Expert Review of Clinical Pharmacology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierj20

Stimulant and hallucinogenic novel psychoactive substances; an update

F Schifano, A Vento, N Scherbaum & A Guirguis

To cite this article: F Schifano, A Vento, N Scherbaum & A Guirguis (2023) Stimulant and hallucinogenic novel psychoactive substances; an update, Expert Review of Clinical Pharmacology, 16:11, 1109-1123, DOI: 10.1080/17512433.2023.2279192

To link to this article: https://doi.org/10.1080/17512433.2023.2279192

Published online: 22 Nov 2023.

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
2023, VOL. 16, NO. 11, 1109–1123
https://doi.org/10.1080/17512433.2023.2279192

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Stimulant and hallucinogenic novel psychoactive substances; an update

F Schifano[a], A Vento[b], N Scherbaum[c] and A Guirguis[a,d]

[a]Psychopharmacology Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Herts (UK); [b]Mental Health Department, Addiction Observatory (Osservatorio sulle dipendenze)- NonProfit Association - Rome, Rome, Italy; [c]LVR-University Hospital, Department of Psychiatry and Psychotherapy, Medical Faculty, University of Duisburg-Essen, Essen, Germany; [d]Pharmacy, Swansea University Medical School, Faculty of Medicine, Health and Life Science, Swansea University, Wales, UK

ABSTRACT

Introduction: The renewed interest in considering a range of stimulants, psychedelics and dissociatives as therapeutics emphasizes the need to draft an updated overview of these drugs' clinical and pharmacological issues.

Areas covered: The focus here was on: stimulants (e.g. amphetamines, methamphetamine, and pseudoephedrine; phenethylamines; synthetic cathinones; benzofurans; piperazines; aminoindanes; aminorex derivatives; phenmetrazine derivatives; phenidates); classical (e.g. ergolines; tryptamines; psychedelic phenethylamines), and atypical (e.g. PCP/ketamine-like dissociatives) psychedelics.

Stimulant and psychedelics are associated with: a) increased central DA levels (psychedelic phenethylamines, synthetic cathinones and stimulants); b) 5-HT receptor subtypes' activation (psychedelic phenethylamines; recent tryptamine and lysergamide derivatives); and c) antagonist activity at NMDA receptors, (phencyclidine-like dissociatives).

Expert opinion: Clinicians should be regularly informed about the range of NPS and their medical, psychobiological and psychopathological risks both in the acute and long term. Future research should focus on an integrative model in which pro-drug websites' analyses are combined with advanced research approaches, including computational chemistry studies so that in vitro and in vivo preclinical studies of index novel psychoactives can be organized. The future of psychedelic research should focus on identifying robust study designs to convincingly assess the potential therapeutic benefits of psychedelics, molecules likely to present with limited dependence liability levels.

ARTICLE HISTORY
Received 6 September 2023
Accepted 31 October 2023

KEYWORDS
Stimulants; hallucinogens; psychedelics; amphetamine-type stimulants; dissociatives

1. Introduction

In today's context, the widespread issues related to drug use span diverse regions, adding to the already complex policy challenges at a domestic level [1]. A significant development is the increasing prevalence of NPS within the drug market. These substances often come with misleading labels or combinations that obscure their composition and pose health risks.

Various definitions of the term 'novel' or 'new' psychoactive substances (NPS) are being used. The term 'new' doesn't necessarily mean entirely new inventions; rather, it refers to substances that have recently become available. Thus, 'new' could encompass a previously unsuccessful pharmaceutical or an old patent that has been 'rediscovered' and marketed for recreational use. Conversely, 'novel' could imply something newly created, a compound that has reentered the recreational drug scene after a period of absence, or a known NPS molecule used in an innovative or unusual way, presenting a sense of novelty [2]. Overall, the focus will be here on NPS being ingested mainly in the context of recreational use. It has to be specified, however, that recreational 'street' drugs are often 'dirty;' they may not contain significant amounts of the NPS and/or might be contaminated with other compounds [3].

Another distinction arises between NPS and Emerging Psychoactive Substances (EPS), where the latter term includes all NPS as well as drugs that may not be brand new but have recently experienced a resurgence or increase in use. This evolving trend introduces new complexities for law enforcement and regulatory frameworks, as the market showcases a wide range of drugs, often with high potency and purity levels [4].

The increasing diversity in drug availability and usage brings forth multifaceted challenges in both health and policy domains. The accessibility of drugs exposes consumers to various psychoactive substances, including newly synthesized variants with poorly understood health effects [5].

Over the past decade, the proliferation of synthetic drugs has continued, but only a subset, such as amphetamine-type stimulants (ATS) like methamphetamine and MDMA, have established solid global markets [1]. Particularly concerning in the Near and Middle East is the prominence of 'Captagon,' containing a range of ATS [6], while South American markets have witnessed an increased distribution of synthetic drugs, including stimulants; hallucinogens; dissociative anesthetics like ketamine; and other NPS. The shift from ephedrine-

CONTACT F Schifano f.schifano@herts.ac.uk Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Herts (UK)

Article highlights

- An updated overview of emerging psychostimulants and psychedelics/hallucinogens is here provided. Their pharmacological effects are discussed, in parallel with the rapidly evolving drug-related scenarios and market trends.
- Focus is here on the following stimulants: amphetamines; methamphetamine; pseudoephedrine; phenethylamines; synthetic cathinones; benzofurans; piperazines; aminoindanes; aminorex derivatives; phenmetrazine derivatives; and phenidates. Ergolines and tryptamines (e.g. typical psychedelics), together with PCP/ketamine-like dissociatives (atypical psychedelics) are here discussed.
- The landscape of the stimulants' and psychedelics' market underwent a transformation in the early 2000s, with the introduction of numerous, potent, and easily available synthetic derivatives of these molecules (e.g. novel psychoactive substances; NPS). NPS gained prevalence within the recreational drug market.
- Healthcare professionals should receive ongoing education regarding the medical, psychobiological, and psychopathological risks associated with the vast range of stimulant and psychedelic NPS. Prospective investigations into NPS long-term effects should be promoted.
- The interest in psychedelics has recently and significantly surged in therapeutic contexts. The future of psychedelic and psychopharmacological research should, and will, strive to employ more robust study designs.

based synthesis to the use of different derivatives of phenyl-2-propanone (P2P), through tartaric acid refinement, in ATS chemical production has been reported, with similar shifts possibly occurring in South-East Asia [4,7] Notably, Afghanistan has emerged as a source of methamphetamine, involving the use of diverted precursors and industrial-grade formic acid [7].

1.1. The relative contributions of the different neurotransmitter pathways in addiction

To better understand the pharmacology of stimulant and psychedelic NPS, it may be of help to briefly summarize the relative contributions of dopamine (DA); noradrenaline (NA); and serotonin (5-HT); together with both adrenergic and trace amine-associated (TAAR1) receptors in their effects related to addiction.

It is felt that *dopamine (DA)* is mainly involved in mechanisms relating to reward and motivation [8,9]. In particular: dopamine D_1 receptors expressed on GABA neurons may be involved in regulating opioid reward by mediating the dopamine neuron activity in the ventral tegmental area (VTA) [10,11]; D2 receptors have been studied for their involvement in alcohol use disorder [12]; D3 receptors' activation may be associated to nicotine reinforcement, conditioned stimuli, and withdrawal [13]; and the D_4 receptor may be a target for attention-deficit hyperactivity disorder (ADHD) [14], a disorder frequently associated with addiction [15].

