Novel Psychoactive Substances: Emerging Drugs of Abuse

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Faculty

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Faculty Disclosure

Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This advanced course is designed for psychologists who are involved in the evaluation or treatment of persons who use novel psychoactive substances or whose past use has resulted in untoward effects.

Accreditations & Approvals

American Psychological Association

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Designations of Credit

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Course Objective

The purpose of this course is to provide psychologists with a comprehensive overview of the pharmacology, evolution, and trends of psychoactive substances, thus enabling them to effectively identify, diagnose, treat, and provide appropriate referrals for patients who use novel psychoactive substances.

Learning Objectives

Upon completion of this course, you should be able to:

1. Describe the history, emergence, and proliferation of novel psychoactive substances.
2. Analyze the effects and management of synthetic cathinones and other amphetamine analogs.
3. Outline the pharmacology and effects of synthetic cannabinoid receptor agonists.
4. Identify other synthetic drugs of abuse and emerging botanical products.
5. Discuss strategies for the assessment, prevention, and treatment of novel drug abuse and/or dependence.

INTRODUCTION

A unique trend in recreational and problematic drug use began to emerge in the United States around 2008, with the introduction and proliferation of previously unknown or unavailable psychoactive substances. By 2015, this trend became an established element of domestic and global recreational drug cultures, and nearly two decades later is the center of a global drug crisis. The United Nations Office for Drug and Crime (UNODC) defines novel or new psychoactive substances (NPS) as "a substance 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" [1]. The use of the word "new" or "novel" does not necessarily refer to the invention of a new drug, but rather indicates a substance has emerged or re-emerged as a psychoactive substance or synthetic drug of abuse. NPS often have similar molecular structures as controlled or banned substances but are slightly modified by manufacturing and/or trafficking organizations with intent to circumvent existing drug laws [1; 12].

Since their emergence, NPS have been known in the market by terms such as "designer drugs," "legal highs," "herbal highs," "research chemicals," and/or "bath salts." Additionally, the term "designer drugs" had been traditionally used to identify synthetic substances that mimic the effects of specific prescription drugs. In recent years, however, the term NPS has been broadened to include other psychoactive substances that mimic the effects of illicit and prescription drugs [1].

The NPS phenomenon is characterized by an evolutionary arms race. New drugs are introduced, become banned, and are rapidly replaced by unregulated substances that become banned and rapidly replaced. Earlier NPS (2008–2012) were originally synthesized in academic or pharmaceutical laboratories for research or clinical use, and some briefly entered clinical practice. Post-2012, NPS generations are more likely to be unknown molecular entities that may be more toxic than previous NPS. Potential substances are introduced if the drug shows interesting market potential, has not been banned under a controlled substance act, and/or there is increasing scarcity of an established drug [1]. NPS market turnover is high, but many NPS resemble their banned parent compound molecularly and pharmacologically [1; 10].

Novel psychoactive substances are marketed and distributed in a variety of ways. Traditionally, NPS were promoted and sold in retail shops (e.g., gas stations, convenience stores, smoke shops) or online in both surface websites and in the deep web as "legal high" substitutes for illicit drugs such as cannabis, cocaine, amphetamines, 3,4-methylenedioxy-methamphetamine (MDMA, or Ecstasy), and lysergic acid diethylamide (LSD). In addition, many NPS can evade urine drug testing, thus appealing to individuals subject to routine or random drug testing.

Today, the majority of NPS are sold online through surface websites and by individual drug dealers using online social media and communication platforms [12]. Information about consumption and direct marketing can be found on YouTube channels, social media networks, and smartphone applications created for these purposes and often do not carry or enforce an age restriction. Marketing is also aimed at those with physical and/or mental health issues and those who may not have the resources available or access to visit a healthcare provider. In this case, NPS is marketed as an over-the-counter alternative to prescription drugs for a variety of conditions and ailments, with the perceived benefit of simplifying the process of obtaining a diagnosis and/or prescription [3; 12]. However, there are substantially greater risks of adverse effects and toxicity syndromes with any of these synthetic drugs, highlighting the need for education among healthcare professionals and the public alike.

Understanding the molecular structures and pharmacology of NPS classes can help clinicians predict their clinical effects and toxicity. NPS may go undetected by drug toxicology screening, but NPS toxicity/overdose is readily managed by identifying the characteristic toxicity syndrome. This helps link substance to clinical effect, and understanding the pharmacologic profiles of the underlying molecular group can facilitate effective patient care [4]. Due to significant chemical diversity within NPS and the continuously mounting number of substances, this course will be broken into six broad substance "effect groups," as identified by the UNODC: synthetic cannabinoid receptor agonists (SCRA); classic hallucinogens; opioid receptor agonists; sedative/hypnotics; and dissociatives [1]. Following emergency department care for NPS toxicity/overdose, many patients experience persistent neuropsychiatric symptoms. These can be effectively managed in the primary care setting but require clinician knowledge and education.

The American Academy of Family Physicians (AAFP) has identified substantial knowledge gaps between published research evidence and clinical care of patients using NPS. The AAFP also states these knowledge deficits can be remedied by continuing education that provides primary care providers with the information necessary to understand the clinical effects of NPS and the assessment, differential diagnosis, and management of medical and neuropsychiatric problems from NPS use [5].

This course will provide the most up-to-date information available on NPS while avoiding the more time-sensitive aspects of this "moving target." Discussion will include the evolution of their use; the pharmacology, mechanism of action, and acute effects of NPS; signs and symptoms of NPS intoxication; differential diagnosis and clinical management of severe adverse effects and toxicity from NPS use; possible long-term adverse effects; and prevention and treatment of NPS abuse and addiction. As NPS carry the potential for severe and fatal toxicity, assessment, diagnosis, and management of toxicity syndromes following their use is detailed.

NPS EMERGENCE AND EXPANSION

THE NPS PHENOMENON

Since early humans first experienced euphoria with psychotropic plants more than 6,000 years ago, creative individuals have explored new ways of achieving drug-induced euphoria without getting in trouble with the law or dying. These same human tendencies—the quest for novel yet legal psychoactive experiences—are driving the NPS phenomenon.

Although NPS emerged domestically in 2008, use has been widespread in Europe for years, prompted by recreational drug scarcity. Banned in 1985, MDMA (also referred to as Ecstasy) has remained very popular for its mild stimulant, euphoric, and entactogenic/empathogenic effects. The standard MDMA chemical precursor, safrole, is extracted from camphor trees (*Cinnamomum camphora*) in Southeast Asia. During the 1990s and 2000s, interdiction of safrole shipments into Europe and safrole oil at extraction sites limited precursor supplies for MDMA production, decreasing MDMA purity and availability in Europe. Another precursor, piperonyl methyl ketone (PMK), is banned, but in 2012, Chinese chemists introduced PMK-glycidate, a precursor easily converted to PMK. This reversed long-term scarcity, and from 2013 to 2015, Europe was flooded with high-potency MDMA pills produced by labs in the Netherlands and Belgium, with reports in 2016 indicating that seizures and stopped shipments were being seen in France, Bulgaria, and Spain, suggesting diversifying trafficking routes [11].

Concurrently, the interception of cocaine shipments into Europe from South America made cocaine scarce and poor in quality. The European emergence of cathinones in the early to mid-2000s filled the void of MDMA and cocaine by promising users a legal-high substitute. Cathinones began replacing MDMA in Ecstasy and were introduced as over-the-counter "bath salt" products. The decreasing MDMA content in Ecstasy coincided with the 2009 emergence of cathinones in the United States, which were promoted as less expensive "legal high" ecstasy and cocaine alternatives [3].

As noted, NPS substances are introduced (or reintroduced) when the drug shows market potential, has not been banned under a controlled substance act, and/or there is increasing scarcity of an established drug [1]. The relative ease of developing, manufacturing, and marketing NPS has made this phenomenon highly adaptable to legal evasion, current cultural climate, and product demand.

NPS EXPANSION AND PROLIFERATION

The Internet is the predominant marketplace for NPS and plays an essential role in the NPS phenomenon through a variety of mechanisms. NPS users and manufacturers are able to utilize the Internet for information on acquisition, synthesis, extraction, identification, and use of these substances. The Internet also serves as the marketplace that connects manufacturers, suppliers, retailers, and end users. It is increasingly common that manufacturers, suppliers, retailers, web-hosting, and payment processing services are based in different countries, and this decentralization of the online drug markets adds to the difficulty for law enforcement control [1; 3; 12].

Information and transactions occur on the "surface web," as well as the "deep web" and "dark web." The deep web is a part of the Internet not accessible to traditional search engines, and includes online banking, social networks, and other restricted pages/profiles typically used for licit activity. The dark web is a small portion of the deep web intentionally hidden and inaccessible through standard web browsers, typically to evade detection of illicit activities. The dark web hosts drug cryptomarkets, which are only accessible through encryption software that provides a high level of anonymity. Cryptomarkets resemble online marketplaces such as eBay and provide sellers and buyers with an infrastructure to conduct transactions and services, including seller and buyer ratings and discussion forums. Cryptocurrencies like Bitcoin are used as the medium of exchange to facilitate anonymous transactions, and stealth packaging is used to facilitate transportation of small quantities of drugs through established commercial channels. Evidence suggests that many illicit drug purchases made on the deep web are intended for resale [3; 12].

Internet facilitation of NPS began in the 2000s. 4-Methylmethcathinone (mephedrone) was "rediscovered" in the early 2000s and marketed as a "legal cocaine" and MDMA substitute and became the most widely used NPS in the European Union by 2009. Internet centrality in seller and user information exchange led to mephedrone being dubbed "the first Internet drug" [17].

In earlier years of retail and Internet sales, NPS were often marketed and disguised as purportedly non-ingestible consumer products, such as "herbal incense" (cannabimimetics), "bath salts" (synthetic cathinones), potpourri, plant food, room deodorizer, and electronic-device cleaner. NPS were typically labeled by distributors "not for human consumption" in order to evade controlled substance analog statutes for which prosecution requires the intent for human consumption. NPS purchased on the Internet were often labeled "research chemicals," "intended for scientific research only," and "not for human consumption" [1; 10].

The profit potential also fuels NPS and pace of expansion. To illustrate, in 2010, a store in Missouri was selling the cannabimimetic product K2 for $20 per 3-gram packet. The owner stated he was making $7,000 per day in K2 sales [18]. Another example was seen with the potent synthetic cathinone alpha-pyrrolidinovalerophenone (alpha-PVP) or "flakka." Emerging in Florida and other U.S. regions in 2014 and 2015, "flakka" was sold to users in quantities as small as 100 mg for as little as $5. Bulk alpha-PVP was being purchased from China (via the Internet) for around $1,500/kg and shipped by worldwide express to local mid-level dealers. One kilogram provided 10,000 doses, yielding $50,000 in sales—$48,500 in profit. This profit margin required a high sales volume. However, the $5 retail price made it affordable for most users, and the high abuse/addiction potential assured repeat business. Younger and poorer populations were targeted as customers, and alpha-PVP was actively targeted to be sold to, and by, homeless individuals. Following the pattern of NPS proliferation, the synthetic cathinone alpha-PVP (a type of "bath salt" also known as "flakka") became known to law enforcement agencies and legisla-

tion. In 2016, China banned 116 NPS, resulting in a dramatic reduction of the drug in the United States, especially Florida; however, the ban in turn opened the market for other similar NPS that could effectively circumvent legal action [19].

Due to the rapid growth in NPS and limited public knowledge, cases of toxicity, overdose, and fatalities skyrocketed during 2014 and 2015. Because many of these new substances were sold locally at retail locations or through local individual dealers, local and regional outbreaks became common, putting additional stress on healthcare professions, EMS, and communities. Especially hard-hit were Broward County, Florida, with county hospitals averaging 20 emergency department admits per day for alpha-PVP overdose or excited delirium, and Washington, DC, where cannabimimetic toxicity led to 439 emergency department admits in one month. Many DC toxicities were excited delirium; two homicides were committed during cannabimimetic-induced excited delirium, with one victim stabbed 40 times on a subway [19; 21].

Non-chemists can synthesize NPS compounds with readily available raw materials or directly obtain the synthetic compounds. Most NPS chemicals are produced in China, in suburban laboratories near Chinese port cities for easy and rapid shipment to North America and Europe using ordinary commercial delivery services. Bulk quantities are also available and may be shipped to wholesalers in the United States and packaged for retail distribution [1; 3].

PROLIFERATION AND TURNOVER IN NPS MARKETS

As noted, the NPS arena is characterized by an evolutionary "arms race" between manufacturers and regulators. The U.S. Drug Enforcement Administration (DEA) broadens prohibition of NPS agents and structures, with manufacturers introducing NPS that circumvent these legislative actions. The hazard from this process is that manufacturer efforts to circumvent new drug laws will lead to NPS entry with greater toxicity and morbidity risk [1].

NPS Epidemic Cycles

A predictable pattern, termed a drug epidemic cycle, has long been observed with some recreational drugs. The cycle begins when the drug first becomes used by a narrow population segment, followed by dramatic increases in its use, possibly fueled by accounts of highly desired effect, perceived safety, or legality. With widespread use come initial reports of addiction or adverse effects from its use, followed by medical and public health alarm, extensive and sometimes sensationalized media reporting, rushed legislation criminalizing its use or possession, and then declining prevalence of its use [17]. This pattern has been shown in the United States using poison control center data to obtain valuable information on population-level trends in the abuse of specific and class-wide substances. According to the American Association of Poison Control Centers, use of synthetic cathinones resulting in toxic effects peaked in 2012 and cannabimimetics reached highest rates in 2015, indicating the turning point in the epidemic cycles [36].

NPS epidemic cycles also depend on sub-groups of people, for example music and club subcultures. It has been shown that music and club cultures and recreational drug preferences have evolved in tandem. Cocaine was favored in the 1970s and 1980s disco scene. Underground raves started appearing in the late 1980s and early 1990s, and MDMA (sold and referred to as Ecstasy) was the favored psychoactive at these events. MDMA remained favored by participants in the domestic rave, club, and warehouse party scenes during the 1990s to early 2000s, along with gamma-hydroxybutyrate (GHB) and ketamine. Other growing scenes were gay nightclubs and circuit parties, with methamphetamine the preferred circuit party drug. Efforts to improve safety through harm-reduction approaches (e.g., testing pills, information dissemination) developed during this period [25].

In the 2000s, electronic dance music grew out of rave culture, with indoor club or warehouse productions and outdoor festivals. Outdoor electronic dance music events are often large, with tens of thousands of participants and corporate sponsorships. These

events have been plagued by NPS-related emergency department admissions and fatalities among participants. Independent harm-reduction groups began offering free drug sample testing to inform participants about the true contents of what was sold to them as MDMA or LSD. However, event promoters and venue owners have banned drug testing groups from admission, concerned that allowing their entrance would appear to condone drug use. This stance is a consequence of the 2003 Reducing Americans' Vulnerability to Ecstasy (RAVE) Act, which holds promoters legally responsible for drug dealing at their events. Some law enforcement members began misinterpreting the harm-reduction services and conflating them with drug promotion [42].

In addition, proliferation of NPS is often seen in persons attempting to avoid drug-testing detection due to probation/parole, seeking employment, residing in a sober facility, or joining the military. Most report using cannabimimetics as a cannabis substitute during drug-testing periods and resuming cannabis when drug testing has ended. In one study, nearly all learned of SCRA from someone using the substances to avoid drug-testing detection.

NPS Regulation

Schedule I is the most restrictive category under the Controlled Substances Act (CSA) and is reserved for drugs with no recognized medical use and a high abuse liability (e.g., heroin, LSD). The DEA has placed numerous NPS into Schedule I. This is an ongoing process, and information about scheduling and a link to the most recent list of Scheduled drugs is found on the DEA website at https://www.dea.gov/drug-information/drug-scheduling [9]. In addition, the Commission on Narcotic Drugs maintains international scheduling decisions, available on the UNODC website at https://www.unodc.org/unodc/en/commissions/CND/Mandate_Functions/Scheduling.html.

Other attempts at regulating NPS are still being developed. The UK responded to emerging NPS by enacting the European Psychoactive Substances Act of 2016, a generic drug legislation pre-emptively banning entire groups of drugs, making it illegal to produce or supply. The goals of the Act were to end NPS sales; end the issue of NPS emerging faster than the government could ban them; reduce NPS use; and reduce NPS-related harm. However, studies have found that there was an opposite effect, and the legislation resulted in manufacturers, dealers, and users shifting to street markets and dark web sales [13]. In the United States, House Bill 1732: Synthetic Drug Control Act of 2017 was introduced to amend the Controlled Substances Act to include several NPS as Schedule I drugs; the HB was not passed. In 2019, the Stop Importation and Manufacturing of Synthetic Analogues (SIMSA) Act was introduced, but no action was taken. This Act has been reintroduced several times, but as of December 2024 has not been passed [22]. Many individual states have enacted legislation to regulate the distribution and use of NPS [2].

