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Review Article

New Psychoactive Substances: Major Groups, Laboratory Testing Challenges, Public Health Concerns, and Community-Based Solutions

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Across communities worldwide, various new psychoactive substances (NPSs) continue to emerge, which worsens the challenges to global mental health, drug rules, and public health risks, as well as combats their usage. Specifically, the vast number of NPSs that are currently available, coupled with the rate at which new ones emerge worldwide, increasingly challenges both forensic and clinical testing strategies. The well-established NPS detection techniques include immunoassays, colorimetric tests, mass spectrometric techniques, chromatographic techniques, and hyphenated types. Nonetheless, mitigating drug abuse and NPS usage is achievable through extensive community-based initiatives, with increased focus on harm reduction. Clinically validated and reliable testing of NPS from human samples, along with community-driven solution, such as harm reduction, will be of great importance, especially in combating their prevalence and the use of other illicit synthetic substances. There is a need for continued literature synthesis to reiterate the importance of NPS, given the continuous emergence of illicit substances in the recent years. All these are discussed in this overview, as we performed another look into NPS, from differentiating the major groups and identifying with laboratory testing challenges to community-based initiatives.

1. Introduction

The United Nations Office on Drugs and Crime (UNODC) uses the term "new psychoactive substances" (NPS), which refer to substances of abuse, in a preparation/formulation or pure form, not controlled by "the 1961 Single Convention on Narcotic Drugs" or "the 1971 Convention on Psychotropic Substances," which may pose a threat to the public health [1, 2]. Many psychoactive substances including the synthetic drugs are increasingly considered as "new psychoactive substances" (NPSs) or "designer drug" (DD). Broadly speaking, NPS refers to any functional/structural analog of controlled substance designed to mimic the psychological and/or pharmacological properties of the original drug, dodging the detection in standard drug test and/or classification as illegal [1, 2]. NPS also includes those designated as performance-enhancing drugs' analogs, e.g., designer steroids [3, 4]. Some NPSs were firstly synthesized in the laboratory by industrial or academic researchers in a concerted effort to develop additional effective derivatives with reduced side effects, shorter onset, and possibly due to ease of applying on patents; later, they were coadopted for recreational purposes [4]. Other NPSs were originally prepared in covert laboratories and mostly affect the adolescents, youths, and adults, including those with or without comorbidities [5, 6]. As the evaluation of safety/efficacy of

NPS, especially those that involve human and animal trials, continues, their use might lead to unexpected side effects, some of which may be lethal. Most NPSs are also traded in the dark web. The dark web has drawn the attention of researchers and law enforcement agencies, largely due to the mode of operations that play a major role in substance abuse. Many of the substances/NPS in dark web offered under already known names often have different contents.

Most NPSs in the market are named bath salts, kryptonite, herbal highs, legal highs, synthetic drugs, research chemicals, party pills, and so on [7, 8], as marketing strategies, often for branding to evade the law and law enforcement agents, as well as to deceive unsuspecting consumers, although some consumers/users of NPS are already aware of these strategies. NPSs do not necessarily mean new invented substances, as many NPSs were originally synthesized many years ago, but mean substances with recent availability at the market [9, 10]. The chemical structures of synthetic drugs (or NPS) often differ from the original illicit substances they mimic, as the synthetic drugs' manufacturers continuously modify their structures in an attempt to beat the law [6]. Whilst some NPSs are promoted as safe, acceptable, and legal alternatives to unlawful drugs [1, 2], even though it may not mean they are safe or lawful, there appears to be no clearly recommended dose [4]. Modifications of recognized active drugs, including their stereoisomers, derivatives, and structural analogues, provide the drugs that might significantly differ in effects from the parent drug they mimic, with reduced side effects, shorter or longer onset, increased potency, and so on [9, 10], having similar effects to existing drugs, although completely different in chemical structures, for example, JWH-018 (AM-678) and tetrahydrocannabinol (one of the psychoactive constituents in cannabis). Besides the nonregulation/quality control, the NPS development may appear as a subfield in drug design and development [9, 10]. The nature of NPS being abused or used has considerably evolved, just like the same way its associated factors are evolving at the same time. Many populations in developed and developing nations have observable patterns/trends and characteristics underpinning factors, primarily responsible for the observable patterns/trends [2, 8]. Efforts that are made are inadequate in containing the increasing trend of substance abuse and to appreciate the evolution for characterizing the patterns of this substance abuse, including factors responsible for the trend. Arguably, this is partly due to the fact that the epidemiology of NPS has not been given adequate attention it deserves all over the world. With recent data and developments on prevalence, the epidemiology of NPS requires more attention than it is currently receiving [2, 8].

Among countries and regions, the definitions of NPS do differ by legislations, not necessarily due to pharmacological/structural classification(s) but also by social and cultural perspectives. However, under the UN conventions, many NPSs are subject to international control, e.g., ADB-FUBINACA (a synthetic cannabinoid) and mephedrone in 2019 and 2015, respectively; different legal control approaches have been taken at state levels in many countries [11–13]. By December 2021, there were about 1124 NPSs, compared to 892 NPS in 2018, as reported by 134 countries, with each reporting one or more NPS, as monitored by the UNODC early warning system [8]. Overall, the market of NPS show effects that resemble those of the international controlled substances, like cocaine, cannabis, heroin, and lysergic acid diethylamide (LSD). A look at the properties of synthetic NPS reported by December 2021 shows that majority are stimulants, which is followed by the receptor agonists of synthetic cannabinoid and hallucinogens, with recent remarkable increase in synthetic opioids [8]. The fast-changing NPS market profile has raised concerns over ambiguity and uncertainty regarding their metabolic, toxicity, and chemical profiles and the associated social, mental, and physical health harms [14, 15]. In this study, insights into NPS epidemiology/prevalence were given, with emphasis on their spread, chemistry, action mechanisms, public and global health concerns, etc., among the major challenges associated with the increasing global emergence of various NPSs including drug rules, public health risks, and resultant mental health crisis. However, the knowledge about NPS's societal adverse effects/harm is still on the rise. Identifying and analyzing the many diverse chemical substances in drug markets is challenging [1]. Risk awareness, monitoring, early warning, information sharing, and community engagement are essential for adequate response to the NPS challenges [7]. Given the continuous emergence of illicit substances particularly in the recent years, there is need for continued studies at various levels to reiterate the socioeconomic and scientific significance of NPS. More so, combating the prevalence across several communities worldwide requires increased community-based initiatives/approaches. Therefore, to supplement existing information, we provide an overview of NPS, from differentiating major groups and laboratory testing to community-based initiatives. The study aimed at providing latest insight into several NPS (synthetic drugs), their associated effects, and their prevalence. It focused more on the NPS (illicit substances) emerging in recent years and provided community-based initiatives and approaches to combat their prevalence in our society. The major groups of NPS and associated substances were extensively covered. An insight into their effects is provided. The study clearly demonstrates the diversity of existing and new psychoactive substances with their various psychoactive effects, structures, mechanism of actions, adverse effects, properties, psychological and pharmacological properties, and widespread use.

2. Materials and Methods

2.1. Search Methods. We thoroughly searched relevant databases such as ScienceDirect, Google Scholar, PubMed/MEDLINE, United Nations Office on Drugs and Crime (UNODC), Google, and other relevant search engines using the following key terms: ("new psychoactive substances" OR "illicit synthetic drugs" OR "designer drug" OR "Chemistry of new psychoactive substances") AND ("Detection of new psychoactive substances" OR "Fight against new psychoactive substances").

Table 1: Description of major new psychoactive substances along with the reason why people keep taking them as well as their potential adverse effects.

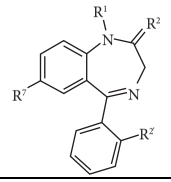
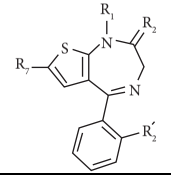
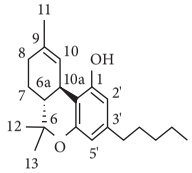
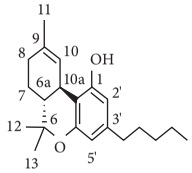
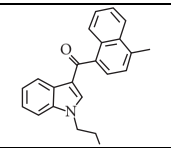
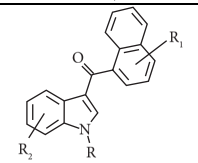
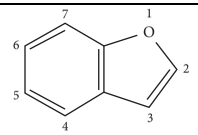
New psychoactive substances	Basic structure	Description	Examples	NPS group	Reason for intake	Adverse effects	References
Benzodiazepines		Benzodiazepines, sometimes referred as "benzos," are a family of psychoactive drugs with core chemical structure being a benzene ring and a diazepine ring fusion. Synthetic benzodiazepines are often taken for nonmedical reasons	Phenazepam, nitrazolam, 4′-chlorodiazepam, pyrazolam, nimetazepam, nifoxipam, norflurazepam, meclonazepam, flunitrazolam, flubromazolam, flubromazepam, fludiazolam, diclazepam, fonazepam, cloniprazepam, clonazolam, bromazolam, adinazolam, 3-hydroxyphenazepam, etc.	Synthetic benzodiazepines (sedatives)	Anxiolytic and hypnotic effects, managing acute stimulant effects, self-treating withdrawal symptoms, and "high"	Confusion, visual and auditory hallucinations, sedative-hypnotic toxidrome, drowsiness fatigue, dizziness, delirium, tachycardia and hyperthermia, agitation, coma, and deep sleep, seizures	[16, 17]
Thienodiazepines		Thienodiazepines belong to a family in benzodiazepines. Thienodiazepines are heterocyclic compounds made of the fusion of a diazepine ring and a thiophene ring. Their structure forms the core of some recreational and pharmaceutical drugs	Desmethyletizolam, fluclotizolam, flubrotizolam, etizolam, deschloroetizolam, deschloroclotizolam, etc	Synthetic benzodiazepines (sedatives)	Hypnotics, sedation, anxiolytic effects, managing acute stimulant effects, "high,", self-treating withdrawal symptoms, etc.	Drowsiness, muscle incoordination/weakness, depression, slurred speech, fainting, headache, confusion, changes in libido, visual disturbances, tremor, etc.	[17, 18]
Classical cannabinoids		Classical cannabinoids are ABC-tricyclics that incorporate a benzopyran moiety and are characterized by (−)-Δ^9-THC (1) and similar compounds with structural resemblance	HU-210, CP 47,497 (and its (C8) homologue cannabicyclohexanol), HU-308, CP 55,940	Synthetic cannabinoids	Euphoria, disinhibition, relaxation, appetite, etc.	Cerebrovascular accidents ("strokes"), renal injury, haemodynamic embarrassment, respiratory complication, cardiovascular impairment, etc.	[19, 20]
Miscellaneous cannabinoids		Many miscellaneous cannabinoids have been reported	JWH-018 benzimidazole analogue, WIN 55,212-2, QMPSB, NNL-1, NESS-040C5, EGMB-CHMINACA, MDA-19, LY-2183240, JTE-907, EG-2201, BAY 38-7271, AB-CHFUPYCA, 5F-MDA-19, 5F-AB-FUPPYCA, etc.	Synthetic cannabinoids	Relaxation, euphoria, disinhibition, appetite, etc.	Morbidity, renal injury, haemodynamic embarrassment, respiratory complication, mortality, seizures, poor coordination, palpitations, withdrawal symptoms, etc.	[21]
Indazole based cannabinoids		Synthetic cannabinoids based on indazole that contain cannabinoid receptor agonists	THJ-2201, SDB-005, PX-2, NPB-22, BiPICANA, APP-BINACA, AMB, ADB-BINACA, 5F-SDB-005, 5F-AMB, 5C-APINACA, 4F-MDMB-BINACA, 4F-ADB, 4CN-ADB, etc.	Synthetic cannabinoids	Disinhibition, euphoria, relaxation, etc.	Confusion, vomiting, paranoia, nausea, intense anxiety, strong compulsion to dose again, persistent cravings, etc.	[22, 23]
Indole based cannabinoids		Synthetic cannabinoids based on indole that contain cannabinoid receptor agonists	Adamantoylindole, naphthoylindoles, quinolinylindoles, benzoylindoles, phenylacetylindoles, 5C-NNEI, 5F-APP-PICA, etc.	Synthetic cannabinoids	Euphoria, appetite, disinhibition, relaxation, etc.	Tachycardia, hypertension, dizziness, chest pain, agitation, drowsiness, protracted vomiting, nausea, confusion, etc.	[24]
Benzofurans		Benzofurans are heterocyclic compounds with fused benzene and furan rings. They have structural similarity to MD(M)A, but differ by the methylenedioxy groups been modified, thus eliminating one of the two oxygens in methylenedioxy ring, making a benzofuran ring	Benzo fury, 5-(2-aminopropyl)benzofuran, 6-(2-Aminopropyl)-2,3-dihydrobenzofuran, 1-(benzofuran-5-yl)-N-ethylpropan-2-amine, etc.	Synthetic empathogens, hallucinogens, and/or stimulants	Empathy, love, euphoria, hallucinogenic effects, stimulant, effects, recreational effects, etc.	Anxiety, panic attack, confusion, dilated pupils, insomnia, paranoia, aggression, hostility, panic, etc.	[25]

Table 1: Continued.

