

Review

New Psychoactive Substances: Health and Legal Challenges

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Abstract: Drug abuse represents a significant public health problem with a growing tendency. As a way of circumventing the strict national and international control of psychoactive substances by regulatory agencies, there is a market release of new substances with psychoactive activity, called New Psychoactive Substances (NPSs). This group of substances encompasses a diverse range of synthetic compounds designed to mimic the effects of traditional illicit substances. As NPSs show stronger psychoactive effects than classical drugs, they pose unique challenges to public health and regulatory frameworks. Additionally, some substances are considered NPSs in some countries but not in others. Therefore, based on a given legal definition, manufacturers can create an NPS that does not fall under that definition and thus is not prohibited. This review critically explores the multifaceted dimensions of the criminal and legal contexts associated with NPSs. It examines the trends of abuse, the intricate network of criminal and legal aspects surrounding these substances, and the crucial warning signs that indicate their emergence, highlighting the health risks posed by these substances. In conclusion, this manuscript addresses the intricate interplay between the pharmacology, risks, and regulatory responses. These multifaceted challenges associated with NPSs will likely provide valuable insights for future research.



Citation: Santos, I.C.; Maia, D.; Dinis-Oliveira, R.J.; Barbosa, D.J. New Psychoactive Substances: Health and Legal Challenges. *Psychoactives* **2024**, *3*, 285–302. <https://doi.org/10.3390/psychoactives3020018>

Academic Editor: Jeremy Carlier

Received: 26 April 2024

Revised: 23 May 2024

Accepted: 29 May 2024

Published: 1 June 2024



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Keywords: new psychoactive substances; trends of drug abuse; forensic aspects; warning signs; public health

1. Introduction

Substance Use Disorder (SUD) represents a growing health problem that transcends geographical boundaries, socioeconomic strata, and cultural settings. Intrinsicly, SUD is a reflex of the human story, as it represents a manifestation of societal challenges, personal struggles, and the intricate interplay of biological, psychological, and environmental factors. Therefore, it significantly challenges public health and individual well-being [1,2].

Over the last few years, we have been facing a high dynamism in the illicit drug market. Up until a few years ago, the illicit drug market was essentially populated by classic drugs, including amphetamine derivatives and other heavy drugs like cocaine or heroin. However, in recent years, we have faced the growing development and release of new drugs in the illicit market, known as New Psychoactive Substances (NPSs; also commonly referred to as “designer drugs” or “legal highs”) [3,4]. Chemically, they represent a category of synthetic or semi-synthetic substances created by modifying the chemical structure of well-known drugs. They include a wide range of substances, such as synthetic cannabinoids, synthetic cathinones (commonly known as “bath salts”), hallucinogens, and stimulants.

Mechanistically, they mimic traditional illicit substances, producing similar or even more pronounced psychoactive effects [4].

The rationale behind their advancement is the development of novel compounds that are not yet classified as illegal, allowing them to circumvent existing drug laws. However, as these substances gain popularity, authorities update regulations to control their distribution and use [5–8].

Despite all these regulatory mechanisms, NPSs are frequently marketed as legal alternatives to traditional illicit drugs. Such an idea creates several risks for human health [9–12]. A significant aspect is the uncertainty about their safety profile, as the development of new compounds is faster than the research into their pharmacological/toxicological effects. Moreover, the need for quality control in terms of their production raises concerns about the purity and potency of these products [13]. In addition, NPSs are marketed and distributed through online platforms, making them easily accessible to a global audience. This online marketing dramatically contributes to the challenges of regulating and controlling these substances. Therefore, users may be exposed to unexpected health risks, including severe physical and psychological reactions [8,12].

This manuscript explores the dynamic environment surrounding NPSs, including the abuse trends, legal frameworks, and critical warning signs associated with their emergence. Thus, it provides a comprehensive understanding of the broader implications of using and distributing NPSs.

2. New Psychoactive Substances: An Overview

New Psychoactive Substances include a wide range of synthetic substances specifically developed to produce psychoactive effects. Such drugs are characterized by a structural diversity created by modifying the molecular structures of existing substances or classical drugs. This structural diversity poses additional challenges for regulatory agencies and authorities, making it difficult to closely control the dissemination and abuse of these substances. This problem is even more fundamental as they are frequently nicknamed legal and safe alternatives to traditional drugs. The coexistence of these drugs in a world of uncontrolled control creates an additional layer of complexity, posing a clear risk to human health [14,15].

Like most illicit drugs, NPS substances are associated with distinct ways of consumption, including smoking, snorting, swallowing, or injecting. Some can be sold as powders, pills, or liquids (e.g., synthetic cathinones), while others are infused on plant material, resembling traditional herbal products (e.g., synthetic cannabinoids). In addition, their consumption is not confined to a specific demographic: it is transversal to distinct age groups, socioeconomic environments, and geographic regions [4,16].

The lack of regulated production and quality control challenges the prediction of NPS abuse effects and potential risks. Users may experience severe adverse reactions, including psychosis, seizures, and even death. Therefore, developing comprehensive and flexible legislation is essential to address the dynamic nature of the NPS market and restrict the consequences for human health [8,17].

NPSs represent a complex and challenging phenomenon in the illicit drug world. The dynamic nature of these substances, coupled with the globalization of their distribution, forces the implementation of advanced research, adaptable regulatory frameworks, and international collaboration to effectively address the risks and consequences associated with NPS use, which constitutes a significant dilemma that is far from being solved [3,18,19].

3. Historical Perspective and Trends of NPS Abuse

The emergence of NPSs has a complex and multifaceted history that began several decades ago. The cultural movements that characterized the decades of the 1960s and 1970s resulted in the first wave of synthetic drugs, with an increase in the recreational use of lysergic acid diethylamide (LSD), amphetamines, and hallucinogens [20]. In the same decades, substances like phencyclidine (PCP) [21] and methaqualone [22] emerged

as a consequence of efforts made by pharmaceutical companies to actively develop novel compounds with psychoactive properties.