NPS OF CONCERN TODAY

Fentanyl

For decades, the NPS market has been dominated by SCRA and synthetic cathinones. However, in the 2010s, opioid receptor agonists, namely fentanyl, have become the deadliest drug threat in the history of the United States [6]. Acetyl fentanyl, with one-third the potency of fentanyl, appeared sporadically in the United States during 2014 and 2015 and resulted in at least 60 fatalities, a probable underestimate, suggesting, and correctly predicting, a fentanyl analog resurgence that began during the opioid crisis [6]. The DEA identified 15 novel fentanyl analogs during 2013–2014; in 2017, they identified 2,825 new fentanyl analogs, marking an increase of nearly 19,000% in less than five years. In 2020, the DEA's National Drug Threat Assessment reported nearly 88% of NPS tested was comprised of opioids, most commonly fentanyl (90% of all opioids), compared with 5.3% benzodiazepines, 3.6% cathinones, and 2.4% cannabimimetics identified. In addition, a high proportion (53%) of samples purchased as fentanyl contained only fentanyl and no other substance, and 31% of fentanyl identifications contained fentanyl and heroin [6; 38].

With potency roughly 100 times greater than morphine and 30 to 50 times greater than heroin, as little as 0.25 mg of fentanyl can be fatal. In addition, there is significant risk that illicit drugs of any type have been intentionally contaminated with fentanyl. Because of its potency, low cost, and ease of access, drug dealers and manufacturers have been found to switch out or mix fentanyl with other drugs, including heroin, methamphetamine, and cocaine, increasing the likelihood of a fatal interaction. Fentanyl is also being falsely sold as a variety of different pharmaceutical drugs and is often manufactured to look like a prescription tablet. In 2023, the DEA seized more than 80 million fentanyl-laced fake pills and nearly 12,000 pounds of fentanyl powder, the equivalent to more than 390 million lethal doses of fentanyl [35].

As a direct consequence of the market becoming dominated by highly potent opioid NPS, especially fentanyl, the rate of overdose deaths has increased remarkably. The monthly rate of all drug overdose deaths in January 2015 (the first year of NPS reporting) was approximately 48,000; among these, 5,800 deaths (12%) were attributed directly to synthetic opioids. Overall, overdose death rates continued to climb before peaking at 113,000 in August 2023, of which 79,000 deaths (70%) were attributed to synthetic opioids. A decrease of 15% in all overdose death rates and 18% in synthetic opioid death rates was noted in June 2024 [23].

Fentanyl and Nitazenes

Despite the decline in synthetic opioid deaths, the DEA warned in the 2024 National Drug Threat Assessment report that fentanyl is still a major issue and is being further complicated by the nitazenes NPS class. Nitazenes are synthetic opioids, like fentanyl, but some nitazenes can match or surpass the potency of already deadly fentanyl. Nitazenes first began appearing in fentanyl mixtures in the United States in 2019. When combined with fentanyl, the effects of both drugs are heightened, which significantly increases the chance of fatal drug poisoning. In 2023, four novel nitazene drugs were identified [6].

Fentanyl and Xylazine

Xylazine is a sedative used in veterinary practice and has historically been thought to be associated with a low risk of illicit use. However, in 2018, the emergency of xylazine combined with the opioid fentanyl produced was identified in the United States, a mixture known as "tranq" in illicit drug markets [6]. In 2023, fentanyl adulterated or associated with xylazine (FAAX) was identified as an emerging drug threat. In 2024, xylazine was found in 36% of fentanyl powder samples submitted to the DEA for testing, and nearly 6% of fentanyl pills were found to be adulterated with xylazine [6; 16].

The growing issue of FAAX is of particular concern, as it complicates the reversal of opioid overdoses with naloxone and is responsible for widespread reports of injection site infections and necrosis resulting in amputations. Furthermore, people chronically exposed to FAAX often struggle with difficult withdrawal symptoms that may present unique treatment challenges compared to opioid withdrawal alone [16].

The Office of National Drug Control Policy released the Fentanyl Adulterated or Associated with Xylazine Response Plan outlining protocols to prevent xylazine-involved overdoses, ease withdrawal symptoms, and manage an effective treatment and recovery process for people with opioid use disorder who are chronically exposed to FAAX [16].

Medetomidine has also been flagged as potential emerging risk, with effects similar to xylazine, but more potent, with higher alpha2-adrenoceptor selectivity, greater lipophilicity, and faster elimination [16].

STIMULANTS

The stimulant effect group represents the largest category of NPS, with nearly 400 individual substances reported to the UNODC. Stimulants include several structural sub-groups, including aminoindanes, phenethylamines, phenidates, phenylmorpholines (phenmetrazines), piperazines, and synthetic cathinones (***Table 1***).

PROFILE OF STIMULANT-EFFECT NPS CATEGORY	
Definition	A chemically diverse group of substances (including phenethylamines, cathinones, aminoindanes, and piperazines) that act as central nervous system (CNS) stimulants by mediating the dopamine, norepinephrine, and serotonin, resulting in a range of effects (e.g., stimulant, enactogenic, hallucinogenic).
Parent Drug(s)	Amphetamine, cocaine, Ecstasy (MDMA), methamphetamine
Common Forms and Routes of Administration	Powder and pill: Injection, smoking, nasal insufflation
Examples of Known Street Names	Bath Salt, Bk-MDMA, Cristal Bath, Ease, Explosion, Flower Power, M1, Magic, MP, Mdmcat, MDAI Gold, Mef, Meow, Neocor, New Ivory Wave, Pink Champagnes, Plant food, Special, Super Coke, Serotini, Ice, U4Euh (Euphoria)
Desired Effects	Facilitation of communication Feelings of emotional closeness to others, or empathy Improved performance at manual or intellectual tasks Increased alertness and energy (physical and emotional) Increased sociability (use at "raves") Mental and physical stimulation Sense of physical and mental well-being and exhilaration Suppression of hunger
Undesired Acute Effects	Anxiety Pronounced auditory and visual hallucinations Convulsions, seizures, arrhythmia, heart failure, cerebral hemorrhage Heat stroke Dilated pupils Fatigue and potential depression Hyperthermia Hyperexcitability, insomnia, talkativeness, irritability, hallucinations Increased heart rate, body temperature, blood pressure, and respiration rate Nausea and vomiting Restlessness Erratic and sometimes violent behavior Serotonergic syndrome
Effects of Chronic Use	Confusion, apathy, confused exhaustion due to lack of sleep Brain as well as liver damage Development of tolerance Possibility of neurotoxicity, psychiatric, and physical problems Malnutrition and weight loss Paranoid psychoses Potential depression, anxiety, fatigue, and difficulty in concentrating Strong psychological dependence and abuse potential

Source: [1; 15; 20] *Table 1*

AMINOINDANES

Aminoindanes were first synthesized in the 1970s and investigated for their significant bronchodilating and analgesic properties, though they were later found to produce psychoactive effects. Aminoindanes are amphetamine analogs, with their molecule characterized by a closed five-membered ring system next to the parent six-membered system. This configuration bestows minimal to no neurotoxicity (in preclinical studies) and higher serotonin than dopamine activation (which dampens drug craving). Together with Internet availability as "research chemicals," these actions form the basis of predictions that aminoindanes will become the next wave of NPS [1; 8; 10].

2-Aminoindane (2-AI) produces a stimulant effect similar to amphetamine but at one-sixth the potency. It also induces an analgesic effect that, in contrast to morphine, does not depress the brain respiratory center and is not counteracted by nalorphine. In contrast to amphetamines, 2-AI does not increase motor activity but does decrease food consumption. 5-methoxy-6-methyl-2-aminoindane (MMAI) is a potent serotonin releaser but minimally inhibits dopamine uptake. By stimulating serotonergic neurotransmission, it can increase secretion of hormones such as adrenocorticotropic hormone. Compared with MDMA, 5-IAI is a greater serotonin and dopamine releaser and minimally inhibits their reuptake. Both are non-neurotoxic. Some 1-AIs are promising candidates for psychosis treatment, and the substituted derivative rasagiline is used in the treatment for Parkinson disease. The finding of potent 5-HT2B receptor full agonist activity with 5-IAI suggests cardiotoxic potential with long-term use, as this mechanism is shared by all drugs that induce heart valvular disease in humans, including fenfluramine, MDMA, and various ergolines [1; 8; 10].

Following oral ingestion of powder or crystals, aminoindanes produce empathogenic and entactogenic effects similar to other serotonin-releasing drugs (such as MDMA) and a mild stimulant effect similar to amphetamine [1; 8].

2-AMINO-5-ARYL-2-OXAZOLINES

Within the stimulant group of 2-amino-5-aryl-2-oxazolines are three distinct sub-families: 2-amino-5-phenyl-2-oxazolines (aminorex), 4-alkyl-2-amino-5-aryl-2-oxazolines (4-MAR and 4,4'-DMAR) and 2-oxazolidinimines (3,4-DMAR). Aminorex, an anorectic stimulant drug, and 4-MAR, a methyl-derivative substance similar to amphetamine or cathinone, were originally synthesized in the 1960s and have been under international control since the 1990s. As of 2023, this group has reported 10 NPS, including six added since 2016 [1; 14].

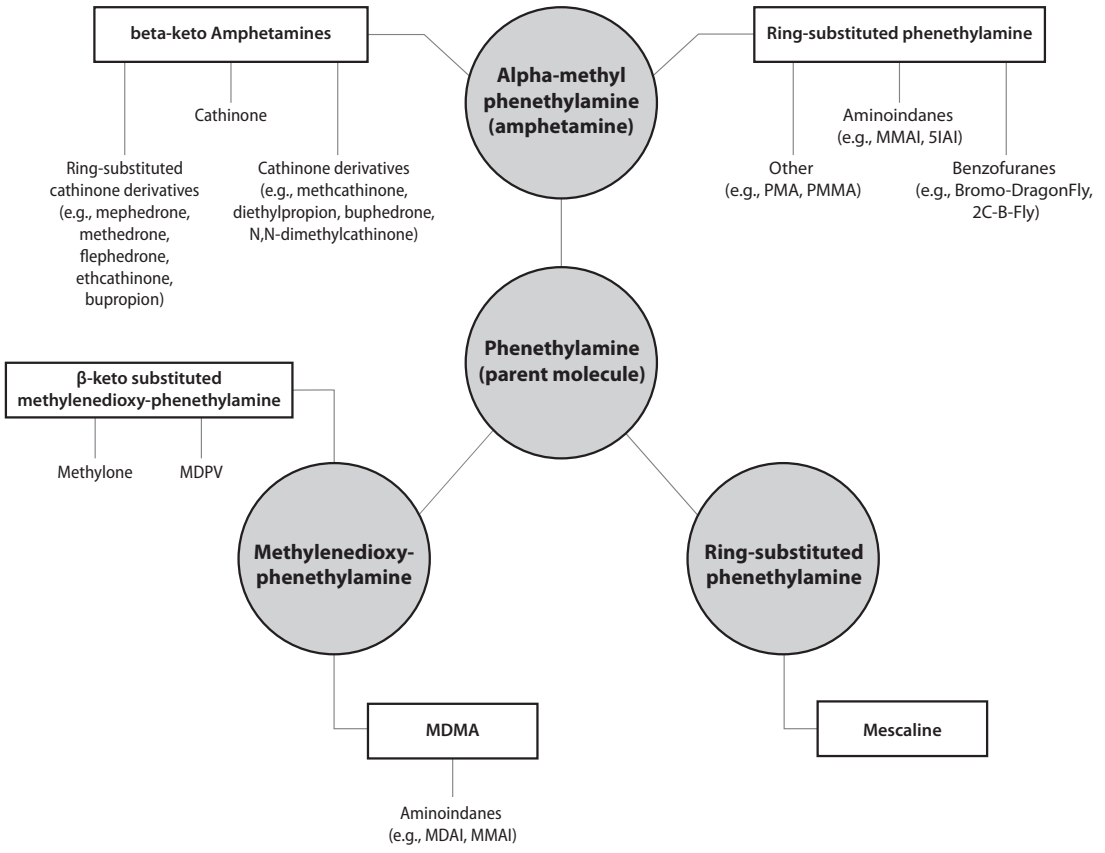
PHENETHYLAMINE DERIVATIVES

An astonishing diversity of structural families and subgroups of NPS and psychoactive drugs have been synthesized from the single parent molecule phenethylamine. Phenethylamines are a broad molecular class that can produce both hallucinogenic and stimulant effects. Phenethylamines fall into three sub-families: ring-substituted phenethylamines, amphetamines, and methylenedioxyphenethylamines. More than 180 phenethylamines have been reported to the UNODC, the majority of which are ring-substituted [1; 8]. For the purposes of this course, phenethylamines (plural) refers to phenethylamine derivatives as a category.

Phenethylamine, or phenylethylamine, is the parent molecule of many psychoactive substances, including synthetic cathinones, benzofurans and benzodifurans, the 2C-, 2D-, and *N*-benzylphenethylamine (NBOMe) series, aminoindanes, mescaline, and the classic recreational drugs amphetamine, methamphetamine, and MDMA (***Figure 1***) [1; 8]. The structural similarity of phenethylamine to the neurotransmitter dopamine is readily apparent.

Phenethylamine contains a phenyl ring joined to an amino group via an ethyl sidechain. In substituted phenethylamines, the phenyl ring, sidechain, and/or amino group is modified by substituting another group for one of the hydrogen atoms [1; 8]. Manipulation of the phenethylamine structure forms new compounds with stimulant, empathogenic, or hallucinogenic effects or their combination, influenced by the location and molecular make-up of the substitution. This section will predominantly cover stimulant phenethylamines; hallucinogenic phenethylamines will be discussed later in this course.

PSYCHOACTIVE DRUGS SYNTHESIZED FROM PHENETHYLAMINE



Source: [1; 8] *Figure 1*

Structure-Function Relationships

Amphetamine is a substituted phenethylamine, formed by adding an alpha-methyl group to yield alpha-methyl-phenylethylamine. Amphetamine is modified to produce substituted amphetamines. Methylation of the terminal amine forms methamphetamine. A methylenedioxy substitution on the phenyl ring forms MDMA. Adding a ketone oxygen group at the beta position of the side-chain forms cathinone, termed beta-keto-amphetamine. Amphetamine, cathinone, and MDMA are likewise parent structures of numerous stimulant and empathogenic (MDMA-like) NPS; cathinone is the parent of most "bath salts" NPS [1; 8; 10].

Mechanism of Action

All phenethylamines produce their stimulant, entactogenic, and/or hallucinogenic effects by increasing synaptic monoamine levels. Dopamine, serotonin (5-hydroxytryptamine or 5-HT), and norepinephrine are the monoamine neurotransmitters. Normally, dopamine, serotonin, or norepinephrine is released into the synaptic cleft, and then cleared from the synapse through uptake by their respective transporter. The last step involves vesicular monoamine transporter-2 (VMAT-2) located on the vesicular membrane. VMAT-2 uptakes the monoamines retrieved from the synapse and packages and stores them in synaptic vesicles for later release [1; 8; 10].

Phenethylamines increase synaptic monoamine levels by acting as inhibitors (blockers) or substrate releasers. Blockers inhibit monoamine transporter (re)uptake by competing with monoamine for binding sites on reuptake transporters to reduce synaptic clearance. Releasers induce the release of newly synthesized monoamine pools and release monoamines from pre-synaptic vesicle stores. The drug molecule permeates the intracellular space to inhibit vesicular reuptake of monoamines within the cell, induce transporter-mediated sodium currents (i.e., depolarization), and initiate transporter-mediated monoamine efflux (i.e., reverse transport or release). Outflow of cytoplasmic monoamines into the synaptic cleft is increased [1; 8; 10].

The net result of increased synaptic monoamine concentration is greater activation of post-synaptic dopamine, norepinephrine, or serotonin receptors, which transmit the amplified electrochemical signaling downstream for relay through various pathways to produce clinical effects of the phenethylamine derivative. Phenethylamines differ by monoamines targeted, relative monoamine activating potencies, and mechanism of monoamine increase (i.e., blockers, releasers, or both). Differences in potency, duration of effect, desired and adverse effects, abuse potential, acute toxicity syndromes, and neurotoxicity potential result from these varied interactions with monoamine systems and from interaction with non-monoamine transmitter systems [1; 8; 10].

Neurotoxicity

Substrate releaser-induced depolarization puts neurons at risk, as seen with methamphetamine-associated dopamine neuron dysfunction and serotonin neuronal depletion from the use of fenfluramines. Releasers also disrupt vesicular storage to induce monoamine release, potentially contributing to persistent functional deficit in monoamine neurons through neurotransmitter depletion and loss of functional transporters. These potential neurotoxic mechanisms are not found in inhibitors [1; 8; 10].

PHENIDATES

Phenidates are a structural sub-group of stimulants that produce a stimulatory effect on the central nervous system and modulate the neurotransmitters dopamine, norepinephrine, and serotonin. The action of these neurotransmitters induces a range of psychostimulant properties. Methylphenidate is a potent reuptake inhibitor of norepinephrine and dopamine, approved to treat attention deficit-hyperactivity disorder (ADHD) and narcolepsy. Analogs of methylphenidate have emerged, with an extension of the carbon side chain (e.g., ethylphenidate, propylphenidate, isopropylphenidate). Structural modification of the phenidate core provides access to the related pipradrol, desoxypipradrol (2-DPMP), and diphenylprolinol (D2PM) psychostimulants. Replacement of the phenyl ring with a 1-naphthyl ring has also been reported. The UNODC has received reports of 10 NPS in this class, including seven phenidates, two prolinols, and one pipradrol derivative [1].