At the brain level, *the serotonergic network* regulates various functions like reward processing, satiety, and impulsivity [16,17]. Some 14 5-HT receptor subtypes have been identified [18]. In particular, recent findings have suggested a key role of 5-HT2C receptors for treating cocaine use disorder and comorbid depression [19]; whilst 5-HT2A; 5-HT1A; 5-HT1B; and a few other receptor subtypes have been involved at various levels in the psychedelics' pharmacodynamic [20–22]; for a better overview of the issue, see below the psychedelics' section.

Noradrenergic regions play pivotal roles in cognitive functions, memory consolidation, and arousal. It has been suggested that some stimulant-related, putative [23], pro-cognitive effects may be due as well to NE transporter (NET) inhibition [24]. This perceived cognitive enhancement is an issue which may increase drug, including nicotine, reinforcement levels [25]. Furthermore, noradrenergic systems exert potent arousal-enhancing actions, and the dysregulation of arousal-related neural systems is implicated in both relapse and addiction [26].

Adrenergic (as opposed to noradrenergic) *receptors* may have a role as well in addiction; indeed, drug reward memories contribute to both craving and increase relapse risks. Propranolol, a nonspecific β-adrenergic receptor antagonist, may be able to somehow delete maladaptive memories associated with nicotine, cocaine and heroin in humans [27]. Furthermore, blockade of peripheral adrenergic β1 receptors by atenolol significantly reduces the cocaine-associated increased ghrelin levels, inhibiting cocaine intake [28].

Finally, *TAAR1*, which is broadly expressed in the monoaminergic system in the brain (e.g. ventral tegmental area (VTA), nucleus accumbens (NAc), dorsal raphe (DR) and substantia nigra (SN)), may play an important role in modulating DA transmission. Indeed, TAAR1 activation inhibits the rewarding and reinforcing effects of drugs from different classes including psychostimulants, opioid and alcohol [29].

1.2. Aims

In this context, the present article aims to provide an updated review concerning emerging psychostimulants and psychedelics/hallucinogens. The pharmacological effects of these molecules will be discussed, considering the evolving complexities and challenges arising from drug-related issues and market trends.

2. Methods

A narrative review was here carried out; the comprehensive search included case reports, research papers, reviews and systematic reviews identified from Medline/PubMed, utilizing a range of relevant keywords including, but not limited to: 'stimulants', 'cathinones', meth/amphetamine", 'hallucinogens', 'psychedelics', 'dissociatives', and 'pharmacology'. The search parameters were refined to focus mainly on both the last 15 years' studies and human subjects' non-medical drug intake. Articles referring to legal stimulants like caffeine or nutritional ergogenic aids were excluded from this study. The categories of molecules here discussed will include: *stimulants* (e.g. amphetamine-type stimulants (ATS): amphetamines, methamphetamine, and pseudoephedrine; phenethylamines; synthetic cathinones; benzofurans; piperazines; aminoindanes; aminorex derivatives; phenmetrazine derivatives; and phenidates); but also *typical* (e.g. ergolines; tryptamines), and *atypical psychedelics* (e.g. PCP/ketamine-like dissociatives).

3. Stimulants

Amphetamine-type stimulants refer to substances such as amphetamines (AMPH) (street names: bennies, black beauties, crank, glass, ice, speed, pep pills, uppers), methamphetamine (METH) (street names: speed, meth, chalk, crystal, crystal meth, ice, crank, Tina) [30] and pseudoephedrine. They exhibit sympathomimetic effects on both the central and peripheral nervous systems mimicking the actions of both adrenaline and noradrenaline [31].

3.1. Stimulants; pharmacodynamics' and related neurotoxicity issues

Functioning as an ATS, methamphetamine (METH) elicits potent indirect agonistic effects on noradrenaline, dopamine, and serotonin receptors, instigating the release of these monoamines in both the central (CNS) and peripheral nervous system. This dynamic activity stems from a complex interplay of mechanisms that enhance neurotransmitter release. These mechanisms involve processes like the redistribution of vesicular stores to the cytosol, intensified reverse transport from the cytosol to the synapse, suppression and reduced expression of membrane transporters, inhibition of monoamine oxidase, and increased tyrosine hydroxylase activity, ultimately leading to heightened dopamine production [32].

Methamphetamine's influence extends significantly across crucial CNS pathways, including dopaminergic, noradrenergic, serotonergic, and opiatergic systems, each intricately linked to specific physiological and cognitive functions [16]. Overall, stimulant variations in dopaminergic engagement contribute to heightened stimulant-like reinforcing effects and an increased potential for abuse [33]. Conversely, serotonergic activity aligns with an entactogenic response akin to MDMA, characterized by a reduced risk of abuse [34,35]. Furthermore, a high or low affinity for the modulation of noradrenergic systems might correlate with varying sympathetic nervous system activation, while the activation of 5-HT2A/1A receptors would likely predict hallucinogenic effects [20].

Stimulant NPS modulate monoaminergic neurotransmission through two primary mechanisms: the inhibition of monoamine transporters and the facilitation of non-exocytotic substrate efflux from these transporters [36]. Additionally, interactions with adrenergic, dopaminergic, serotonergic, and TAAR1 receptors contribute to the mechanism of action of the diverse stimulant NPS [22,37]. Moreover, some stimulant NPS exhibit substrate properties at vesicular monoamine transporters (VMATs) and exert inhibitory effects on monoamine oxidases [36].

A range of studies have substantiated the impact of high ATS doses on dopamine (DA) and serotonin (5-HT) systems' toxicity [38]. Potential contributors to stimulant NPS-induced neurotoxicity include cytotoxicity, mitochondrial dysfunction, oxidative stress, neuronal apoptosis and activation of glial cells in the brain [39–41]. In particular, METH-induced neurotoxicity may involve transcription factors, activation of apoptotic pathways stemming from mitochondria and endoplasmic reticulum, and participation of neuroinflammatory mechanisms [42]. METH use has been associated with both stroke and Parkinson's disease [43]. However, if all striatal DA neuronal markers are decreased in Parkinson's disease, levels of only some (e.g. DA and DA transporters) are below normal in METH users [44].

Overall, it is important to distinguish acute versus chronic effects of ATS, although it is not clear how much exposure to either of these drugs is required for the toxicity to present [45]. Neurodegeneration involving decreased levels of dopamine (DA) and its metabolites, along with loss of dopamine transporters (DAT) and serotonin transporters (5-HTT), have been observed in the brains of human, long-term, METH users [46,47]. Furthermore, METH users show substantial reduction in gray matter in cortical and hippocampal [48] brain regions, and changes in white matter integrity [47]. Chronic users of MDMA may display selective dysfunction of serotonergic neurons, raising concerns about potential neurodegenerative changes [49]. Combination of MDMA with the legal stimulant caffeine may increase their respective neurotoxic effects [50].

3.2. ATS (amphetamine; methamphetamine; and pseudoephedrine)

These molecules exhibit chemical and functional resemblances to the monoamine neurotransmitters dopamine, noradrenaline, and serotonin. Structurally, ATS are derivatives of phenethylamine, whilst MDMA/ecstasy and its analogues contain a phenethylamine and a methylenedioxy ring, which make them similar to serotonin. On the other hand, cathinones differ from AMPHs by incorporating a β-ketone group into the phenylethylamine structure (for an overview of these issues, see [33]).