The decade of the 1980s made a crucial mark in the field of NPSs with the advent of the so-called designer drugs [23], synthesized to mimic the effects of controlled substances while evading legal regulations [24]. To face such a scenario, in 1986, the United States of America introduced the Federal Analog Act, which aimed to control substances structurally similar to controlled drugs (but only if intended for human consumption). This allowed the United States to strengthen the legal gaps that manufacturers were utilizing to introduce novel designer drugs onto the illicit market [25,26].

The last decade of the 20th century was crucial for the advent of NPSs. We faced an incredible increase in the widespread popularity of 3,4-methylenedioxymethamphetamine (MDMA) in rave cultures and nightclub scenes [27,28]. Such a generalization inflamed the chemical industry. This resulted in an exponential increase in the synthesis of new derivatives of existing drugs to create novel psychoactive drugs with more potent effects than those of classical compounds [29]. Therefore, the efforts made during this decade significantly contributed to the evolution of the designer drug market.

The advent of the internet at the beginning of the 21st century represented the final blow to the globalization of the NPS market. The internet facilitated the rapid spread of information and allowed for online “trafficking” of drugs, which pushed the NPS market toward a less controlled scenario [30,31]. In line with this, it assisted in the rapid emergence of NPSs, including synthetic cannabinoids and synthetic cathinones, frequently sold, although wrongly, as legal alternatives to traditional drugs.

Although the diversity of NPSs continues to expand, with new compounds regularly entering the market, agencies and authorities all over the world have been making increased efforts to control globalization and the prevalence of illicit NPS use. Such efforts include temporary bans on specific substances or the implementation of comprehensive legislation targeting entire classes of compounds. However, the global picture poses demanding challenges for legislators and law enforcement agencies that continue in the present.

Nowadays, with the more refined power of the pharmaceutical industry, we are facing an ever-increasing number of novel psychoactive substances being introduced into the illicit market. In 2021, European Union Member States seized a record 8.5 tons of NPSs, corresponding to approximately 400 drugs. In 2022, the EMCDDA monitored around 930 NPSs, with 41 first reported in Europe in 2022 [32]. In Europe, the number of young adults (aged 15 to 34) that used NPSs last year (excluding ketamine and GHB) varied significantly. In Latvia, only 0.1% of young adults reported using these drugs, while in Romania, it was as high as 5.1% [32]. For 15- to 16-year-old students, a survey from 2019 revealed that the lifetime use of NPSs ranged from 0.9% to 6.6%. Mainly, the lifetime use of synthetic cannabinoids ranged from 1.1% to 5.2%, while that of synthetic cathinones ranged from 0.2% to 2.5% [32]. Nevertheless, regulatory agencies have not been able to follow the dynamic nature of the market, and therefore, we have been facing continuous obstacles and limitations in the control of NPS dissemination and abuse.

4. Categories of New Psychoactive Substances

New Psychoactive Substances encompass a wide range of substances, including synthetic and semi-synthetic cannabinoids, synthetic cathinones, phenethylamines, aminoin-danes, piperazine designer drugs, synthetic opioids, tryptamines, and dissociative drugs. A brief description of each class is provided below and illustrated in Figure 1.

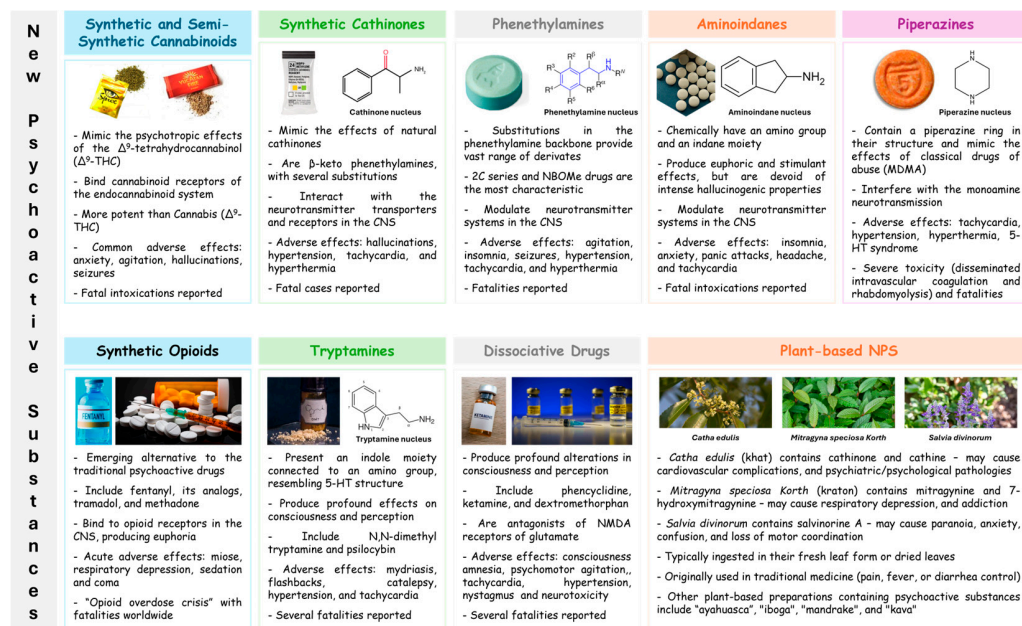


Figure 1. Main characteristics of different categories of NPSs.

4.1. Synthetic and Semi-Synthetic Cannabinoids

Synthetic cannabinoids, frequently called synthetic marijuana or “spice”, are synthetic drugs that mimic the psychotropic effects of Δ -9-tetrahydrocannabinol (THC), the psychoactive component in natural cannabis.