The substances D2PM and 2-DPMP are selective and very potent monoamine transporter inhibitors without substrate-releasing properties. This pharmacologic profile closely resembles MDPV and alpha-PVP and predicts high risk of abuse potential and psychiatric morbidity. First appearing in 2010 as "Ivory Wave," clinical toxicity from 2-DPMP/D2PM is long-lasting (24 to 72 hours), with sympathomimetic symptoms of hypertension, agitation, and hallucinations [1; 8].

PHENYLMORPHOLINES

Phenylmorpholines are a family of orally active stimulants derived from the controlled substance phenmetrazine (Preludin), developed in the mid-1950s as an appetite suppressant; this class is sometimes referred to as phenmetrazines, named after the parent drug. Like other stimulants, this NPS works by modulating dopamine and norepinephrine transporters. The synthetic approaches to phenylmorpholines can easily be adapted to access ring-modified analogs. Subsequently, 13 novel phenylmorpholines have been reported to UNODC [1; 8].

PIPERAZINES

Piperazines are a group of stimulants that have been considered "failed pharmaceuticals." Some of them had been evaluated as potential therapeutic agents by pharmaceutical companies but never brought to the market. More than 20 piperazine NPS have been reported to the UNODC; the most widely known and studied is1-benzylpiperazine (BZP). Studies have indicated that BZP is approximately 10% of the potency of amphetamine and produces similar toxic effects. The substances trigger the release of dopamine and norepinephrine whilst inhibiting the uptake of dopamine, norepinephrine, and serotonin [1; 8].

SYNTHETIC CATHINONES

In plural, cathinones and amphetamines refer to all synthetics/derivatives of the respective parent. Most stimulant NPS are cathinones, but NPS amphetamines have also emerged as significant drugs of abuse.

History

More than 120 years ago, cathinone, the parent compound of this drug class, was isolated from *Catha edulis* (khat), a plant cultivated and chewed as a recreational and stimulant drug in Africa and the Arabian Peninsula for centuries. Beginning with the synthesis of methcathinone in 1928 and mephedrone in 1929, many cathinone derivatives and analogs were synthesized and investigated or introduced into clinical use as anorectics, CNS stimulants, or antidepressants. Overall, problems with abuse and dependence have limited their clinical utility. Methcathinone was used in the former Soviet Union as an antidepressant in the 1930s and 1940s but was removed from clinical use due to problems with its abuse. It has been most widely used as a drug of abuse in countries formerly part of the Soviet Union. Another derivative, pyrovalerone, is a stimulant first synthesized in 1964. It was investigated for use in treating chronic fatigue, lethargy, and obesity but was withdrawn due to abuse and dependency in users. Methylone was created and patented by Jacob Peyton and Alexander Shulgin in 1996 as an antidepressant but never entered clinical use. MDPV was developed by Boehringer Ingelheim in 1969 and subsequently prescribed for chronic fatigue and lethargy before its abuse liability became apparent [1; 57].

As of 2024, only two cathinones are in clinical use in the United States. Diethylpropion is used as an anorectic but is infrequently prescribed due to abuse and dependence liability and better available options. It has also shown neurotoxicity in preclinical studies. The most successful cathinone derivative is bupropion, a ring-substituted cathinone widely used in the United States and Europe as an antidepressant and smoking-cessation aid under the brand names Wellbutrin and Zyban. This drug has been shown to have liability for misuse and abuse when used in methods other than intended(crushing to ingest nasally or intravenously, or by smoking) creating a milder cocaine-like effect [58].

The first documented large-scale abuse of synthetic cathinones occurred with methcathinone in the former Soviet Union in the 1970s and 1980s. Clandestine methcathinone manufacture first appeared in the United States in Michigan in 1991, followed by significant problems with abuse in the early 1990s [58]. In Europe, novel cathinone compounds emerged later in the 1990s, immediately followed by the rising prominence of "bath salts," which began appearing in the United States in 2009 [1; 57].

Molecular Structures

Cathinone and its derivatives are closely related to phenethylamine, MDMA, and the classic stimulants amphetamine and methamphetamine in use in various settings since the 1930s. Cathinone, amphetamine, and MDMA are parent molecules of all known synthetic cathinones on the NPS market sold through the Internet, retailers, or street dealers [1; 8].

As discussed, adding an alpha-methyl group to phenethylamine forms amphetamine. Methylation of the terminal amine then forms methamphetamine and greater CNS potency. Some cathinones are beta-ketone analogs of amphetamines. The parent cathinone is formed by adding a ketone oxygen group at the beta-carbon position on the amino side-chain of amphetamine, making cathinone its beta-keto analog (or bk-amphetamine). A ketone group added to methamphetamine forms methcathinone and the *N*-methyl derivative of cathinone [1; 58].

MDMA is formed by a methylenedioxy substitution on the phenyl ring of amphetamine. Other cathinones are formed from MDMA and derivatives by adding a ketone group; thus, MDMA forms methylone or bk-MDMA; methylenedioxyethylamphetamine (MDEA or "Eve") forms ethylone or bk-MDEA; and *N*-methyl-1,3-benzodioxolylbutanamine (MBDB) forms butylone or bk-MBDB [1; 58].

The molecular structure of cathinone is modified to form new cathinones through *N*-alkylation, which is achieved by substitutions in the phenyl (aromatic) ring or at the alpha-carbon position. Cathinones without ring substitution produce mainly stimulant effects. Ring substitution with a secondary or cyclic amino group (usually alkyl, alkoxy, or methylenedioxy) confers varying degrees of entactogenic and other effects similar to MDMA. All cathinones, whether or not ring substituted, possess primary stimulant properties [17; 58].

Mechanism of Action

As with amphetamines and MDMA, the subjective and physiologic effects of cathinones result from increased synaptic concentrations of the monoamines dopamine, norepinephrine, and serotonin. In addition to those discussed for phenethylamines, cathinones inhibit monoamine oxidase (MAO), especially MAO-B, reducing the breakdown of dopamine and phenethylamine [8; 58].

Pharmacologic Sub-Groups of Cathinones

Several cathinones and amphetamine derivatives are grouped by mechanisms of action resembling classic stimulants, which can help in the understanding of their clinical effects. Cathinone derivatives have been categorized into four sub-families based on chemical structure, with novel drugs being created by slightly altering each structure [1; 57]:

- *N*-alkylcathinones: Characterized by alkyl substitutions in the amino group and possible alkyl or halogen substituent at any possible position of the aromatic ring. The first synthetic cathinones, including ethcathinone, ephedrone, mephedrone, flephedrone, buphedrone, and pentedrone, are part of this group.
- *N*-pyrrolidino cathinones: Characterized by a pyrrolidinyl substitution in the amino group and possible alkyl or halogen substitutions in the aromatic ring and/or alkyl substitutions in the α-carbon of the side chain. Most frequently encountered in the designer drug market.
- Methylenedioxy-*N*-alkyl cathinones: Characterized by the addition of a methylenedioxy-group to the aromatic ring (either the 2,3- or 3,4-isomer) and alkyl substitutions in the amino group, and possible alkyl- substitutions both in the α -carbon of the side chain and in the aromatic ring. Includes the compounds methylone, pentylone, and butylone. In terms of their structure and pharmacologic effect, these compounds are quite similar to MDMA.
- Methylenedioxy-*N*-pyrrolidine cathinones: Characterized by the addition of a methylenedioxy-group to the aromatic ring (either the 2,3- or 3,4-isomer) and a pyrrolidinyl substitution in the amino group and possible alkyl substitutions both in the α-carbon of the side chain and in the aromatic ring.

Cocaine-MDMA-Mixed Cathinones

Similar to cocaine, cocaine-MDMA-mixed cathinones show a ratio of dopamine versus serotonin inhibition ranging from 1 to 5 (dopamine>serotonin). With methylone, ethylone, and butylone, their corresponding non-beta-keto analog entactogens MDMA, MDEA ("Eve"), and MBDB are 10-fold more selective for serotonin compared with dopamine. These cathinones are more dopaminergic in monoamine transporter inhibition activity than their serotonergic entactogen analogs. Overall, the cocaine-MDMA-mixed cathinones are comparable to MDMA in monoamine-releasing activity, although the overall pharmacologic effects of mephedrone and methylone share the dopamine system-stimulating properties of amphetamine and methamphetamine [1; 58].

Mephedrone is equally potent at dopamine and serotonin inhibition. It is a more potent releaser of dopamine than MDMA and produces a rapid and pronounced increase in nucleus accumbens dopamine levels, similar to amphetamine and unlike MDMA. However, mephedrone produces strong increases in extracellular serotonin similar to MDMA and unlike amphetamine.

Methylone is a slightly more potent dopamine inhibitor than a serotonin inhibitor. It has been found to elevate extracellular monoamine levels in the nucleus accumbens, similar to MDMA. Ethylone is an equipotent dopamine, serotonin, and norepinephrine inhibitor and releases serotonin. Butylone also releases serotonin, but it is a slightly more potent dopamine than serotonin inhibitor.

Naphyrone shows a monoamine uptake transporter inhibition profile similar to cocaine, with equal potency at all three transporters and no monoamine releaser activity. Naphyrone is structurally related to pyrovalerone and its derivative MDPV, but it is functionally distinct due to its greater absolute and relative serotonin-inhibiting potency [43].

MDMA-Like Para-(4)-Substituted Methcathinones and Amphetamines

This group of NPS includes mephedrone, 4-ethylmethcathinone (4-EMC), 4-FMC, 4-bromomethcathinone (4-BMC or brephedrone), 4-FA, and 4-fluoromethamphetamine (4-FMA). Substances in this group are more serotonergic (i.e., have a lower dopamine/serotonin ratio) than their amphetamine, methamphetamine, and methcathinone analogs [58; 44].

The 4-methyl, 4-ethyl, and 4-bromo groups show enhanced serotonergic properties versus the 4-fluoro group. The para-substituted amphetamines release norepinephrine and dopamine; 4-FA, 4-FMA, 4-MEC, and 4-EMC also release serotonin (similar to MDMA). Most para-substituted amphetamines show 5-HT2A receptor affinity, without relevant 5-HT2B receptor activation. The enhanced direct and indirect serotonergic agonist properties of para-substituted amphetamines/cathinones are associated with greater MDMA-like effects [58; 44].

Methamphetamine-Like Cathinones

Cathinone and methcathinone show pharmacologic profiles highly similar to their non-beta-keto analogs amphetamine and methamphetamine, including their relative monoamine transporter inhibition profiles with high inhibitory potencies at dopamine and low potencies at serotonin. They are potent releasers of dopamine but not of serotonin [1; 58].

Flephedrone inhibits dopamine but not serotonin, similar to its analog 4-FA. It has a dopamine/serotonin selectivity profile equal to the methamphetamine-like cathinones, but with higher 5-HT2A receptor binding and agonism, similar to mephedrone and MDMA [1; 58].

Pyrovalerone Cathinones

Pyrovalerone and its derivative MDPV are very potent dopamine inhibitors—at least 10-fold more potent than cocaine and methamphetamine. They are weak serotonin inhibitors and thus show dopamine/serotonin inhibition ratios greater than 100.

MDPV and pyrovalerone are also highly potent norepinephrine inhibitors. Pyrovalerone and MDPV do not produce dopamine efflux, and the activity of pyrovalerone-derivative cathinones is purely transporter uptake inhibition [58; 44].

Bupropion

Bupropion is a ring-substituted cathinone and a dopamine and norepinephrine reuptake inhibitor. Its close structural and functional similarity with psychoactive cathinones suggests it may be beneficial in the treatment of cathinone addiction and craving. There is some evidence of benefit in treating selected methamphetamine-dependent patients with bupropion, although effectiveness has not been consistently shown [58].

Para-(4)-Phenyl-Substituted Amphetamines

PMA and PMMA are potent norepinephrine and serotonin transporter inhibitors and releasers and have been sold as MDMA. However, they are substantially more toxic. In 2014, PMA/PMMA sold as MDMA led to 29 deaths in the UK [1; 14].

4-MTA, the methyl-thio analog of PMA, has dominant serotonergic action and a high risk of serotonin toxicity. Methedrone is the beta-keto analog of PMMA, and whether this cathinone carries the toxicity of its parent compound is not known [1; 58; 43].

Characteristics of Specific Cathinones

Mephedrone

Mephedrone can produce the sought-after entactogenic effects of MDMA, particularly the feeling of enhanced emotional and physical connection to others. Other desired effects include intense stimulation, alertness, euphoria, sociability and talkativeness, moderate sexual arousal, perceptual distortions, and intensification of sensory experiences. The numerous unwanted effects are common to all cathinones and result from hyper-dopaminergic, hyper-adrenergic, and hyper-serotonergic output. The effects are often followed by intense compulsion to re-dose. Tolerance develops quickly, and brief drug effect and urge to re-dose can lead users to ingest successive doses, often in excess of 1 g [1; 8; 58].

Following single-dose mephedrone, brain dopamine peaks in 20 minutes and returns to baseline within two hours, 10 times faster than MDMA and two times faster than amphetamine. Dopamine levels increase 496% following a single dose of mephedrone, compared with 412% with amphetamine and 235% with MDMA. Serotonin levels increase by 941% with mephedrone, 165% with amphetamine, and 911% with MDMA. An intranasal dose of 25–75 mg or an oral dose of 150–250 mg can induce intense craving and compulsion to re-dose—stronger than that experienced with MDMA. Intranasal users rate mephedrone as more addictive than cocaine. Mephedrone alone is not neurotoxic to dopamine neuron terminals, but its co-administration with MDMA, amphetamine, and methamphetamine enhances neurotoxicity [1; 8; 58].

Methylone

Relative to MDMA, 100–200 mg oral methylone produces calm euphoria, alertness, restlessness, a strong feeling of empathy, and milder stimulation. Unlike methamphetamine, methylone is a weak motor stimulant, and unlike MDMA, methylone induces minimal hyperthermia and little long-term cortical or striatal amines alteration. It has shown antidepressant effects and demonstrates little long-term cortical or striatal amine alteration. The side effect profile primarily reflects sympathomimetic activity. Fatalities attributed to methylone often involve polysubstance use [1; 8; 58].

MDPV

Entering the domestic NPS market in late 2010, MDPV quickly rose in prominence and notoriety. Its pharmacologic actions closely resemble pyrovalerone and alpha-PVP. Rapid blood-brain barrier penetration confers high potency. Full effects peak at 90 minutes and last three hours. Relative to cocaine, MDPV shows 50-fold greater dopamine potency and 10-fold greater norepinephrine potency, predictive of pronounced sympathomimetic stimulation and euphoria.

MDPV imposes risks from the slim dose-response margin between desired (2–10 mg oral) and adverse (>10 mg oral) effects. Effects include physical and mental stimulation, increased sociability, euphoria, and potentially severe prolonged panic attacks, agitation, anhedonia, confusion, intense paranoia, and depression. An unpleasant comedown, significant craving, compulsion to re-dose, and rapid tolerance are often reported. Users have repeatedly re-dosed from intense craving and to counteract unpleasant comedown symptoms, increasing the risks of overdose and toxicity. More than other cathinones, MDPV is linked to excited delirium syndrome [1; 8; 58] .

4-MEC

4-MEC is a methcathinone derivative that produces stimulant, euphoric, and empathogenic effects. 4-MEC users frequently report multiple re-dosing and difficulty refraining from re-dosing if more 4-MEC is available. Tolerance quickly develops [1; 8].

Routes of Administration

As noted, mephedrone can be nasally ingested (snorted), but most cathinones are orally ingested. They cannot be smoked because their free bases are highly labile. Mephedrone, MDPV, 4-MEC, and pentedrone are water soluble, allowing injection. Mephedrone has been injected with heroin to simulate IV heroin/cocaine effects ("speedball") [8; 58]. Other ingestion approaches are "bombing," with mephedrone powder wrapped in cigarette paper and swallowed, and "keying," an approach to get a crude dose estimate by dipping a car or house key into powder and then ingesting nasally. It is thought the powder from five to eight "keys" amounts to 1 gram [1; 8].

Side Effect Profile

The side effect profile of cathinones reflects relative contribution from dopamine, serotonin, and/or norepinephrine activation. Sympathomimetic effects common to all cathinones include tachycardia, tremor, sweating, hypertension, mydriasis, or hyperthermia. Excessive dopamine release can induce psychosis and confusion, while excessive serotonin release can induce myoclonus, nausea and vomiting, and agitation. Additional possible side effects include seizures, bruxism, prolonged panic attacks, insomnia, headache, tinnitus, vertigo, muscle twitching, dizziness, altered vision, short-term memory problems, anhedonia, depression, and suicidal thoughts. Cathinones closely resemble amphetamines in molecular structure, but differ by greater potential for severe and protracted adverse effects, potentially even from a single dose [1; 58].

Severe Adverse Effects and Excited Delirium Syndrome

Excited delirium syndrome is a life-threatening and potentially fatal state of agitated delirium and autonomic dysregulation. It is the most severe manifestation of toxicity/overdose with cathinones use. Cannabimimetics and other NPS can also induce excited delirium, but cathinones-induced excited delirium is the most documented in scientific literature and the lay media.

Cathinones-induced agitated delirium or psychosis may persist for weeks, even from a single dose. Close to 80% of patients presenting for emergency medical care following cathinone use exhibit agitation ranging from mild to severe psychosis requiring chemical and physical restraint. With severe agitation, the patient may require restraint and transport to a medical setting by law enforcement personnel. Agitation can be exacerbated by concurrent use of alcohol or other drugs, such as cocaine. Dramatic cases of disorganized and agitated behavior manifesting in severe aggression, violence, homicidal combative behavior, self-mutilation, or suicide have received media coverage due to injury and loss of life. Delusions of persecution and auditory hallucinations during binge use have been described in users with a negative history of psychosis [41].