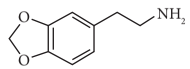
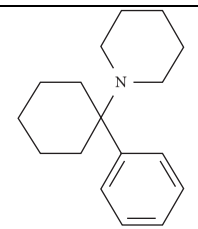
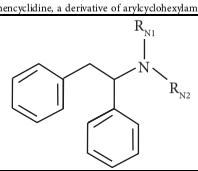
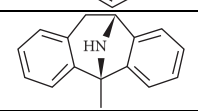
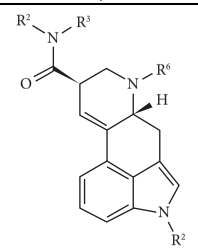
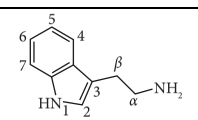
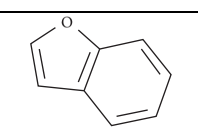
New psychoactive substances	Basic structure	Description	Examples	NPS group	Reason for intake	Adverse effects	References
Substituted methylenedioxyphenethylamines (MDxx)	 Methylenedioxyphenethylamine, an MDxx	Substituted methylenedioxy- phenethylamines are a large family of phenethylamines derivatives, which includes several psychoactive drugs that function as psychedelics, entactogens, entheogens, and/or stimulants	5-methyl-MDA, difluoromethylenedioxyamphetamine, ethylenedioxymethylamphetamine, ethylone, eutylone, dimethylone, 5-methoxymethylone, butylone, dibutylone, 5-methylethylone, dipentylone, ethylbenzodioxolylbutanamine, methylbenzodioxylbutanamine, methylenedioxyhydroxyamphetamine, methylenedioxyethylamphetamine, N-tert-butyl-methylone, methylenedioxyhydroxymethamphetamine, N-propylbutylone, methylbenzodioxylpentanamine, methylbenzodioxylbutanamine, methylenedioxyhydroxyamphetamine, methylenedioxyethylamphetamine, N-tert-butyl-methylone, methylenedioxyhydroxymethamphetamine, N-propylbutylone, etc.	Synthetic empathogens, psychedelics, entactogens, entheogens and/or stimulants	Empathy, emotional closeness, love, recreational effects, etc.	Dehydration, increased perspiration, etc.	[26]
Arylcyclohexylamines (arylcyclohexanamines or arylcyclohexamines)	 Phencyclidine, a derivative of arylcyclohexylamine	Arylcyclohexylamines contain a unit of cyclohexylamine with attached aryl moiety located geminal to the amine. They have NMDA receptor antagonistic, μ-opioid receptor agonistic, and dopamine reuptake inhibitory properties	Ketamine, phencyclidine, bromoketamine, 2-fluoroketamine, eticyclidinone, fluoroeticyclidinone, deoxymethoxetamine, 2-trifluoromethyldeschloroketamine, hydroxyeticyclidine, 3-methylrolicyclidine, methoxydine, deschloroketamine, eticyclidine, methoxetamine, isopropyloxetamine, 2-meo-2-deschloroketamine, n-ethylketamine, etc.	Synthetic hallucinogens (dissociative)	Hallucinations, anesthesia, dream-like states, dissociation, sensory deprivation, etc.	Ataxia, nystagmus, confusion, nausea, agitation, muscle rigidity, amnesia, hallucinations, slurred speech, disorientation, renal impairment, tachycardia, hypertension, etc.	[27, 28]
Diarylethylamines		Diarylethylamines are NPS that produce dissociative effects similar to those of arylcyclohexylamine dissociatives, although they have different chemical structure	2-MeO-ephenidine, 2-chloro-ephenidine, diphenidine, fluorolintane, ephenidine, 2-MeO-diphenidine, methoxphenidine, N-methylephenidine, etc.	Synthetic hallucinogens (dissociative)	Hallucinations, anesthesia, dissociation, etc.	Sensory deprivation, confusion, nausea, agitation, muscle rigidity, amnesia, hallucinations, slurred speech, disorientation, etc.	[29]
Misc		A misc, known as dizocilpine (MK-801), is an uncompetitive N-Methyl-D-aspartate antagonist	Dizocilpine, *N*-methylhexahydrofluorenamine, 1,3-dimethylbutylamine, camfetamine, tert-Amyl alcohol, larocaine, amfonelic acid, bromantane, pagoclone, mephtetramine, methylhexanamine, methyldifluoromodafinil, etc.	Synthetic hallucinogens (dissociative), stimulants, and sedatives	Dissociative effects, recreational experience, hallucinogenic effects, etc.	Amnesia, residual deficits in thinking, agitation, muscle rigidity, amnesia, etc.	[30]
Lysergamides		Lysergamides are amide derivatives of the lysergic acid (an alkaloid), and include various substances with potent antagonist and/or agonist activities at many serotonin and dopamine receptors	Methylisopropyllysergamide, 1-cyclopropionyl-6-Allyl-6-Nor-LSD, 1-butanoyl-LSD, 1-propionyl-LSD, 1-cyclopropionyl-LSD, N-Morpholinyllysergamide, 1-acetyl-LSD, etc.	Synthetic hallucinogens (psychedelic)	Psychedelic experience, hallucinogenic effects, euphoria, mystical experiences, novel thought, etc.	Hysterical behavior, unpredictable hallucinations recurrence, life-threatening hyperthermia, hyperactivity, confusion, aggression, agitation, mydriasis, hyperthermia, etc.	[31, 32]
Tryptamines		Tryptamines are monoamine alkaloids synthesized by decarboxylating amino acid tryptophan; tryptamines are an indolamine metabolites of tryptophan, an essential amino acid; NPS and drugs with tryptamine moiety are usually serotonin receptors' substrates	Diethyltryptamine, diisopropyltryptamine, ethacetin, ethipracetin, ethocin, depracetin, deprocin, ethylpropyltryptamine, indapex, ipracetin, miprocin, psilacetin, iprocin, lucigenol, metacetin, methylcyclopropyltryptamine, methylethyltryptamine, methylisopropyltryptamine, etc.	Synthetic hallucinogens (psychedelic)	Psychedelic effects, hallucinogenic experience, euphoria, etc.	Confusion, anxiety, drowsiness, excessive hallucinations, aggression, agitation, mydriasis, moderately severe dysphoria, hyperthermia, hypertension, tachycardia, nausea, depression, etc.	[33, 34]
Benzofurans		Benzofurans are the heterocyclic compound with fused furan and benzene rings	5-MeO-benzofuranethanamine, 5-MeO-DiBF, etc.	Synthetic hallucinogens (psychedelic)	Psychedelic effects	Severe pulmonary *side effects*, cough, hypoxia, exertional dyspnea, weight loss, etc.	[25, 35]

Table 1: Continued.

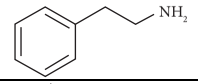
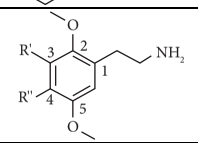
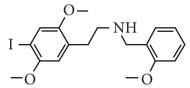
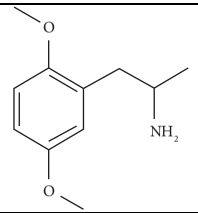
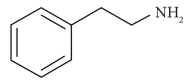
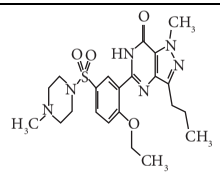
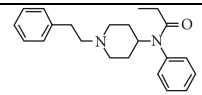
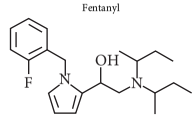
New psychoactive substances	Basic structure	Description	Examples	NPS group	Reason for intake	Adverse effects	References
Phenethylamines		NPS or drugs with phenethylamine moiety have similar chemical structure as dopamine, but the benzene ring substitution results in drugs with a higher serotonin receptors' affinity	Isoproscaline, allylescaline, escaline, proscaline, methallylescaline, etc.	Synthetic hallucinogens (psychedelic)	Psychedelic effects, stimulation, euphoria, mystical experiences, thought associations, etc.	Hallucination recurrence, hyperactivity, confusion, aggression, agitation, depression, mydriasis, etc.	[36]
2C-x (2C)		2C-x are class of psychedelics derived from 2,5-dimethoxy-phenethylamine; 2c-*x* comprise of a psychedelic phenethylamines family having methoxy groups on a benzene ring's 2 and 5 positions	2C-B, brolphetaminil (2C-B-AN), 2C-D, *β*-methoxy-2C-B, 2C-M, europa (2C-E), 2C-C, 2C-B-FLY, jelena (2C-iP), 2C-I, 2C-G, 2C-P, *β*-methoxy-2C-D, *β*OH-2CB, HOT-7, *β*k-2C-B, etc.	Synthetic hallucinogens (psychedelic)	Psychedelic effects, mystical experiences, hallucinogenic experience, euphoria, etc.	Agitation, hyperthermia, hypertension, aggression, hallucinations, state of unease, seizures, violence, etc.	[26]
25-NB (25*x*-NB*x* or NB*x*x)		The 25-NB series, also known as the NBOMe compounds, is a serotonergic psychedelics family. They selectively act as serotonin 5-HT_{2A} receptor agonists, and are substituted phenethylamines derived from the family of 2C	25B-NBF, cimbi-5, (25I-NBOMe, N-bomb, solaris), 25C-NBF, cimbi-21 (25I-NBF), 2CBCB-NBOMe, cimbi-27 (25I-NBOH), 25B-NBOH, nova (25B-NBOMe or cimbi-36), pandora (25C-NBOMe or cimbi-82), 25C-NBOH, divination (25D-NBOMe), 25E-NBOMe, cimbi-29 (25I-NBMD), mescaline-NBOMe, etc.	Synthetic hallucinogens (psychedelic)	Psychedelic effects, hallucinogenic experience, euphoria, recreational use, etc.	Altered reality, uncontrolled movements (tremor), cold feet, hallucination, headache, dizziness, confusion, memory loss, anxiety, agitation, weakness, upset stomach, etc.	[37, 38]
4-Substituted-2,5-dimethoxyamphetamines (DO*x*)		4-Substituted-2,5-dimethoxyamphetaminesis a family of substituted amphetamine derivatives with methoxy groups at positions of 2 and 5 of the phenyl ring, and an alkyl or halogen substituent at the 4th position of phenyl ring. They act as highly selective partial agonists of 5-HT_{2B}, 5-HT_{2A}, and 5-HT_{2C} receptor	2,5-Dimethoxy-4-(ethoxymethyl)amphetamine, 2,5-dimethoxy-4-ethylamphetamine, 2,5-dimethoxy-4-chloroamphetamine, 2,5-dimethoxy-4-ethoxyamphetamine, 2,5-dimethoxy-4-amylamphetamine, 2,5-dimethoxy-4-bromoamphetamine, 2,5-dimethoxy-4-butylamphetamine, 2,5-dimethoxy-4-(methoxymethyl)amphetamine, etc.	Synthetic hallucinogens (psychedelic)	Psychedelic effects, mental stimulation, hallucinogenic experience	Hyperactivity, confusion, aggression, agitation, *bad* trips, more physical *effects*, etc.	[26]
Miscellaneous polycyclic phenethylamines (tetralin-type and Indane-type phenethylamines)		Tetralin-type and indane-type phenethylamines are vaguely related to their amphetamine analogues. Just a nontryptamine indole has been sold	Indanylaminopropane, 5,6-methylenedioxy-N-methyl-2-aminoindane (*MDMAI*), 5,6-methylenedioxy-2-aminoindane (MDAI), *N-methyl-2-AI*, 5-(2-Aminopropyl)indole, etc.	Synthetic hallucinogens, empathogens, and stimulants	Empathogenic effects, recreational effect, feel more awake, stimulation, chatty and "up"	Increased heart rate, increased blood pressure, slight hyperthermia, restlessness, anxiety, diuresis, anorexia, tachycardia, dilated pupils (mydriasis), jaw clenching, agitation, panic attacks, excessive sweating, insomnia, disorientation, tremor etc.	[39, 40]
Phosphodiesterase type 5 inhibitors (PDE5 inhibitors)	 Sildenafil, a PDE5 inhibitor	PDE5 inhibitors are typically used to treat pulmonary hypertension and erectile dysfunction	Piperidinoacetildenafil, nitrosoprodenafil, thiosildenafil, sulfoaildenafil, piperidinovardenafil, lodenafil, hydroxythiohomosildenafil, alldenafil, hydroxyacetildenafil, homosildenafil, gendenafil, aminotadalafil, acetildenafil, etc.	Synthetic inhibitors	Penile erection, ChemSex, pulmonary hypertension, etc.	Headache, dizziness, nasal congestion, flushing, dyspepsia, rhinitis, muscle aches, back pain, risk of neonatal mortality, etc.	[41, 42]
Opioids	 Fentanyl  2-fluoroviminol	Opioids exert pharmacologic actions similar to that of morphine and other opium components. They act on opioid receptors, producing morphine-like effects	Fentanyl, 2-fluoroviminol, 3-methylbutyrfentanyl, 4-fluoroisobutyrfentanyl, bromadol, bucinnazine, 4-methoxybutyrfentanyl, dipyanone, 2,2′-difluorofentanyl, 3-methylfentanyl, 4-chloroisobutyrfentanyl, 4-fluorobutyrfentanyl, 4-fluorofentanyl, p-hydroxy-butyrylfentanyl, acrylfentanyl, α-methylfentanyl, acetylfentanyl, brorphine, metonitazene, norbromadol, butonitazene, clonitazene, acetoxymethylketobemidone, butyrfentanyl, bromadoline, cyclopentylfentanyl, desmethylprodine, desmethylmoramide, cyclopropylfentanyl, crotonylfentanyl, diphenpipenol, etazene, desnitroetonitazene, etonitazene, isotonitazene, methoxyacetylfentanyl, etc.	Synthetic opioids (sedatives)	Euphoria, anxiolysis, drowsiness, relaxation feelings, etc.	Vomiting, respiratory depression, nausea, constipation, CNS depression, apnoea, dizziness, deaths, rhabdomyolysis, acute lung injury, diffuse alveolar haemorrhage, noncardiogenic pulmonary oedema, etc.	[8, 43]

Table 1: Continued.

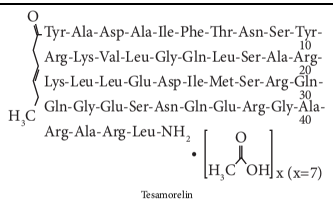
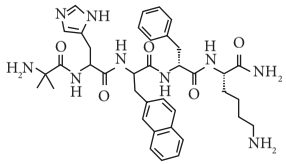
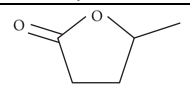
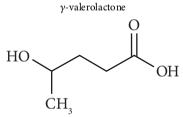
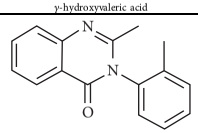
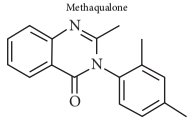
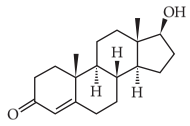
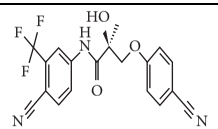
New psychoactive substances	Basic structure	Description	Examples	NPS group	Reason for intake	Adverse effects	References
Peptides	 Tesamorelin  Ipamorelin	GHRH analogues stimulate the release of growth hormone. Agonists of the growth hormone secretagogue receptor regulate energy homeostasis and body weight	GHRH analogues (tesamorelin, sermorelin, CJC-1295, CJC-1293, etc.); growth hormone secretagogue receptor agonists (ipamorelin, ibutamoren, GHRP-6, GHRP-2, examorelin, etc.); other examples (melanotan II, melanotan, delta sleep - inducing peptide, carnosine, bremelanotide, bpc-157, etc.)	Synthetic peptides	Regulate body weight and energy homeostasis, stimulate growth hormone, etc.	Vomiting, abdominal pain, nausea, tiredness, headache, arthralgia (joint pain), diarrhea, weakness, muscle pain, etc.	[44, 45]
Gamma-hydroxybutyric acid (GHB) analogues	 γ-valerolactone  γ-hydroxyvaleric acid	Gamma-hydroxybutyric acid analogues are drugs that have chemical structures similar to gamma-hydroxybutyric acid (GHB). Their ingestion produces physiological effects closely related to the effects closely associated with the abuse of GHB	γ-valerolactone, γ-hydroxyvaleric acid, γ-butyrolactone, 1,4-butanediol	Synthetic sedatives	Relaxation, mild euphoria, athletic-performance enhancer, recreational effects	Drowsiness, depressed breathing, nausea, agitation, visual disturbances, dizziness, drowsiness, amnesia, death, unconsciousness, neurotoxicity, etc.	[46, 47]
Methaqualone analogues	 Methaqualone  Methylmethaqualone	Methaqualone analogues are designed to mimic methaqualone, a hypnotic and sedative drug	Methylmethaqualone, nitromethaqualone, mecloqualone, mebroqualone, etaqualone, afloqualone	Synthetic sedatives	Hypnotic and sedative effects, relaxation, recreational effects, socializing effects, etc.	Delirium, convulsions, nervous system shutdown, vomiting, kidney failure, hypertonia, hyperreflexia, coma, cardiac arrest, respiratory depression, death, etc.	[48, 49]
Androgenic anabolic steroids	 Testosterone	Androgenic anabolic steroids are approved for medical uses and are also illicitly used as performance-enhancing drugs for building muscle mass/strength. Anabolic steroids are known as "designer steroids" when they are designed to evade sport doping tests. Anabolic steroids are also called anabolic-androgenic steroids, and are steroidal androgens, which include the natural androgens, such as testosterone, and synthetic androgens, which are similar to testosterone in effects and structure	Testosterone based (testosterone, methyltestosterone, dianabol, halotestin, 4-chloro-testosterone, boldenone, adrenosterone, turinabol, 11-ketotestosterone); estranes (trestolone, trenbolone, tetrahydrogestrinone, genabol, nandrolone, mibolerone, methyltrenbolone, dimethyltrienolone, dimethandrolone); DHT based (winstrol, prostanozol, oxymetholone, oxandrolone, methyl-1-testosterone, superdrol, metenolone enanthate, mesterolone, mestanolone, epiandrosterone, drostanolone, dihydrotestosterone, desoxymethyltestosterone, 1-testosterone, dihydroboldenone)	Synthetic steroids and androgens	Enhancing performance, stimulate muscle growth and appetite, build muscle mass/strength etc.	Decreased high-density lipoprotein, high blood pressure, increased low-density lipoprotein, acne, liver damage, heart impairment, strokes, myocardial infarction, etc.	[3, 4, 50]
Selective androgen receptor modulators (SARMs)	 Ostarine, a nonsteroidal SARM	Selective androgen receptor modulators (SARMs) are a novel class of androgen receptor ligands. They are intended to maintain the desirable muscle building effects of anabolic steroids while reducing undesirable androgenic actions (*e.g.*, increased risk of prostate cancer)	YK-11, S-40503, S-23, ostarine, BMS-564,929, andarine, AC-262,356, etc.	Synthetic steroids and androgens	maintain the desired anabolic steroids' muscle building effects (*e.g.*, preventing muscle loss and osteoporsis), while decreasing the unwanted androgenic actions (*e.g.*, risk of prostate cancer)	Reduce HDL levels, dyspepsia, nausea, constipation,	[51, 52]

Table 1: Continued.