ATS are found in various forms, including free bases or salts, tablets or powder, and crystalline forms, which are generally lacking in odor and possess a bitter taste. The methods of administration encompass intravenous injection (referred to as 'slamming'), oral ingestion, smoking, inhalation, intrarectal administration (known as 'booty bumping'), and intravaginal methods [33].

Generally, ATS are absorbed through the gastrointestinal tract and reach their highest plasma concentrations around 3–6 hours after non-injectable administration. Overall, for both amphetamine and methamphetamine, the bioavailability levels increase to approximately 90% when in a smokable formulation. ATS are associated with high distribution levels and, thanks to their lipid solubility, they can cross the blood-brain barrier, placenta, and enter breast milk. ATS are mainly metabolized by CYP2D6 and are then eliminated through urine [33].

Following immediate consumption of ATS, there are commonly observed sympathomimetic effects like increased alertness, heightened blood pressure, bronchodilation, and elevated heart rate ([51], renal and hepatic impairment, arrhythmias [52], high body temperature, and loss of consciousness. Notably, METH users exhibit signs and symptoms of Parkinsonism [53]. They can also lead to mydriasis, enhanced communicativeness, increased motivation, reduced appetite, and insomnia.

Psychopathological issues such as feelings of euphoria, anxiety, and paranoia can be routinely observed as well. Conversely, with a high and/or chronic ATS intake, the related neurotoxic effects can result in cognitive impairments, weakened memory and attention, and deficits in executive functions like decision-making and information processing [42,54]. These can also lead to seizures [55], hemorrhagic strokes, psychosis [56], METH mouth bruxism [57], hypertension, coronary artery disease, hyperthermia, hyperreflexia, and METH-related tactile hallucinations [58]. Extended ATS usage can foster addictive behavior [32].

The combined use of methamphetamine and potent opioids like heroin or fentanyl is commonly referred to as a 'goofball.' Although historically less common than the cocaine and heroin speedball, this combination appears to be increasing in prevalence [59,60] The convergence of synthetic opioids with stimulants has contributed to the current rise in mortality rates [61], termed as the 'fourth wave' [62].

3.3. Phenethylamines

Often grouped under MDMA/ecstasy derivatives [63,64], phenethylamines form a diverse chemical class encompassing molecules with various activities such as stimulants, entactogens, and psychedelics [41,65,66]. Phenethylamines are synthetic compounds available in tablet, capsule, and powder forms.

Methylenedioxymethamphetamine (MDMA/ecstasy) shares structural similarities with mescaline and amphetamine. Commonly known as 'ecstasy' or 'MD,' remains a popular choice among young individuals and club-goers due to its stimulant effects. With a half-life of 4–6 hours, MDMA stimulates the release of both 5HT and DA, with these effects being likely to underlie its abuse potential [67]. Furthermore, MDMA stimulates central and peripheral α- and β-adrenoceptors, and its actions are influenced by physical exertion, dehydration, and heat. Certain individuals, like poor metabolizers with the CYP450 2D6 polymorphism, can experience severe and fatal reactions, including hyperthermia, convulsions, coagulation issues, rhabdomyolysis, organ failure and even fatalities [49,68].

The phenethylamine category includes both: the 2C-series drugs like 2C-B, 2C-D, and 2C-E; the 'fly;' and the N-methoxybenzyl/NBOMe series drugs [69]. Compounds in the 'fly' series, particularly 'Bromo-DragonFly'/'B-fly,' are potent and long-lasting, with adverse effects that can persist for up to three days [69]. The market for NBOMe compounds has grown alongside the decreased availability of lysergic acid diethylamide (LSD). In recent times, a range of other psychedelic phenethylamines like 4-MTA, 6-APB, 4,4'-DMAR, and PMA have emerged [35]. The psychoactive effects of these compounds vary with dosage, ranging from stimulant effects at lower doses to hallucinogenic and entactogenic effects at higher doses. Those compounds with high 5-HT/DA ratios, such as MDMA, 2C-series drugs, and benzofurans like 3C-bromo-dragonfly, are considered entactogenic substances. Conversely, high DA/5-HT ratios (e.g. MDA) are indicative of strong stimulant experiences [69,70]

The consumption of phenethylamines can lead to various effects including appetite loss, tachycardia, hypertension, anxiety, nausea, headache, dizziness, skin irritation, hyperthermia, convulsions, respiratory problems, and even organ failure and death [69]. Psychotic symptoms are linked to high-dosage intake [20].

3.4. Pseudoephedrine and ephedrine

Pseudoephedrine and ephedrine are naturally occurring alkaloids derived from various species of Ephedra spp. within the Ephedraceae family [71]. Pseudoephedrine indirectly stimulates alpha-adrenergic receptors, leading to the release of endogenous noradrenaline from neuronal granules, and directly stimulates alpha, beta1-, and beta2- adrenergic receptors [72,73]. While its effects resemble those of ephedrine, they are slightly less pronounced. Moreover, pseudoephedrine is less likely to induce tachycardia and elevate systolic blood pressure. In terms of central effects, it is milder than amphetamine, whereas its peripheral effects align more closely with epinephrine [74]. Pseudoephedrine takes about 30 minutes to take effect, reaches its peak action within 1–4 hours, has a duration of action of 4–12 hours, and a biological half-life of 3–16 hours [71]. The molecule is one of the different cough/cold, over-the-counter (OTC) medicines with a potential of misuse [74], with 'misuse' (as opposed to 'dependence') being the intentional and inappropriate use of a product other than as prescribed or not in accordance with the authorized product information [75]. 'Russian Cocktail' includes ephedrine consumed together with potassium permanganate and acetylsalicylic acid diluted in water [76]. To address the potential utilization for the production of the controlled substance methylamphetamine, the United Kingdom has implemented measures to regulate products containing pseudoephedrine and ephedrine in order to mitigate associated risks.

3.5. Cathinones

The category of synthetic cathinones encompasses a range of more than 180 distinct molecules [75]. The first-generation synthetic cathinones, which are derivatives of the natural psychoactive compound found in khat leaves (cathinone), include methcathinone, 4-methylmethcathinone (known as mephedrone), 3,4-methylenedioxy-N-methylcathinone (methylone), and 3,4-methylenedioxypyrovalerone (MDPV). A subsequent generation features compounds like 4-fluoromethcathinone (referred to as flephedrone) and α-PVP (α-pyrrolidinopentiophenone). Structurally resembling amphetamine-type stimulants, synthetic cathinones fall under the category of β-ketone analogues. The dominant psychoactive pharmacophore group is phenethylamine, and its derivatives constitute a significant portion of the available NPS on the illegal drug market [3,66].

Synthetic cathinones are predominantly inhibitors of the serotonin (SERT), dopamine (DAT), and noradrenaline transporter (NET) [3].

These molecules can be classified into three categories:

- Compounds resembling cocaine/MDMA (3,4-methylenedioxy-N-alkylated cathinones, such as butylone), which function as inhibitors of serotonin, dopamine, and norepinephrine reuptake transporters (SERT, DAT, and NET) and as agents that release serotonin.
- Compounds resembling methamphetamine (N-alkylated or ring-substituted cathinones, like buphedrone), which operate as inhibitors of SERT, DAT, and NET and as substances that release dopamine.
- Cathinones resembling pyrovalerone (N-pyrrolidine cathinones, e.g. MDPV), which exhibit high potency in inhibiting DAT and do not induce the release of monoamine substrates [3,77]; for an overview, see also [78].