The bizarre, aberrant behavior during cathinone-induced psychosis encountered by poison control and emergency medical experts led to their description as embodying the combined worst attributes of methamphetamine, cocaine, phencyclidine, LSD, and MDMA. In a case series, poison control experts in Kentucky and Louisiana described their encounters with individuals displaying "aggressive violent behavior, hallucinations, and paranoia in higher percentages than previously reported" following synthetic cathinone use [59]. Behavioral descriptions included those who were found "jumping out of a window to flee from non-existent pursuers; requiring electrical shock (Taser) and eight responders to initially subdue the patient; repeatedly firing guns out of the house windows at 'strangers' who were not there; walking into a river in January to look for a friend who was not there; leaving a 2-year-old daughter in the middle of a highway because she had demons; climbing into the attic of the home with a gun to kill demons that were hiding there; and breaking all the windows in a house and wandering barefoot through the broken glass" [59]. Also described was a patient fatality from a self-inflicted gunshot wound while delusional. Investigation into possible causality in each of these cases found that MDPV was present in every case and that MDPV was the sole cause of the behavioral toxicity [59].

MDPV has been the primary cathinone detected in patients hospitalized for synthetic cathinone toxicity and overdose in the United States and has become the cathinone most responsible for excited delirium. MDPV cross-reacts with the phencyclidine (PCP) immunoassay used in hospitals, suggesting some cases of severe neuropsychiatric toxicity following MDPV use may have been falsely attributed to PCP. In addition to paranoia, psychosis, and agitation associated with all cathinones, high-dose MDPV use can induce extreme anxiety and intense prolonged panic attacks, aggressive behavior, "superhuman" strength, combativeness, and potentially terrifying hallucinations [58; 41].

The first case report of fatality following acute MDPV toxicity described a sequence beginning with arrival to the emergency department, where the patient went into cardiac arrest with pulseless electrical activity. Despite rapid aggressive intervention that restored spontaneous circulation, the patient subsequently developed coagulopathy, rhabdomyolysis, renal failure, hepatic failure, and anoxic brain injury and ultimately died [56].

Numerous cases of organ damage and other life-threatening sequelae have been documented following cathinone use, including acute tubular necrosis and renal failure resulting from severe renal tubular vasospasm and elevated creatine kinase [60]. Seizure activity or anion gap metabolic acidosis has resulted from excessive anaerobic metabolism induced by excessive systemic monoamine elevation. Several fatalities following mephedrone use were linked to severe hyponatremia and cerebral edema. MDPV exposure in one patient led to fulminant hepatic failure and disseminated intravascular coagulation. Most fatalities following cathinone use have resulted from aggression/self-harm in the context of severe agitation and psychosis [56; 61].

SYNTHETIC CANNABINOID RECEPTOR AGONISTS

Cannabis refers to the natural cannabis plant, primarily *Cannabis sativa* or *C. indica*. Cannabinoids are any natural or synthetic compounds with pharmacologic activity resembling the primary psychoactive effects of cannabis plants (via delta-9-tetrahydrocannabinol or THC) through cannabinoid receptor (CB)-1 or CB2 activity. Synthetic cannabinoid receptor agonists (SCRA), or cannabimimetics, have been called "synthetic marijuana," which can be misleading because while these substances functionally resemble THC, they also produce a range of pharmacologic and clinical effects uncharacteristic of cannabis (***Table 2***) [1; 8; 18].

PROFILE OF SYNETHIC CANNABINOID RECEPTOR AGNOIST (SCRA)-EFFECT NPS CATEGORY	
Definition	Substances that bear structural features that allow binding to one of the known cannabinoid receptors and produce effects similar to those of delta-9-tetrahydrocannabinol (THC). THC is the only known psychoactive component in cannabis. SCRA is often laced onto herbal products. Also known as cannabinoids or cannabimimetics.
Parent Drug(s)	Marijuana, THC
Common Forms and Routes of Administration	Powder and pill: Injection, smoking, nasal insufflation Tablets and capsules: Oral consumption Crystals: Nasal insufflation, smoking Liquid: IV and IM injection, nasal insufflation, smoking
Examples of Known Street Names	Bath Salt, Bk-MDMA, Cristal Bath, Ease, Explosion, Flower Power, M1, Magic, MP, Mdmcat, MDAI Gold, Mef, Meow, Neocor, New Ivory Wave, Pink Champagnes, Plant food, Special, Super Coke, Serotini, Ice, U4Euh (Euphoria)
Desired Effects	Facilitation of communication Feelings of emotional closeness to others, or empathy Improved performance at manual or intellectual tasks Increased alertness and energy (physical and emotional) Increased sociability (use at "raves") Mental and physical stimulation Sense of physical and mental well-being and exhilaration Suppression of hunger
Undesired Acute Effects	Anxiety Pronounced auditory and visual hallucinations Convulsions, seizures, arrhythmia, heart failure, cerebral hemorrhage Heat stroke Dilated pupils Fatigue and potential depression Hyperthermia Hyperexcitability, insomnia, talkativeness, irritability, hallucinations Increased heart rate, body temperature, blood pressure, and respiration rate Nausea and vomiting Restlessness Erratic and sometimes violent behavior Serotonergic syndrome
Effects of Chronic Use	Confusion, apathy, confused exhaustion due to lack of sleep Brain as well as liver damage Development of tolerance Possibility of neurotoxicity, psychiatric, and physical problems Malnutrition and weight loss Paranoid psychoses Potential depression, anxiety, fatigue, and difficulty in concentrating Strong psychological dependence and abuse potential
Source: [1; 15; 20]	*Table 2*

The psychoactive components of SCRAs are primarily manufactured in China. These bulk chemicals are shipped as powder or dissolved in acetone or other solvents to U.S. distributors, who spray or coat the compound onto dried herbs and package the product for retail sales as herbal incense or potpourri. Of the numerous brands cannabimimetics have sold under, "Spice" has the highest name recognition and has become synonymous with cannabimimetic products. Herbal products saturated with SCRAs were introduced in Europe in 2004 and the United States in 2008, marketed as legal-high alternatives to cannabis. Spice products were smoked until the entrance of oral/e-liquid/injectable SCRA formulations for use in e-cigarettes or vaping. Identically labeled products vary by cannabimimetic dosage, composition, and concentration. Some products contain multiple cannabimimetic agents and other substances identified in samples as psychoactive herbs and plants, benzodiazepines, tryptamines, phenethylamines, NBOMe compounds, cathinones, and opioids [45].

The actual herbal plant materials in cannabimimetic products are listed on the packaging, typically a combination of purportedly psychoactive plants such as Indian warrior (*Pedicularis densiflora*) and Lion's tail (*Leonotis leonurus*). Some of the plants may have been chosen because of their actual historical use as cannabis substitutes, but little is known of their pharmacology and toxicology and concern has been raised over potential heavy-metal residue content [45].

When these products first appeared in Europe, it was thought the mixture of legal herbs produced the "high." However, laboratory analysis revealed SCRAs as the psychoactive constituent. Identification of the true psychoactive drug was delayed by several plausible factors, including psychoactivity from the labeled botanical products, the complex evaluation methods necessary, the addition of large amounts of masking agents such as vitamin E (tocopherol) to conceal the active substance, and distribution through legal Internet or retail establishments instead of clandestine production and illegal distribution that would have led to law enforcement interception and analysis. Consumer perception in the United States that herbal smoking blends were safe, legal cannabis alternatives with the "high" produced by the proprietary herbal combinations persisted as their use became widespread [45].

DEVELOPMENT AND INTRODUCTION AS NPS

Cannabimimetics entering domestic NPS markets between 2009 and 2012 were "rediscovered" molecules originally developed for research or clinical use. Following the discovery of THC in the 1960s, researchers synthesized numerous cannabimimetics during concerted efforts to isolate the psychoactive effects from desired therapeutic properties by modifying the THC structure. Their synthesis was described in scientific publications and later replicated for NPS market entry. Earlier cannabimimetic molecules bear a prefix denoting their origin. The first THC analogs were synthesized at Hebrew University, and these molecules are designated HU- (e.g., HU-210). The best known, nabilone and dronabinol, received U.S. Food and Drug Administration (FDA) approval in 1985 for the treatment of chemotherapy-induced nausea and vomiting. In the 1970s, Pfizer developed the cyclohexylphenols (CP) series and their *N*-alkyl homologues. John W. Huffman and his team at Clemson University synthesized more than 450 cannabinoids during the 1990s to study interactions between molecular structure, receptor activity, and physiologic response. Their structural groups are indoles, pyrroles, and indenes. These substances bear the prefix JWH- (e.g., JWH-018) [15; 45; 46].

Newer cannabimimetics fluorinate the aliphatic side chain of older indole-based substances to strongly increase potency; this may also enhance blood-brain barrier penetration. For example, fluorinated JWH-018 forms AM-2201, and fluorinated UR-144 forms XLR-11. AB-FUBINACA, AB-CHMINACA, and similar substituted indazole compounds have been introduced using this method. Many indazole compounds are fluorinated, and all are very potent, with high CB1 binding affinity. Receptor binding affinity is one potency test, with a lower affinity constant value indicating increased potency [8; 18].

PHARMACOLOGY

THC and cannabimimetics bind and activate CB1 receptors to produce their euphoric effects. Compared to the partial CB1 agonist THC, full agonist cannabimimetics have greater potency, with toxicity and overdose potential uncharacteristic of cannabis. As a partial agonist, THC is limited in the extent it activates CB1 and shows a direct dose-response effect until a plateau is reached, with further dose escalation failing to increase drug effect. This partial agonist property contributes to the infrequent toxicity from cannabis use and the perception of cannabis as a "safe" drug. In contrast, the full CB1 agonist cannabimimetics do not possess a dose-response plateau and further use increases overdose and toxicity risk [45; 46].

Cannabimimetics produce a substantially greater drug effect than THC, with CB1 receptor binding affinities 5 to 10,000 times greater and significantly higher dose-response efficacy. CB1 agonists inhibit GABAergic neurons that project to the nucleus accumbens, which disinhibits nucleus accumbens dopaminergic neurons that activate the mesolimbic dopaminergic pathways and contribute to the rewarding properties and abuse potential of cannabinoids. Because cannabimimetics more powerfully activate CB1, they produce more intense euphoria and reward. This greater inhibition of GABA-mediated neurotransmission also disrupts the balance of GABA/glutamate release in neuronal projections from the prefrontal cortex, which over-activates dopaminergic systems in the prefrontal cortex and striatum, inducing paranoia, agitation, anxiety, psychoses, and convulsions [18; 45; 46].

Importantly, evidence and growing consensus indicates that absence of cannabidiol (CBD) in the presence of THC strongly contributes to more frequent, severe toxicity. Cannabidiol is a cannabinoid and natural constituent of cannabis with demonstrated anxiolytic, antipsychotic, and anticraving effects. The presence of cannabidiol in cannabis is thought to counter the psychotomimetic and anxiogenic properties of THC in a concentration-dependent manner. Cannabidiol is absent in cannabimimetics, which may increase the risks of acute psychosis [1; 18; 46].

Many SCRAs possess indole-derived structures similar to serotonin, which may facilitate 5-HT2A receptor dysfunction associated with hallucinations, psychosis, and serotonin syndrome. Some cannabimimetics show additional activity as *N*-methyl-D-aspartate (NMDA) receptor antagonists and/or MAO inhibitors. This may increase the risk of serious drug interaction toxicity. Cannabimimetic products are often contaminated with clenbuterol, a beta2-adrenergic receptor agonist that potentiates sympathomimetic effects and may result in hypertension, tachycardia, nausea/vomiting, chest pain, and myocardial infarction [1; 45; 46].

Synthetic cannabinoids are a group are dynamic and evolving group, with more than 300 individual substances having been reported to UNODC. Synthetic cannabinoids can be divided in to eight sub-groups [1].

TYPES OF SYNTHETIC CANNABINOIDS

Naphthoylindoles

The naphthoylindole sub-group of SCRA was independently synthesized by John W. Huffman (JWH-series) and Alexandros Makriyannis (AM-series) to identify the structural requirements for selective binding affinity to the CB1receptor. Despite a negligible selectivity for CB1, synthetic cannabinoids containing *N*-alkylated tail groups bearing four to six carbon atoms demonstrated effective hydrophobic interactions with the binding pocket of the receptor, leading to an increase in affinity, whereas shorter (or longer) *N*-alkyl groups decreased affinity significantly [1]. Replacement of the N-pentyl group, with either an N-5-fluoropentyl or N-5-cyanopentyl group, resulted in substantial increase in CB1 affinity. Chemical substitution of the ketone bridge with a methylene linker led to naphthylmethylindoles (e.g. JWH-175), which have a weaker affinity for the CB1 receptor compared to naphthoylindoles. However, modification of the 1-naphthyl head group, through the introduction of 4-alkoxy- (JWH-081) or 4-halo-substituents (JWH-398) provided access to active cannabimimetics. The most marked increase in potency was observed in 4-alkyl-substituted naphthoylindoles, which led to the JWH- and AM-series (specifically JWH-018 and AM-2201), which dominated the synthetic cannabinoid market for a period [1].

Phenylacetyl- And Benzoylindoles

Simplified naphthoylindole derivatives, where the 1-napthyl group was replaced with either a phenylacetyl or benzoyl group were also developed to probe binding to the CB1 receptor. In the case of the phenylacetylindole (JWH-167) the affinity for the CB1-receptor was 10 times less than observed for JWH-018. However, the introduction of 2-alkyl- (JWH-251), 2-alkoxy- (JWH-250) or 2-halo-substituents (JWH-311, JWH203, and JWH-249), led to improved binding [1].

Substitution of the naphthalene group of JWH-018, with a 2-iodophenyl motif results in the benzoylindole derivative AM-679, which exhibits a similar level of binding to CB1 as JHW-018. As with the naphthoylindole family, subsequent replacement of the *N*-pentyl group, in the AM-679 with an *N*-5-fluoropentyl tail, resulted in a substantial increase in CB1 affinity (AM-694) [1].

Acylindoles

The SCRA 3-acylindole derivatives, such as JWH-018 and AM-2201, emerged in globally in the late 2000s. They are characterized by non-aromatic, bulky alicyclic head groups, such as the adamantylindoles (e.g., AB-001) and tetramethylcyclopropylindoles (e.g., UR-144). As with the naphthoylindole series, the replacement of the *N*-pentyl group with an *N*-5-fluoropentyltail resulted in substantial increase in CB1 affinity and led to the emergence of cannabinoids such as 5F-AB-001 and XLR-11 [1].

Acylindazoles

Similar to the emergence of acylindoles, a variety of acylindazole SCRAs have also emerged. These substances, such as THJ-018, and THJ-2201, feature a modified indazole core but retain specific head and tail groups for optimal CB1 -receptor affinity [1].

Indole- and Indazolecarboxylates

In the early to mid-2010s, the NPS market pivoted toward SCRA analogs in which the acyl-linker was substituted by either an ester or an amide linker (e.g., indole-an indazole carboxylates, carboxamides). As with previous classes, affinity for CB1-receptor binding were retained [1].

In 2013, the first two indolecarboxylate SCRAs reported were the quinoline-8-yl derivatives, BB-22 (QUCHIC) and PB-22 (QUIPIC). Cannabimimetic binding of PB-22 was improved by sequential replacement of the quinoline-8-yl- group for a 1-naphthyl-group (CBL-018) and subsequent introduction of terminal fluorine into the *N*-pentyl tail, leading to a ten-fold increase in CB1 affinity (NM2201).

Replacing the *N*-pentyl tail (in PB-22) with either an *N*-4-fluorobenzyl group or with an *N*-5-fluoropentyl chain resulted in FDU-PB-22, FUB-PB-22, and 5F-PB-22 [1].

Indazolecarboxylates are closely related to the indolecarboxylate family of cannabinoids, and some derivatives have been reported to UNODC, including the CBL-018, CBL-2201 analogs, SDB-005, 5F-SDB-005 25, quinoline-8-yl analogs, 5F-NPB-22 51, 52, FUB-NPB-22 53, adamantan-1-yl-1H-indazole-3-carboxylates: APINAC 54–57 and 5F-AKB-57 [1].

As a result of their inherent metabolic instability/toxicity, both the indoleand indazolecarboxylate families have been entirely replaced by the more stable amide (indole- and indazolecarboxamide) classes [1].

Indole- and Indazolecarboxamides

In 2012, APICA and its fluorinated derivative, 5F-APICA, became the first indolecarboxamide SCRAs in the NPS market, of which both exhibited moderate CB1 receptor affinity. As a result, a "mix and match" modification of the *N*-alkyl tails and replacement of the bulky adamantyl head group for either phenyl (*N*-phenyl-SDB-006), benzyl (SDB-006 and 5F-SDB-006), or 1-naphthyl(NNEI, 5F-NNEI; 5Cl-NNEI, and FDU-NNEI) groups led to a wide variety of products [1].