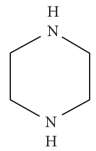
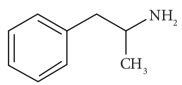
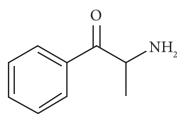
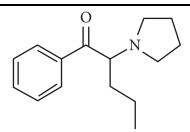
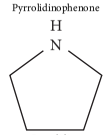
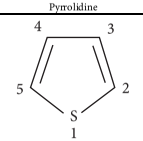
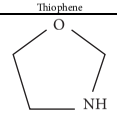
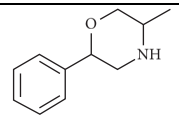
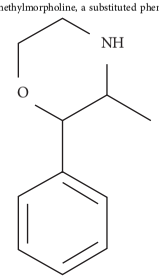
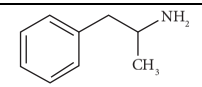
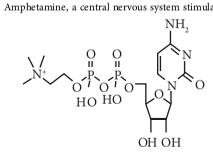
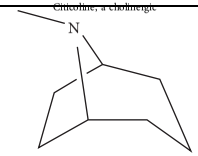
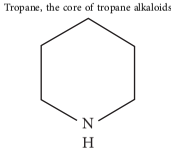
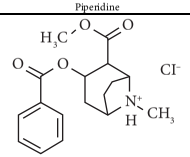
New psychoactive substances	Basic structure	Description	Examples	NPS group	Reason for intake	Adverse effects	References
Piperazines		Piperazines consist of a 6-membered ring containing two atoms of nitrogen at opposite positions. NPS that contain piperazines have MDMA-like effects (ecstasy). They mimic serotonin that activates 5-HT receptor subtypes, which release dopamine and norepinephrine	Benzylpiperazine, dibenzylpiperazine, 3-chlorophenylpiperazine, 4-methoxyphenylpiperazine, methoxypiperamide, 4-fluorophenylpiperazine, methylbenzylpiperazine, piperonylpiperazine, trifluoromethylphenylpiperazine, etc.	Synthetic stimulants	Ecstasy, recreational experience, etc.	Hyperthermia, nausea, agitation, hypertension, palpitations, vomiting, headache, paranoia, etc.	[53, 54]
Amphetamines		Amphetamines (substituted amphetamines) include a family of stimulants, hallucinogens, entactogens, etc., having a phenethylamine core with the alpha carbon linked to a methyl group, resulting in amphetamine, and extra substitutions. They are central nervous system stimulants	2-fluoroamphetamine, N,alpha-diethylphenylethylamine, 2-fluoromethamphetamine, meta-methamphetamine, β-phenylmethamphetamine, 3-fluoroamphetamine, 3-fluoromethamphetamine, 4-chloromethamphetamine, 4-fluoroamphetamine, 4-chloroamphetamine, 4-fluoroselegiline, 4-methylamphetamine, 4-fluoromethamphetamine, 4-bromoamphetamine, 4-methoxyamphetamine, methamnetamine, 3-fluoroethamphetamine, 3-methoxy-4-methylamphetamine, 4-methoxymethamphetamine, 4-methylthioamphetamine, etc.	Synthetic stimulants	Cognitive enhancer, performance enhancer, recreational effects, aphrodisiac, euphoriant, etc.	Hypertension, Raynaud's phenomenon, hypotension, blurred vision, dry mouth, increased heart rate (tachycardia), sexual effects in men (frequent erections, erectile dysfunction, prolonged erections, etc.), nosebleed, appetite loss, excessive teeth grinding, profuse sweating, etc.	[14, 55]
Cathinones ("Bath salts")		Cathinones include certain stimulants and entactogens, which are cathinone derivatives and have a phenethylamine core with the beta carbon bonded to a ketone group and the alpha carbon bonded to an alkyl group, along with extra substitutions. Cathinone (also called β-keto-amphetamine or benzoylethanamine) are monoamine alkaloid found in khat (*Catha edulis*) and have chemical similarity to cathine, methcathinone, ephedrine, and other amphetamines	Dimethoxyethylpentedrone, 4-bromomethcathinone, 4-chlorobutylcathinone, ephylone, 2-chloromethcathinone, 2-methylmethcathinone, 2-methylmephedrone, 2-fluoromethcathinone, 2-methylethcathinone, 3,4-dimethyl-N-ethylpentedrone, 3-chloromethcathinone, 3-fluoromephedrone, 3-methoxymethcathinone, 3-ethylethcathinone, 3-fluoromethcathinone, flephedrone, 4-fluoro-N-isopropylpentedrone, 4-ethylethcathinone, α-methylamino-butyrophenone, ethcathinone, 4-methylbuphedrone, benzedrone, 3-methylmethcathinone, 4-chloroethcathinone, etc.	Synthetic stimulants	Stimulant effects, euphoria, wakefulness, enhanced alertness, productivity, awareness, endurance, motivation, etc.	Irritability, insomnia, loss of appetite, increased heart rate, increased arousal, increased blood pressure, rhabdomyolysis and peripheral organ damage, etc.	[8, 56]
Pyrrolidinophenones and pyrrolidines	 Pyrrolidinophenone  Pyrrolidine	Pyrrolidinophenones (also known as pyrovalerones) are cathinones (βk-amphetamines) that have a pyrrolidine group. Pyrrolidines are amphetamines that have a pyrrolidine group	Centroton, α-pyrrolidinopropiophenone, diphenylprolinol, 2-diphenylmethylpyrrolidine, 3′,4′-methylenedioxy-α-pyrrolidinopropiophenone, α-pyrrolidino-2-phenylacetophenone, 4′-methyl-α-pyrrolidinopropiophenone, α-phenyl-pyrovalerone, α-pyrrolidinobutiophenone, βk-prolintane, α-pyrrolidinobutiothiophenone, 4′-chloro-α-pyrrolidinopropiophenone, 2′-methyl-α-pyrrolidinopentiophenone, naphyrone, 4′-bromo-α-pyrrolidinopentiophenone, indapyrophenidone, 2′,4′-dimethyl-α-pyrrolidinopropiophenone, etc.	Synthetic stimulants	Improved alertness, endurance, productivity, arousal, awareness, wakefulness, recreational effects, psychostimulation, etc.	Increased arousal, increased heart rate, poor sleep, increased blood pressure, CNS and cardiovascular toxicities, etc.	[57–60]
Thiophenes	 Thiophene	Thiophenes are synthetic stimulant drugs which are amphetamine or cathinone analogues, where thiophene replaced the phenyl ring	Methiopropamine, thiothinone, mephedrene, thiopropamine, cyclo-methiodrone, etc.	Synthetic stimulants	*Psychedelic*-like effects, stimulating effects,	Tachycardia, reduced consciousness, agitation, confusion, hallucinations, increased creatine kinase, sedation, hypothermia, etc.	[61–63]
Oxazolidines		Oxazolidines are five-membered ring compounds with three atoms of carbon, an oxygen atom, and a nitrogen atom. The NH group and O atom are the 3 and 1 positions, respectively. In derivatives of oxazolidine, there is always one atom of carbon between the atoms of N and O (otherwise, it becomes an *isoxazolidine*)	4′-bromo-4-methylaminorex, 4′-Fluoro-4-methylaminorex, 4,4′-Dimethylaminorex, 4′-chloro-4-methylaminorex, etc.	Synthetic stimulants	Improved alertness, awareness, recreational effects, psychostimulation, etc.	Increased arousal, increased heart rate, increased blood pressure, anxiety, etc.	[64, 65]

Table 1: Continued.

New psychoactive substances	Basic structure	Description	Examples	NPS group	Reason for intake	Adverse effects	References
Phenylmorpholines (substituted phenylmorpholines) and Phenmetrazines	 2-phenyl-5-methylmorpholine, a substituted phenylmorpholines  Phenmetrazine	Phenylmorpholines are family of stimulants that contain a phenethylamine skeleton with the terminal amine fused into a morpholine ring. Substituted phenylmorpholines (alternatively known as substituted phenmetrazines) are derivatives of phenylmorpholine or of phenmetrazine (a psychostimulant drug). Phenmetrazines are substituted amphetamine having a morpholine ring	Isophenmetrazine, 3-fluorophenmetrazine, phenmetetrazine, N-ethylphenmetrazol, 3-chlorophenmetrazine, methylmorphenate, phenetrazine, etc.	Synthetic stimulants	Stimulant effects, anorectic effects, antidepressant-like effects, euphoria, suppressing appetite, recreational effects, etc.	Insomnia, dizziness, nausea, vomiting, irritability, upset stomach, dry mouth, diarrhea, etc.	[66]
Nootropics	 Amphetamine, a central nervous system stimulant  Citicoline, a cholinergic	These drugs enhance cognition in healthy people. In particular, the classes of stimulants that demonstrate cognition-enhancing effects in humans act as direct agonists or indirect agonists of dopamine receptor D_1, adrenoceptor A_2, or both types of receptor in the pre-frontal cortex. Racetams are often marketed as cognitive enhancers and sold over the counter. Cholinergics are typically analogues and compounds of choline	Central nervous system stimulants (amphetamine, methylphenidate, eugeroics, caffeine, nicotine); cholinergics (citicoline, choline bitartrate, L-alpha glycerylphosphorylcholine, *etc.*); Racetams (phenylpiracetam, aniracetam, piracetam, oxiracetam)	Synthetic stimulants and nootropics	Cognition-enhancing effects, "high," motivation, attention, improve task saliency, improve task performance, wakefulness, alertness, improved memory, creativity, etc.	Decrease learning, physiological discomfort, anxiety, etc.	[67–69]
Tropanes and piperidines	 Tropane, the core of tropane alkaloids  Piperidine	Tropane alkaloids are found in plants that belong to the families erythroxylaceae (*e.g.*, coca) and Solanaceae (*e.g.*, deadly nightshade, mandrake, tomato, potato, henbane, datura, etc.). Piperidine and its derivatives are abundant building blocks for synthesizing several fine chemicals and pharmaceuticals. Piperidine can be obtained from black pepper, *Petrosimonia monandra*, Aizoaceae (*Psilocaulon absimile*), etc.	2-benzhydrylpyrrolidine, 4-fluoroethylphenidate, 3,4-dichloromethylphenidate, 4′-fluorococaine, 4-benzylpiperidine, 4-fluoromethylphenidate, benocyclidine, desoxypipradrol, ethylphenidate, ethylnaphthidate, methylnaphthidate, isopropylphenidate, meprylcaine, 4-nitro-dimethocaine, diphenidine, pipradrol, propylphenidate, etc.	Synthetic stimulants, opioids, and dissociatives	Getting high, recreational effects, hallucinogenic experiences, stimulating experience, presumed medicinal effects, etc.	Nausea, abdominal pain, depression, irritability, cardiac disorders, vomiting, irregular breathing patterns, salivation, muscle weakness, headache, dizziness, fatigue, hepatotoxicity, nephrotoxicity, sore throat, coughing, dizziness, altered blood pressure, etc.	[70]
Cocaine analogues		Cocaine analogue is any artificial construct of novel chemical compound derived from the structure of cocaine. The resulting substance has strong similarity to cocaine	Dimethocaine, erythroxyline, R-allococaine, isococaine, S-allococaine, etc.	Synthetic stimulants	Getting high, feeling of alertness, recreational effects, euphoria, stimulating experience, power and energy, etc	Nose bleeds, collapse, central nervous disorders, paranoid delusions, fast heart rate, etc	[9, 14, 58, 59, 70]

2.2. Inclusion Criteria. For an article to be considered in this review, the paper had to meet the following inclusion criteria: Firstly, it must have been published by peer-reviewed sources. Secondly, it must have used acceptable research methods and reported the effects of new psychoactive substances or possible solution thereof. We also made use of articles published in English language and also considered those in other languages which must have been translated to English language. Although our main focus was on recently published articles, we also considered articles published some years ago without year restrictions and followed the development over the years. We evaluated the title, abstract, methodology, and references of each article.

2.3. Exclusion Criteria. We excluded articles that did not strictly focused on new psychoactive substances. We also exclude articles that mostly focused on other psychoactive substances that are not considered new psychoactive substances. Duplicate articles were screened and only one was retained.

The data/information was then stratified into paragraphs and subparagraphs accordingly, with emphasis on action mechanisms, chemical structures, intended intoxicating effects, and modes of use. Many psychoactive substances were reported, starting from the most commonly used ones to the infrequently used ones. This study may not have covered all sources but almost all reliable sources for information on NPS were extensively covered. The study did not focus on the emerging psychoactive substances from plants, as it mostly focused on synthetic psychoactive substances.

3. Differentiating the New Psychoactive Substances (NPS) and Their Global Public Health Concerns

Table 1 summarises the different psychoactive substances elaborated by examples, the major groups situated, and the reasons that underpin intake, as well as their potential adverse effects. NPS lists include benzodiazepines [16, 17], thienodiazepines [17, 18], classical cannabinoids [19, 20], miscellaneous cannabinoids [21], indazole based cannabinoids [22, 23], indole-based cannabinoids [24], and benzofurans [25, 35], as well as substituted methylenedioxyphenethylamines (MDxx) [26]. Also, Table 1 includes arylcyclohexylamines (arylcyclohexanamines or arylcyclohexamines) [27, 28], diarylethylamines [29], misc [30], lysergamides [31, 32], tryptamines [33, 34], phenethylamines [36], 2C-x (2C) [26], 25-NB (25x-NBx or NBxx) [37, 38], 4-substituted-2,5-dimethoxyamphetamines (DOx) [26], and miscellaneous polycyclic phenethylamines (tetralin-type and Indane-type phenethylamines) [39, 40], as well as phosphodiesterase type 5 inhibitors (PDE5 inhibitors) [41, 42]. Opioids [8, 43], peptides [44, 45], gamma-hydroxybutyric acid (GHB) analogues [46, 47], methaqualone analogues [48, 49], androgenic anabolic steroids [3, 4, 50], selective androgen receptor modulators (SARMs), piperazines [53, 54], amphetamines [14, 55], and cathinones ("Bath Salts") [8, 56] are also shown in Table 1. Additionally, pyrrolidinophenones and pyrrolidines [57–60], thiophenes [61–63], oxazolidines [64, 65], phenylmorpholines (Substituted phenylmorpholines)/phenmetrazines [66], nootropics [67–69], and tropanes, as well as piperidines [70] are collated in Table 1.