The pharmacokinetic characteristics of cathinones depend on each specific analogue [31]. Cathinones such as MDPV display higher lipophilicity compared to other synthetic stimulants, facilitating substantial penetration of the blood-brain barrier and an increased volume of distribution. The incorporation of electrophilic elements like fluorine further enhances their lipophilic nature, contributing to their potency, which is associated with an intensified and prolonged 'party drug' experience [79].

With mephedrone, the most well studied cathinone, reported effects include low mood, loss of appetite, sleep difficulties, paranoid ideation, cognitive impairment, altered perception, agitation, hallucinations, delusions, amnesia, confusion, violence, and suicidal thoughts. Positive effects have also been reported, such as euphoria, improved psychomotor speed, alertness, and talkativeness (for an overview, see [80]).

Acute intoxication induced by cathinones can be associated with the serotonin syndrome, marked by traits such as aggression, hyperthermia, psychotic conditions, catatonia, and excited delirium [69]. Additionally, acute intoxication may give rise to problems like dehydration, high blood pressure, rapid heartbeat, kidney and liver dysfunction, disturbances in electrolyte levels, metabolic toxicity, cerebral edema, and even fatalities [63]. Instances of suicides by hanging and fatalities resulting from firearm injuries have been frequently documented along with deaths attributed to toxicity [81].

3.6. Piperazines

The primary compound within the piperazine group, known as N-benzylpiperazine (BZP) possesses a standard structure characteristic of CNS stimulants. Structurally resembling amphetamine and initially created for antidepressant purposes, BZP induces the release of DA and NE while concurrently blocking the reuptake of dopamine DA, NE, and 5-HT [35]. In the past, benzylpiperazine (BZP) was found in counterfeit MDMA/XTC tablets. BZP acts as a 5-HT2A receptor agonist, which accounts for its hallucinogenic effects at higher dosages. Its impact is akin to that of amphetamine but of a lesser intensity. Piperazine toxicity can lead to seizures, occurring in as many as one in five patients, and it has also been associated with hyponatremia, serotonin syndrome, and renal failure [69]. Other piperazines include: meta-chlorophenylpiperazine (mCPP), which is the primary metabolite of trazodone/nefazodone; and trifluoromethylphenylpiperazine (TFMPP), which is at times identified in so called 'ecstasy' tablets and which interacts with the serotonin transporter [82]. Some countries have seen a recent rise in this molecule consumption [83].

3.7. Benzofurans

'Benzofury' molecules (e.g. 5-and 6-APB; King, 2014) are typically consumed recreationally at parties and in polydrug abuse settings. Whilst mostly influencing the serotonergic pathways, and mildly the dopaminergic system, rewarding, entactogenic and stimulant effects are being reported (for a review, see [84]).

3.8. Aminoindanes; thiophenes

Although distinct from phenethylamines, compounds like the thiophene bioisosteres of amphetamine, as well as specific conformationally-restricted variants like aminoindanes [85], have been discovered in drug seizures [86]. Among these, the fully synthetic 5,6-methylenedioxy-2-aminoindane (MDAI) stands out as an analogue of 3,4-methylenedioxymethamphetamine (MDMA). Despite its development dating back to the 1990s, widespread misuse of MDAI didn't emerge until around 2010. In response to the ban on mephedrone in the UK in April 2010, MDAI quickly gained attention as an advertised alternative [87].

3.9. Aminorex derivatives

Aminorex analogues encompass compounds that were previously unsuccessful as pharmaceuticals but have resurfaced as substances of abuse, along with newly synthesized compounds designed exclusively for recreational use by clandestine chemists [88]. Consequently, these substances share both pharmacological and neurochemical similarities with amphetamines and cocaine. One such derivative is 4,4'-dimethylaminorex (4,4'-DMAR, often referred to as 'Serotoni'), which was linked to approximately 30 deaths in Europe between 2013 and 2014. Similar to amphetamine-type stimulants, 'Serotoni' is a potent releaser of dopamine and noradrenaline while also inhibiting the serotonin transporter. It can be administered through snorting or ingestion, producing effects like euphoria, increased alertness, and agitation that can last for several hours. Notably, cases of hyperthermia and cardiorespiratory problems associated with its use have also been documented (for an overview, refer to [89]).

3.10. Phenmetrazine derivatives

In the realm of phenmetrazine derivatives, a compound called 3-fluorophenmetrazine (3-FPM), derived from the anorectic agent phenmetrazine, has emerged in the recreational drug market [90,91]. Phenmetrazine is recognized for its ability to elevate extracellular monoamine levels via an amphetamine-like mechanism. Mayer et al. [92] conducted studies on 3-FPM and its positional isomers, namely 2-FPM and 4-FPM, to assess their interactions with DAT, NET, and SERT transporters. Their

findings demonstrated that 2-FPM, 3-FPM, and 4-FPM inhibited uptake mediated by DAT and NET, showing potencies comparable to cocaine. However, their effects on SERT were less potent. Moreover, each of these FPM compounds induced the release of monoamines from rat brain synaptosomes in a concentration-dependent manner.

3.11. Phenidates; cognitive enhancers

In conjunction with modafinil, methylphenidate is being utilized as a cognitive enhancer on a global scale. Notably, students frequently acquire prescription stimulants not for recreational purposes, as seen with substances like amphetamine or methylphenidate, but rather to augment their academic performance [23]. Stimulants prescribed for ADHD treatment, even at doses relevant for clinical use, demonstrate cognitive enhancements linked to fronto-striatal pathways, both in individuals with ADHD and those without the condition [23].

Despite not being fully understood in humans, methylphenidate is thought to inhibit dopamine reuptake in the striatum without inducing dopamine release. According to Carlier et al. [93], numerous analogues of methylphenidate have recently emerged in the illicit market as NPS stimulants. These include ethylphenidate, 3,4-dichloromethylphenidate, 3,4-dichloroethylphenidate, 4-fluoromethylphenidate, 4-fluoroethylphenidate, methylnaphthidate, ethylnaphthidate, isopropylphenidate, propylphenidate, 4-methylmethylphenidate, and N-benzylethylphenidate. Among these, ethylphenidate has been associated with 28 fatalities, although it was directly implicated as the cause of death in only 7 cases; 3,4-dichloromethylphenidate was linked to 1 death (for a comprehensive review, refer to [93]).

4. Hallucinogens: classical and atypical (dissociative) psychedelics

4.1. Definitions and categorization issues

Psychedelics have lately been capturing significant attention because of their therapeutic potential, albeit still largely under investigation, for a range of neuropsychiatric disorders [94,95]. While the term '*hallucinogen*' is used to describe a wide range of different types of psychoactive molecules [96], *psychedelics* (e.g. the subclass of hallucinogenic drugs whose primary effect is to trigger non-ordinary mental states and an apparent expansion of consciousness [97,98]) refer here specifically to tryptamines (e.g. psilocin, 5-Meo-DALT); ergolines/lysergamides; and the vast range of phenethylamines (e.g. mescaline and 2C-B) [99], which have been discussed in the previous paragraphs. Overall, it has been suggested that psychedelic/entactogenic phenethylamines are weak reinforcers, as opposed to remaining hallucinogenic psychedelics which are non-reinforcers [100]. Atypical hallucinogen compounds induce analogous effects through different mechanisms [66].