Semi-synthetic cannabinoids are derived from naturally occurring cannabinoids such as THC and cannabidiol (CBD) [33]. Their synthesis involves the chemical modification of these natural compounds to produce new molecules with distinct properties. Common modifications include the addition of functional groups, alteration of the carbon skeleton, and cyclization. Examples of substances included in this category include 1,1-Dimethylheptyl-11-hydroxy-tetrahydrocannabinol (HU-210), synthesized by modifying the terpene structure of THC [34], and hexahydrocannabinol (HHC), a hydrogenated derivative of THC that is also a naturally occurring phytocannabinoid [35].

These substances are chemically designed to bind cannabinoid receptors of the endocannabinoid system in the brain and peripheral tissues as THC, producing psychoactive effects [35–37]. However, synthetic and semi-synthetic cannabinoids are distinct from natural cannabis and can be much more potent, leading to unpredictable and potentially dangerous outcomes [35,37].

They are usually produced in clandestine laboratories by chemically substituting already existing molecular structures, allowing manufacturers to stay ahead of regulatory efforts. In addition, the specific chemical composition can vary greatly, making it challenging to accurately predict their effects [38].

The use of synthetic and semi-synthetic cannabinoids has been associated with a variety of adverse effects, including anxiety, agitation, hallucinations, seizures, and, in extreme cases, severe risks to life. However, the long-term effects of repeated use are poorly understood [39]. Fatalities associated with synthetic cannabinoids have been reported [40,41].

In 2022, the Early Warning System of the European Union received reports of 24 new synthetic cannabinoids, increasing the total number under monitoring to 245 [32]. In addition, in 2021, there were seizures totaling 242 kg of low-THC herbal cannabis material containing synthetic cannabinoids, compared to 37 kg in 2020 and 200 g in 2019 [32].

4.2. Synthetic Cathinones

Synthetic cathinones, also known as “bath salts”, are a group of synthetic stimulant drugs that belong to the larger family of substances known as cathinones [42–44]. Cathi-

nonones, naturally occurring stimulants, are found in the leaves of the khat plant (*Catha edulis*), native to East Africa and the Arabian Peninsula [45,46]. Synthetic cathinones mimic the effects of these natural stimulants, but they are chemically designed to produce more potent and, most of the time, unpredictable psychoactive effects [42,43]. Their emergence as NPSs in the early 20th century coincided with increasing regulatory control over traditional illicit drugs [47].

Chemically, these compounds share a β -keto phenethylamine backbone, with several substitutions at the alpha carbon and other positions. These structural modifications result in distinct pharmacological profiles, allowing their classification into three main groups. (1) Synthetic cathinones with cocaine–MDMA mixed effects that non-selectively inhibit the reuptake of neurotransmitters and promote serotonin (5-HT) release. This group includes compounds like mephedrone, methylone, ethylone, and butylone. (2) Synthetic cathinones with effects similar to methamphetamine that preferentially inhibit dopamine and noradrenaline reuptake transporters (DAT and NAT, respectively) and promote dopamine release. Compounds like methcathinone, fluoromethcathinone (4-FMC), and 4-chloromethcathinone (clephedrone) are included in this group. (3) Pyrovalerone cathinones, which possess the pyrrolidine moiety and selectively inhibit DAT and NAT but do not interfere with monoamines' release. This group includes pyrovalerone and 3,4-methylenedioxypropylpyrovalerone (MDPV) [42,44,48]. Therefore, the psychostimulant properties of synthetic cathinones come from their interaction with neurotransmitter systems.

The use of synthetic cathinones is particularly relevant for recreational purposes, including in nightclubs, music festivals, and parties, as they produce stimulant and empathogenic effects. Due to their chemical diversity, their effects on human health can vary significantly and largely depend on the dose, the route of administration (usually consumed orally), individual susceptibility, and concomitant use of other drugs. However, their classical acute effects include agitation, delusions, hallucinations, hypertension, tachycardia, and hyperthermia [44]. Although the long-term effects of synthetic cathinone consumption are not fully understood, evidence suggests potential cognitive impairment, psychiatric disorders, and cardiovascular problems [44]. In 2021, 3-methylmethcathinone (3-MMC) was involved in 68 acute drug toxicity presentations across 5 Euro-DEN Plus hospitals [32]. Additionally, the consumption of synthetic cathinones has been associated with severe toxicity, including neurotoxicity (reviewed in [49]), and fatalities [50,51].

In 2021, more than 47% of the quantity of NPSs seized in the European Union (total of 8.5 tons) was attributed to three cathinones: 3-chloromethcathinone (3-CMC), 3-MMC, and 4-chloromethcathinone (4-CMC) [32].

4.3. Phenethylamines

Phenethylamine drugs represent a diverse class of compounds increasingly prevalent in society due to their wide-ranging effects on the central nervous system, including stimulant and psychoactive effects. Chemically, they are characterized by the presence of a phenethylamine backbone in their chemical structure, with substituent groups introducing a vast range of derivatives with distinct pharmacological profiles.

The discovery of phenethylamine drugs started in the early 20th century with P-methoxymethamphetamine, also known as PMMA, in 1938 [52] due to the scientific and cultural attention that was paid to amphetamine and mescaline. The late 20th century was characterized by the introduction of the 2C series of phenethylamines, which show aromatic ring substitutions [e.g., 2-(4-ethyl-2,5-dimethoxyphenyl)ethanamine, also known as 2C-E] or the D series, which represent amphetamines with aromatic substitutions (e.g., 1-(4-iodo-2,5-dimethoxyphenyl)propan-2-amine, also known as DOI) [53]. Subsequently, the introduction of a methoxybenzyl group on the nitrogen of the 2C series gave rise to the NBOMe drugs (e.g., 2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine, also known as 25I-NBOMe). Although initially synthesized in the early 21st century, NBOMe drugs only reached the illicit market in 2010. They show potent agonism activity on 5-HT_{2A} receptors, resulting in hallucinogenic effects more robust than those seen with

the 2C drugs [54]. This class of drugs also incorporates the benzodifurans, which include compounds like 5-(2-aminopropyl)benzofuran (5-APB) or 6-(2-aminopropyl)benzofuran (6-APB) [55].