Although most NPSs have been stimulants, anabolic steroids, or hallucinogens, the diversity of likely compounds seem limited by patent and scientific literature; recent years have been characterized by the extensive range of substances sold as NPS [6, 7], which include several synthetic sedatives (e.g., premazepam, methylmethaqualone), synthetic stimulants (*e.g.*, geranamine, mephedrone, desoxypipradrol), and synthetic analogues of Viagra (sildenafil), reported as herbal aphrodisiac products' active compounds [71, 72]. Synthetic cannabinoids that are believed to have emerged in December 2008 include two compounds, (C8)-CP 47,497 and JWH-018, first reported as active components in blends for herbal smoking, and sold as alternatives tomarijuana [73]. Many synthetic cannabinoid agonists, including novel compounds, keep appearing (e.g., AB-001, RCS-4, and RCS-8) scanty in scientific literature and considered as invented by synthetic drug manufacturers. Besides, there are recent reports that have demonstrated why NPS is of global public health concern. Many effects of NPS are yet to be collected and accounted for but are often directly experienced by users/consumers; also, many NPSs actually leave the market before they are identified, perhaps after at least one death case has been attributable to them. By studying the psychoactive substances' prevalence in hospitalised patients in Moscow and Oslo via cross-sectional/observational fashion, Gamboa et al. [74] showed that many patients used at least one medicinal drug with psychoactive effects, especially opiates and benzodiazepines. Elsewhere, to understand the prevalence of NPS usage among patients undergoing drug detoxification, Specka et al. [9] analyzed responses of 295 patients and observed that majority of the patients were multiple substance users and opiate-dependent. Many users reported long-term usage, suggesting the prevalence of the use of many NPSs that go unreported. Around 32% said they used synthetic cannabimimetics throughout lifetime, although only in a few occassions. One of the major reasons for their usage was that NPSs were unable to be detected by drug treatment facility or drug tests in prisons [9]. Herbal drugs, cathinones, or other NPSs seem rarely used throughout lifetime, with strong lifetime and recent uses of cocaine, cannabis, opiates, benzodiazepines, etc. [9]. Additionally, 18% of the patients reported that they used unprescribed pregabalin regularly throughout lifetime, while 20% recently made use of pregabalin [9]. Pregabalin is among many drugs that are misused; gabapentin and pregabalin were recently reclassified as class C, scheduled V, and scheduled 4 controlled substances in the UK, US, and Australia, respectively [75]. Other countries have also restricted their use.

In the South Eastern part of Nigeria, especially between late 2020 and mid-2022, there has been high prevalence in the use of illicit substances and NPS [76]. In 2022, positive drug tests hit two-decade high among the US workers, and

mostly driven by increased positive marijuana tests, along with positive tests for other illicit substances [77]. Increase in the use of NPS worldwide, from Africa to South and North Americas and Asia-Pacific to Europe, presents high risks. Another novel development is the use of research ligands for cosmetic rather than strictly recreational purposes, such as grey-market Internet sales of the nonapproved alpha-melanocyte-stimulating hormone tanning drugs known as melanotan peptides [78]. What is new is the wide range of substances now being explored, the aggressive marketing of products that have been intentionally mislabeled, the growing use of the Internet, and the speed at which the market reacts to control measures [79]. Mephedrone and the cathinones somewhat marked a turning point for designer drugs, turning them from lessknown, ineffective substances to powerful substances capable of competing with classical drugs on the black market [54, 80, 81]. Mephedrone dramatically became more popular in 2009 and was prohibited in many countries mainly due to media panic [80, 81]. Since then, there has been an increased emergence of other cathinones aimed at mimicking mephedrone effects with more customer base. As stated earlier, in general, as of 2022, there are more than 1124 NPSs worldwide, reported by the UNODC early warning system [8].

Intense NPS side effects include seizures, aggression, agitation, potential development of dependence, and acute psychosis. Users of NPS have often been hospitalized and presented with severe intoxications, sometimes leading to unconsciousness or even death. Short-term physical effects that have been reported include rapid heartbeat, higher blood pressure, difficulty eating, difficulty sleeping, vomiting, nausea, shakiness, and dizziness, while long-term effects include kidney damage, respiratory difficulties, cardiovascular illness, liver damage, and impaired immunity [10, 77, 78].

4. Major New Psychoactive Substances (NPS): Action Mechanisms, Chemical Structures, Adverse Effects, and Toxicity

In this section, further discussions into major NPS are performed, grouped from synthetic cannabinoids (such as JWH-018), phencyclidine-type substances (such as methoxetamine), synthetic cathinones (such as α-pyrrolidinopentiophenone, 4-methylethcathinone), phenethylamines (such as 25H-NBOMe), aminoindanes (such as 5,6-methylenedioxy-2-aminoindane), tryptamines (such as α-methyltryptamine), plant-based substances (such as kratom), and piperazines (such as 1-(3-chlorophenyl) piperazine) to other substances such as 1,3-dimethylamylamine [8, 80]. Additionally, respective action mechanisms, chemical structures, intended intoxicating effects, modes of use, and associated harms to mental and physical health per group are highlighted.

4.1. Synthetic Cannabinoids. Synthetic cannabinoids are a group of NPS, typically in cannabis plants, which able to bind same receptors (such as cannabinoid receptor type 1) attached by cannabinoids (tetrahydrocannabinol and cannabidiol), which should not be confused with synthetic endocannabinoids (as they differ in many aspects) or synthetic phytocannabinoids (tetrahydrocannabinol or cannabidiol) [22, 82]. Synthetic cannabinoids were officially identified and reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) for the first time in 2008, originally used as herbal cannabis alternatives, especially to evade detection in the settings that subject substances to forensic tests, including the military, prisons, and sports programmes [73]. Since then, they are spread worldwide in varying potencies, structures, and forms and at present, represent the most structurally varied and biggest group of NPS [83, 84]. The EMCDDA and other relevant bodies have recently increased monitoring for substance abuse. The UNODC reported around 326 synthetic cannabinoids identified by the end of 2021 [85]. Synthetic cannabinoids are usually produced and transported from manufacturing nations as bulk powders, which when dissolved in solvents, e.g., methanol or acetone, get spread on paper (to reduce detection risk) or inert material from plant (similar to traditional cannabis) and either directly smoked or mixed with tobacco, with inhalation as the major usage route [86]. Synthetic cannabinoids are fraudulently or illicitly sold, for example, as cannabidiol or delta-9-tetrahydrocannabinol (d9-THC) and detectable in some preparations, e.g., powders/liquids in vaping device or capsules/tablets similar to ecstasy [20, 87].

Synthetic cannabinoids interact with the endocannabinoid system, involved in many human physiological functions like appetite, pain sensation, immunoregulation, cognition performance, motor control, gastrointestinal motility, respiratory performance, cardiovascular functions, etc. (Table 2) [10, 102, 103]. Positive effects due to usage include euphoria, disinhibition, relaxation, etc., which are related to the effects of delta-9-tetrahydrocannabinol, the major psychoactive constituent in traditional cannabis [23, 104]. Synthetic cannabinoids adversely affect health to cause cerebrovascular accidents ("strokes"), renal injury, haemodynamic embarrassment, respiratory complication, cardiovascular impairment, etc. [103, 105, 106]. Numerous reports of severe morbidity and mortality have emerged from synthetic cannabinoids, like in prisons/secure settings and among the homeless [23, 107]. Most synthetic cannabinoids are (cannabinoid) receptors' agonists designed to mimic tetrahydrocannabinol, which are naturally occurring (cannabinoid) with strongest CB_1 receptor binding affinity linked to marijuana's "high" or psychoactive effects [22, 108]. Negative effects in users include seizures, poor coordination, palpitations, withdrawal symptoms, confusion, vomiting, paranoia, nausea, intense anxiety, strong compulsion to dose again, and persistent cravings [109, 110].

4.1.1. Action Mechanism. Synthetic cannabinoids primarily interact with the endocannabinoid system, along with its G protein-coupled receptors, namely, the cannabinoid receptor type-1 and the cannabinoid receptor type-2. They mostly interact with the former and less with the latter [89].

Table 2: Structural classifications of synthetic cannabinoids.

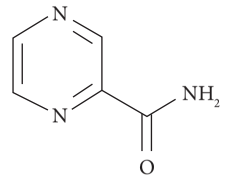
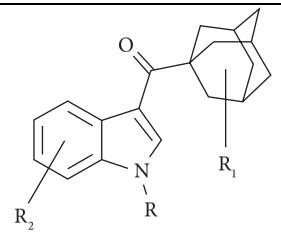
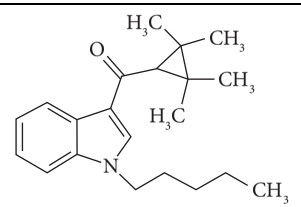
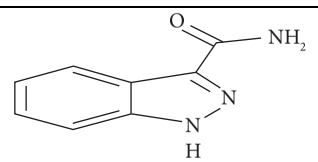
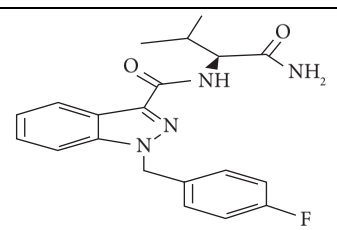
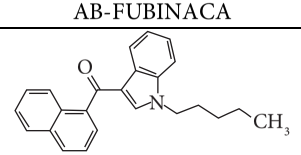
Classification	Structure	Examples	References
Pyrazolecarboxamides		AB-CHFUPYCA, 5F-AB-FUPPYCA	[87, 88]
Indazole carboxamide or adamantoylindoles		APICA, 5F-AKB-48, STS-135	[88, 89]
Tetramethylcyclo-propylcarbonylindoles	 UR-144	UR-144, XLR-11, XLR-11, A-796,260, A-834,735, XLR-12	[89, 90]
Indazole-3-carboxamides		AB-FUBINACA, AB-CHMINACA, PX-2, PX-3	[88, 90]
Indazole carboxamides	 AB-FUBINACA	AB-FUBINACA, AB-PINACA	[90–92]
Naphthoylindoles		AM-2201, AM-1221, JWH-007, JWH-200, JWH-018, JWH-073, WIN-55,212-2, JWH-398	[88, 92, 93]

Table 2: Continued.

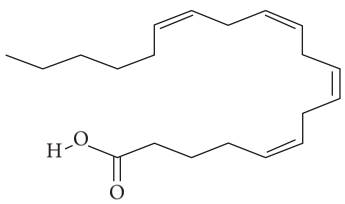
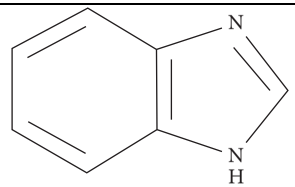
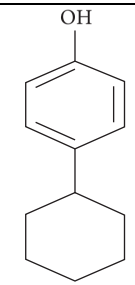
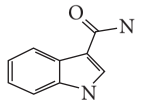
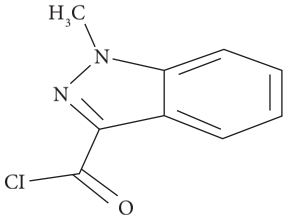
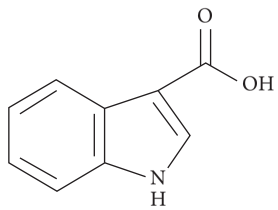
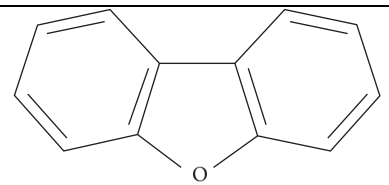
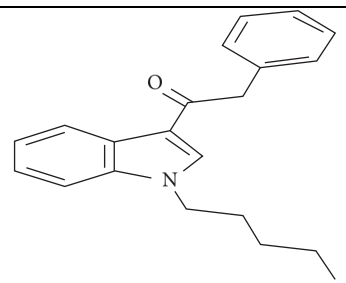
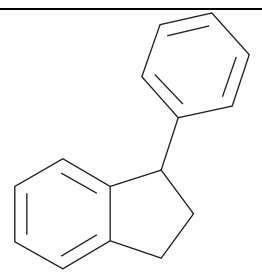
Classification	Structure	Examples	References
Eicosanoids		AM-883, O-585, AM-1346, O-689	[87, 88, 93]
Benzimidazoles		AZD-1940, AZ-11713908	[94, 95]
Cyclohexylphenols		CP-55,940, CP-47,947	[96, 97]
Indole-3-carboxamides		CUMYL-CBMICA, CUMYL-BICA, org 28611, org 28312	[88, 96, 97]
Tetramethylcyclo-propylcarbonylindazoles		FAB-144	[89, 91, 92]

Table 2: Continued.

Classification	Structure	Examples	References
Indole-3-carboxylates or aryloxycarbonylindole		FDU-PB-22, FUB-PB-22	[98, 99]
Dibenzopyrans		JWH-056, JWH-051	[98, 99]
Phenylacetylindoles		JWH-203, JWH-167	[98, 99]
Naphtylindenes		JWH-176, JWH-171	[99–101]

The cannabinoid receptor type-1 is widely spread in the brain, with concentrated amounts found in the basal ganglia, hippocampus, and neo-cortex, where they modulate the release of presynaptic neurotransmitter and contribute to many modulations of brain functions, including reward, memory, executive, and emotional functions [24, 90]. Figure 1 shows the major localized sites and associated functions of the cannabinoid receptor type-1 in humans (Figure 1(a)) as well as the subcellular cannabinoid receptor type-1 localization (Figure 1(b)) [91]. Considering this, the cannabinoid receptor type-2 was at first believed to be restricted to peripheral tissues and immune cells but recently was found in brain stem neurons and cerebellum, where their functions have been clearly described [92]. However, how these two receptors exactly modulate the effects of synthetic cannabinoids and the exact differences between the clinical effects of synthetic cannabinoids and traditional cannabis remain insufficiently described, although recent studies suggest mitochondrial homeostasis disruption or cannabinoid receptors' biased signaling [89, 93].

Receptors' roles in the endocannabinoid system in zebrafish and possible cannabis effects in humans have been debated by Bailone et al. [94]. Synthetic cannabinoids contain no cannabidiol, potentially associated with the toxicity exerted by these compounds compared to natural cannabis [95]. Synthetic cannabinoids would possess binding affinity and stronger potency compared to delta-9-tetrahydrocannabinol at cannabinoid receptors [95–97], with full agonists properties compared to the partial agonist activities of delta-9-tetrahydrocannabinol, having potency 10 to 200 times greater than that of delta-9-tetrahydrocannabinol [93, 94]. To further demonstrate this, Figure 2 shows the drug interactions and endocannabinoid pathways in the synapse. Besides the endocannabinoids (e.g., arachidonolyethanolamine (AEA)) formed in the membrane phospholipids' postsynaptic terminal and the "retrograde" released into the synaptic cleft, Figure 2 shows that after being bound to one cannabinoid receptor on presynaptic membrane, the pathways of intracellular signaling would be activated, which involves cyclic-adenosine monophosphate (c-AMP) and G_i (inhibitory G-protein) and modifies ion channels (K^+, Ca^{++}). Lastly, the principal NT release from presynaptic membrane would be reduced. EC inactivation in the synaptic cleft occurs by either monoacylglycerol lipase (MAGL, cleaves 2-AG), enzyme fatty acid amide hydrolase (FAAH, cleaves AEA), or cell reuptake [98]. Some researchers have shown that illicit substance users, like those of synthetic cannabinoids, could be 30 times more likely to be admitted into an emergency unit over those of traditional cannabis [106].

4.1.2. Chemical Structures. Synthetic cannabinoids can be grouped into different chemical classes, including benzoylindoles, the URB-class, classical cannabinoids, naphthoylindoles, cyclohexyl-substituted phenols, and carbazoles [99]. Novel synthetic cannabinoids are commonly designed by clandestine and legitimate chemists, and they vary by removing or adding a substituent group, which makes the pharmacological profile of NPS introduced to the market much more difficult to monitor and predict [100]. Synthetic cannabinoids are somewhat structurally similar to delta-9-tetrahydrocannabinol and are called synthetic cannabinoids because of their pharmacological action mechanisms. As a result, except specifically added to reference databases, they usually go undetected in the screening procedures used in conventional drug, including urine tests.