4.2. The psychonauts' psychedelics

The landscape of the psychedelics market underwent a transformation in the early 2000s, marked by the introduction of numerous synthetic derivatives of LSD, tryptamines, and phenethylamines, classified as NPS [63,64,74,101–103]. These synthetic analogues, often significantly more potent than their natural counterparts, became available for purchase and gained prevalence within the recreational drug market.

Concurrently, alongside the emergence of these 'modern' psychedelic NPS, there has been a parallel surge and consolidation of a contemporary form of shamanism [104]. This involves a new wave of drug experimentation carried out by enthusiasts of NPS, referred to as e-psychonauts [105,106]. These individuals define themselves as either 'techno-shamans' or 'sailors of the mind/soul,' since they aim at exploring their inner realms using psychedelic NPS and sharing their experiences online [106]. Interestingly, the drug consumption patterns of these psychonauts exhibit striking similarities to ancient shamanic ritual plant usage [104]. In the era of NPS, these explorers of the mind have access to a diverse array of new psychedelic compounds, allegedly facilitating novel inner explorations and profound mental journeys into uncharted territories.

Against this background, Catalani et al. [99] embarked on a study to: categorize psychedelic molecules sourced from psychonaut websites and NPS online resources; and compare the findings from the NPSfinder® tool with data from the European Monitoring Centre for Drug and Drug Addiction (EMCDDA) and United Nations Office for Drugs and Crime (UNODC) databases. NPSfinder®, an automated crawling software, was developed to continuously scan a list of URLs and extract pertinent information, such as chemical/street names and formulae, to aid in the identification of NPS. The outcomes revealed a total of 1344 psychedelic NPS detected by NPSfinder® between November 2017 and February 2020, almost 10 times greater than the combined figures reported by UNODC and EMCDDA. Significantly, 994 of these molecules, primarily phenethylamines but also including 65 tryptamines and 16 lysergamides, were identified as (potential) novel psychedelics not previously recognized by the UNODC and EMCDDA. These findings underscore the enthusiastic interest of psychonauts, and potentially of a broader community of 'recreational' drug users, in both classical and novel psychedelics, hinting at a substantial discord between online and real-world NPS scenarios.

More recently, Mallaroni et al. [107] delved into the prevalence of novel phenethylamines, tryptamines, and lysergamides among users of Novel Psychedelics (NPs), comprising 1180 participants. They contrasted the occurrence and types of different psychedelic adverse events (AEs) through logistic regressions. Notably, novel phenethylamines exhibited the highest usage prevalence at 61.5%, followed by tryptamines at 43.8%, and lysergamides at 42.9%. In comparison to phenethylamines, users of tryptamines and lysergamides displayed significantly lower odds for overall physical AEs. Furthermore, Lea et al. [108] undertook a content analysis of discussions about *psychedelic*

microdosing on the online platform Reddit. Reported benefits encompassed cognitive and creative enhancements, reduced depression and anxiety, and improved social interactions. However, limitations were also identified, including concerns related to adverse physical effects, the use of illegal substances, increased anxiety, occasional 'off' days, short-term benefits, and apprehensions about dependence and drug-related risks.

4.3. Psychedelics; pharmacodynamic issues

A common thread across all psychedelics is their shared pharmacodynamic activities, including agonism/partial agonism of the 5-HT2A, 5-HT2C (linked to anxiety and panic [109]), and 5-HT1A receptors [22]. Furthermore, LSD exhibits a pronounced affinity for additional 5-HT receptor subtypes, such as 5-HT1B, 5-HT1D, 5-HT7, and 5-HT6 [21,22]; psilocin may exert its pharmacological action by enhancing neuroplasticity and increasing the expression of neurotrophic factors such as BDNF; DMT may act on 5-HT1A, 5-HT1B, and 5-HT2A; and finally mescaline should be seen as an agonist of 5-HT2A; 5-HT2C receptors, and α2A adrenergic receptor s(for thorough overview, see [110]).

Overall, the newer phenethylamines' NBOMe derivatives demonstrate enhanced affinity for 5-HT2A and 5-HT2C receptors, while tryptamine derivatives impact serotonin reuptake and release through 5-HT1A, 5-HT2A, and 5-HT2C receptors. The 4-Iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25I-NBOMe) hallucinatory activities seem to be related with the increase in extracellular glutamate level-mediated via cortical 5-HT_{2A} receptors [111]. Furthermore, Miliano et al [112] demonstrated that administration of 25I-NBOMe may affect DA transmission in the nucleus accumbens (NAc) shell in rodents. Conversely, the chronic rats' administration of the highly selective 5-HT2A receptor agonist 2-(4-Bromo-2,5-dimethoxyphenyl)-N-(2-methoxybenzyl)etanoamine (25B-NBOMe) has been found to be associated with development of tolerance in both neurotransmitters release and hallucinogenic activity [113].

Psychedelic compounds also interact with other receptors/transporters, including vesicular monoamine transporter 2 (VMAT2), sigma-1 receptors, SERT, and TAAR. Notably, mescaline's hallucinogenic potency is comparatively lower, while LSD stands out with the highest potency [22].

Activation of 5-HT2AR plays a pivotal role in inducing visual hallucinations, 'mystical' subjective states, out-of-body experiences (OBEs), and the modulation of fear circuits. Notably, hallucinogenic experiences induced by these substances tend to be 'dream-like,' with individuals retaining insight ('meta-awareness') that they are hallucinating. This insight stands in contrast to dopaminergic hallucinations, where such awareness is lost [109]. The selective 5-HT2AR inverse agonist, pimavanserin, has been considered for the treatment of specific perceptual disturbances [109]. Moreover, the role of 5-HT2AR in the antidepressant-like effects of psychedelics has been debated. Qu et al. [114] demonstrated that the rapid antidepressant-like effects of lisuride, a non-hallucinogenic psychedelic analogue with 5-HT2AR and 5-HT1AR agonism, were not associated with 5-HT2AR-related psychedelic effects.

Serotonin receptors, in particular, 5-HT2A, play a pivotal role in mediating the effects of psychedelics by activating distinct signal transduction pathways within neurons. This cascade results in changes in gene expression, neural plasticity through synapse and dendrite remodeling, and alterations in spiking dynamics. At the network level, these effects manifest as shifts in regional activation and functional connectivity, often involving central hubs like the default-mode network [115,116].

Bedford et al. [117] employed regression dynamic causal modeling (rDCM) during resting-state functional magnetic resonance imaging (fMRI) to investigate the neural mechanisms of LSD. They analyzed data from randomized, double-blind, placebo-controlled trials involving 45 participants who received 100 µg LSD and placebo in two resting-state fMRI sessions. The results indicated enhanced interregional connectivity and reduced self-inhibition under LSD, implying a perturbation of the brain's excitation/inhibition balance.

Finally, microglia, the resident immune cells of the CNS, play a pivotal role in regulating neuroplasticity and the brain's inflammatory environment. VanderZwaag et al. [118] revealed that psychedelics like psilocybin, LSD, ketamine, and propofol modulate microglial phagocytic activity and the release of inflammatory mediators through pathways involving sigma-1 receptors, serotonergic and γ-aminobutyric acid signaling, and tryptophan metabolism. Moreover, serotonin, apart from its neurotransmitter role, serves as a hormone with vasoconstrictor, pro-inflammatory, and pro-nociceptive actions in various peripheral organs, tissues, and cells [119].