Phenyl- and benzyl-substituted indolecarboxamides generally exhibit weaker binding to the CB1 receptor compared to their adamantyl- and 1-naphthyl counterparts. The exception to this trend is the sub-family of (2-phenylpropan-2-yl)- (or cumyl-) CB1 agonists, which show significant increases in potency compared to their progenitors SDB-006 and 5F-SDB-006. Several 7-azaindole-3-car boxamide derivatives (also known as the 7AICA-series) have also emerged in the synthetic cannabinoid market, including 5F-AKB-48-7N, CUMYL-5F-P7AICA, CUMYL-4CN-B7AICA, and 5F-PCN [1].

Indazolecarboxamides are a direct extension of the indolecarboxamide family of cannabinoids, where the indole core is replaced with an indazole. Since 2012, various derivatives have been reported, for example SDB-005, 5F-SDB-005 (and analogs); MN-18, and 5F-MN-18. Other examples are the adamantan-1-yl-1H-indazole-3-carboxamides and cumyl-derivatives. These derivatives all show significant increases in cannabimimetic CB1 potency compared to their indole counterparts [1].

Amino Acid Amides

This is an important sub-family within the broader indole- and indazolecarboxamide series of synthetic cannabinoids, which include the valinamides (AB-series), tert-leucinamides (ADB-series), and/or phenylalaninamide (APP-series). The incorporation of esters like, methyl valinate (AMB- or MMB-series), ethyl valinate (AEB- or EMB-series), methyl tert-leucinate (MDMB-series), and/or ethyl tert-leucinate (EDMB-series) is also possible [1].

Unlike the previously discussed cannabimimetics, which are achiral, these SCRAs contain an asymmetric carbon. In theory, these compounds are present in two enantiomeric forms, dependent on the source and enantio-purity of the precursor chemicals used. In most cases, a higher potency at the CB1 receptor is observed for the (S)-enantiomer over the (R)-enantiomers. In seized samples, the more active enantiomer appears to predominate [1].

As with previous generations, the indole-valinamide synthetic cannabinoids with *N*-alkylated tail groups bearing 4 or 5 carbons exhibit nanomolar CB1 affinity (e.g., AB-PICA). Modification of the *N*-pentyl group, with either an *N*-5-fluoropentyl- (5F-AB-PICA) or aromatic *N*-4-fluorobenzyl- (AB-FUBICA), tail resulted in substantial increase in CB1 affinity.

Compounds containing other side chains such as *N*-4-cyanobutyl (4CN-AB-BUTICA), *N*-cyclohexylmethyl (AB-CHMICA), and *N*-penten-4yl (AB-4en-PICA) have also been reported. Replacement of the indole core with an indazole (e.g., AB-PICA versus AB-PINACA) leads to a ten-fold increase in potency in each congeneric derivative. A similar increase in CB1-binding affinity was seen within the analogous indoleand indazole-tert-leucinamide [ADB-series] derivatives. The same was not observed in the APP-series derived from phenylalanidamide, where the presence of the bulky aromatic group significantly reduces CB1 cannabimimetic activity in many cases. Further chemical modification of the tail groups or replacement of the core with a 7-azaindole scaffold in the most active ADB-series resulted in an increase in the variety of potent and potentially more harmful analogs on the market [1].

An extension of this sub-family has also emerged, where the amino acid amide group was replaced with either a commercially available chiral methyl valinate (AMB- or MMB-series), ethyl valinate (AEB- or EMB-series), methyl tert-leucinate (MDMB-series), or ethyl tert-leucinate (EDMB-series) group. Similar to the AB-, ADB-, and APP-series, in most cases, a higher potency at the CB1 receptor is observed for the (S)-enantiomer over the (R)-enantiomers. The AMB-/MMB- and MDMB-series of derivatives bearing *N*-4-fluoropentyl, *N*-5-fluoropentyl and *N*-penten-4-ylgroups show the same trends, except for in terms of binding affinity as their amide counterparts with indazoles observed to be more potent than indoles and the tert-leucinate derivatives more potent than the valinate derivatives [1].

The *N*-4-fluorobenzyl-, *N*-cyclohexylmethyl-, *N*-4-cyanobutyl-, *N*-5-chloropentyl-, and 7-azaindole derivatives show similar trends in terms of their CB1 -binding affinities as their corresponding amide counterparts. A small number of ethyl valinate (EMB-) and tert-leucinate (EDMB-) derivatives have also been reported [1].

Carbazoles and γ-Carbolines

After the national control of some indoles, indazole, and benzimidazole-derived synthetic cannabinoids, the NPS market again shifted towards previously unexplored chemical structures. In 2014, tricyclic synthetic cannabinoids, such as the carbazole and γ-carboline were first identified and exhibited moderate CB1 affinity. Between 2017 and 2020 several γ-carboline analogs have emerged in which the *N*-pentyl tail has been replaced with either a *N*-5-halopentyl or cycloalkyl group [1].

N-Alkylisatin-Acylhydrazones

In 2021, new substances with previously unencountered and/or not well-characterized structural modifications appeared on the market, including the weak CB1 binding *N*-alkylisatin-acylhydrazone, MDA-19 (also known as BZO-HEXOXIZID), and its related analogs [1]

ACUTE EFFECTS

Natural cannabis and cannabimimetics overlap mechanistically through CB1 receptor binding and activation to produce the shared subjective effects of relaxation, euphoria, perceptual changes (e.g., altered sense of time, intensified sensory experiences), cognitive impairment (e.g., amnestic symptoms, slowed reaction time), and the physiologic effects of xerostomia, conjunctival injection, and tachycardia. Acute changes in mood, anxiety, perception, thinking, memory, and attention are common to both. Agitation, aggression, paranoia, anxiety, and psychoses are common with cannabimimetic use and less common or rare with cannabis use. As discussed, the more frequent and severe psychosis, agitation, and sympathomimetic effects with cannabimimetic use reflect greater potency, full CB1 agonist action, and absence of CBD [1; 8; 45].

The quality and intensity of adverse effects also differ. Unlike cannabis, cannabimimetics can induce severe agitation, psychosis, and paranoid delusions; command hallucinations are more likely with prolonged, heavy use. The greatest safety concern is psychosis, which can occur in persons without previous history and persist five months or longer. Young and first-time users may be particularly vulnerable to cannabimimetic-induced psychoses. The severity of distress during panic attacks and other psychologic effects has driven some cannabimimetic users to suicide [1; 8; 45].

Cannabimimetic use has repeatedly led to excited delirium, and some users die before reaching an emergency department. Others may seek emergent care for paranoia, hallucinations, or physical violence emergencies. Increased activity from severe agitation and struggle can lead to rhabdomyolysis and the risk of renal failure. Seizures can induce anoxia, hyperthermia, acidosis, and long-term end-organ damage; these are fatal in 2% of cases [1; 8; 45].

CLASSIC HALLUCINOGENS

The classic hallucinogenic effect group contains substances that elicit their pharmacologic effect through interaction with serotonin and dopamine receptors in the central nervous system. Included in this group are three distinct structural sub-groups: hallucinogenic phenethylamines, tryptamines, and lysergamides (***Table 3***).

HALLUCINOGENIC PHENETHYLAMINES

As noted, phenethylamines are a class of NPS that can have stimulant and/or hallucinogenic effects depending on the position and identity of functional group substituents on the phenethylamine core. More than 180 individual phenethylamine NPS have been reported to the UNODC, 80 of which are hallucinogenic. Among the reported hallucinogenic phenethylamines, 80% possess a 2,5-dimethoxy substitution pattern on the aromatic ring, characteristic of "classic hallucinogens."

The classic hallucinogens within the phenethylamines are represented by the 2C-series and NBOMe analogs, and the 2D-series. Addition of methoxy-groups at the 2 and 5 positions of phenethylamine, with any hydrophobic substitution at the 4 position, confers hallucinogenic activity and produces the 2C-series. Adding a 2-methoxybenzyl (MeOB) unit onto the nitrogen molecule of 2C drugs confers substantially greater potency and forms the NBOMe series. The hallucinogenic properties of 2C drugs are further enhanced by introducing a methyl-group at the alpha-carbon, providing access to ring-substituted amphetamine derivatives, known as D-series hallucinogens. All ring-substituted phenethylamines are potent serotonin (5-HT2A) receptor agonists, and many have strong activity in other receptor complexes [1].

Additional hallucinogens, or the remaining 20% not considered "classic hallucinogens," are compounds containing the 2,5-dimethoxy substitution, -3,5-dimethoxy substitution, and trimethoxy substitution, or are NBOMe variations of amphetamines, mescaline analogues, and the "Fly" compounds (benzofurans and benzodifurans) [1].

The 2C-Series Phenethylamines

The 2C-series sub-group is the largest of the three hallucinogenic phenethylamines. The powerful hallucinogen 2C-B was the first 2C synthesized, in 1974, by simple alterations to the natural phenylethylamine molecule mescaline. The more commonly encountered 2Cs in the United States are 2C-B and 2C-T-7, known by the street names Nexus, Bromo, Blue Mystic, and T7 [1; 15].

The effect following oral use in the lower dose range (<8 mg for 2C-B and 10–50 mg for 2C-T-7) lasts six to eight hours and is often described as relaxation, awareness of integration between sensory perception and emotional state, and euphoria with increased body awareness and enhanced receptiveness of visual, auditory, olfactory, and tactile sensation. Dosing in the upper limits results in greater stimulant effects and a state of substantially greater intoxication. Even higher dosing produces LSD-like visual

PROFILE OF CLASSIC HALLUCINOGENIC-EFFECT NPS CATEGORY	
Definition	A chemically diverse group of substances (e.g., ring substituted phenylethylamines, tryptamines, lysergamides) that mediate specific seroton in-receptor activities and produce hallucinations; these substances may also possess residual stimulant activity. Also known as psychedelics.
Parent Drug(s)	2C-B, LSD, DMT
Common Forms and Routes of Administration	Powder: Nasal insufflation, oral consumption Tablet and capsules: Oral consumption Liquid: IV and IM injection, nasal insufflation, inhalation (via water, pipe/bong/cigarette, blunt, or vaping) "Blotter paper:" Oral consumption
Examples of Known Street Names	2C-B, 25I, BOM-25, BOMCI, 25I-NBOMe, Bees, Bromo, Cimbi-5, Dots, Erox, Legal acid, N-boom, Nbomb, NE-BOME, Nexus, Smiles, Smiley paper, Solaris, STP (Serenity, Tranquility, Peace), Venus
Desired Effects	Alterations in thought, mood, and sensory perception, or "mind expansion" Sense of empathy Facilitation of communication Increased sociability
Undesired Acute Effects	Change in perception of time, "slowing" of time, sleepiness Difficulty focusing General changes in consciousness Looping or out of control thinking Hot flashes and/or cold chills Nausea, vomiting Pupil dilation Scrambled communication Slight increase in heart rate Unusual body sensations (body energy, chills, facial flushing, goosebumps) Vasoconstriction, swelling of feet, hands and face, peripheral numbness Yawning
Effects of Chronic Use	Risk of neurological damage, such as progressive encephalopathy and quadriparesis Increased heart rate, high blood pressure, exceptionally high fever Excessive acid in blood Seizures Rapid destruction of muscle tissue Acute kidney injury Potential violent, erratic behavior, agitation, and aggression
Source: [1; 15; 20]	*Table 3*

and auditory effects and potentially extremely fearful hallucinations and morbid delusions. User reports of 2C drug effects describe a blend of MDMA-like empathy and entactogenic effects with LSD-like psychedelic effects. 2C-B is used primarily as a club drug in the rave culture and circuit party scene, where some users ingest 2C-B in combination with LSD (a "banana split") or MDMA (a "party pack"). Several fatalities have been reported from co-ingestion of 2C-T-7 and MDMA [51; 53].

Possible adverse effects include nausea, vomiting, agitation, tachycardia, hypertension, respiratory depression, seizures, psychosis, and suicidal thoughts. Excited delirium with agitation and violent behavior, hyperactivity, hyperthermia, and cardiopulmonary arrest have been documented following 2C use. Immediate action is required with excited delirium, hyperthermia, and seizure activity, because presence of vomiting, agitated behavior, and seizures are risk factors for fatal 2C toxicity [1; 18].

The 2D-Series Phenethylamines

The introduction of a methyl-group in the alpha position of 2C-series substances provides access to ring-substituted amphetamine derivatives, known as the D-series. Included are 4-iodo-2,5-dimethoxyamphetamine (DOI) and the trimethoxyamphetamines (TMA-2 and TMA-6). Compared with the 2C-series, D-series substances are metabolically stable to monoamine oxidases in the body, making them significantly more potent with a duration of action up to three times greater (6 to 10 hours versus 16 to 30). Reported adverse effects associated with the use of D-series derivatives include agitation, tachycardia, mydriasis, hallucinations, severe limb ischemia, seizures, liver and renal failure [1; 8].

The NBOMe Compounds

The *N*-benzylphenethylamines (NBOMe) series was first developed in the early to mid-2000s for the purpose of researching mammalian serotonin receptor distribution. Initial Internet discussion and law enforcement attention both occurred in 2010. They are commonly known by the street names N-Bomb, Smiles, 25I, 25C, and 25B [32].

As noted, the NBOMes are synthesized from 2C phenethylamines by the addition of a 2-methoxybenzyl (MeOB) unit onto the nitrogen molecule. This molecular appendage confers greater potency than its 2C counterpart; for example, the dose of 2C-I is roughly 20 mg versus 50–100 mcg with 25I-NBOMe. The hallucinogenic effects are mediated by highly potent and selective agonist activity at 5-HT2A receptors [1; 32].

The NBOMe series is sold as powder, liquid solution, or soaked into blotter paper. NBOMe appears in products sold as LSD, a widespread counterfeiting practice that is encouraged by the cheaper cost of NBOMe. This poses a potentially serious health risk to the user, who instead of ingesting the physiologically benign LSD, unsuspectingly ingests NBOMe and risks potentially severe and fatal adverse effects [33].

The effects of NBOMe last 6 to 10 hours with sublingual ingestion. Users report desired effects of euphoria, mental/physical stimulation, feelings of love/empathy, altered consciousness, and unusual body sensations. Negative effects include confusion, shaking, nausea, insomnia, paranoia, and intense negative emotions. Users with severe NBOMe toxicity show violent, severely agitated, and hallucinating presentations and require hospitalization, as hyperthermia, tachycardia, hypertension, seizures, metabolic acidosis, elevated creatine kinase, and acute renal injury are usually present. Even small amounts can cause seizures, cardiac and respiratory arrest, and death. Many fatalities have occurred following NBOMe use, typically preceded by excited delirium [1; 32].

Benzofurans and Benzodifurans

Benzofurans include 1-(benzofuran-5-yl)-propan-2-amine (5-APB), 6-APB, and their dihydro-derivatives 5-APDB and 6-APDB. Benzofurans are analogs of MDMA and MDA, first synthesized in the 1990s at Purdue University for researching structure-activity relationships of MDMA-like molecules. In 2010, 5/6-APB entered the UK market as an MDMA replacement "legal high" under the brand name Benzofury (derived from benzofuran) and became very popular. Other benzofurans include IAP and 5-APDI, which replace both oxygen atoms of MDA with methylene groups; 5- and 6-API, which replace the oxygen atom in the heterocyclic rings of 5/6-APB with a nitrogen atom; and 5-MAPB, an *N*-methyl analog of 5-APB [1; 8; 15].

Benzofurans are dopamine, norepinephrine, and serotonin inhibitors, with greatest potency at dopamine and norepinephrine receptors. As full 5-HT2B agonists, 5/6-APB may be cardiotoxic with long-term use. User reports describe an empathogenic and stimulant effect, with 5-APB more potent than 6-APB. Several fatalities have been attributed to benzofurans, with hyperpyrexia noted in several cases. Emergency department admissions for benzofuran toxicity have noted tachycardia, elevated blood pressure, and fever [1; 8].

Benzodifurans are termed the "fly" drugs in reference to their insect-resembling molecular structure. They include tetrahydrobenzodifuranyl (Fly), 2C-B-Fly, 3C-B-Fly, and the most potent and widely used drug of this category, benzodifuranyl aminoalkane (Bromo-Dragonfly or B-Fly). The phenyl ring bound between two dihydrofuran rings in B-Fly produces much greater potency and duration of action than most phenethylamine derivatives. B-Fly mechanism of action is mediated primarily by agonist activity at 5-HT2A receptors and, to some degree, 5-HT1 and 5-HT2C receptors [1; 8; 15].

Recreational use of B-Fly was first noted in 2001 and became widespread in 2008, primarily through Internet mediation [63]. B-Fly is sold for oral use in blotter paper or liquid. Following a typical 200–800 mcg dose, the onset of effects can take six hours. Many users assume the initial dose ineffective and ingest another dose or other substances. The drug effect commonly lasts two to three days and is described as profound hallucinations (mainly visual, with geometric patterns and lights), sound alterations, a sense of connection/belonging with other realities, a sense of peace and well-being, emotional stimulation, and meeting with metaphysical entities. Commonly reported adverse effects include nausea and vomiting, headache, tachycardia, elevated blood pressure, lung collapse, gastrointestinal disturbances, muscle tension, tremor, anxiety, panic attacks, arrhythmias, heart murmurs, convulsions, flashbacks, memory disturbances, confusion, and paranoid ideation. Several fatalities have been reported in Europe, but attribution is unclear, as polysubstance use (particularly with ketamine) is common with B-Fly [1; 8; 15].