Pharmacologically, phenethylamine drugs modulate neurotransmitter systems in the central nervous system (CNS) through reuptake inhibition or direct agonism/antagonism of neurotransmitter receptors [56]. Thus, according to their pharmacological profile, they can be categorized as stimulants, hallucinogens, empathogens, and entactogens.

Common adverse effects of these drugs are agitation, loss of appetite, nausea, hypertension, tachycardia, hyperthermia, insomnia, and seizures. Phenethylamines with hallucinogenic properties may also induce or exacerbate psychological/psychiatric conditions (anxiety and psychosis) [57]. Additionally, the consumption of phenethylamines has been associated with cases of severe toxicity and fatalities [58–60].

4.4. Aminoindanes

Among the different categories of NPSs, aminoindanes have gained increased interest [4]. Although they were initially developed and investigated for therapeutic purposes, including as vasoactive and bronchodilator agents [61], potent non-narcotic analgesics [62], or monoamine oxidase inhibitors with potential anti-Parkinson activity [63], their euphoric and stimulant effects (e.g., euphoria, enhanced empathy, and alterations in perception) rapidly led to their emergence as drugs of abuse [64].

Chemically, their molecular structure includes an amino group and an indane moiety. The indane ring allows for synthesizing several derivatives that may show more pronounced and unpredictable effects than the classical drugs [65]. Notably, 5,6-methylenedioxy-2-aminoindane (MDAI) has emerged as a significant aminoindane on the drug abuse market. While lacking the intense hallucinogenic effects of classic psychedelics (e.g., LSD or psilocybin), it gained notoriety in recreational drug scenarios for its empathogenic effects, characterized by increased feelings of empathy, sociability, and emotional openness. Other aminoindanes, including 5,6-methylenedioxy-N-methyl-2-aminoindane (MDMAI), 2-aminoindane (2-AI), 5-iodo-2-aminoindane (5-IAI), 5-methoxy-6-methyl-2-aminoindane (MMAI), and 5-methoxy-2-aminoindane (MEAI), have also emerged as a new generation of NPSs [66].

Pharmacologically, aminoindanes modulate neurotransmitter systems in the CNS by mechanisms involving reuptake inhibition or direct agonism of neurotransmitter receptors. For example, MDAI and 5-IAI strongly inhibit SERT and NAT while promoting 5-HT release. In contrast, 2-AI preferentially inhibits NAT and promotes the release of both 5-HT and dopamine [67,68].

Common adverse effects of these drugs include tachycardia, agitation, hallucinations, headache, insomnia, anxiety, and panic attacks [69]. In addition, fatal intoxications have been associated with abuse of this class of drugs [70].

4.5. Piperazines

Piperazine designer drugs constitute a group of synthetic substances containing a piperazine ring in their structure, designed to mimic the effects of traditional, controlled drugs of abuse, such as MDMA and other amphetamines [24].

This class of compounds encompasses a large variety of substances, with the most representative examples including benzylpiperazine (BZP), 1-(3,4-methylenedioxybenzyl) piperazine (MDBP), 1-(3-chlorophenyl) piperazine (*m*CPP), 1-[3-(Trifluoro-methyl)-phenyl] piperazine (TFMPP), and 1-(4-Methoxyphenyl)piperazine (MeOPP) [24].

Pharmacologically, piperazine designer drugs interfere with monoamine neurotransmission with distinct patterns. TFMPP preferentially blocks the 5-HT reuptake transporter (SERT), whereas *m*CPP inhibits both SERT and NAT with similar potencies. They also bind to several serotonergic, adrenergic, dopaminergic, and histaminergic receptors. In contrast, BZP is a selective NAT inhibitor devoid of affinity at the monoamine receptors [67]. Their clandestine synthesis renders their composition and potency unpredictable, as formulations

frequently contain a mixture of compounds, including piperazine derivatives, stimulants, hallucinogens, adulterants, and other contaminants. Consequently, the variability of formulations contributes to the unpredictability of their pharmacological effects and safety profiles, creating another layer of complexity regarding the health risk [24].

These drugs are associated with a range of acute adverse effects, including tachycardia, hypertension, hyperthermia, dehydration, seizures, and 5-HT syndrome. Additionally, psychological symptoms such as short temper, confusion, anxiety, depression, and paranoia, have been linked to the use of piperazine designer drugs [71]. Moreover, the consumption of these drugs has been associated with severe toxicity, including disseminated intravascular coagulation and rhabdomyolysis [72], as well as with fatalities [73,74].

4.6. Synthetic Opioids

Synthetic opioids are increasingly emerging on the illicit market as an alternative to the more traditional psychoactive compounds that are regulated. Their abuse potential is a direct consequence of their higher potency and selectivity, presenting a significant public health problem due to the associated morbidity and mortality [75].

This class of compounds encompasses a large variety of substances, including fentanyl analogs, tramadol, and methadone [76]. Mainly, fentanyl and its analogs, such as carfentanil and acetylfentanyl, are potent synthetic opioids with 50–100 times higher potency than morphine, a natural opioid found in opium [77]. For illicit purposes, these substances are usually synthesized in clandestine laboratories [75].