4.4. Psychedelics; tryptamines, LSD and lysergamides

Tryptamines feature an indole structure, with a benzene ring fused to a pyrrole ring along with an ethylamine chain at the C3 position. Variations in the ethylamine chain, such as methyl groups and functional groups at other positions, yield compounds like psilocybin, psilocin (the active metabolite of psilocybin), DMT, 5-MeO-DMT, 5-MeO-AMT, 5-MeO-DALT, 4-HO-DALT, 5-MeO-DIPT and 5-MeO-DMT, 4-AcO-MET (4-acetoxy-N-methyl-N-ethyltryptamine) and many others which have appeared on the drug scene over the last few years [120].

Some tryptamines are found in nature, e.g. Delosperma species plants (containing dimethyltryptamine/DMT; 5-MeO-DMT); hallucinogenic fungi (psilocin; 4-OH-DMT) and amphibians (bufotenin) [69]. Mescaline is a phenethylamine alkaloid from the Mexican peyote cactus, whilst psilocybin is derived from varieties of the fungus *Psilocybe* ('magic mushrooms') that grow in many countries. Experiences with mescaline and psilocybin are similar.

Tryptamines generally undergo metabolism by monoamine oxidase (MAO) enzymes, necessitating methods such as sniffing, smoking, or injection for enhancing their bioavailability. Conversely, when ingested orally, DMT's effects are enhanced by MAO inhibitors, and this is the case of Ayahuasca. This is a concoction made with the contribution of both the DMT-containing Psychotria viridis and Banisteriopsis caapi, rich in the MAO-inhibitors' harmala alkaloids [121,122]. The primary clinical outcomes associated with tryptamines include visual

hallucinations, changes in sensory perception, distortion of one's body image, feelings of depersonalization, pronounced fluctuations in mood, and the presence of anxiety or panic. Adverse effects may encompass agitation, tachyarrhythmia, and significant rise in body temperature. Winstock et al. [123] analyzed data collected from the Global Drug Survey, an anonymous online questionnaire administered between November and December 2012, which received 22,289 responses. The lifetime prevalence of DMT usage was 8.9% ($n = 1980$), with a past-year prevalence of 5.0% ($n = 1123$). DMT was most commonly administered via smoking and induced a potent, brief, and highly psychedelic experience, with relatively few adverse effects or a noticeable 'come down.' Notably, it attracted a higher percentage of new users compared to other psychedelics. Presently, tryptamine derivatives continue to emerge on the online drug market as NPS [107].

Ergolines, exemplified by the semi-synthetic compound LSD, are derived from the ergot fungus and subsequently subjected to chemical refinement. An effective LSD oral dose typically amounts to approximately 30 µg, and its half-life (t1/2) stands at around 3 hours. Tachyphylaxis, characterized by acute tolerance, can develop in response to LSD use [78]. Recent analogues of LSD include 1-propionyl-D-lysergic acid diethylamide hemitartrate (1P-LSD), D-lysergic acid amide (LSA, also known as 'Morning Glory seeds'), and 1-acetyl-N, N-diethyllysergamide (ALD-52, often referred to as 'Orange Sunshine Acid') [69]. Additional lysergamides introduced more recently encompass 1cP-AL-LAD, which has been identified in recreational 'blotter' samples available online [124]; N, N-diethyl-1-propanoyl-6-(prop-2-en-1-yl)-9,10-didehydroergoline-8β-carboxamide (1P-AL-LAD), a compound that converts to AL-LAD [125]; 1-Valeroyl-LSD (also known as 1-valeryl-LSD, 1-pentanoyl-LSD, 1 V-LSD, or 'Valerie'), potentially serving as an analogue of ALD-52, 1P-LSD, and 1B-LSD, and potentially hydrolyzing to LSD as a prodrug [126]; 1-butanoyl-LSD (1B-LSD), a constitutional isomer of 1-propanoyl-6-ethyl-6-nor-lysergic acid diethylamide (1P-ETH-LAD) that could serve as a prodrug for LSD [127]; lysergic acid morpholide (LSM-775), which may yield mild LSD-like effects [128]; N6-allyl-6-norlysergic acid diethylamide (AL-LAD) and (2'S,4'S)-lysergic acid 2,4-dimethylazetidide (LSZ), both exhibiting comparable potency to LSD [129]; and ETH-LAD and 1P-ETH-LAD, the latter of which might function as a prodrug [130].

These compounds induce hallucinations or illusions, where perception is disrupted and individuals seem to perceive sights, sounds, or odors that are not actually present [69,78]. Responses to these drugs can vary significantly based on expectations, existing mental state, personality, and environment (e.g. 'set and setting'). Preparing individuals can influence the likelihood of a positive 'trip' versus a negative experience. Visual distortions and changes in object shapes and significance can occur. Auditory acuity can heighten, while time perception may become distorted, slowing down, or accelerating. The user might experience relaxation, elation, fear, or depression. Depersonalization and dream-like states might also manifest. The effects generally last for a few hours, contingent on the dose, followed by intervals of normality that extend progressively [78].

Somatic symptoms and signs encompass nausea, dizziness, paresthesias, weakness, drowsiness, tremors, dilated pupils, and ataxia. Effects on the cardiovascular and respiratory systems tend to fluctuate and likely correlate with varying levels of anxiety. Long-term effects could include the development of hallucinogen-persisting perception disorder (HPPD) [131].

4.5. Atypical psychedelics: dissociatives

The hallucinogenic effects attributed to PCP-like substances (such as ketamine, methoxetamine, and various others) are linked to their antagonistic activity on central NMDA receptors, agonism of 5-HT2A receptors, and strong affinity for mu/delta/sigma opioid receptors [69]. Notable subjective effects, often referred to as the 'K-hole' [132] encompass a sense of dissociation from both one's surroundings and one's own body, accompanied by auditory and visual hallucinations, unusual thought patterns, euphoria, and visual distortions [81]. These experiences are accompanied by certain associated risks, including potential trauma, incidents of drowning, hypothermia-related fatalities, traffic accidents, and notable urinary dysfunction issues [81].

4.6. Phencyclidine (PCP)

Phencyclidine (PCP), commonly known as 'angel dust,' induces analgesia in humans without rendering them unconscious but with inducing amnesia, a phenomenon termed dissociative anesthesia. Its pharmacological action involves acting as an antagonist on NMDA glutamate receptors. PCP can be insufflated in the form of a dry powder or smoked, with cigarettes sometimes dipped in a solution of phencyclidine dissolved in an organic solvent. An overdose of phencyclidine can trigger agitation, intense emotional releases, hallucinations, and psychosis. In severe cases, it can lead to seizures, coma, hyperthermia, muscular rigidity, and rhabdomyolysis (for an overview, see [69]).

4.7. Ketamine

Ketamine (often referred to as K or special K) produces effects comparable to those of phencyclidine. It is utilized as a brief-acting general anesthetic and can be administered through injection as a liquid, inhalation as a powder, or ingestion as a tablet. Functioning as an NMDA antagonist, it induces perceptual shifts and hallucinations akin to those caused by LSD. Additionally, it elicits dissociative analgesia, which poses a risk of significant harm. Inhalation of vomit can lead to nausea, vomiting, and even fatality. Ketamine has also been exploited as a substance for date rape. Mounting evidence indicates its potential to cause severe, lasting bladder damage [133].