TRYPTAMINES

Tryptamines are monoamine alkaloids synthesized by decarboxylation of tryptophan and are quite varied. They include natural neurotransmitters (e.g., serotonin, melatonin); hallucinogens found in plants, fungi, and animals (dimethyltryptamine [DMT], 5-MeO-DMT, bufotenin); synthetic pharmaceutical products (e.g., sumatriptan and zolmitriptan to treat migraine); and various synthetic hallucinogenic compounds, such as alpha-methyltryptamine (AMT), diisopropyltryptamine (DiPT), 5-MeO-DiPT, 5-MeO-AMT, diethyltryptamine (DET), and 5-MeO-DET [1; 8]. Use of tryptamines for psychoactive effect began in the late 1950s with psilocybin, the natural ingredient in certain mushroom species. Synthetic tryptamines appeared on the illicit drug market in the United States during the 1990s .

More than 60 individual tryptamine NPS have been reported to the UNODC. Tryptamines have an indole ring structure (a fused pyrrole and benzene double-ring) joined to an amino group by a 2-carbon side chain. Psychoactive effects are closely related to their structural influence on receptor affinity. Tryptamines produce dominant hallucinogenic/psychedelic effects as 5-HT2A/1A/2C receptor agonists. Alpha methylation leads to stimulant activity, as with AMT and 5-MeO-AMT. Many synthetic tryptamines are monoamine releasers, increasing the risks of serotonin syndrome and sympathomimetic toxicity. With primarily serotonergic action, tryptamines lack reinforcement and abuse liability. NPA tryptamines are grouped by structure into three categories: indole ring-unsubstituted tryptamines, 4-position ring-substituted tryptamines (e.g., psilocybin), and 5-position ring-substituted tryptamines.

Indole Ring-Unsubstituted Tryptamines

Introduction of methyl- or ethyl-branching into the ethylamino sidechain, provides access to alpha-methyltryptamine (AMT), 5-MeOAMT, and alpha-ethyltryptamine (AET). AMT and AET were developed as antidepressants in the 1960s by Upjohn but were withdrawn from brief clinical use due to the risk for psychoses and other adverse effects. With a 15–40 mg oral dose of AMT, effects have onset in three to four hours. Visual hallucinations, altered sensory perception, and euphoria persist for 12 to 24 hours. Frequently reported adverse effects include anxiety, nausea, moderately severe dysphoria, and next-day depression. AET produces psychedelic, stimulant, and entactogenic effects but may induce serotonin neurotoxicity [1; 8; 39].

Other indole ring-unsubstituted tryptamines include DMT, DET, dipropyltryptamine (DPT), and DiPT. DPT was synthesized in the 1950s and was first used in 1973 as an adjunct to psychotherapy in the treatment of alcoholism. An oral dose of 100–250 mg induces psychedelic effects, with increased music and color intensity, flashes of light and sparkles, ego loss, and seeing apparitions of faces. These effects last two to four hours [1; 8; 39].

4-Position Ring-Substituted Tryptamines

Psilocybin (4-phosphoryloxy-*N*,*N*-dimethyltryptamine), is a 4-position ring-substituted tryptamine, producing hallucinogen effects similar to those of LSD and mescaline, and is the major active constituent several species of hallucinogenic mushrooms ("magic mushrooms"). Psilocybin is rapidly dephosphorylated to psilocin (4-hydroxy-*N*,*N*-dimethyltryptamine, 4-HO-DMT) by alkaline phosphatase. Although psilocin and psilocybin have been available on the illicit market since the 1960s, the recreational use of other 4-substituted tryptamines is a more recent development, fueled by marketing and distribution via the Internet. It has been documented that most 4-substituted tryptamines produce psilocybin-like psychedelic effects [1; 39].

5-Position Ring-Substituted Tryptamines

All 5-position ring-substituted tryptamines inhibit monoamine reuptake but have few monoamine releasing effects. 5-MeO-AMT is a psychedelic tryptamine with structural similarity to amphetamines. Oral use of 2.5–4.5 mg produces effects lasting 12 to 18 hours. Excessive dosing can induce sympathomimetic effects and has led to several hospitalizations and fatalities [40].

5-MeO-DiPT, termed Foxy or Foxy Methoxy, was first synthesized by Andrew Shulgin and emerged as a drug of abuse in 1999. The effects resemble 2C-B, with a psychoactive threshold of 4 mg. Doses of 6–20 mg produce full-blown effects that peak at 60 to 90 minutes and last three to six hours. The initial nausea and muscular hyperreflexia are followed by euphoria, relaxation with emotional enhancement, talkativeness, and behavioral disinhibition. Higher doses can produce abstract closed-eye imagery [40]. Adverse effects include restlessness, agitation, gastrointestinal distress, muscle tension, and rhabdomyolysis. Fatalities have been associated with 5-MeO-DiPT [1].

5-MeO-MiPT or "Moxy" is an analog of 5-MeO-DiPT. Following an oral dose of 4–6 mg, this drug produces euphoria, increased tactile sensations, relaxation, and visual distortions that dissipate by 10 hours, followed by difficulty sleeping [40].

LYSERGAMIDES

The semi-synthetic drug (+)-lysergide (LSD) is one of the most potent hallucinogenic substances known. LSD is derived from lysergic acid, an alkaloid found in a fungus, *Claviceps purpurea*, that grows on rye and other grains. The group of lysergamides are hallucinogenic NPS with effects similar to those of LSD. Sixteen lysergamides have been reported to the UNODC, including analogs with structural modifications of LSD such as 1-acetyl-LSD (ALD-52), 1-methyl-LSD (1M-LSD, MLD-41), 1-cyclopropylmethanoyl-LSD (1cP-LSD), 1-propionyl-LSD (1P-LSD), 1-butyryl-LSD (1B-LSD), 1-valeryl-LSD (1V-LSD), and lysergic acid 2,4-dimethylazetidide (LSZ) [1; 8].

The pharmacology and mechanism of action of LSD is still not completely understood. It has affinity for serotonin receptors and its hallucinogenic effects have been linked to its agonist activity at the 5-HT2A receptor. LSD can have a duration of action as long as 10 to 12 hours, although this can be dependent on its interaction with individual users. In addition, whether the user experiences desired effects or unwanted negative effects (a "good trip" versus a "bad trip") strongly depends on the mental state of the user and the setting. As an example, the same dose in the same user of the same drug may produce good or bad trips, depending on circumstances of use. Thus, the type of effects produced are subject to different confounding factors and can be extremely unpredictable [1; 8].

PROFILE OF DISSOCIATIVE-EFFECT NPS CATEGORY	
Definition	These substances form a class of hallucinogens which modulate effects of the *N*-methyl-D-aspartate (NMDA) receptor in the brain and produce feelings of detachment and dissociation of the self and the environment; these substances may also have stimulant effects.
Parent Drug(s)	Phencyclidine (PCP), ketamine
Common Forms and Routes of Administration	Powder: Inhalation, nasal insufflation, oral consumption, injection Pills: Inhalation, nasal insufflation, oral consumption, injection
Examples of Known Street Names	Angel Dust, DOA (dead on arrival), Hoy, Killer Weed, Magic Dust, Peace Pills, Rocket Fuel, Space Basing (PCP with crack)
Desired Effects	Alterations in thought, mood, and sensory perception, or "mind expansion" Out of body experiences Sense of empathy Facilitation of communication Increased sociability
Undesired Acute Effects	Hallucinations, image distortion, severe mood disorders, mental confusion, amnesia Loss of comprehension of the immediate environment, often accompanied by a sense of strength and invulnerability Numbness of the extremities Slurred speech Loss of coordination Potential acute anxiety, paranoia, and violent hostility, or schizophrenia-like psychosis Potential convulsions, coma Shallow respiration with increased rate of breathing, blood pressure and heart rate, flushing, and profuse sweating. Blank stare, rapid involuntary eye movement and/or watering of eyes
Effects of Chronic Use	Development of tolerance and strong psychological dependence "Flashbacks," or a short-lived vivid re-experience of part of a previous "trip" can occur days to months after taking the last dose, leading to disorientation, anxiety and distress Impaired memory Speech difficulties, stuttering or the inability to speak
Source: [1; 15; 20]	*Table 4*

DISSOCIATIVES

Dissociative substances form a class of hallucinogens that produce feelings of detachment and dissociation from self and the environment; effect is due to antagonism of ionotropic *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system. Dissociatives can be classified into two sub-groups: phencyclidine-type substances and 1,2-diarylethylamines (***Table 4***).

PHENCYCLIDINE-TYPE SUBSTANCES

Phencyclidine or PCP, a dissociative with hallucinogenic properties, was discovered in 1956 by Parke-Davis. Initially showing great promise as a potent anesthetic, evidence of the alarming adverse effects delirium, hallucinations, and violent behavior led to PCP being declared "clinically unacceptable," halting clinical trials in 1965. However, recreational use of PCP was widespread in the late 1970s, prompting efforts to isolate useful from undesirable properties. Since then, more than 300 PCP analogs have been identified [8; 15].

Several analogs known as "arylcyclohexylamines" have been developed by modifying two key regions of the PCP structure. PCP analogs are part of the arylcyclohexylamine family of dissociatives; when a cyclohexane ring is substituted with a cyclohexan-2-one group, beta-keto-arylcyclohexylamines, or ketamine, is produced. PCP and ketamine are structurally similar, although in the same way that arylcylohexylamines share commonality with PCP, beta-keto-arylcyclohexylamine NPS are structurally related to the dissociative anesthetic, ketamine.

The first arylcyclohexylamine NPS sold online was the low-potency PCP analog methoxydine (4-MeO-PCP) in 2008 [30]. The ketamine analog methoxetamine (MXE) or 2-(3-methoxyphenyl)-2-(ethylamino)-cyclohexanone was developed as an alternative free of urinary tract morbidity. After its 2010 Internet entrance, it became the most popular dissociative NPS. Compared with ketamine, the 3-methox substituent provides higher serotonin transporter affinity and euphoria and greater duration/potency from the *N*-ethyl group [15; 34; 54].

Both PCP and ketamine are NMDA receptor antagonists and inhibit the reuptake of dopamine, norepinephrine, and serotonin. These dissociative effect-type NPS produce sedation, immobility, amnesia, and marked analgesia. Compared to PCP, ketamine is less potent as an anesthetic, has a faster onset and shorter duration of action of 30 to 60 minutes (versus 4 to 8 hours for PCP) [54; 34]. Acute PCP intoxication results in a wide range of behavioral and psychological effects and has been claimed to cause violent behavior. Severe adverse effects, such as hypertension and lung edema, have been reported in relation to ketamine use. However, these effects may be related to poly substance use [8; 54; 34].

1,2-DIARYLETHYLAMINES

Another class of NMDA receptor antagonists to emerge on the NPS market are the 1,2-diarylethylamines. These NPS share structural similarities to arylcyclohexylamines, but are less conformationally restricted due to the removal of the cyclohexane core. The first 1,2-diarylethylamine to appear on the market was 1-(1,2-diphenylethyl)piperidine (diphenidine) in 2013, shortly followed by its 2-methoxy analog 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine (2-methoxphenidine, 2-MXP), and *N*-ethyl-1,2-diphenylethylamine (ephenidine) in 2015 [1; 8].

OPIOID RECEPTOR AGONISTS

Opioid receptor agonists are a chemically diverse group of central nervous system depressants mediated through interaction with opioid receptors and inhibitory neurotransmitters. The term "opioid" is a generic term applied to a variety of substances including naturally occurring opiates (e.g., opium and morphine), synthetic opioids (e.g., fentanyl and tramadol), semi-synthetic opioids (e.g., heroin), as well as NPS in the opioid effect category (***Table* 5**) [1; 15].

More than 120 opioid receptor agonists have been reported to UNODC and can be classified into five distinct sub-groups: fentanyl analogs; U-series substances; nitazenes; piperazines; and miscellaneous, which include any derivatives structurally unrelated to the other four sub-groups [1].

FENTANYL ANALOGS

Fentanyl analogs are a group of short-acting, highly potent synthetic opioids with narcotic analgesic properties. While four fentanyl analogs (alfentanil, remifentanil, sufentanil, and fentanyl itself) have been approved for medical use to manage severe pain and in anesthesia, many fentanyl analogs are derived from substances that have been researched for pharmaceutical use but have never been marketed. The UNODC has received reports of more than 80 fentanyl analogs [1; 8].

Fentanyl analogs can be described as having the 4-anilinopiperidine structure as its core, with four possible sites of modification.

PROFILE OF OPIOID RECEPTOR AGONIST-EFFECT NPS CATEGORY	
Definition	A chemically diverse group of central nervous system depressants that bear structural features allowing binding to specific opioid receptors, resulting in morphine-like analgesic effects. Also known as synthetic opioids.
Parent Drug(s)	Opioids (morphine, fentanyl, methadone, buprenorphine)
Common Forms and Routes of Administration	Powder: Injection, Smoking, nasal insufflation, injection Tablets and pills: Oral consumption, smoking, inhalation, injection Crystals: Nasal insufflation, oral or rectal consumption, injection "Blotter paper:" Oral consumption
Examples of Known Street Names	Apache, Bupe, China white, Chocolate-Chip Cookies, Dollies, Doxylam, Doxylan, Drop Dead, meth, synthetic heroin, Subs, Tems, Wafers
Desired Effects	Alertness Euphoria Analgesia Relaxation
Undesired Acute Effects	Anemia, peripheral edema Dizziness, fatigue, headache Drowsiness, constipation, sweating Muscle rigidity Respiratory depression, sedation, sleepiness Nausea, vomiting
Effects of Chronic Use	Constipation Development of dependence and tolerance Potential cardiac arrest or severe anaphylactic reaction Withdrawal symptoms (sweating, anxiety, diarrhea, bone pain, abdominal cramps, shivers)
Source: [1; 15; 20]	*Table 5*

U-SERIES

Another sub-group of opioid receptor agonists that have been reported to UNODC are the "U-Series" compounds. The substances can be differentiated into two families, the cyclohexylbenzamides (e.g., U-47700 and AH-7921) and phenylacetamides (e.g., U-48800, U-50488, and U-51754) [1].

Due to the presence of two chiral centers, the synthesis of U-47700 can lead to four potential stereoisomers. However, the reported synthesis of U-47700 (and its derivative or phenylacetamide analogs) into the desired (and active) trans-(1R, 2R)-isomer of this class is straightforward. U-4770 has one-tenth of the potency of fentanyl and about 7.5 times the potency of morphine in animal studies. The structurally related cyclohexylbenzamide analog, AH-7921, is a synthetic opioid with similar potency to morphine. AH-7921 was never marketed, possibly due to its highly addictive properties and risk of respiratory depression observed in animal studies. In 2015, it was placed under international control as a Schedule I substance within the Single Convention on Narcotic Drugs of 1961, and in 2017, U-47700 was also placed in the same convention. Since then, related derivatives have emerged such as cyclohexylbenzamide- (e.g., isopropyl-U-47700; 3,4-methylenedioxy-U-47700; U-47931E, "bromadoline" and U-49900) and phenylacetamide-derived synthetic opioids (e.g., U-48800; U-50488 and U-51754) [1].

NITAZENES

Another group of synthetic opioids that have emerged is analogs of the internationally controlled substances clonitazene and etonitazene. The first nitazene reported to UNODC, isotonitazene, emerged in 2019, and since then, 18 substances have emerged. This family of synthetic opioids has a potency several times higher than morphine; etonitazene is 70 times and isotonitazene is 500 times more potent. The reported substances can be differentiated into two sub-families, which include nitrobenzimidazoles (e.g., isotonitazene), and benzimidazoles (e.g., metodesnitazene) [1].

PIPERAZINES

The smallest group of opioids receptor agonists that have been reported to UNODC are classified as piperazines and include two cinnamylpiperazines and one phenethylpiperazine. Additionally, AP-237 ("bucinnazine"), a pharmaceutical opioid prescribed for pain management in cancer patients, can be considered the structural parent of the analogs 2-methyl-AP-237 and para-methyl-AP-237. In 2019, the 2-methyl-AP-237 appeared on the NPS market. This substance possesses analgesic activity but is less toxic than AP-237 in animal studies [1]

MISCELLANEOUS SYNTHETIC OPIOIDS

The miscellaneous synthetic opioid group is made up of a diverse range of synthetic opioids, that in some cases express certain structural similarities to opioid analgesics under international control but have never been marketed as a pharmaceutical and lack a common core. One example is the phenethylpiperidine, brorphine, which has a similar chemical structure to the opioid bezitramide.

SEDATIVES/HYPNOTICS

Substances within the sedative/hypnotic effect group are CNS depressants that suppress, inhibit, or decrease brain activity through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), suppressing nerve signals and facilitating sedation. CNS depressants include benzodiazepines, barbiturates, methaqualone, and gamma-hydroxybutyric acid (GHB) (***Table 6***) [1; 15].

BENZODIAZEPINES

The largest structural group of CNS depressants are benzodiazepines, which are widely used in medicine as anticonvulsants, anxiolytics, hypnotics, sedatives, skeletal muscle relaxants, and tranquilizers. Several benzodiazepines (BZDs) have been synthesized for use as pharmaceuticals and more than 40 have been placed under international control. Benzodiazepine-type NPS have re-appeared in recent years, often marketed in forms of presentation that are similar in appearance to legitimate medicines containing benzodiazepines [1]. The benzodiazepine NPS flunitrazepam (trade name Rohypnol) and its derivatives became famously intertwined with drug-facilitated sexual assault or "date rape" as early as the 1970s; the term "getting roofied" is now synonymous with being exposed to any date rape drug in any structural NPS subgroup [1; 62].