Pharmacologically, synthetic opioids bind to opioid receptors in the CNS, producing analgesia, euphoria, and respiratory depression (also used as antitussive drugs). The acute adverse effects of synthetic opioids include miosis, respiratory depression, sedation, and coma. Chronic abuse can lead to opioid dependence, tolerance, and withdrawal syndrome. Moreover, the clandestine production of synthetic opioids frequently results in variations in the purity and composition, increasing the likelihood of adverse reactions [75,76]. Thus, due to their potent pharmacological effects and unpredictable potency, synthetic opioids pose significant health risks.

Since 2009, authorities have identified 74 new opioids being sold on the European drug market. In 2022, they identified one new substance (compared to six in 2021 and ten in 2020). Data from 2021 report 740 seizures of synthetic opioids registered by the Early Warning System of the European Union. Of these seizures, 45% contained carfentanil and 22% contained isotonitazene. In addition, authorities have seized 8.2 kg of material, where 4.9 kg (59%) contained carfentanil and 1.9 kg (23%) contained isotonitazene. Therefore, fentanyl analogs represent the most identified drugs [32]. In line with these observations, the illicit abuse of synthetic opioids has contributed to a rise in opioid-related overdoses and fatalities worldwide. Particularly in North America, the illegal distribution of fentanyl and its analogs over recent years has led to the “opioid overdose crisis”, with substantial impacts on human health [78,79].

4.7. Tryptamines

Tryptamines represent a class of psychoactive substances that produce profound effects on consciousness and perception. From ancient rituals to contemporary cultural movements, tryptamines have been used for medicinal purposes, as a trigger of spiritual experiences, or to promote artistic inspiration or altered states of consciousness. However, due to their euphoric, hallucinogenic, and mind-altering effects, some tryptamines have emerged on the illicit market as drugs of abuse [80].

These compounds can occur naturally in plants of the genera *Acacia*, *Mimosa*, *Anadenanthera*, *Chrysanthemum*, *Psychotria*, *Desmanthus*, *Pilocarpus*, *Virola*, *Prestonia*, *Diplopterys*, *Arundo*, and *Phalaris*, among others, or be chemically synthesized in clandestine laboratories. Classic examples of tryptamines include *N,N*-dimethyltryptamine (DMT), the primary active substance in the psychoactive brew “ayahuasca” [81], and psilocybin, present in *Psilocybe* spp. mushrooms [82]. In addition, several synthetic tryptamines, including

5-MeO-DALT (5-methoxy-*N,N*-diallyltryptamine) [83] and 4-AcO-DMT (4-acetoxy-*N,N*-dimethyltryptamine) [84], exhibit pronounced psychoactive effects and have emerged on illicit drug markets as substitutes for classic psychedelics [85].

Chemically, tryptamines present an indole moiety connected to an amino group, a structure resembling 5-HT. Consequently, tryptamines primarily act as agonists of 5-HT receptors. Notably, the agonism on the 5-HT_{2A} receptor is responsible for altering the perception of reality and hallucinations [24]. They also activate 5-HT_{1A} receptors, which contributes to their psychedelic effects [86]. In addition, tryptamines also bind adrenergic, dopaminergic, and histaminergic receptors [87] and interact with SERT, DAT, and NAT, promoting neurotransmitter release [88].

The characteristic adverse effects of tryptamines include loss of appetite, sweating, mydriasis, restlessness, disorientation, amnesia, catalepsy, tachypnea, hypertension, and tachycardia [24,89,90], some of which are associated with interference in 5-HT-dependent mechanisms. Additionally, long-term flashbacks and psychological disturbances like acute psychosis may also occur [24,91]. Fatal intoxications by tryptamines have also been reported [92–94].

4.8. Dissociative Drugs

Dissociative drugs represent a class of compounds capable of inducing profound alterations in consciousness and perception. While initially developed for medical and therapeutic purposes due to their anesthetic and analgesic properties, their characteristic psychoactive effects, such as “out-of-body” and “near-death” experiences, as well as their euphoric, hallucinogenic, or sensory-enhancing properties, have led to their rapid dissemination as drugs of abuse in contemporary society.

Among the most well-known dissociative drugs are phencyclidine (PCP), ketamine, and dextromethorphan (DXM). Pharmacologically, these drugs act as antagonists on *N*-methyl-*D*-aspartate (NMDA) receptors, a subtype of ionotropic glutamate receptor, thus blocking the transport of ions, particularly Ca²⁺ [95]. Since the excitatory effect of glutamate is blocked, pain perception ceases and environmental responses become compromised [96]. The inhibition of NMDA receptors is the primary mechanism behind the psychoactive effects of these drugs.

Common acute adverse effects of these drugs include psychomotor agitation, consciousness, amnesia, tachycardia, hypertension, and nystagmus [97]. In addition to their acute effects, long-term use of dissociative drugs may have consequences for brain structure and function. For example, long-term use of ketamine has been associated with neurotoxicity [98], cognitive impairments [99], and psychiatric disturbances, such as psychosis and mood disorders [100–102]. Several cases of overdose involving dissociative drugs, including ketamine [103], PCP [104], 3-methoxyphencyclidine [105], or DXM [106,107], have been implicated in fatal intoxications. In 2021, from the 8.5 tons of NPSs seized in the European Union, 9.9 tons (11%) were attributed to ketamine [32].

4.9. Plant-Based New Psychoactive Substances

Recently, there has been growing interest and concern regarding the emergence of plant-based NPSs. These include khat (*Catha edulis*), kratom (*Mitragyna speciosa* Korth), and *Salvia divinorum*. Usually, these substances are ingested in their fresh leaf form, although dried leaves are also accessible. Given their characteristics, they are commonly chewed, smoked, infused, or brewed for consumption as tea. Traditional medicine originally used them to manage several conditions, including pain, fever, or diarrhea [4,108].