Five major synthetic cannabinoids categories include eicosanoids, classical cannabinoids, aminoalkylindoles, nonclassical cannabinoids, and hybrid cannabinoids. Classical cannabinoids are tetrahydrocannabinol analogs which are based on dibenzopyran ring and include dronabinol and nabilone [111]; HU-210 is among the common synthetic classical cannabinoids. Nonclassical cannabinoids include cyclohexylphenols. Hybrid cannabinoids are a combination of the structural features of classical cannabinoids and nonclassical cannabinoids [111]. Aminoalkylindoles have structural dissimilarity to tetrahydrocannabinol and include phenylacetylindoles (JWH-250), benzoylindoles (AM-2233), and naphthoylindoles (JWH-018) [24, 101]. Aminoalkylindoles are considered the most synthetic cannabinoids in the blend of synthetic cannabinoid, largely because they can be synthesized easily than classical cannabinoids and nonclassical cannabinoids [101]. Eicosanoid synthetic cannabinoids are endocannabinoids analogs, e.g., anandamide. Endocannabinoids are naturally occurring cannabinoids in the body.

4.1.3. Adverse Effects and Toxicities. Considering that synthetic cannabinoids activate cannabinoid receptor type-1 and the cannabinoid receptor type-2, most of their effects are similar to tetrahydrocannabinol effects. The effects can be achieved at low doses, as several synthetic cannabinoids have more potency than marijuana, coupled with the fact that the users usually do not know what they exactly get and how potent it is [112]. There have been many reports about mild to moderate to severe effects of synthetic cannabinoids, including tachycardia, hypertension, dizziness, chest pain, agitation, drowsiness, protracted vomiting, nausea, and confusion, which usually have a limited duration and require only supportive treatment [113, 114]. The most common death causative mechanisms following the use of synthetic cannabinoids include the central nervous system (CNS) depression, behavioral risks, e.g., wandering into traffic, falling from elevated platform, self-harm, suicide, etc., and cardiovascular effects [114]. Evidence suggests that renal impairment can result from synthetic cannabinoids direct toxic effects on the kidney, instead of indirect effects caused by dehydration due to vomiting [112]. Many severe physical harms to health due to the use of synthetic cannabinoid have also been described, including multiple organ failure, convulsions, delirium, intracranial haemorrhage, pulmonary embolism, seizures, rhabdomyolysis syndrome, ventricular arrhythmias, supraventricular arrhythmias, and hyperemesis syndrome [115–118]. Severe harms associated with mental health include psychosis, paranoia, self-inflicted injury, suicide, indiscriminate aggression, and violence towards people [119–121].

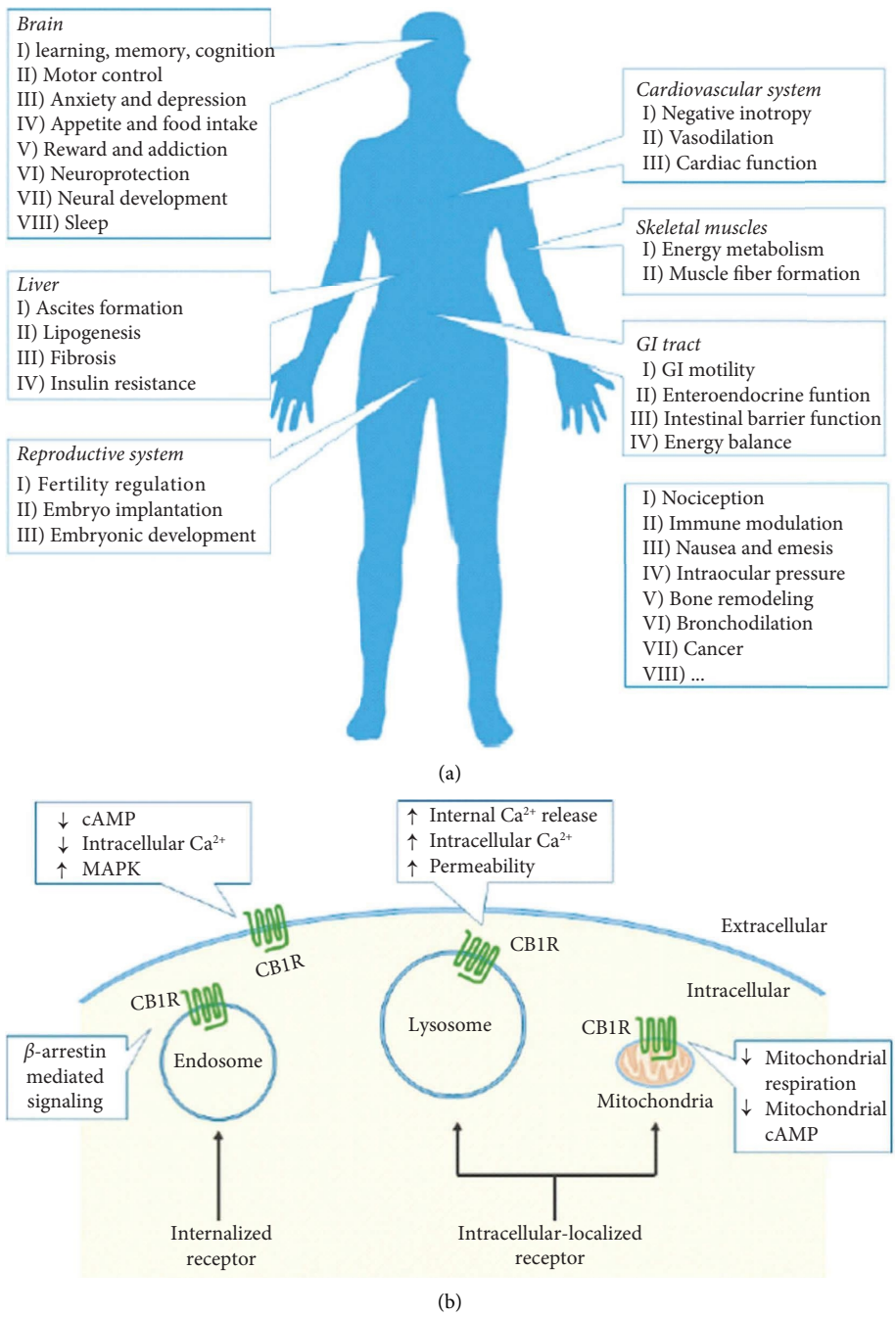


Figure 1: (a) Major localized sites and associated functions of the cannabinoid receptor type-1 in humans; (b) subcellular cannabinoid receptor type 1 localization (adapted from [91]). Cannabinoid receptor type-1 is widely spread in the brain and modulates the release of presynaptic neurotransmitter and many brain functions.

The use of synthetic cannabinoids is associated with white matter abnormality in young adults and adolescents and might result in psychosis vulnerability and cognitive impairment [122]. MRI brain changes linked to toxicity of synthetic cannabinoids showed leptomeningeal enhancement, demyelinating injury, hypoxic-ischaemic brain injuries, embolic stroke, etc. [122, 123]. The MRI findings can be a reflection of the various endocannabinoid system actions, including its roles in regulating cerebral perfusion, mitochondrial function, and inflammatory responses. Acute or repeated use of synthetic cannabinoids are associated with the impairment of executive functions [124]. Strong psychological withdrawal syndromes following their use were described to cause a high potential for synthetic cannabinoids addiction, where people used them every 30 min for the avoidance of feeling sick [125]. Concerns for public health exist about synthetic cannabinoids use in water pipes or vaping devices and the consequent severe lung injuries' development, such as diffuse alveolar hemorrhages and acute respiratory distress syndromes [126, 127].

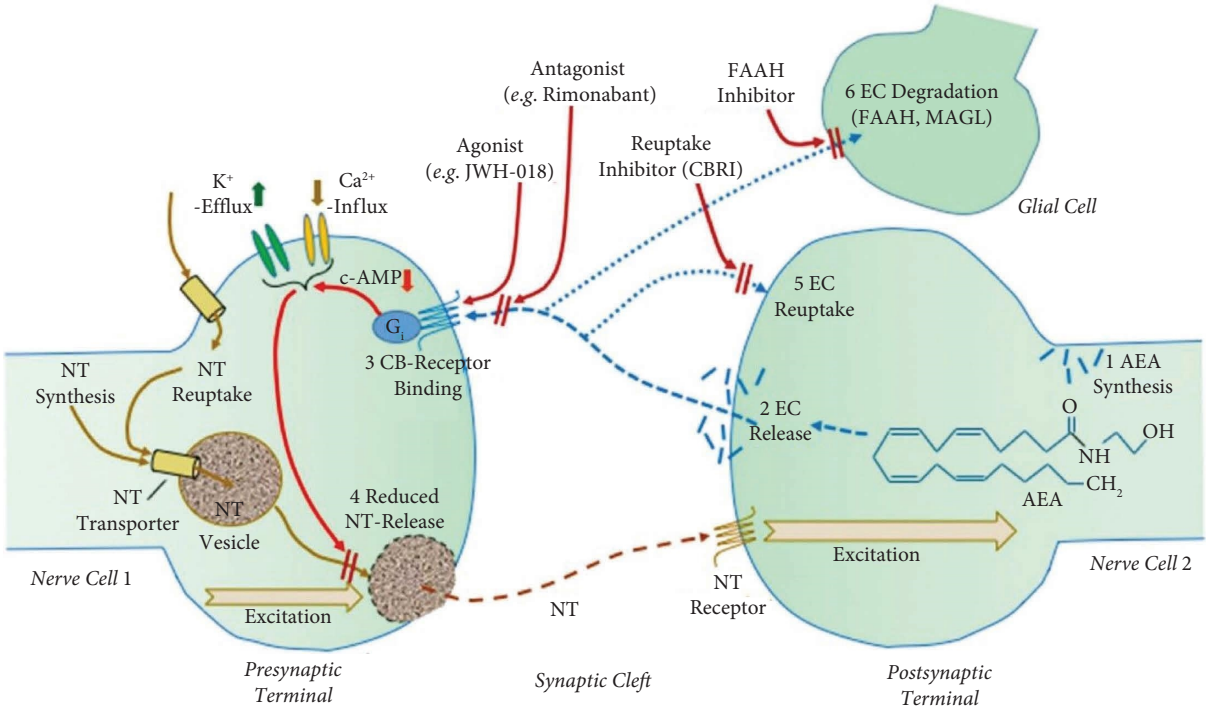


Figure 2: Drug interactions (red) and endocannabinoid pathways (blue) in the synapse. Endocannabinoids (e.g., arachidonolyethanolamine (AEA)) is formed in the membrane phospholipids' postsynaptic terminal and the "retrograde" released into the synaptic cleft (adapted from [98]).

4.2. Synthetic Opioids. Synthetic opioids are laboratory-manufactured drugs designed to mimic the chemical structure of the opioids (opiates), which are substances obtained from opium poppy (*Papaver somniferum*) [128, 129]. Opioids are substances that exert effects on the opioid receptors and produce effects similar to those of morphine [130]. Synthetic opioids exert opiate-like effects. Examples of synthetic opioids include fentanyl, carfentanil, tramadol, U-47700, 3-methylfentanyl, furanylfentanyl, methadone, butyrylfentanyl, carfentanil, and acetylfentanyl [128]. Fentanyl and carfentanil are more common examples that can be lethal. Codeine and morphine are the most common prescription as pain medications [43]. Synthetic opioids are designed by modifying each of opioids' chemical structures. Opioids' chemical structure is divided into the ones based on the 4,5-epoxymorphinan ring (such as morphine), diphenylheptylamines (such as methadone), and phenylpiperidines (e.g., fentanyl). Synthetic opioids are designed to bind same receptors that opiates bind to in the brain, such as Mu (μ), kappa (κ), and delta (δ) opioid receptors, producing similar effects, including anxiolysis, euphoria, drowsiness, and relaxation feelings. Side effects of synthetic opioids include vomiting, nausea, respiratory depression, constipation, and dizziness. [43, 131]. Vandeputte et al. [129] described brorphine and isotonitazene as two current stars in the firmament of synthetic opioid, which sequentially dominated the opioid market for NPS in 2019 and 2020. The international reports on deaths caused by opioid epidemic have been debated and studied [43, 131, 132]. The UNODC reported that synthetic opioids are increasing recently, with over 112 synthetic opioids reported to the UNODC Early Warning Advisory as in December 2021 [8]. Some synthetic opioids such as fentanyl and carfentanil are under international control. Evidence suggests a worrying upsurge in the availability of mixture of fentanyl and heroin, which is more affordable and easily available than heroin alone, resulting in an increased mortality and morbidity risks for users, who are often not aware of the synthetic opioid addition [133, 134].

4.2.1. Action Mechanism. The analogues of synthetic opioids interact with the receptors of G protein-coupled opioids in the spinal cord and brain partial to full agonists at μ, κ, and δ opioid receptor subtypes, with μ opioid receptor selectivity [135, 136]. μ opioid receptors agonism exerts the main opioids pharmacologic effects, such as respiratory depression, dependence development, euphoria, and analgesia [137]. Several synthetic opioids significantly have more potency than the traditional opioids. Fentanyl's potency is 50–200 times higher than that of morphine, while carfentanil's potency is around 10,000 times more than that of morphine; all of them act on mu opioid receptor [135, 138]. The effects of synthetic opioids on human body are related to those of other opioids, from black tar heroin to percocet. The drugs are agonists of opioids receptor and primarily act on the spinal cord and the brain [128, 139].

4.2.2. Adverse Effects and Toxicities. Synthetic opioids use to get intense "highs," which commonly leads to an escalation

with possible overdose. The adverse effects of synthetic opioids range from mild effects, such as dizziness, constipation, vomiting, nausea, and pruritus, to severe effects, such as CNS depression, apnoea, and respiratory depression [129, 140]. Synthetic opioids intoxication is associated with rhabdomyolysis, diffuse alveolar haemorrhage, acute lung injury, and noncardiogenic pulmonary oedema [141, 142]. Withdrawing from synthetic opioids might cause distress that may be psychological and physiological in nature [74, 136]. Mortality and morbidity statistics may not be a true reflection of the actual situation because synthetic opioids users might recover, e.g., from an overdose of mixed synthetic opioid and heroin when there is administration of naloxone and the heroin will be the documented illicit drug instead of synthetic one [136, 140, 143].

4.3. Synthetic Stimulants. Synthetic stimulants are NPSs that increase the activities of the body and the central nervous system and are invigorating and pleasurable or have sympathomimetic effects. They comprise of many base compounds, including cathinones ("Bath Salts"), piperazines, tryptamines, phenethylamines, and aminoindanes, among which synthetic cathinones are by far the most studied and the largest group [54, 80]. As of today, synthetic stimulants are the largest NPSs monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the UNODC Early Warning Advisory [8, 144]. They make up 34% of the 1224 NPSs reported in over 134 countries as in December 2021 [8]. Synthetic stimulants are designed to mimic the effects and structures of controlled traditional stimulants, including cocaine, amphetamines, and caffeine [14]. They are made in form of many formulations and inhaled, insufflated, used rectally, smoked, injected, or swallowed; they are mostly taken in form of tablet/pill [80]. They promote increase in neurotransmitters' synaptic availability, mainly serotonin and dopamine. Dopamine plays significant roles in learning, reward, motivation, and arousal, while serotonin contributes to happiness feelings and sense of emotional connection (entactogenic). Crack contains similar chemical structure as cocaine but in a distinct form and often used in place of cocaine. Synthetic stimulants have actions on the two neurotransmitter systems at different degrees, which accounts for the differing desirable and undesirable effects [58, 59], which include much-desired experiences, e.g., euphoria, energy boost and alertness, increased feelings of compassion/empathy, libido, sociability, improved self-confidence, and sense of relaxation and inner peace [145, 146]. Synthetic stimulants also have adverse effects, including high potential for addiction, severe intoxications associated with neuropsychiatric, neurological, cardiac, and metabolic complications, with increased fatality risks [147, 148].