BZDs can be classified into eight sub-groups based on chemical structure: 1,4-benzodiazepines; 1,5-benzodiazepines; imidazolobenzodiazepines; triazolbenzodiazepines; 2,3-benzodiazepines; thienotriazolodiazepines; thienodiazepines; oxazolodiazepines [1]. More than 30 benzodiazepine-type NPS have been reported to UNODC and primarily belong to the three sub-families: 1,4-benzodiazepines, triazolobenzodiazepines, and thienotriazolobenzodiazepines [1].

PROFILE OF SEDATIVE/HYPNOTIC-EFFECT NPS CATEGORY	
Definition	These substances are central nervous system depressants, with actions derived from their activation of receptors in the GABA receptor complex in the brain.
Parent Drug(s)	Benzodiazepines, barbiturates, methaqualone, gamma-hydroxybutyric acid (GHB)
Common Forms and Routes of Administration	Powder: Oral consumption Tablets and capsules: Oral consumption Liquid: Oral consumption, injection Liquids (gel) in capsules: Injection
Examples of Known Street Names	714s, Barbitos, Barbs, Benzos, Blue bomb, Canasson rouge, Candy, Cherry meth, Cloud-9, Double trouble, Downers, Fantasy, G, Goop, Georgia Home Boy, GHB, Goofballs, Lemons, Ludes, Mandrax, Nerve pills, Nimbies, Parest, Peanuts, Pinks, Quaalude, Rainbows, Reds and blues, Red birds, Red devils, Reds, Scoop, Seggy, Sleep, Sleepers, Sleeping pills, Yellow jackets
Desired Effects	Feelings of calmness, relaxation, sociability, and well-being in individuals with anxiety Improved coping with situational pressure or psychological problems Promotes growth hormone effects of alleged stimulation of muscle growth Reduced inhibition, euphoria, mild hallucinations Relief of tension, mental stress, anxiety Relief of side effects associated with withdrawal of other drugs or overstimulation
Undesired Acute Effects	Dilation of pupils Diminished emotional responses to external stimuli, such as pain Extreme, unpredictable emotional reactions and mental confusion or disorientation Potential impairment of muscle coordination, clumsiness, dizziness, low blood pressure, or feinting Potential stupor, unconsciousness, coma Reduced mental activity and alertness, drowsiness, lethargy, Impairment of clarity of thought and judgement Respiratory and cardiac depression, weak and rapid heart rate, suppression of cough reflex Slurred or poor control of speech
Effects of Chronic Use	Abrupt cessation may lead to withdrawal syndrome (insomnia, anxiety, perceptual hypersensitivity, tremors, irritability, nervousness, faintness, nausea, vomiting, progressive restlessness, temporary sleep disturbances, and possible delirium and life-threatening convulsions Bronchitis, pneumonia Development of tolerance strong psychological and physical dependence Headache, irritability, confusion, memory impairment, depression insomnia and tremor Potential blackouts Severe depression and amnesia In conjunction with other central nervous system (CNS) depressants, adverse effects are exacerbated

Source: [1; 15; 20] *Table 6*

While some benzodiazepine-type-NPS have been placed under international control in recent years, there is limited pharmacological and toxicological information on most substances that have emerged. The use of benzodiazepines along with opiates or other CNS-depressant drugs highly increases the risk of overdose and death. Although deaths involving benzodiazepines may be under-reported, they are rare without the concurrent use of other drugs [1].

BARBITURATES

The barbiturates are synthetic CNS depressants that were once used widely in health care but now are mainly used as antiepileptics, an adjunct to anesthesia, and less commonly as antianxiety medication. As with benzodiazepines, individual barbiturate drugs differ in the onset and duration of action and potency. Barbiturates have a low therapeutic index (a comparison of the amount that produces the therapeutic effect and that results in toxicity) and overdosing can therefore be fatal. As a result, they have been largely replaced on both the licit and illicit market by the benzodiazepines [15].

METHAQUALONE

A number of sedative/hypnotic NPS derived from methaqualone have also emerged. Methaqualone is a CNS depressant with sedative/hypnotic, anticonvulsant, antispasmodic, and local anesthetic properties. This substance was withdrawn from the pharmaceutical market in many countries because of issues of abuse and it is under international control. NPS within this group that have been reported to UNODC include etaqualone, mebroqualone, methylmethaqualone, and nitromethaqualone [1; 15].

GAMMA-HYDROXYBUTYRIC ACID (GHB)

The psychoactive drug GHB is derived from the GABA neurotransmitter and is mediated through its activation of specific excitatory GHB receptors and inhibitory GABA receptors. GHB has also been shown to affect the dopamine neurotransmitter system. The CNS depressant GHB produces sedation and anesthesia and medically has been used in anesthesia, as an aid for alcohol or opioid withdrawal, and in patients with insomnia and/or clinical depression. The NPS and its derivatives have also been associated with drug-facilitated sexual assault. It is also generated in the body after ingestion of the solvents gamma-butyrolactone (GBL) or 1,4-butanediol [15; 19].

NPS OF NATURAL ORIGIN (BOTANICALS)

KHAT

Catha edulis is a flowering shrub native to East Africa and the Arabian Peninsula. Its leaves are chewed for psychoactive effect and are referred to as khat (or alternatively, qat, kat, Chat, Miraa, or Quaadka). Khat has been widely used since the thirteenth century as a recreational drug in Africa and the Middle East [47]. The acute effects of khat include euphoria, increased alertness and energy, hyperactivity, anorexia, and decreased fatigue; many users report feeling relaxed and talkative. The sympathomimetic effects mimic those of amphetamines. Following the 90- to 180-minute effect, users report diminished concentration, numbness, and insomnia [47]. Widespread khat use in the United States is unlikely.

SALVIA DIVINORUM

Salvia divinorum is a member of the mint family native to Oaxaca, Mexico, and has been used by Mazatec shamans for divination and spiritual healing for more than 500 years. It is used in the United States for its intense hallucinogenic effects, sometimes under the street names Sally-D, Diviner's Sage, Magic Mint, and Mystic Sage. Salvinorin A, the primary psychoactive constituent, is a potent and selective kappa opioid receptor agonist that, unlike LSD, psilocybin, and DMT, lacks serotonin receptor activity. Salvinorin A is the most highly potent known hallucinogen found in nature [48].

Salvia is usually taken by smoking the dried leaves, which produces a rapid onset with peak effect within two minutes and dissipation by 20 to 30 minutes. User reports describe intense, highly unusual experiences of changes in spatial orientation, sensations of energy or pressure on different areas of the body, revisiting childhood memories, cartoon-like imagery, and contact with entities. Other descriptions include dysphoria, uncontrolled laughter, a sense of bodily loss, overlapping realities, hallucinations, bright lights, vivid colors and shapes, and body or object distortions. Adverse effects can include incoordination, dizziness, and slurred speech. No clinically meaningful changes occur in cardiovascular parameters. *Salvia divinorum* and salvinorin A are not currently DEA scheduled, but several states have enacted regulatory controls for either or both agents [48].

KRATOM

Kratom (*Mitragyna speciosa korth*) is a tree indigenous to Southeast Asia, used by natives for its therapeutic and recreational effects (as an opium substitute) and to manage opioid withdrawal symptoms. In the United States, kratom was once promoted as a legal psychoactive product, but was a Schedule I drug in 2016 [49].

Mitragynine is the primary active alkaloid of kratom. Kratom leaves are ingested by chewing or boiling into tea. The effects last two to five hours. Low doses produce increased alertness, physical energy, talkativeness, and sociable behavior. High doses produce an opioid-like effect with sedation and euphoria. Undesired effects include nausea, itching, sweating, dry mouth, constipation, increased urination, and loss of appetite [49].

Addiction to kratom has been documented and is associated with anorexia, weight loss, insomnia, skin darkening, dry mouth, frequent urination, and constipation. Isolated cases of psychosis have occurred from chronic use. A withdrawal syndrome is also characterized, with hostility, aggression, emotional lability, muscle and bone ache, and jerky movement of the limbs.

ASSESSMENT, DIAGNOSIS, AND TREATMENT OF NPS TOXICITY

Patients presenting for medical attention following NPS use may exhibit intact or altered mental status. Mentally lucid patients may be intensely distressed with anxiety or panic, highly concerned with physical symptoms, or both. Symptoms are typically isolated and not systemic. If possible, information from patient history-taking and interview, together with patient signs and symptoms, directs management. However, patient presentations with altered mental status are not amenable to history-taking or interview, in which case management is directed by identifying the specific toxicity syndrome. Most toxicity/overdose symptoms are expressed through common pathways that allow markedly similar interventions despite pharmacologic diversity of causal NPS agent(s). This is fortunate, as toxicology confirmation of ingested NPS is rarely possible.

GENERAL ASSESSMENT

An attempt should be made to obtain information from all patients, with added information from lucid, coherent patients. The initial approach to assessing NPS intoxication and toxicity is evaluation of presenting signs and symptoms. With cathinone use, this may include mydriasis, excited delirium syndrome, and sympathomimetic toxidromes. Cannabimimetic intoxication may present with conjunctival injection, signs/symptoms of cannabis intoxication with THC-negative urine drug screen, and sudden-onset psychosis not otherwise explained. Being subject to urine drug testing (e.g., active military duty, probation/parole) should be considered a risk factor for cannabimimetic use. A standard toxicology screening of illicit drugs should be obtained to anticipate drug interaction toxicities or the need for closer/prolonged monitoring.

Clinicians should have a working knowledge of NPS and other substances common to their region to facilitate recognition of toxicities. Knowledge of NPS street names can improve patient communication/rapport. Patients should be directly asked about recent NPS use, especially younger patients with signs/symptoms of possible substance-related toxicity. Inconsistencies between observed and expected presentations from self-reported or screen-detected drug class may indicate NPS use. If the patient and/or friend or family member has additional unused NPS and/or the package, the brand and possible NPS should be identified. Any unused NPS may be sent for laboratory analysis.

If severe muscle spasms, swelling and pain in the extremities, or seizures are present, a laboratory workup should be obtained, including complete blood count, metabolic panel, cardiac enzymes, and creatine kinase for suspected rhabdomyolysis. Very high lactic acid concentration, very low pH, and high creatinine/creatine kinase suggests rhabdomyolysis, metabolic acidosis, and potential renal failure.

NPS TOXICITY SYNDROMES

The constellation of signs and symptoms in severe NPS toxicities reflects dysregulation of autonomic, sympathetic, dopaminergic, and/or serotonergic systems. These are termed syndromes or toxidromes. It is important to consider polysubstance ingestion before, during, and after NPS use, as it is common and can occur without intent by the frequent addition of multiple NPS and other psychoactives to NPS products. NPS users often co-ingest cocaine, amphetamines, MDMA, caffeine, hallucinogens, *Mitragyna speciosa* (kratom), and/or cathinones to enhance stimulant and entactogen effects; alcohol and beta-blockers to suppress tachycardia; zopiclone to produce visual hallucinations; pregabalin, omeprazole, and domperidone to counteract stomach pain; and cannabis and benzodiazepines to counteract anxiety. Self-administration of the second-generation antipsychotic drug olanzapine has become widely endorsed on Internet forums as the "ideal" molecule to terminate NPS-related psychotic crises/"bad trips," typically at a dosage range of 5–50 mg/day. In addition, it has been found that some users of this drug intended to augment, but not replace, pre-established use patterns of cocaine and MDMA. This pattern increases the risks of drug interaction toxicities in users [1; 8; 27].

Importantly, data suggest polysubstance use may be more or less prevalent in users of specific NPS, rather than endemic. Several studies found significantly higher rates of mono-substance use in cannabimimetic-related emergency department admissions than in patients with synthetic cathinone-related admissions. This may importantly influence management of patients with acute NPS toxicity [26; 27].

Excited Delirium Syndrome

Excited delirium syndrome, also referred to more recently as agitated delirium, is the most serious NPS-induced toxicity, is a severe, life-threatening state of agitated delirium and autonomic dysregulation. This syndrome is characterized by sympathetic hyperarousal (e.g., hyperthermia, vital sign abnormalities, metabolic acidosis), delirium (altered consciousness with diminished awareness of one's environment), rhabdomyolysis, and agitated or violent behavior. Patients with excited delirium are incoherent and combative; emergency department arrival is often by EMS transport or police escort in physical restraints. Many sustain traumatic injuries before first responder contact and intensely struggle even when struggle is futile, resulting in self-harm. Some patients may strip naked, reflecting the combined hyperthermia and altered mental status [28; 58].

Stimulant toxicity resulting in excited delirium syndrome has been described with MDMA, cocaine, amphetamine, and more recently, NPS such as cathinones and cannabimimetics. The hyper-dopaminergic state associated with intoxication with these drugs overloads dopamine circuitry with electrochemical signaling, triggering a surge in extreme motor hyperactivity, delirium, agitation, and violent behavior. Action pathways lead to peripheral sympathomimetic stimulation that predisposes to cardiac arrhythmia and cardiomyopathy, and with sufficient activation of the neurocardiac axis, sudden death. Autopsy results have shown a diminished concentration of D3 dopamine receptors relative to controls, suggesting a deficit in normal compensatory measures in response to rapid changes in dopamine levels [28; 58].

Hyperthermia contributes to excited delirium-associated morbidity and mortality and primarily results from agitation that drives muscular hyperactivity, rhabdomyolysis, and renal failure. Even with patient survival of an initial cardiac arrest, persistent hyperthermia contributes to the developing coagulopathy, rhabdomyolysis, and multisystem organ failure [41; 58].

Effective Calming of Patients with Excited Delirium Syndrome

The ability of EMS or emergency department staff to safely subdue patients with excited delirium has been elusive. Delays in medical treatment and the use of conventional restraints can be fatal. The behavioral symptoms of excited delirium impose a serious safety hazard to EMS, emergency department staff, and the patient. TASER and physical restraints are standard control measures but produce further destruction of muscle tissue, exacerbating the risks of subsequent renal failure and cardiopulmonary collapse. Benzodiazepines and haloperidol are used by some EMS to calm patients with excited delirium before attempting emergency transport. In this setting, IV administration is usually impossible, intramuscular administration delays the onset, and the dose required to sedate violent patients risks adverse hemodynamic and respiratory complications. Antipsychotic drugs interfere with already-compromised dopamine function [30].

Intramuscular ketamine has rapid onset and efficacy, a wide therapeutic window, and favorable side effect profile. It is becoming favored by EMS for calming patients with excited delirium before emergency transport with support from several studies. However, some patients develop laryngospasm and hypoxia, resolved by endotracheal intubation. In one study of 52 patients receiving ketamine 4 mg/kg IM, effective sedation and medical control was achieved within 150 seconds in 96% of cases; all remained sedated following emergency department arrival (mean: 19 minutes) [31]. In another study of 35 agitated, combative patients with possible excited delirium, 91% were successfully sedated by ketamine IM (mean dose: 324 mg), 17% required additional post-ketamine sedation by EMS or emergency department staff, and 23% required post-ketamine intubation. Emergence reactions, well described with ketamine, also developed but were resolved with benzodiazepines. Rapid calming from ketamine reduces extreme physiologic stress from extended struggles with police and continued agitation with physical restraints. Excited delirium syndrome requires IV initiation to begin end-organ, life-preserving treatment, which is nearly impossible until severely agitated, combative patients are sedated [30; 31].

Sympathomimetic Toxidrome

Sympathomimetic toxidrome resembles excited delirium, differing by dominant hyperadrenergic symptoms of tachycardia, hypertension, nausea/vomiting, and diaphoresis and a lack of violent agitation. Excited delirium syndrome and sympathomimetic toxidrome can co-occur. The presumed underlying hyperdopaminergic and hyperadrenergic states of excited delirium and sympathomimetic toxidrome, respectively, are intertwined. As such, co-occurrence in NPS toxicity is probably frequent, and management is highly similar [15; 18].

Serotonin Syndrome

Serotonin syndrome is a state of excess serotonin activity from serotonergic agent overdose or synergistic toxicity. Serotonin syndrome shares some features with excited delirium and sympathomimetic toxidrome, but patients are rarely aggressive and violent. Patients typically present with psychomotor agitation, and cognitive (e.g., confusion, delirium), neuromuscular (e.g., akathisia, ataxia, myoclonus, hyper-reflexia), and autonomic (e.g., dizziness, nausea/vomiting, tachycardia, sweating) symptoms. It can be differentiated from sympathomimetic toxidrome by the presence of shivering, rigidity, myoclonus, and hyper-reflexia. Serotonin syndrome is characterized by a rapid onset of neuromuscular symptoms with markedly increased muscle tone, along with shivering, tremors, hyper-reflexia, akathisia, ataxia, and myoclonus. Sweating may decrease and contraction of opposing muscle groups generates heat more rapidly than vasodilatation, leading to hyperpyrexia and cardiovascular instability. The mortality rate is 10% to 15% [8; 15].