Recent ketamine-like substances emerging from the NPS market include N-Ethyl-1,2-diphenylethanamine (ephenidine), a diarylethylamine that has gained popularity among recreational users seeking dissociative hallucinogenic effects [134]. Another example is 2-oxo-PCE, associated with a cluster of acute intoxications characterized by impaired consciousness (84%), confusion (60%), abnormal behavior (44%), hypertension (80%), tachycardia (40%), and seizures (16%) [135]. Additionally,

[2-(2-fluorophenyl)-2-(ethylamino)cyclohexan-1-one (2F-NENDCK)] has also emerged as a ketamine-like drug [136].

4.8. Methoxetamine (MXE)

Methoxetamine (MXE), a dissociative substance belonging to the arylcyclohexylamine class, has been present on the designer drug market as a substitute for ketamine since 2010 [137]. Costa et al [138] were the first to provide a detailed characterization of the neurotoxic effects of methoxetamine in different brain regions in an experimental model; they found that repeated administration of MXE may be associated with persisting behavioral idiosyncrasies and neurotoxicity in rats.

Marti et al. [139] indicated that MXE shares ketamine-like discriminative and positive rewarding effects in rats, influences brain processes related to cognition and emotional responses, and could be linked to neurological, sensorimotor, and cardiorespiratory alterations in mice. In vivo microdialysis study revealed that a single intravenous administration of MXE significantly impacted serotonin levels in the rat medial prefrontal cortex and nucleus accumbens. In vitro electrophysiological investigations also suggested the involvement of the GABAergic and glutamatergic systems in the central effects of MXE.

5. Discussion

This review offers an updated exploration of the pharmacological effects associated with various novel recreational drugs, encompassing stimulants, psychedelics, and dissociatives. There is a pressing need for clinicians to stay informed about these substances, which continue to attract recreational use. Moreover, the renewed consideration of these compounds for therapeutic applications, coupled with the surge in clinical trials focusing on conditions such as depression, cluster headaches, migraines, anxiety, and obsessive-compulsive disorder, underscores the importance of comprehending the pharmacodynamics of these drugs [95].

In essence, the actions of these drugs are centered on perturbations within diverse neurotransmitter pathways and receptors. This includes a) elevation of central dopamine levels, a hallmark of many of these substances such as novel psychedelic phenethylamines, synthetic cathinones, and other new stimulants; b) activation of various subtypes of 5-HT receptors, observed with novel psychedelic phenethylamines, recent tryptamine and lysergamide derivatives, as well as hallucinogenic plants and fungi; and c) antagonistic effects on NMDA receptors, characteristic of phencyclidine-like dissociatives [63].

5.1. Coping with a range of 'unknown,' drug-related, clinical and toxicity issues

Given the likely abundance of some 4,300 NPS (as indicated by Schifano et al [64], it proves challenging for both medical professionals in Accident and Emergency Departments and mental health practitioners to remain well-informed about the continuously expanding repertoire of NPS entering the dynamic drug landscape. This emerging trend raises legitimate concerns.

Traditional toxicology assessments can merely detect a limited subset of abused substances, and the comprehensive identification of the extensive array of NPS necessitates costly and time-consuming screening procedures conducted within specialized facilities [63,64,74]. Conversely, the utilization patterns of these NPS often involve sporadic use, and potential somatic and mental side effects may act as deterrents against the establishment of addictive consumption habits; in many instances; because of the pronounced toxicity exhibited by specific psychedelic NPS, such as the NBOMes [22,99]; and overall hallucinogens' limited abuse liability levels [140], individuals may be engaging in experimental use only [141]

Furthermore, the pharmacodynamic of psychedelics can elicit phenomena congruent with their effects. This includes the induction of paranoid and elaborate systematic delusions, shifts in mood toward hypomanic states, as well as episodes of suicidal ideation and depressive states [96]. In a study conducted by Martinotti et al [142] involving 110 inpatients, a substantial majority (70%) acknowledged the use of multiple substances, with a third (33%) reporting the use of more than two substances. Among these, 44 individuals (40%) were stimulant users, and 49 (45%) were users of psychodysleptics. Notably, a positive correlation was found with a lifetime diagnosis of bipolar disorder ($p = 0.013$).

In instances where the usage of these substances remains sporadic, any ensuing psychotic features tend to be reversible. However, when consumption becomes more frequent and involves higher doses, there is a heightened risk of developing enduring psychotic disorders [69]. Addressing this matter, Martinotti et al. [143] conducted an examination of the prevalence of prolonged psychiatric symptoms among individuals who reported substance use in Ibiza nightclubs. Of the 10,163 subjects seeking medical assistance within the club's medical-nursing facilities, 223 necessitated transfers to hospital emergency rooms. Among these, 110 individuals eventually required psychiatric hospitalization. A notable majority of these patients (82.7%) had a history of previous mental health issue. For individuals without a positive psychiatric history, the odds of requiring hospitalization changed by a factor of 0.076. Once again, it appeared from here that the use of club drugs could potentially induce psychiatric consequences necessitating hospitalization, particularly in individuals who already exhibit vulnerability.

Emerging psychedelic substances might exhibit considerable levels of toxicity [22], thereby rendering their consumption inherently unsafe [78]. Beyond the acute medical and psychopathological effects associated with psychedelics, recreational usage of certain molecules has, on numerous occasions, resulted in near misses and fatalities, even after prompt medical intervention [22]. Of particular note are incidents linked to substances like NBOMes, synthetic tryptamines (such as alpha-methyltryptamine and 'Foxy' – 5-methoxy-N, N-diisopropyltryptamine), bromo-dragonFLY, and 2,5-dimethoxy-4-bromoamphetamine (DOB) [69,144,145].

6. Conclusions

Healthcare professionals should receive ongoing education regarding various NPS, including their methods of consumption, desired psychoactive effects, unique combinations with

other drugs, as well as the medical, psychobiological, and psychopathological risks associated with them. Indeed, in line with Martinotti et al [142], future research should prioritize gaining a deeper comprehension of the psychopathological impacts associated with particular substances, defining specific signs and symptoms to aid in distinguishing diagnoses, and conducting prospective investigations into their long-term effects. To enhance precision and conduct a comprehensive examination of NPS pharmacology, our current research endeavors involve an integrative approach. This approach combines web-based analyses with more advanced research methods, including ongoing quantitative structure-activity relationship (QSAR) studies, molecular docking, and in silico investigations. These investigations aim to yield valuable insights regarding which NPS within specific categories (e.g. emerging stimulants or contemporary psychedelics) exhibit greater receptor affinities, potentially indicating higher clinical potency. Data gathered from selected molecules will subsequently inform the design of additional in vitro and in vivo/preclinical studies.

7. Expert opinion

Several noteworthy observations have surfaced in this paper, which may be of considerable interest to the reader when juxtaposed with findings from just approximately five years ago. These observations include:

a. The substantial increase in the availability of recreational psychedelics and stimulants within the recent time-frame;
b. The notable proliferation of research publications over the same period, focusing on the investigation of stimulants and psychedelics for various medical and psychopathological conditions.

From both clinical and psychopharmacological perspectives, these two phenomena (e.g. a and b) appear to be heading in distinct directions. As a result, it may be pertinent to first discuss each of these aspects separately before attempting to arrive at reasoned conclusions that can shed light on these differing trends.