The psychoactive effects of khat come from its active constituents, including cathinone and cathine. These compounds can induce a state of increased energy, alertness, and euphoria. In addition, they also suppress appetite and fatigue. Long-term use of khat has been associated with several adverse effects, including cardiovascular complications, psychiatric/psychological pathologies, and dependency [45,46].

Kratom contains several active alkaloids, including mitragynine and 7-hydroxymitragynine, which are the most prevalent and pharmacologically active. These alkaloids primarily act on opioid receptors in the brain, resulting in analgesic, euphoric, and sedative effects [109,110]. Of note, mitragynine, at lower doses, exhibits stimulating properties, while 7-hydroxymitragynine is associated with more potent opioid-like effects [111]. The effects of kratom depend on the dosage and individual sensitivity, and they include increased energy, sociability, relaxation, and pain management. On the other hand, adverse effects associated with kratom use include nausea, vomiting, constipation, respiratory depression, and addiction [112].

The active compound responsible for *Salvia divinorum* psychoactive effects is salvinorin A, a potent κ -opioid receptor agonist [113]. Unlike other hallucinogen compounds, salvinorin A does not modulate serotonergic neurotransmission but interacts with opioid receptors in the brain, causing intense alterations in body perception, consciousness, dissociative states, ego dissolution, and sensory experiences [114]. The most significant adverse effects of *Salvia divinorum* include paranoia, anxiety, confusion, and loss of motor coordination [115].

Other plant-based NPSs include “ayahuasca”, which contains the psychoactive compound DMT, that is classified in the tryptamines category [116]. Additionally, “magic mushrooms” contain the bioactive molecule psilocybin, which is also included in the tryptamines category [117]. Other plant-based psychoactive substances exist, such as “iboga”, “mandrake”, and “kava”, although some of them remain unclassified as NPSs [4].

These substances represent a paradigm shift in drug use, posing unique challenges and opportunities for public health, regulatory bodies, and the whole of society.

5. Legal and Criminal Aspects Related to New Psychoactive Substance Abuse

The emerging growth of NPSs is a problem for legal systems worldwide. The general challenges of NPS legislation are depicted in Figure 2.

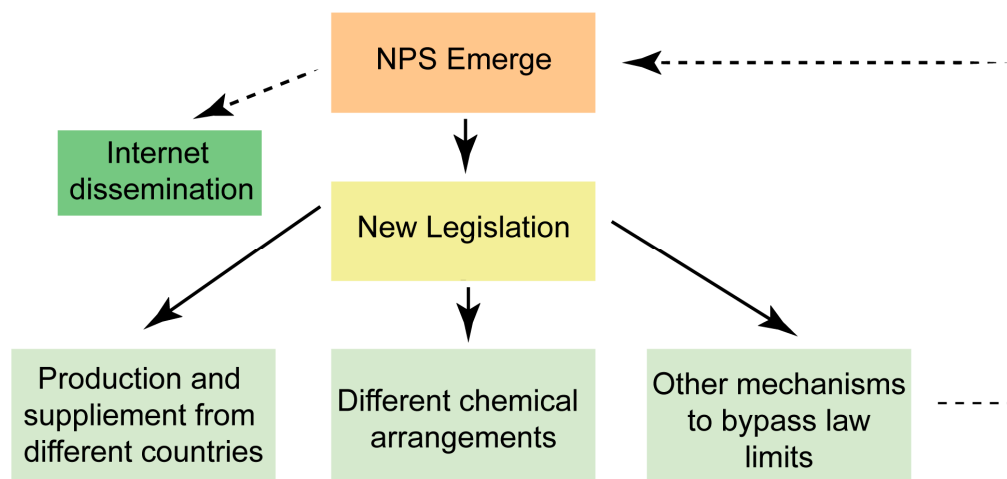


Figure 2. General challenges of NPS legislation.

The term NPS is given by legal definitions that are only sometimes accepted. This means that a particular substance can be considered an NPS in some countries, whereas in others, it cannot be. Based on a given legal definition, manufacturers can create an NPS that does not fall under those definitions and thus is not prohibited. NPSs started by being sold on the open market since they have not been restricted by national/international legislation. The internet disseminates the promotion and commercialization of these substances almost instantaneously. NPS sellers and producers are also fast enough to reinvent themselves and bypass legal limits (Figure 2). For instance, they created a system named “Methspresso”, which allows them to overcome the limits of the law. Customers can legally acquire some drugs and convert them into psychoactive compounds at home simply by heating them in

hydrochloric acid for six hours [118]. This means that regulation is always one step behind NPS emergence, potentiating the cat and mouse game.

Individual and global efforts are being made within legal systems around the world. As NPSs evolve, those systems try to follow the tendencies by creating new legislation, optimizing the existing legislation, or creating agencies to study and follow the risks posed by NPSs [3]. In Europe, the European Union (EU) and individual Member States have been working to speed up all the processes [119,120]. The main advantages and disadvantages of NPS legalization are summarized in Figure 3.