Synthetic cocaine derivatives (cocaine analogues) have been among the widely used NPSs. Dimethocaine (DMC), a synthetic cocaine derivative, is commonly consumed and distributed as NPS with no safety testing. DMC is usually metabolized by N-deethylation, hydroxylation, or N-acetylation. In general, cocaine analogues are often artificial constructs of a novel chemical compound derived from the molecular structure of cocaine, with the resulting products having strong similarity to cocaine, which may have altered chemical functions [14, 59]. Within the analogues derived from the cocaine structure, we maintain 3β-benzoyloxy or similar functionality on a skeleton of tropane, in comparison to other related stimulants. Most semi-synthetic cocaine analogues that are made/studied include the following classes of compounds: 3β-phenyl ring substituted analogues, 3β-carbamoyl analogues, stereoisomers of cocaine, *N*-modified analogues of cocaine, 2β-substituted analogues, piperidine homologues of cocaine, 6/7-substituted cocaines, 3β-alkyl-3-benzyl tropanes, and 6-alkyl-3-benzyl tropanes [9, 14, 58, 59, 70].

4.3.1. Action Mechanism. Synthetic stimulants increase the monoamine neurotransmitters dopamine and serotonin and to a lesser extent, noradrenaline (NE) concentration in the synaptic cleft, which then mediate the stimulatory effects [149, 150]. Two distinct mechanisms are responsible for the increase in monoamine concentration in the synaptic cleft. Firstly, there is stimulation of nonexocytotic neurotransmitter release by inhibiting the vesicular monoamine transporter-2 (VMAT2) and reversing the transporter influx, thereby stimulating neurotransmitter release from the cytosolic pool or synaptic vesicles. Secondly, there is inhibition of the uptake of neurotransmitters from the synaptic cleft by inhibiting the plasma membrane transporters, which are responsible for the uptake of dopamine, serotonin, and NE [6].

4.3.2. Chemical Structures. Phenethylamine is the common pharmacophore group that induces the psychoactive effects shown by synthetic stimulants, and its derivatives represent no less than 37% of NPSs found in the markets of illicit drugs [151]. Some synthetic stimulants having structural similarity to pyrovalerone, including 3,4-methylenedioxypyrovalerone, have high lipophilicity in comparison to other synthetic stimulants, and as a result, their blood-brain barrier penetration capacity is very high, so do their distribution volume, leading to longer tissue and plasma half-life [152]. Occurrence of electrophilic groups, e.g., fluorine, may alter the lipophilic capacity of the analogues of synthetic stimulants, consequently affecting their potency, a much-desired quality by users seeking to have the effect of the definitive new party drug with more potency, longer effects, and a better "high" [150]. Synthetic cathinones made to have similar chemical structure and effects as the natural cathinone obtained from khat leaves. While the common second generation of synthetic cathinone consists of α-pyrrolidinopentiophenone (α-PVP), flephedrone (4-fluoromethcathinone or 4-FMC) and its positional isomer 3-FMC (or 3-fluoromethcathinone), and 4-methylethcathinone (4-MEC or 4-methyl-N-ethylcathinone), and the first-generation includes methcathinone, 3,4-methylenedioxypyrovalerone, 3,4-methylenedioxy-N-methylcathinone, and 4-methylmethcathinone (mephedrone, 4-MMC) [145, 146].

Table 3: Common 25-NB derivatives.

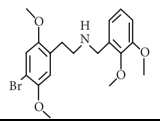
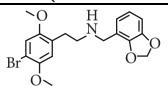
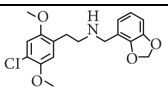
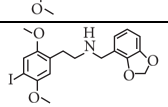
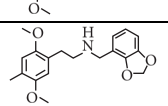
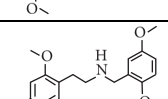
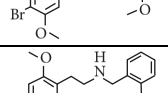
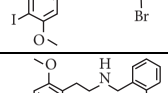
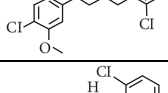
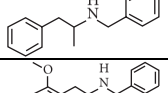
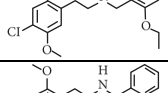
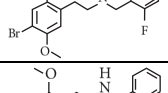
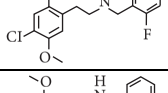
Common name	Chemical structure	R_1	R	Chemical name	Cyc	References
25B-NB23DM		H	2,5-dimethoxy-4-bromo	*N*-(2,3-dimethoxybenzyl)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	2,3-dimethoxyphenyl	[37, 38, 187]
25B-NBMD		H	2,5-dimethoxy-4-bromo	*N*-(2,3-methylenedioxybenzyl)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	2,3-methylenedioxyphenyl	[187, 188]
25C-NBMD		H	2,5-dimethoxy-4-chloro	*N*-(2,3-methylenedioxybenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	2,3-methylenedioxyphenyl	[187, 189, 190]
25I-NBMD		H	2,5-dimethoxy-4-iodo	*N*-(2,3-methylenedioxybenzyl)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	2,3-methylenedioxyphenyl	[37, 38, 187–191]
25D-NBMD		H	2,5-dimethoxy-4-methyl	*N*-(2,3-methylenedioxybenzyl)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminoethane	2,3-methylenedioxyphenyl	[38, 188, 189, 191]
25B-NB25DM		H	2,5-dimethoxy-4-bromo	*N*-(2,5-dimethoxybenzyl)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	2,5-dimethoxyphenyl	[187, 188, 190]
25I-NBBr		H	2,5-dimethoxy-4-iodo	*N*-(2-bromobenzyl)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	2-bromophenyl	[187, 190]
25C-NBCl		H	2,5-dimethoxy-4-chloro	*N*-(2-chlorobenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	2-chlorophenyl	[187, 189]
Clobenzorex		methyl	H	*N*-(2-chlorobenzyl)-1-phenyl-2-aminopropane	2-chlorophenyl	[37, 38, 187–191]
25C-NBOEt		H	2,5-dimethoxy-4-chloro	*N*-(2-ethoxybenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	2-ethoxyphenyl	[37, 189, 190]
25B-NBF		H	2,5-dimethoxy-4-bromo	*N*-(2-fluorobenzyl)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	2-fluorophenyl	[188, 189]
25C-NBF		H	2,5-dimethoxy-4-chloro	*N*-(2-fluorobenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	2-fluorophenyl	[37, 38, 187–191]
25I-NBF		H	2,5-dimethoxy-4-iodo	*N*-(2-fluorobenzyl)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	2-fluorophenyl	[37, 38, 187–191]

Table 3: Continued.

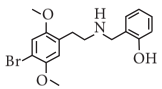
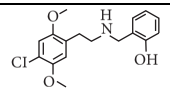
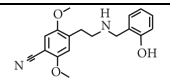
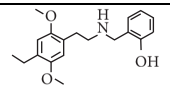
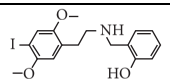
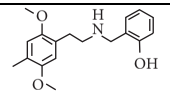
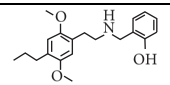
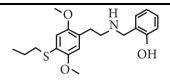
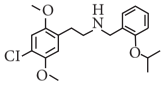
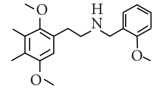
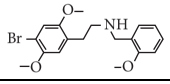
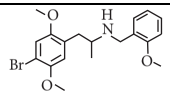
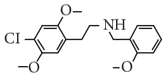
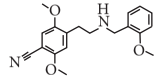
Common name	Chemical structure	R_1	R	Chemical name	Cyc	References
25B-NBOH		H	2,5-dimethoxy-4-bromo	*N*-(2-hydroxybenzyl)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	2-hydroxyphenyl	[190, 191]
25C-NBOH		H	2,5-dimethoxy-4-chloro	*N*-(2-hydroxybenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	2-hydroxyphenyl	[37, 190]
25C*N*-NBOH		H	2,5-dimethoxy-4-cyano	*N*-(2-hydroxybenzyl)-1-(2,5-dimethoxy-4-cyanophenyl)-2-aminoethane	2-hydroxyphenyl	[188, 190]
25E-NBOH		H	2,5-dimethoxy-4-ethyl	*N*-(2-hydroxybenzyl)-1-(2,5-dimethoxy-4-ethylphenyl)-2-aminoethane	2-hydroxyphenyl	[187, 188, 190]
25I-NBOH		H	2,5-dimethoxy-4-iodo	*N*-(2-hydroxybenzyl)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	2-hydroxyphenyl	[37, 38, 187–191]
25D-NBOH		H	2,5-dimethoxy-4-methyl	*N*-(2-hydroxybenzyl)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminoethane	2-hydroxyphenyl	[38, 188, 190]
25P-NBOH		H	2,5-dimethoxy-4-propyl	*N*-(2-hydroxybenzyl)-1-(2,5-dimethoxy-4-propylphenyl)-2-aminoethane	2-hydroxyphenyl	[37, 38, 188]
25T7-NBOH		H	2,5-dimethoxy-4-(propylthio)	*N*-(2-hydroxybenzyl)-1-[2,5-dimethoxy-4-(propylthio)phenyl]-2-aminoethane	2-hydroxyphenyl	[189, 191]
25C-NBOiPr		H	2,5-dimethoxy-4-chloro	*N*-(2-isopropoxybenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	2-isopropoxyphenyl	[187, 188, 190]
25G-NBOMe		H	2,5-dimethoxy-3,4-dimethyl	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-3,4-dimethylphenyl)-2-aminoethane	2-methoxyphenyl	[189, 190]
25B-NBOMe		H	2,5-dimethoxy-4-bromo	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	2-methoxyphenyl	[37, 38, 187–191]
DOB-NBOMe		methyl	2,5-dimethoxy-4-bromo	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane	2-methoxyphenyl	[37, 38, 187–191]
25C-NBOMe		H	2,5-dimethoxy-4-chloro	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	2-methoxyphenyl	[188–190]
25C*N*-NBOMe		H	2,5-dimethoxy-4-cyano	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-cyanophenyl)-2-aminoethane	2-methoxyphenyl	[37, 188, 189]

Table 3: Continued.

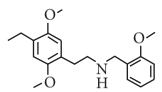
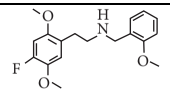
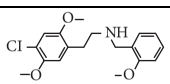
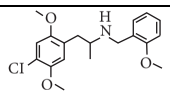
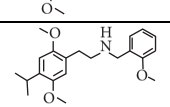
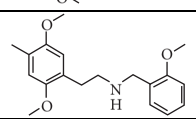
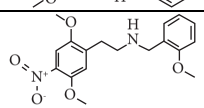
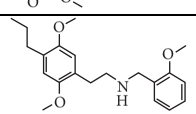
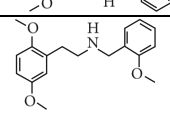
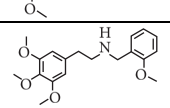
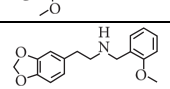
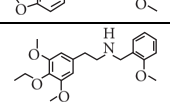
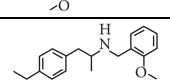
Common name	Chemical structure	R_1	R	Chemical name	Cyc	References
25E-NBOMe		H	2,5-dimethoxy-4-ethyl	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-ethylphenyl)-2-aminoethane	2-methoxyphenyl	[38, 188, 191]
25F-NBOMe		H	2,5-dimethoxy-4-fluoro	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-fluorophenyl)-2-aminoethane	2-methoxyphenyl	[189–191]
25I-NBOMe		H	2,5-dimethoxy-4-iodo	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	2-methoxyphenyl	[188–190]
DOI-NBOMe		methyl	2,5-dimethoxy-4-iodo	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane	2-methoxyphenyl	[37, 38, 187, 188, 190, 191]
25iP-NBOMe		H	2,5-dimethoxy-4-isopropyl	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-isopropylphenyl)-2-aminoethane	2-methoxyphenyl	[37, 38, 187, 188, 190]
25D-NBOMe		H	2,5-dimethoxy-4-methyl	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminoethane	2-methoxyphenyl	[187–191]
25*N*-NBOMe		H	2,5-dimethoxy-4-nitro	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminoethane	2-methoxyphenyl	[37, 188–190]
25P-NBOMe		H	2,5-dimethoxy-4-propyl	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxy-4-propylphenyl)-2-aminoethane	2-methoxyphenyl	[187–190]
25H-NBOMe		H	2,5-dimethoxy	*N*-(2-methoxybenzyl)-1-(2,5-dimethoxyphenyl)-2-aminoethane	2-methoxyphenyl	[187–190]
NBOMe-mescaline		H	3,4,5-trimethoxy	*N*-(2-methoxybenzyl)-1-(3,4,5-trimethoxyphenyl)-2-aminoethane	2-methoxyphenyl	[187–190]
MDPEA-NBOMe		H	3,4-methylenedioxy	*N*-(2-methoxybenzyl)-1-(3,4-methylenedioxyphenyl)-2-aminoethane	2-methoxyphenyl	[187, 189, 191]
NBOMe-escaline		H	3,5-dimethoxy-4-ethoxy	*N*-(2-methoxybenzyl)-1-(3,5-dimethoxy-4-ethoxyphenyl)-2-aminoethane	2-methoxyphenyl	[188–190]
4-EA-NBOMe		methyl	4-ethyl	*N*-(2-methoxybenzyl)-1-(4-ethylphenyl)-2-aminopropane	2-methoxyphenyl	[37, 38, 187–191]

Table 3: Continued.

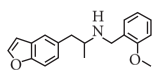
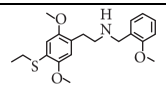
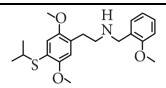
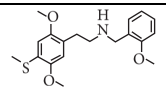
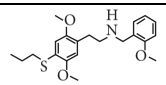
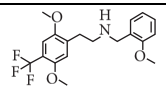
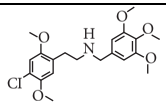
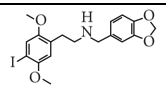
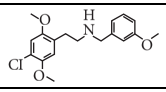
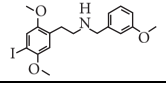
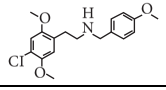
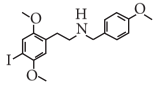
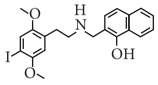
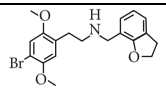
Common name	Chemical structure	R_1	R	Chemical name	Cyc	References
5-APB-NBOMe		methyl	benzofura*N*-5-yl instead of phenyl	*N*-(2-methoxybenzyl)-1-(benzofura*N*-5-yl)-2-aminopropane	2-methoxyphenyl	[37, 38, 187–191]
25T2-NBOMe		H	2,5-dimethoxy-4-(ethylthio)	*N*-(2-methoxybenzyl)-1-[2,5-dimethoxy-4-(ethylthio)phenyl]-2-aminoethane	2-methoxyphenyl	[37, 187, 188, 190]
25T4-NBOMe		H	2,5-dimethoxy-4-(isopropylthio)	*N*-(2-methoxybenzyl)-1-[2,5-dimethoxy-4-(isopropylthio)phenyl]-2-aminoethane	2-methoxyphenyl	[187, 190, 191]
25T-NBOMe		H	2,5-dimethoxy-4-(methylthio)	*N*-(2-methoxybenzyl)-1-[2,5-dimethoxy-4-(methylthio)phenyl]-2-aminoethane	2-methoxyphenyl	[37, 38, 191]
25T7-NBOMe		H	2,5-dimethoxy-4-(propylthio)	*N*-(2-methoxybenzyl)-1-[2,5-dimethoxy-4-(propylthio)phenyl]-2-aminoethane	2-methoxyphenyl	[187, 188, 190, 191]
25TFM-NBOMe		H	2,5-dimethoxy-4-(trifluoromethyl)	*N*-(2-methoxybenzyl)-1-[2,5-dimethoxy-4-(trifluoromethyl)phenyl]-2-aminoethane	2-methoxyphenyl	[187, 188, 191]
C30-NBOMe		H	2,5-dimethoxy-4-chloro	*N*-(3,4,5-trimethoxybenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	3,4,5-trimethoxyphenyl	[190, 191]
25I-NB34MD		H	2,5-dimethoxy-4-iodo	*N*-(3,4-methylenedioxybenzyl)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	3,4-methylenedioxyphenyl	[187, 188, 191]
25C-NB3OMe		H	2,5-dimethoxy-4-chloro	*N*-(3-methoxybenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	3-methoxyphenyl	[37, 38, 187–191]
25I-NB3OMe		H	2,5-dimethoxy-4-iodo	*N*-(3-methoxybenzyl)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	3-methoxyphenyl	[188, 189, 191]
25C-NB4OMe		H	2,5-dimethoxy-4-chloro	*N*-(4-methoxybenzyl)-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	4-methoxyphenyl	[188, 189, 191]
25I-NB4OMe		H	2,5-dimethoxy-4-iodo	*N*-(4-methoxybenzyl)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	4-methoxyphenyl	[187, 189–191]
25I-N2Nap1OH		H	2,5-dimethoxy-4-iodo	*N*-[(1-hydroxynaphthale*N*-2-yl)methyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	1-hydroxynaphthale*N*-2-yl	[37, 187–191]
25B-NMe7DHBF		H	2,5-dimethoxy-4-bromo	*N*-[(2,3-dihydrobenzofura*N*-7-yl)methyl]-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	2,3-dihydrobenzofura*N*-7-yl	[37, 187–191]

Table 3: Continued.