Acute Hyponatremia

Acute hyponatremia has led to numerous MDMA fatalities. These deaths usually result from prolonged (8 to 12 hours) dancing to electronic dance music (e.g., techno, house). Indoor settings with poor ventilation and high ambient temperature contribute further. Hyperthermic complications from MDMA stem from exertional hyperpyrexia, hyponatremia, and serotonin syndrome [27; 42].

Anticholinergic Toxidromes

Anticholinergic toxidromes can resemble NPS toxicity, with altered consciousness, agitation, confusion, disorientation, delirium, hallucinations, tachycardia, tachypnea, and hyperthermia. Sympathomimetic toxidrome may be differentiated from anticholinergic toxidromes by presence of marked diaphoresis (instead of dry skin) and lack of bowel sounds [8; 18]. The presence of neuromuscular abnormalities is specific to serotonin syndrome and is not seen in patients with anticholinergic toxidromes.

DIFFERENTIAL DIAGNOSIS

Rapid identification of NPS-induced toxicity is essential in patients who present with agitation, altered mental status, hyperthermia, and autonomic dysregulation. Conditions that resemble NPS toxicity should be ruled out first (***Table 7***); in addition, current medications should be reviewed to rule out potential psychiatric side effects that can mimic NPS-induced toxicity (***Table 8***) [28; 29]. This narrows the field to identify the NPS toxicity syndrome or toxidrome.

Medical Conditions

A GABA agonist withdrawal syndrome from substances such as alcohol or benzodiazepines is a common medical condition that shares autonomic hyperarousal, agitation, and altered mental status with NPS toxicity. Neurologic trauma or disease, including traumatic brain injury, hydrocephalus, brain tumor, and subarachnoid or intracerebral hemorrhage, can produce an intense autonomic dysregulation syndrome similar to that seen with NPS use. These patients may also display hypertension, fever, tachycardia, tachypnea, and pupillary dilation [1; 28; 30].

Some psychiatric disorders may have similar presentations to acute NPS toxicity, including bipolar disorder and paranoid schizophrenia. Patients may display an emotional rage reaction in response to acute psychologic stressors. In addition, psychotropic drug withdrawal and emergent symptoms from medication noncompliance may precipitate symptoms similar to an excited delirium or serotonin syndrome.

Systemic inflammatory response syndrome (SIRS) is related to systemic inflammation, organ dysfunction, or organ failure, and is broadly classified as infectious or noninfectious. With infection, the condition is termed sepsis. Noninfectious SIRS origins include trauma, burns, pancreatitis, ischemia, and hemorrhage, and dysregulated and uninhibited pro-inflammatory pathways result in altered mental status, fever, or hyperdynamic vital signs [28].

POSSIBLE CONDITIONS ACCOUNTING FOR AGITATION, FEVER, ALTERED MENTAL STATUS, AND HYPERDYNAMIC VITAL SIGNS		
Medical	**Substance-Induced**	**Toxidromes**
GABA-agonist substance withdrawal Malignant catatonia Systemic inflammatory response syndrome Encephalitis Post-head injury with autonomic dysfunction syndrome	Cocaine Methamphetamine Ketamine Phencyclidine MDMA Tryptamines Cathinones	Serotonin syndrome Malignant hyperthermia Anticholinergic toxicity Neuroleptic malignant syndrome
GABA = gamma-aminobutyric acid.		
Source: [28]		*Table 7*

MEDICATIONS THAT MAY MIMIC NPS-INDUCED TOXICITY	
Medication	**Commonly Associated Side Effect**
Antiepileptic agents	Delirium, psychosis, irritability
Beta blockers	Delirium, psychosis, depression
Corticosteroids and anabolic steroids	Mood changes
Interferon	Depression
Benzodiazepine (withdrawal)	Anxiety, agitation
Fluoroquinolones	Restlessness, irritability
Isoniazid	Delirium
Sulfonamide antibiotics	Delirium
Acyclovir/ganciclovir	Hallucinations
Psychostimulants, dopaminergic agents (e.g., anti-Parkinson agents)	Psychosis, agitation, irritability
Over-the-counter cough and cold preparations	Delirium, confusion, hallucinations
Anticholinergics (diphenhydramine, benztropine, trihexyphenidyl)	Delirium
Marijuana	Disassociation, apathy, amotivation
Opioids	Anxiety, irritability
Phencyclidine, hallucinogens	Hallucinations, aggression, lability, mood swings
Stimulants (cocaine, amphetamine)	Paranoia, psychosis, depression, hallucinations
Source: [29]	*Table 8*

Encephalitis of viral, bacterial, fungal, or autoimmune origin can manifest in neuropsychiatric disturbances and altered mental status with severe headache, fever, confusion, agitation, personality changes, seizures, hallucinations, or impairment in speech or hearing. Limbic encephalitis of paraneoplastic origin can produce severe neuropsychiatric symptoms, marked agitation, and autonomic dysfunction [28].

Malignant catatonia is a neuropsychiatric syndrome seldom seen clinically, is highly lethal, and initially presents as nonspecific insomnia and mood changes, progressing to severe anxiety, delusions, hallucinations, and agitation. Other symptoms can include severe, nonpurposeful hyperkinetic movements, high fever, tachycardia, and labile blood pressure [28].

Endocrine system disorders can appear as agitation, autonomic instability, and fever. In thyrotoxic crisis, cardiac failure, arrhythmia, or hyperthermia can result from a massive surge in thyroid hormone. Tumors of the sympathetic ganglia can produce hypertension, tachycardia, sweating, and panic attacks from increased sympathetic tone. Less commonly, fever and delirious agitation may be noted [28]. In patients with diabetes, hypoglycemia may precipitate violent outbursts and an appearance of intoxication. Hypoglycemia may be diagnosed rapidly and conclusively via blood glucose testing and glucose response.

MANAGEMENT OF ISOLATED ADVERSE EFFECTS

Most nonpsychiatric symptoms of NPS toxicity appear self-limited and resolve within one to several days with supportive treatment. Panic attacks, intense anxiety, agitation, or paranoia can be treated with benzodiazepines. Antipsychotics are second-line agents for more severe agitation or paranoia because they increase the risk of seizure if cathinones or phenethylamines were taken [30].

MANAGEMENT OF NPS TOXICITY SYNDROMES

The similar core features of NPS toxicities allow symptom-directed management independent of (presumed) causal substance. Management of common core features and those specific to excited delirium, sympathomimetic toxidrome, and serotonin syndrome is discussed in this section.

Immediate Interventions

If treatment of excited delirium or sympathomimetic toxidrome is neglected, delayed, or inadequate, the outcome is often multiple end-organ damage or death. The most essential aspect of the management of cathinone toxicity is rapid, aggressive sedation with benzodiazepines. Benzodiazepines are the agents of choice because they decrease excessive heart rate, blood pressure, neural stimulation, and muscular activity; prevent seizures; protect against physical violence; and reduce muscular hyperactivity that drives fever, rhabdomyolysis, and renal failure. Benzodiazepines have a wide safety margin and, contrary to common belief, do not dangerously decrease cardiovascular or respiratory parameters unless used with potent sedatives. Immediate calming may require IM lorazepam, midazolam, or ketamine to allow for safe placement of IV access. With access in place, IV diazepam may be initiated, the preferred agent for effective rapid titration because full onset of each dose occurs within five minutes, allowing repeat dosing without the "overshooting" risk with slower-onset lorazepam. Patients may require very high doses for effective sedation. Propofol or barbiturates in those appearing refractory to high-dose benzodiazepine [18; 28; 30]. Antipsychotic drugs interfere with already-compromised systemic dopaminergic function and should be avoided in patients with suspected excited delirium.

Management of serotonin syndrome targets agitation, hyperthermia, and autonomic dysfunction. Benzodiazepines are preferred to induce sedation and reduce muscle rigidity. With causal substance(s) typically unidentified and benzodiazepine efficacy across NPS toxicity syndromes, benzodiazepines should be used instead of serotonin antagonists [30].

All toxicities with hyperpyrexia require aggressive cooling through high-rate IV fluids and external cooling measures. The combination of sedation, fluids, and cooling reverses hyperthermia and metabolic acidosis and prevents further muscular and hepatorenal injury. Enteral or parenteral vasodilators should be used for persistent hypertension, while beta-blockers should be avoided because unopposed alpha-receptor stimulation can induce systemic vasoconstriction. Sodium bicarbonate may be considered for rhabdomyolysis and acidosis. Antipyretics are ineffective for hyperthermia because the origin is increased muscular activity, not hypothalamic temperature dysregulation [30].

Post-Discharge Care

Following resolution of the autonomic storm and return to normal reflexes and muscle tone, clinicians should be aware that psychosis, dysphoria, and irritable unrest can persist in patients hospitalized for NPS toxicity after medical stability is achieved. These lingering psychiatric symptoms best respond to dopamine blockade with neuroleptics. This aspect of persistent cathinone toxicity makes post-hospital care challenging and heightens the importance of care providers in multiple specialties to understand this toxidrome and the associated phases of illness [30; 41]. Fatalities following cannabimimetic use have occurred in patients discharged home with lingering paranoia and depression.

NPS USE DISORDERS

NPS ABUSE POTENTIAL

Multiple lines of evidence have captured the abuse and addiction potential of synthetic opioids, including fentanyl analogs and the cathinones.

The abuse potential of synthetic cathinones and other opioid receptor agonists can be predicted by pharmacologic activity. The ratio of dopamine to serotonin influences episodic (i.e., recreational) versus compulsive (i.e., addictive) use patterns. Cathinones release more dopamine than serotonin (similar to methamphetamine and cocaine), which predicts drug craving, urge to re-dose, and addiction liability. Drugs that release higher serotonin than dopamine levels (e.g., MDMA) tend to have a dampening effect on craving and urge to re-dose and a lower abuse potential [1; 58]. Frequent high-dose opioid use induces tolerance, dependence, craving, and a withdrawal syndrome with cessation characterized by depression, anxiety, sleep disorders, and fatigue, with craving, anhedonia, and anergia that can last several weeks. Class-wide, withdrawal symptoms include depression, impulsivity, anhedonia, and cognitive complaints of poor concentration and attention [18].

The abuse liability of many other NPS is anecdotal, and while pharmacologic profiles can help predict risks of craving and compulsive use (as discussed), little is known of the prevalence, natural history, or withdrawal syndromes in patients with heavy/prolonged use [3]. An indicator of abuse potential NPS can broadly be determined by the scheduling of substances (Schedule I–IV), as outlined in the 1961 and 1971 international drug control treaties [8].

ASSESSMENT AND TREATMENT OF NPS USE DISORDERS

Engagement

Helping motivate and empower patients with NPS use disorder to seek help is a challenge. Research suggests many patients with NPS use disorder do not identify as needing conventional drug treatment or do not want to seek help due to the illicit nature of NPS. Hospitalization for NPS overdose/toxicity presents an excellent window of opportunity (the "teachable moment") for advising patients to decrease their substance use or to engage them in treatment. Provider awareness and patient education are cornerstones of public health initiatives to confront the new challenges from NPS. Simple admonitions are insufficient, and adolescents/younger adults are wary of any communication with a judgmental, heavy-handed abstinence tone [50]. Patients identified with any substance use disorder in the emergency department or inpatient setting should be linked to information on local and national addiction treatment resources (***Table 9***).

Patient Motivation/Empowerment to Change

Because patients with problematic NPS use may be ambivalent about changing behavior, clinicians should demonstrate respect for patient autonomy by expressing empathy without confrontation. Providing appropriate, accurate information on the relative risks and unknown harms of NPS empowers patients in making informed decisions to continue NPS use, attempt to quit, or seek treatment [50].

RESOURCES FOR PATIENTS WITH SUBSTANCE USE DISORDER, INCLUDING NPS
211 Dial 211 to identify local counseling or substance use disorder treatment programs 211.org
American Addiction Centers https://americanaddictioncenters.org
Substance Abuse and Mental Health Services Administration National Helpline: 800-622-4357 https://findtreatment.gov
USAGov https://www.usa.gov/substance-abuse
Source: Compiled by Author *Table 9*

In the primary care setting, patients with NPS-related problems may present with concerns over their NPS use or with problems they suspect are NPS-related. Alternatively, patients may describe an NPS-related problem without linking it to NPS use. Motivational interviewing is suggested because this technique is proven useful in resolving patient ambivalence over change with numerous clinical conditions. This approach involves first appreciating and addressing patient concerns and withholding advice until greater clarity emerges. This empowers active patient participation and facilitates positive behavioral change. To begin this process, gain patient permission before questioning about substance use. If granted, mention confidentiality. If concern is from a family member, explore further, ask about their coping, and provide info on relevant support if needed [50]. With assessment of patients acknowledging drug use-related problems, invite active patient contribution by asking open-ended questions, such as:

- "Tell me about your drug use."
- "What is your drug use during an average week?"
- "What concerns do you have?"
- "You mentioned discomfort when urinating—how might that be related to your drug use?" (e.g., ketamine abuse associated with urinary complications)

To help build rapport, ask about drug jargon and drug effects. Giving feedback with specific reference to patient concerns can help patients re-frame their drug use and consequences.

After the basic situation and clinical picture has been established, the next steps should be determined. Further questions may include:

- "Where would you like to go with this next?"
- "Is there anything I can specifically help with?"

This can involve further information about the presenting problem or drug use, harm-reduction advice, guidance on managing physical or psychiatric problems, exploration of abstinence, or specialist referral.

Patients who clearly link drug use with a problem are likely to ask questions and be receptive to expert input. Apply a circular process to engage patient interest:

- "Would you like to know some more about how MDPV can affect your mood?"
- "When people use stimulants over a weekend and don't get any sleep, it can reduce chemicals in the brain that help keep our mood stable and feeling happy."
- "How does that fit with your experience?"

Avoid assuming the patient wants to change or needs expert help to change. Instead, introduce the concept of change by asking:

- "We've discussed some concerns you have, and how they might be related to your drug use. Where do we go from here?"
- "Would you like to do something about your drug use?"

If a patient expresses the wish to change, ask how he or she might do this and whether professional support is needed. In patients unsure about what they should do, consider harm-reduction advice. As little is known about NPS, give general harm reduction advice such as limiting use, a period of cessation to observe improvement in health concerns, and total avoidance in high-risk patients (e.g., those with a history of psychiatric illness, addiction). The appointment should end with permission to revisit the subject in the future [50].

Treatment of NPS Use Disorders

Patients in treatment for NPS use disorder may need to address premorbid or NPS-induced psychiatric or medical conditions or symptoms. As with other patients, those recovering from NPS use disorder probably require long-term support, professional contact, and possibly multiple short-term acute treatment episodes. Treatment typically involves components similar to those in general use, including individual and group counseling, cognitive-behavioral therapy, motivational enhancement therapy, and 12-step facilitation. Family members should be considered for involvement in the treatment program, especially with adolescent or young adult patients. Little data are available to guide pharmacologic management of acute and post-acute NPS withdrawal symptoms and ongoing NPS craving. Treatment is more complex for patients with backgrounds of polysubstance abuse, young age at initiation of regular drug use, lingering neuropsychologic impairment, or psychiatric disorders. Patients with intermittent NPS use in social settings may perceive they have less of a problem [30; 50]. Encouragement of 12-step program involvement, such as Narcotics Anonymous, can provide patients with the means for support, a non-substance-using social network, and other benefits conducive to recovery.

HARM REDUCTION

Harm reduction neither condones nor condemns drug use, but instead recognizes that some risks from recreational NPS use can be mitigated. DanceSafe is the largest harm-reduction organization for North American nightlife/electronic dance music communities. Efforts by DanceSafe are directed at non-addicted recreational users, who comprise the largest number of drug users but are underserved by conventional harm reduction that targets addicted users. DanceSafe objectives include reducing drug misuse and empowering users to make informed decisions about their health and safety by providing unbiased educational literature on the effects/risks of specific drugs; remote and, when possible, on-site adulterant screening (drug testing); on-site free water and electrolytes to help prevent hyperthermia; free ear plugs; free safe sex tools to avoid pregnancy and sexually transmitted infections; and first point of contact for adverse drug effects [52]. Many other American and European harm-reduction groups use common objectives and methods.

Due to the widespread use and severe consequences of the fentanyl epidemic, harm reduction in the form of public naloxone education and use training has been made available. Information on naloxone and how to obtain it for personal or community assistance is available at https://www.factsfightfentanyl.org [37].

PREVENTION

The most effective measure against problems from NPS use is preventive, especially in educating and informing adolescents, young adults, and the general public. An abundance of helpful educational materials are available that target specific age groups, educators, parents, healthcare workers, and the public and that address health and medical consequences and the legal status of NPS [8].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

As a result of the evolving racial and immigration demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because specific details about the patient's history are crucial to diagnosing NPS toxicity, effective communication is required. Communicating effectively is more challenging when the patient's primary language differs from that of the practitioner. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

CONCLUSION

NPS are broadly diverse in molecular structure and pharmacology. Many carry potential risks of serious adverse psychiatric effects or life-threatening toxicity. Frequent inclusion of multiple psychoactive substances in NPS products increases the risk of toxic drug interaction. Intrinsic NPS properties, their frequent adulteration with other substances, and highly prevalent polysubstance ingestion heighten risks of overdose and toxicity reactions urgently requiring medical care. NPS market growth is likely to continue and evolve in the near future, making it essential for primary care providers to understand the spectrum of emerging drugs in order to identify and manage potential acute and persistent effects.

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