Advantages	Disadvantages
<ul style="list-style-type: none"> → Regulation and Control: Allows for the implementation of regulations and controls over the production, distribution, and sale of NPS, ensuring higher standards of quality and safety. → Reduction of the Black Market: decrease the black market associated with NPS, discouraging criminal activity and illegal trade. → Safe Access: Consumers have access to NPS from safe and reliable sources, reducing the risk of exposure to adulterated or dangerous substances. → Information and Education: implementation of educational and informational programs about the risks and benefits of NPS, empowering consumers to make more informed decisions. → Harm Reduction: implementantation of harm reduction measures such as needle exchange programs, substance purity testing, and access to health and support services to reduce harms associated with NPS use. → Therapeutic Potential: access for research purposes and development of potential therapeutic applications of NPS, offering new treatment options for specific medical conditions. 	<ul style="list-style-type: none"> → Public Health Risks: Increase access and availability of NPS, potentially raising public health risks including overdoses and dependency issues. → Normalization of Use: Normalize the use of NPS in society, leading to increased consumption and potentially contributing to public health problems. → Regulatory Challenges: Effectively regulating and controlling the NPS market can be challenging. → Youth Impact: The legal availability of NPS may increase accessibility of these substances to youth, heightening the risk of drug initiation. → Potential for Abuse: Increase recreational use and abuse of these substances, especially if adequate prevention and treatment measures are not implemented. → International Pressures: Resistance and criticism from international organizations and countries maintaining stricter prohibition policies, creating diplomatic tensions and political challenges.

Figure 3. Summary of the advantages and disadvantages of NPS legalization.

Different legal measures have been adopted within different law systems for NPS producers, consumers, or sellers. In the UK, NPS production, supplement, or supplement offers are considered offenses that penalize individuals with up to a maximum of 7 years of imprisonment [121]. Nevertheless, the prohibition and the criminalization of the trafficking and consumption of such NPSs seem mostly ineffective in discouraging their use and avoiding the increase in NPS-related public health problems. Indeed, different national legislative approaches that either consist of bans on specific groups of drugs according to the effect on the user (as is the case in the UK) or based on precisely defined chemical families of substances (as is the case in Germany) have failed to decrease NPS-related criminality and addiction [122,123]. Instead, the restriction caused by general drug legislation led to an increase in purchases on the illicit market, together with traditional drugs [123]. For instance, China’s restriction on the trafficking and production of illicitly manufactured fentanyl and its analogs led to a decrease in direct shipments to the USA. Still, it did not prevent the opioid crisis in the latter country. This is mainly explained by the fact that NPSs are often shipped in small quantities that are difficult to trade [124]. However,

other countries provide these NPSs. In Europe, due to legal restrictions imposed by China regarding some synthetic cathinones and the supply disruption caused by COVID-19, authorities assisted a change in the production and trafficking of NPSs from China to India [125].

Nevertheless, as mentioned in the previous section, regardless of the adverse effects of NPSs, some of them can be used for medical purposes. For instance, some fentanyl precursors were needed for therapeutic drug production, and this constitutes an exception to China's production and trafficking prohibition [123,126–128]. Thus, with the ban on the use and production of NPSs, states may be depriving communities of using some of the benefits of NPSs, particularly for health purposes [118].

Therefore, reflecting on the risks and benefits of penalizing these substances is important. There are many critics of the ban and the punishments associated with NPSs who argue that such measures lead to an increase in the death rates related to NPSs and an increase in sales on the illicit market rather than in head shops, where information about the dosage and potency could be provided and the quality control can be accessed [118]. Thus, these critics defend the idea that the only ones who will benefit from the NPS ban are the drug dealers and organized crime groups that can add more products to their catalogs to sell. On the other hand, they can try to convert NPS users to more traditional drugs once they are more expensive and the level of addictivity is higher. Another issue concerning NPS legislation is related to its applicability if the psychological activity of a substance is difficult to prove in court [118].

Indeed, the *Lancet Commission Report* pointed out not only the regulatory and legislative bodies as being responsible for the opioid crisis in the USA but also the medical profession and healthcare systems [124]. The lack of awareness, reliable literature, and training within medical departments is a limiting step in identifying, diagnosing, and efficiently treating NPS intoxications [118,129]. Despite these, the number of patients presenting with NPS-related symptoms is increasing, forcing healthcare professionals to develop their skills [130]. This results in a lack of confidence among healthcare professionals in treating NPS toxicity, seeking information from other colleagues, users, media, training, and drug- and alcohol-monitoring information systems [118].

Although NPS use carries numerous dangers, the truth is that it cannot be seen as a black-and-white subject since their use for medical purposes brings considerable advances in reducing, for instance, pain. These dual effects are two sides of the same coin that must be weighed when it comes to acting and making decisions to stop the NPS crisis.

6. Warning Signs of New Psychoactive Substance Abuse

The idea that “good decisions rely on good data” motivated the EU to develop a three-step legal framework consisting of early warning, risk assessment, and control measures. The main goals rely on rapid detection, assessment, and response to NPS threats. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), in close cooperation with Europol, is responsible for the early warning and risk assessment, and the European Commission oversees the proposal of control measures to stop NPS harms. This system is seen as a model that led to the EMCDDA establishing profound collaborations with the World Health Organization (WHO) and the United Nations Office on Drugs and Crime (UNODC).

Between 1997 and 2021, the EMCDDA monitored 884 NPSs that appeared in Europe [125]. Interestingly, from 2016 to 2021, an average of 50 NPSs per year emerged on the European drug market, corresponding to half of the NPSs observed in 2014 and 2015. The EMCDDA attributed this drop to global efforts to control and restrict the sales of NPSs in Europe and the restrictions imposed on several countries [125]. Synthetic cathinones were the second largest category of NPS monitored by EMCDDA in 2021. The legal restrictions imposed in countries that were mainly responsible for the production and supply of synthetic cathinones increased the number of illicit laboratories based in Europe dedicated to producing these NPSs [125]. Dismantling these laboratories brings about health risks

based on the risk of explosion and public and environmental hazards due to chemical waste [125,131].