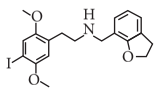
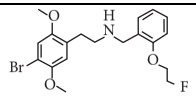
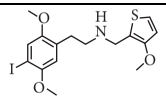
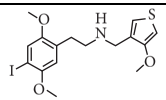
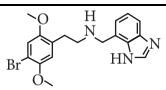
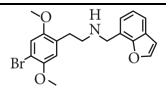
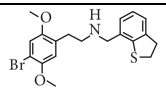
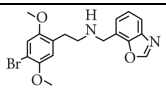
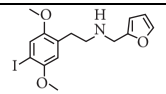
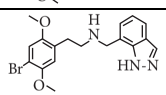
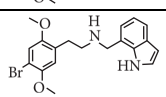
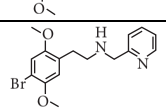
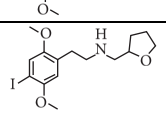
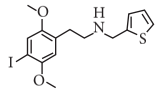
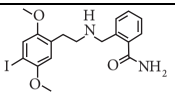
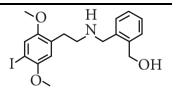
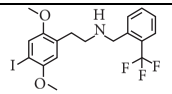
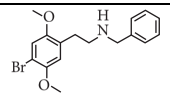
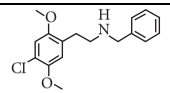
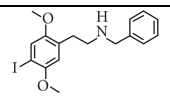
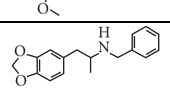
Common name	Chemical structure	R_1	R	Chemical name	Cyc	References
25I-NMe7DHBF		H	2,5-dimethoxy-4-iodo	*N*-[(2,3-dihydrobenzofura*N*-7-yl)methyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	2,3-dihydrobenzofura*N*-7-yl	[188–190]
FECIMBI-36		H	2,5-dimethoxy-4-bromo	*N*-[(2-fluoroethoxy)benzyl]-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	2-(2-fluoroethoxy)phenyl	[189–191]
25I-N3MT2M		H	2,5-dimethoxy-4-iodo	*N*-[(3-methoxythiophe*N*-2-yl)methyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	3-methoxythiophe*N*-2-yl	[37, 38, 190]
25I-N4MT3M		H	2,5-dimethoxy-4-iodo	*N*-[(4-methoxythiophe*N*-3-yl)methyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	4-methoxythiophe*N*-3-yl	[37, 38, 190]
25B-NMe7Bim		H	2,5-dimethoxy-4-bromo	*N*-[(benzimidazol-7-yl)methyl]-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	Benzimidazol-7-yl	[187–191]
25B-NMe7BF		H	2,5-dimethoxy-4-bromo	*N*-[(benzofura*N*-7-yl)methyl]-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	benzofura*N*-7-yl	[187, 190, 191]
25B-NMe7BT		H	2,5-dimethoxy-4-bromo	*N*-[(benzothiophe*N*-7-yl)methyl]-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	benzothiophe*N*-7-yl	[37, 38, 187–191]
25B-NMe7Box		H	2,5-dimethoxy-4-bromo	*N*-[(benzoxazol-7-yl)methyl]-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	Benzoxazol-7-yl	[187–190]
25I-NMeFur		H	2,5-dimethoxy-4-iodo	*N*-[(fura*N*-2-yl)methyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	fura*N*-2-yl	[187–190]
25B-NMe7Indz		H	2,5-dimethoxy-4-bromo	*N*-[(indazol-7-yl)methyl]-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	indazol-7-yl	[187, 188, 191]
25B-NMe7Ind		H	2,5-dimethoxy-4-bromo	*N*-[(indol-7-yl)methyl]-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	indol-7-yl	[37, 38, 187–191]
25B-NMePyr		H	2,5-dimethoxy-4-bromo	*N*-[(pyridi*N*-2-yl)methyl]-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	pyridi*N*-2-yl	[37, 187, 190]
25I-NMeTHF		H	2,5-dimethoxy-4-iodo	*N*-[(tetrahydrofura*N*-2-yl)methyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	tetrahydrofura*N*-2-yl	[37, 187, 190]

Table 3: Continued.

Common name	Chemical structure	R_1	R	Chemical name	Cyc	References
25I-NMeTh		H	2,5-dimethoxy-4-iodo	*N*-[(thiophe*N*-2-yl)methyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	thiophe*N*-2-yl	[187, 189, 191]
25I-NBAm		H	2,5-dimethoxy-4-iodo	*N*-[2-(carbamoyl)benzyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	2-(carbamoyl)phenyl	[38, 189–191]
25I-NBMeOH		H	2,5-dimethoxy-4-iodo	*N*-[2-(hydroxymethyl)benzyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	2-(hydroxymethyl)phenyl	[188, 189, 191]
25I-NBTFM		H	2,5-dimethoxy-4-iodo	*N*-[2-(trifluoromethyl)benzyl]-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	2-(trifluoromethyl)phenyl	[187–190]
25B-NB		H	2,5-dimethoxy-4-bromo	*N*-benzyl-1-(2,5-dimethoxy-4-bromophenyl)-2-aminoethane	Phenyl	[187, 188, 190]
25C-NB		H	2,5-dimethoxy-4-chloro	*N*-benzyl-1-(2,5-dimethoxy-4-chlorophenyl)-2-aminoethane	Phenyl	[37, 38, 187–191]
25I-NB		H	2,5-dimethoxy-4-iodo	*N*-benzyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminoethane	Phenyl	[187–190]
MDBZ		methyl	3,4-methylenedioxy	*N*-benzyl-1-(3,4-methylenedioxyphenyl)-2-aminopropane	Phenyl	[37, 38, 187, 190, 191]

Synthetic cathinones have structural similarity to amphetamine stimulants, and chemically, they are known as the analogues of β-ketone due to the = O (carbonyl group) in the beta carbon [145, 146, 150].

4.3.3. Adverse Effects. Synthetic stimulants were originally made for the treatment of Parkinson's disease, depression, and/or obesity but were withdrawn because of concerns about their abuse and potential harmful effects. But in recent years, some synthetic stimulants have been used as nootropics or cognitive enhancers and for weight loss [153, 154]. The acute mental health and physical effects associated with synthetic stimulants usage are because of sympathomimetic toxicities that can present as hyperthermia, agitation, hypertension, nausea, tachycardia, palpitations, vomiting, and headache, which are more common; seizures, collapse, paranoia, and hallucinations are less frequent [154, 155]. Severe effects, including significant rhabdomyolysis and peripheral organ damage have been rarely described, while cases of deaths are often associated with serotonin syndrome, cardiac arrest, hyperthermia, and hypertensive crises. Functional MRI (fMRI) of rodents showed that 3,4-methylenedioxypyrovalerone administration causes functional connectivity desynchronization between the striatum and prefrontal cortex and the insular cortex and nucleus accumbens [153, 156]. *In vitro* studies on hepatic, neuronal, and skeletal muscle cells showed potential cytotoxicity of exposure to synthetic stimulant, including glutathione depletion, mitochondrial dysfunction, activation of apoptosis, and oxidative stress, which aggravate under hyperthermia, although relevance of these mechanisms to their *in vivo* effects have not been fully established [157, 158]. Many health concerns have been linked to synthetic stimulants. There is growing "slamming" practice during ChemSex. ChemSex is a sexual activity undertaken under the influence of stimulant (psychoactive) drugs, e.g., mephedrone and often involves many participants. The stimulant drugs are injected to improve, prolong, or facilitate sexual activities, raising concerns related substance use disorders, along with increased risk of sexually transmitted diseases, blood-borne transmission of virus, and injection site injury [159, 160]. Increased NPS injection, such as synthetic stimulants, has been associated with increased HCV contiguous infection [160]. Synthetic stimulants are detected in many products with cognitive ability and "brain health" enhancement claims, as well as those that target athletes seeking performance enhancement [161, 162]. Those diagnosed with attention deficit hyperactivity disorder (ADHD) turn to online search for synthetic stimulants to ameliorate their symptoms [163]. The harmful interactions between prescription drugs and synthetic stimulants, while decreasing the drugs therapeutic efficacy or increasing their toxicity, have been described [159, 164].

Case reports indicated that synthetic stimulants may cause ischemic infarction, α-PVP, and acute intrasubarachnoid and parenchymal haemorrhages and have been association with ST-elevation myocardial infarction (STEMI) along with multiple intracardiac thrombi [158]. Persistent globipallidi hyperintensity on T1-weighted MRI has been described in people having this rare syndrome; the use of intravenous methcathinone (M-CAT) for more than 6 months have been associated with significant disability with no improvement in spite of drug cessation [165]. The use of M-CAT has also been linked to rare syndrome of manganese-associated Parkinson disease and cognitive impairment, known as ephedrone encephalopathy.

4.4. Synthetic Dissociatives. Dissociatives are a group of hallucinogens that distort sound and sight perception and produce detachment feelings (i.e., dissociation) from self and/or the environment [166]. Although several drugs can cause such actions, the uniqueness of dissociatives lies in their production of hallucinogenic effects, including hallucinations, anesthesia, dream-like states, dissociation, and sensory deprivation [166]. Arylcyclohexylamine (e.g., ketamine, methoxetamine (MXE), and phencyclidine (PCP)) and diarylethylamine are the two major dissociatives' classes. Phencyclidine was originally synthesised as an anaesthetic in 1956 but withdrawn from use largely due to its abuse potential and undesirable side effects. However, ketamine is still used as a vital medicine in both pain management aspects and specialist anaesthesia and is under study a fast-acting antidepressant [28, 167, 168]. The classes of dissociatives function as N-methyl-d-aspartate receptor (NMDAR) antagonists. Usage routes include intravenous injection, oral ingestion, inhalation, and nasal insufflation. The much-desired experiences include the sense of disconnecting between thoughts, consciousness, identity, and memory, tactile and sensory distortions, and depersonalization and euphoria [28, 167]. Severe adverse effects that are commonly encountered include bladder injury, renal injury, and neurological impairment.

4.4.1. Action Mechanism. Similar to phencyclidine and ketamine, dissociative diarylethylamine and arylcyclohexylamine drugs relatively act as noncompetitive and selective antagonists at the ionotropic glutamatergic N-methyl-d-aspartate receptor [28, 167, 168]. Their affinity to N-methyl-d-aspartate receptor strongly correlates with their potent clinical properties in exerting dissociative effects. The channels of N-methyl-d-aspartate receptor play a significant role in synapse formation and synaptic plasticity underlying learning, memory, and neural networks formation during development in CNS. Ketamine predominantly acts at the N-methyl-d-aspartate receptors, while phencyclidine, methoxetamine, 3-MeO-PCE, 3-MeO-PCP, and 4-MeO-PCP act at serotonin receptors, which could provide an explanation of their extra toxicity [28, 167, 168].

4.4.2. Chemical Structure. All the first-generation dissociatives are simple phencyclidine derivatives. The arylcyclohexylamine structure has 3 different regions, which include a basic amine function, a substituted cyclohexane ring, and an aromatic ring. They involve an amino or aryl substitution, with no cyclohexane ring alteration. The

cyclohexane ring retention provides the affinity to N-methyl-d-aspartate receptor and the consequent potency [169]. Dissociatives latest generation, diarylethylamines, include 2-MeO-diphenidine (1-[1-(2-methoxyphenyl)-2-phenylethyl] piperidine) and diphenidine (1-(1,2-diphenethyl) piperidine) and also have structural similarity to phencyclidine (PCP) [29].

4.4.3. Harmful Effects. The use of dissociatives in palliative care, depression, and pain management are still underway [170, 171]. Adverse effects that are common across the two classes of dissociatives include ataxia, muscle rigidity, amnesia, hallucinations, slurred speech, nystagmus, confusion, nausea, agitation, disorientation, renal impairment, tachycardia, hypertension, and diaphoresis [172]. Severe adverse effects include many fatal intoxications, severe bladder and kidney damage, rhabdomyolysis, and cerebellar toxicity. *In vitro* studies demonstrated that MXE has the potential to alter monoamine metabolism and inhibit neuronal activities [172, 173]. In rats, repeated mMXE parenteral administration leads to the stimulation of mesolimbic dopaminergic transmission and affects behaviour and brain functions. Another study reported that repeated MXE parenteral administrations interfered with memory and caused anxiety-related states [174]. The study also showed that MXE caused persistent dopaminergic neurons damage in the mesocorticolimbic and nigrostriatal systems and also serotonergic neurons in the core of nucleus accumbens [174]. Human use of MXE is linked to acute neurological impairment, such as altered motor coordination and psychomotor agitation, with urinary tract and chronic bladder toxicity shown in mice [175]. Case studies showed severe adverse effects, such as sinus bradycardia, seizures, and hyponatremia and neurological damage with significance in cerebellar toxicity and many fatalities due to intoxication [176].

4.5. Synthetic Hallucinogens. Hallucinogens are several psychoactive drugs that alter consciousness as a result of alterations in perception, thoughts, and mood, among many other alterations [177]. Hallucinogens are mostly categorized as deliriants, psychedelics, or dissociatives. Dissociatives (as shown in the section on dissociatives) are also hallucinogens. Deliriants induce a delirium state in users, which is characterized by inabilities to control one's action and extreme state of confusion; psychedelics are prominently characterized by visual alteration; while dissociatives produce catalepsy, analgesia, and amnesia at anaesthetic doses [177, 178]. Hallucinogens are usually subdivided into 3 major classes, namely, lysergamines, phenethylamines, and tryptamines [36, 179]. Majority of hallucinogens has common mechanism of serotoninergic activity's 5-HT2A receptor modulation, even though there has been an increase in understanding of the glutamatergic system's role, and also, many dissociative hallucinogens have κ opioid receptors activity [36]. Usage routes include intravenous injection, buccal/sublingual administration, oral ingestion (as blotter paper or pill), nasal insufflation, and inhalation [174, 179]. Serotonin is distributed throughout the spinal cord and the brain and involves in controlling many perceptual, regulatory, and behavioural systems, such as sensory perception, mood, muscle control, sexual behaviour, body temperature, and hunger. Common experiences sought by users include joy, euphoria, mystical experiences, providing psychedelic, novel thought associations, broadening and accelerating the content and processes of thought, increase in insight and creativity, and altered perception of space/time [177, 178]. Adverse effects of hallucinogens include complications of sympathomimetic and serotonergic toxicity, and many mental health crises [180, 181]. The 25-NB series, also known as the NBOMe compounds, is a serotonergic psychedelics family (as shown in Table 2).

4.5.1. Action Mechanisms. Phenethylamine derivatives mainly have interactions with cortical serotonin receptors, having the maximum 5-HT2A receptors affinity [182, 183]. The derivatives of NBOMe have lower 5-HT1A receptors affinity and higher 5-HT2C and 5-HT2A receptors affinity in comparison to their 2C analogues. Tryptamine derivatives have 5-HT2C, 5-HT2A, and 5-HT1A receptors affinity and may lead to the inhibition of reuptake and increase in serotonin release [33]. Analogues of lysergic acid diethylamide (LSD) activate both 5-HT2A and 5-HT1A receptors [183]. 5-HT2A receptors activation causes the release of glutamate and α-amino-3-hydroxymethyl-5-4-isoxazolpropionic (AMPA) glutamatergic receptors activation, consequently increasing information processing and cortical activity [184]. Synthetic hallucinogens also work partly by temporary disruption of communication between the spinal cord and brain chemical systems. They may also interfere with serotonin action, a chemical in the brain that regulates sensory perception, mood, body temperature, sleep, hunger, intestinal muscle control, sexual behavior, etc. [183, 184].

4.5.2. Chemical Structure. The synthetic hallucinogens' largest group is the phenethylamine derivatives (2,5-dimethoxyphenethyl-amines), with small lipophilic substituent at 4^{th} position, called the 2C series as they have 2 atoms of carbon between the amino group and benzene ring. Additional derivatives are mostly and exclusively modified chemically at the phenyl ring. N-benzylmethoxy ("NBOMe") group introduction can result in increased derivatives potency [185]. Tryptamines are monoamine alkaloids synthesized by decarboxylating amino acid tryptophan and include compounds like N,N-dimethyltryptamine (DMT), alpha-methyltryptamine (AMT), 5-methoxy-N,N-disopropyltyptamine (5-MeO- DIPT) "foxy methoxy," and N,N-diallyl-5-methoxytryptamine (5-MeO-DALT). They have structure of indole ring, a pyrrole ring, and a bicyclical combination of benzene ring, with an $-NH_3^+$ attached to a side chain of 2-carbon [33]. Synthetic derivatives of derivative LSD of ergot alkaloid, e.g., N1-butyryl-lysergic acid diethylamide (1B-LSD), 1-propionyl-lysergic acid diethylamide (1P- LSD), and acetyl-LSD (ALD-52) have different pharmacological profile and can significantly differ in their effect [32, 186].

4.5.3. Adverse Effects. A class of NPS known as 25-NB derivatives is summarized in Table 3.

There are increased studies and interest on hallucinogen-based compounds, their usage and synthetic derivatives for treating anxiety, substance misuse disorders and depression, and as a psychotherapy adjunct. The data lack sufficient evidence for use beyond scientific trials, although they are encouraging [192–194]. The primary adverse effects commonly reported in nonclinical studies include confusion, drowsiness, hallucinations, aggression, agitation, mydriasis, hyperthermia, hypertension, and tachycardia [195–198]. Severe adverse effects linked to phenethylamine derivatives include serotonin syndrome, seizures, psychosis, and multiorgan failure [196]. Severe tryptamine derivatives' adverse effects include renal failure, prolonged delusions, some reported fatalities, and rhabdomyolysis. The adverse effects of LSD derivatives include exhaustion, thermoregulation impairment, imbalance, difficulty concentrating, and cardiovascular instability [199]. Case studies reported severe but fairly rare complications associated with synthetic hallucinogens toxicity, including an "excited delirium" picture with violence, severe aggression, acute pulmonary oedema, and severe agitation, clonus and hyperreflexia, and acute hyperthermia resulting in death [181, 192].

4.6. Synthetic Benzodiazepines. Synthetic benzodiazepines are often taken for nonmedical reasons [17]. The underlying motivation for their use overlaps with clinical usefulness, including anxiolytic and hypnotic effects and for managing the acute stimulants' effects or for self-treating withdrawal symptoms; however, they lead to the production of subjective "high" [16, 200]. Users also experience amnesic, anticonvulsant, and muscle relaxant effects [201]. A diazepine ring and a benzene ring combination is the base structure, with individual compounds widely varying based on the base structure additions, e.g., Imidazo compounds (midazolam), Triazolo compounds (alprazolam), 2-keto compounds (diazepam), 7-nitro compounds (clonazepam), and 3-hydroxy compounds (temazepam) [200].

4.6.1. Mechanism of Action. New benzodiazepines are known to exert their effects by interacting at "gamma-aminobutyricacid-A" (GABA-A) receptors in a similar way as prescription benzodiazepines [202]. GABA-A receptors are ligand-gated and inotropic receptor ion channels, with different subunit compositions that respond to the GABA inhibitory neurotransmitter. Synthetic benzodiazepines may improve GABA's positive allosteric modulators effects through binding to a site of receptor different from GABA binding site, leading to muscle relaxant, anticonvulsant, sedative, antianxiety, and hypnotic effects [200, 203]. Another action mechanism includes mitochondrial translocator protein 18 kDa (TSPO) activation, which causes neuroactive steroids synthesis, including allopregnanolone. Instead of GABA-A receptor, 4-chlorodiazepam (Ro 5-4864) attaches to this protein, resulting in anxiogenesis and increased seizures' risk [204]. Some synthetic benzodiazepines activate AMPA glutamate receptor, resulting in the quick closing and opening of an ion channel that can be permeated by cations (potassium, sodium, and calcium); inhibition of this leads to the inhibition of CNS fast excitatory synaptic transmissions. A competitive antagonist at this receptor is tofisopam, which does not have GABA-A activities and can induce anxiolytic actions with no sedative effects, unlike other benzodiazepines [205].

4.6.2. Adverse Effects. The adverse effects of novel synthetic benzodiazepines appear to be not fully understood [206]. Adverse effects of synthetic benzodiazepines include sedative-hypnotic toxidrome, drowsiness fatigue, confusion, visual and auditory hallucinations, dizziness, delirium, tachycardia and hyperthermia, agitation, coma, deep sleep, and seizures [205, 207]. Sudden cessation can result in withdrawal symptoms, including convulsions, insomnia, anxiety, restlessness, and panic attacks [208]. Many fatalities have also documented, along with the additional risk regarding toxicity because of the long half-life and slow onset of actions of some synthetic benzodiazepines; long half-life toxicities are more prolonged; slow onset users consume extra doses than normal [209, 210]. Bentazepam is implicated in chronic hepatitis [211].

5. NPS Laboratory Testing: Challenges and Strategies

Some of the major challenges for forensic and clinical testing of NPS hang on the vast number/varieties of currently available NPS, accompanied by the rate by which new ones emerge all around the world, with the NPS developers often designing ways to avoid detection. As laboratory tests can only be developed for NPS after they emerge on the market, tests for NPS continuously lag behind the available varieties of NPS, i.e., laboratory tests are often left racing after the ever-changing targets. The test for NPS in forensic and clinical laboratory settings can be complex, as their routine testing in people that present with toxicity related to recreational drug is not usually undertaken, and also the test kits' reliability and validity considerably vary in the detection of these numerous new substances [212, 213]. Additionally, under clinical practices, patients are usually treated based on the toxicity pattern they present with, with the turnaround time for comprehensive and standard NPS screening often meaning that results are usually unavailable within the frame of time that may alter the patient's clinical management [20, 213]. Moreover, the designs of the tests also have to consider that NPS users will likely make use of extra over-the-counter medicine, other illicit substances, and that other illicit drugs may contaminate the preparations of NPS or dissolve in the diluents [212–215]. The regulatory and testing agencies recognize the present limitations in available timely clinical testing when patients present with acute toxicity of NPS, and at present, the recommended diagnoses for toxicity are primarily

made on clinical features instead of by testing [6]. The toxidromes of NPS may have high nonspecificity, and users may simultaneously take several NPSs or other materials, making it difficult for identifying a possible causative class(es) of NPS from only clinical features. Per se, clinically validated and reliable NPS testing from human samples will be of value and importance. Many techniques have been used for detecting NPS, for example, immunoassays, colorimetric tests, mass spectrometric, chromatographic, and hyphenated types. However, few tests relatively have the capacity to detect over 50 types of NPS [216]. For instance, colorimetric tests rely on a target compound-reagent reactions to generate a detectable change in colour. Portable and easy to operate with little need for prepreparation of sample, colorimetric tests have some demerits, which include cross-reactivities due to false-positive results, user variation in detecting changes in colour, and the limited distinct NPS that can be tested for in one sample [6, 216]. However, immunoassay testing of NPS provides quick testing with high suitability for noninvasive detection, e.g., dissolved drugs and urine samples. Lateral flow immune-chromatography has been applied for trials involving harm reduction where opiate users self-tested drugs for fentanyl presence [217, 218]. Commercial immunoassays appear mostly operational for relatively small NPS selections, although their sensitivity may have limitations, as shown by a cross-reactivity study involving five commercial kits for immunoassay that did not detect 14% (13–94) tested NPS samples [218]. Mass spectrometry tandem gas (or liquid) chromatography (GC-MS or LC-MS) provides more specific and sensitive techniques for identifying individual NPS, providing room for NPS quantification in biological samples by allowing the testing of samples from many biological samples, such as saliva, blood, hair, dried blood samples, urban wastewater, and urine [219, 220]. Samples require preliminary laboratory preparation for the use of these techniques. However, the supposed techniques known as "dilute and shoot" have been validated to allow more rapid biological samples preparation for LC-MS [221]. "Liquid chromatography with quadrupole time of flight mass spectrometry" (LC-QTOF MS) has shown some level of superiority to GC-MS for the detection of many NPSs in serum samples.

Hyphenated techniques to detect NPS include GC-MS, although they may be limited in detecting organic compounds, applicable to street-collected samples of illicit synthetic drugs that contain inorganic chemicals, some of which may interfere with the detection of target analytes [20]. Hyphenated techniques are very useful in detecting and anlyzing a wide range of chemical and biological compounds [222]. Potential interference of the inorganic substances needs consideration particularly in developing GC-MS sensing methods for NPS. Zubrycka et al. [20] profiled 5647 samples obtained from streets, including marijuana and novel illicit drugs. Samples were analyzed with GC-MS, and a total of 53 illicit drugs were identified, with mostly detected compounds like cocaine, Δ-9-tetrahydrocannabinol, 4-chloromethcathinone, N-ethylhexedrone, amphetamine, 4-chloroethcathinone, and α-pyrrolidinoisohexaphenone. Krotulski et al. [223] showed that LC-MS could be employed in forensic toxicological evaluation of new synthetic opioids. Besides, Blanckaert et al. [224] characterized etonitazepyne, a new pyrrolidinyl-containing2-benzylbenzimidazole opioid sold online using specialized techniques. Several techniques have been developed for the detection of NPS with various limits of detection and accuracy.

6. Community-Based Initiatives to Combat NPS and Harm Reduction (HR)

Harm reduction (HR) involves practical-base ideas and strategies aimed at decreasing the negative consequences linked to the use of drugs. It reduces health behaviours' negative consequences without their necessary elimination. HR programs' benefits are widely recognized since maintenance drugs, e.g., methadone, emerged in the 1990s [225, 226]. Common HR programs include naloxone distribution, overseen injection sites, exchange of syringe and needle, purity and content checking of drug, opioid replacement therapy, low-threshold and targeted primary health care counselling, and psychosocial support [2]. They showed to be cost effective and sustainable for reducing the use of drug and its associated harms and improve users' treatment engagement [227]. In spite of these benefits, a number of healthcare practitioners striving to improve health behaviours of patients do not integrate daily-based HR in combating NPS among the teeming population [225]. While HR is among the major strategies for drug control and prevention, several hindrances are stillobstructing its viable approach. A growing number of new drugs have appeared on the market, and especially, synthetic drugs have become a significant concern for many countries [228, 229]. For example, synthetic drugs account for 80% of drug use in south-east Asian countries [228, 229]. The application of a single harm reduction intervention, such as methadone or other maintenance therapies, is reported to be significantly less effective against synthetic drugs [227, 230, 231]. In responding to political instability and social threat occasioned by illicit synthetic drugs (or NPS), many nations tightened users' mandatory treatment and arrest policies. However, compulsory treatments may not have lasting effects in reducing the abuse of drug, indicating that the relapse rate remains high following the period of treatment [232]. HR initiatives are encouraged for developing novel sustainable strategy to NPS problem. Challenges facing implementing interventions at the community level exist, including in developed nations. Additionally, many synthetic drugs users deny suffering from drug related problem and as a result do not opt for treatment [2, 233]. Many of them also fear for community stigmatization. The evidence of community-based HR that supports drug users with mental disorders has been demonstrated in many studies, including the one done in Vietnam [234]. Michel et al. [234] reported the prevalence of mental conditions in drug users and suggested that peer support is important to reduce substance use disorders and improve mental health. HR initiative can utilize community-based approaches for psychological support and screening. It can engage local organizations, interest groups, NGOs, relevant government agencies, schools, universities, psychiatrists, etc., to detect, prevent, and treat users with mental conditions or prevent

drug abuse entirely. Drug users who receive psychiatric care from the community have significant improvement in their mental disorders. Michel et al. [234] reported that in a year, the rates of suicide risks, depression, and psychotic disorder in affected patients significantly reduced from 42.4%, 80.6%, and 44.7%, to 22.9%, 15.9%, and 21.8%, respectively. Similarly, in south eastern part of Nigeria, community-based initiatives were introduced to combat drug abuse [76]. The initiatives have yielded positive outcomes since then, leading to reduction in the use of NPS. Harm reduction infused into community-based initiatives have been shown to help many with the prevalence of drug abuse and use of NPS. Many community-based initiatives used in many other intervention measures can also be employed to tackle excess use and abuse of NPS [235–240]. Fasakin et al. [241], Corazza et al., [242], and Johansen et al. [243] also suggested putting many factors into consideration for reducing the prevalence of NPS abuse. Monitoring activities on Web and supporting innovative Web-based prevention programmes are also essential for combating NPS diffusion and preventing its prevalence [242, 243]. According to the WHO, over 270 million people (5.5% world population) with age 15 to 64 years had used psychoactive substances, and over 35 million people are estimated to be affected by substance use disorders [244]. Over 0.5 million annual deaths are associated with NPS/drug use, which include over 150 000 female and 350 000 male deaths. Recently, synthetic opioids-related deaths alone have changed the trends of mortality in some developed countries. Worldwide, it is estimated that almost 11 million people inject NPS or drugs [244]. All these deaths and abuse can be prevented or at least significantly reduced with the solutions highlighted in this study.

7. Conclusion

In this work, another look into NPS has been performed, specifically from differentiating the major groups, identifying with laboratory testing challenges, to community-based initiative, which we have been holistically described. The NPS largely appears to mimic the psychological and/or pharmacological properties of the original drugs, which are designed to evade the detection by the standard drug test and/or being classified as illegal. Despite this, many substances continue to be detected at the drug market every year, especially in recent years. Among various grouping of NPS, they are mainly grouped into synthetic stimulants, synthetic cannabinoids, synthetic hallucinogens, synthetic opioids, benzodiazepines, and dissociatives. As the safety and efficacy of NPS have not undergone thorough evaluation involving human and animal trials, their use may cause unexpected side effects, which may even be lethal. Some of the major challenges for forensic and clinical testing of NPS are the vast number and varieties of the NPS currently available, accompanied by the rate by which new ones emerge all around the world, with the NPS developers often designing ways to avoid detection. There is a need for increased community-based HR strategies that supports drug users with mental disorders. There is a need for increased access to advanced techniques of immunoassays, colorimetric tests, mass spectrometric techniques, chromatographic techniques, and hyphenated technique commonly employed for NPS detection to reach developing countries to help them in early combat as well as detection of the issue.

Data Availability

The data used for this research are available on request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

CGA did the conceptualization; MS, NBM, MPA, SM, IOA, CKE, and VSI did the methodology,; CGA looked after validation and visualisation; CGA provided the resources,; CGA, MS, MPA, NBM, SM, IOA, CKE, and VSI curated the data; CGA, MS, NBM, SM, IOA, CKE, and VSI did the writing—original draft preparation; CGA did the writing—review and editing; CGA and SM supervised. All authors have read and agreed to the published version of the manuscript.

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