A deep concern regarding NPSs centers on the facility of diffusion of these substances promoted by the internet (Figure 3). As some NPSs can be used for medical purposes, some of the effects of NPS use are already known. However, numerous NPSs lack information about safety, toxicity, and long-lasting effects. This means that most of the effects of NPSs will only be recognized when many people are exposed to the substances. The purity and composition of these substances are also health threats. The use of synthetic stimulants was developed to treat patients who have Parkinson's disease, obesity, and depression [14,132,133]. More recently, they have been used as cognitive enhancers (commonly used by students or professionals who need to focus when working in stressful environments), to enhance athletes' performance and to help people lose weight [14,134,135]. The use of synthetic stimulants during sexual practices with multiple partners to enhance sexual performance, commonly without protection, potentiates the transmission of sexual diseases [14,136]. Additionally, the consumption of these substances by students, athletes, and people suffering from attention deficit hyperactivity disorder, who order them from the internet or other places without consulting a health professional, increases the risk of drug toxicity (by interacting with other drugs prescribed by physicians) or can result in the therapeutic efficacy being reduced [137]. The addiction potential of synthetic cannabinoids is also a concern since it was reported that users need to consume them every 30 min to avoid feeling unwell [14,138–140]. The high potency of some NPSs is also an issue because it increases the probability of developing severe acute poisoning. This poisoning can be massive and constitute a risk to life. Thus, much pressure within healthcare units can be exerted, resulting in high financial costs for governments [125,141].

7. Concluding Remarks

In the field of drug abuse, it has become evident that addressing the challenges posed by NPSs requires a holistic and dynamic approach that integrates researchers, legislators, and public health initiatives. Notably, NPSs' increasing diversity highlights the need for continuous monitoring and research. The legal scenario surrounding NPSs is complex, but, most of the time, it is not accompanied by the rapid development of restrictive measures to control their consumption and dissemination. In addition, the patterns of abuse of NPSs are dynamic, which reinforces the need for constant adaptation of international agencies and authorities to implement suitable procedures to deal with this problematic situation. Therefore, proactive legal measures involving comprehensive and adaptable strategies are essential to limit the proliferation of these substances in the shadow of legal ambiguity. Indeed, this would require strengthened international collaboration to make information-sharing, legislative approaches, and enforcement strategies effective.

In line with this, the identification of emerging warning signs associated with NPS abuse is crucial for timely intervention and prevention efforts. The unpredictable nature of these substances necessitates increased knowledge among healthcare professionals, educators, and the public. Public health initiatives should focus on disseminating accurate information, providing resources for early detection, and fostering a collaborative approach to address the potential harms of NPS use.

By encouraging a comprehensive understanding of NPS dynamism, forensic aspects, and warning signs, this work opens up new perspectives for a proactive and adaptable approach to mitigating the impact of these substances on individuals and society. Therefore, in the future, the collective responsibility of staying informed and the collaboration between different disciplines and research fields will be pivotal in preserving public health and human well-being in the face of the challenges posed by NPSs.

8. Future Perspectives

The use of NPSs is a problem that has persisted for decades and has, regardless of cultural differences, managed to gather some consensus among different countries. Given

the issue’s complexity, various governments have attempted to adopt different measures to curb the growing spread of NPSs, which in many cases have proved ineffective. However, some additional measures can be proposed (Figure 4).

Future perspectives to control the growing spread of NPS	→ Implement policies and cooperation systems among different countries
	→ Consider a multidisciplinary effort that takes into account the country’s geopolitical and social matters
	→ Limit the industry’s influence either in the political or regulation, or in medical prescription (relevant for opioids)
	→ Correct recognition of the risks and benefits for drug-approval purposes, and implementing methods for responsible prescription (relevant for opioids)
	→ Reinforcement of the substance abuse disorders’ system and the stimulation of new responses for addiction
	→ Raise awareness and train healthcare professionals to address the abuse of NPS
	→ Bring public awareness to this problem (better information likely renders more conscious choice)
	→ Develop more sensitive laboratory tests to detect NPS

Figure 4. Summary of the main measures that can be proposed to control the growing spread of NPSs worldwide.

The problem of NPSs is highly complex and involves not only medical and biological aspects but also psychological, sociological, and cultural considerations. Thus, it seems clear that a one-shot approach to this problem is not possible or effective. Instead, considering country, geopolitical, and social matters, a multidisciplinary effort must be undertaken. In 2022, the Lancet Commission identified several issues that exacerbated the opioid crisis in the USA and Canada and proposed several approaches to deal with an emerging opioid pandemic not only in the USA and Canada but also worldwide. First, the commission pointed out that the opioid crisis is a multi-system regulatory failure that must be overcome by limiting the industry’s influence on the political situation, regulation or medical prescription. Secondly, given the dual nature of opioids, a strategy based on the recognition of the risks and benefits for drug-approval purposes, as well as implementing methods for responsible prescription and prevention of certain diseases where opioids can be used on prescription, must be taken. The reinforcement of the substance abuse disorder system and the stimulation of new responses for addiction are proposed to be adopted [124]. These recommendations were inspired by opioid crises that represent a relevant subject in North America. However, we believe that such recommendations can be extrapolated to deal with NPS issues, especially when it comes to addiction.

It is equally important to raise awareness and train healthcare professionals to address the abuse of NPSs, as well as to increase public awareness of this problem. Indeed, individuals who are better informed are likely to make more conscious choices and, consequently, may choose not to consume NPSs. At this level, promoting societal debates on the decriminalization of such drugs may lead to reasonable solutions to address this phenomenon.

Continued efforts should also be made to develop more sensitive laboratory tests to detect NPSs. As suggested by other authors [8], it appears that the only way to curb the use of NPSs is through implementing policies and cooperation systems among different countries. However, despite the solution seeming simple and evident, and some countries beginning to take steps in that direction, its practicability is proving challenging due to the complexity of international relations.

Author Contributions: Conceptualization, D.J.B.; figure preparation, I.C.S. and D.J.B.; writing—original draft preparation, I.C.S., D.M. and D.J.B.; writing—review and editing, I.C.S., R.J.D.-O. and D.J.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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