7.1. Stimulant and psychedelics as recreational drugs of abuse

The recent study by Catalani et al. [99] has indicated that the number of psychedelic new psychoactive substances (NPS) identified through a web-based search conducted between 2017 and 2020 may amount to approximately 1350 different molecules. Moreover, this same research group has identified approximately 950 of these compounds as potential novel psychedelics, which are currently under discussion and, arguably, accessible to drug enthusiasts. Consequently, it is reasonable to conclude that this particular segment of the recreational drug market holds significant appeal for consumers who continually seek unique and uncharted hallucinogenic experiences.

However, as discussed here, this situation raises genuine concerns from both medical and psychopathological perspectives. For the vast majority of these substances, there is a lack of fundamental knowledge encompassing basic, pre-clinical, and clinical pharmacology, including acute treatment and management approaches. Additionally, there are evident apprehensions regarding the effectiveness of toxicological drug screening tests, as psychedelics and most stimulants are not typically detectable in acute treatment settings.

7.2. Stimulant and psychedelics as therapeutic psychopharmacological agents

Concurrently with the notable increase in the use of certain psychedelics and stimulants by recreational users, there has been a significant discussion surrounding the therapeutic potential of drugs belonging to these same classes. Following almost five decades of legal restrictions against their utilization, psychedelics have garnered attention from researchers seeking alternative treatments, primarily for neuropsychiatric conditions [146] and pain-related disorders [147]. Psilocybin, for instance, is currently being investigated for its potential benefits in treating treatment-resistant depression [148], while the use of dissociative psychedelic substances like ketamine and esketamine has expanded treatment options for depressive disorders [149]. Moreover, Sarmanlu et al. [150] have emphasized the resurgence of clinical, scientific, and public interest in treating posttraumatic stress disorder (PTSD) with the assistance of classical psychedelic phenethylamines, such as MDMA.

Despite the resurgence of interest in psychedelic compounds, heralded as a significant development in the field of psychiatry in recent decades, several clinical, pharmacological, and methodological challenges remain in the early stages of exploration (for a comprehensive examination of this matter, refer to Munafo' et al. [151]). Indeed, it is essential to critically assess the efficacy, safety, and tolerability data from published trials within the context of their inherent methodological limitations.

In this context, challenges related to placebo control and maintaining the integrity of blinding are particularly intricate and unique. This complexity arises because psychedelics are associated with vivid perceptual disturbances, and these effects are only discernible in individuals who have received the active compound. Additionally, conventional practice in psychedelic, dissociative, and phenethylamine trials has typically involved the exclusion of individuals with psychiatric comorbidities and those with a history of substance misuse. From this perspective, questions arise about the therapeutic outcomes of psychedelic interventions for individuals already using 5-HT2AR-blocking antipsychotic medications like quetiapine and olanzapine. Moreover, there are concerns regarding the potential psychopathological consequences associated with single or multiple administrations of psychedelics, such as self-harm, paranoid disturbances, persistent depersonalization or derealization, excessive mood elevation, and the development of enduring hallucinogen use disorders, as extensively discussed in this paper.

7.3. ... and what will happen over the next 5 years or so?

It has become evident that the interest in stimulants and psychedelics has significantly surged in both recreational and therapeutic contexts over the past five years. Could these seemingly distinct matters be interconnected in some way? Intriguingly, it has been proposed that the perception of relative safety associated with psychedelic use [148] may have led the general public, especially vulnerable individuals, to consider self-administering either a standard dose or possibly a 'microdose' of psychedelics [151] for alleviating anxiety and mood-related concerns [91] as well as enhancing cognitive performance [23]

It is postulated here that the future of psychedelic and psychopharmacological research over the next five years should, and will, strive to employ more robust study designs. This should involve incorporating, in addition to a placebo control, an active control condition, such as a genuinely psychoactive placebo or a non-hallucinogenic yet still effective substance capable of mimicking the subjective and acute effects of the psychoactive drug being investigated. In this context, the pharmacological insights here provided regarding stimulants and psychedelics can aid in identifying the appropriate drug comparator.

While the prospect of selecting the right molecule from a pool of thousands might seem challenging, preliminary in silico investigations can offer valuable insights into which new psychoactive substances within specific categories (e.g. emerging stimulants or contemporary psychedelics) exhibit stronger receptor affinities, potentially indicating greater clinical potency. Information gathered from these selected molecules will subsequently guide the design of additional in vitro, in vivo/preclinical, and clinical studies.

Funding

This paper was not funded.

Declaration of interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer declarations

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. UNODC. 2023. The synthetic drug phenomenon. [cited 2023 Aug 2]. Available from: https://www.unodc.org/res/WDR-2023/WDR23_B3_CH1_Synthetic_drugs.pdf
2. Corkery JM, Orsolini L, Papanti D, et al. From concept(ion) to life after death/the grave: the 'natural' history and life cycle(s) of novel psychoactive substances (NPS). Hum Psychopharmacol. 2017;32(3). doi: 10.1002/hup.2566
3. Guirguis A, Corkery JM, Stair JL, et al. Intended and unintended use of cathinone mixtures. Hum Psychopharmacol. 2017;32(3). doi: 10.1002/hup.2598
4. EMCDDA. Methylphenidate. European monitoring centre for drugs and drug addiction, EU drug market: methamphetamine. LU: Publications Office. 2022 [cited 2023 Aug 2]. Available from: https://www.emcdda.europa.eu/publications/eu-drug-markets/methamphetamine_en
5. UNODC. 2022. Afghanistan's 'tablet K' – a Forensic insight into an emerging synthetic drug market. Global SMART Update (Vienna, Austria). [cited 2023 Aug 2]. Available from: https://www.unodc.org/LSS/announcement/Details/66069555-1009-4f55-8a33-f992ea49fbc4
6. Mohaddes Ardabili H, Akbari A, Rafei P, et al. Tramadol, captagon and khat use in the Eastern Mediterranean Region: opening Pandora's box. BJPsych Int. 2022;19(3):58–62. doi: 10.1192/bji.2021.53
7. INCB. 2022. Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances. [cited 2023 Aug 2]. Available from: https://www.incb.org/incb/en/precursors/technical_reports/precursors-technical-reports.html
8. Di Chiara G. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. Behav Brain Res. 2022;137(1–2):75–114. doi: 10.1016/S0166-4328(02)00286-3
9. Weinstein AM. Reward, motivation and brain imaging in human healthy participants - a narrative review. Front Behav Neurosci. 2023;17:1123733. doi: 10.3389/fnbeh.2023.1123733
10. Li X, Zheng Y, Zhao X, et al. Relationship between the role of muscarinic M_3 receptors in morphine-induced conditioned place preference and the mesolimbic dopamine system. Neurosci Lett. 2022;786:136774. doi: 10.1016/j.neulet.2022.136774
11. Hosseinzadeh Sahafi O, Sardari M, Alijanpour S, et al. Shared mechanisms of GABAergic and opioidergic transmission regulate corticolimbic reward systems and cognitive aspects of motivational behaviors. Brain Sci. 2023;13(5):815. doi: 10.3390/brainsci13050815
12. Mattioni J, Vansteene C, Poupon D, et al. Associated and intermediate factors between genetic variants of the dopaminergic D2 receptor gene and harmful alcohol use in young adults. Addict Biol. 2023;28(3):e13269. doi: 10.1111/adb.13269
13. Butler K, Le Foll B, Di Ciano P. The role of dopamine D3 receptors in tobacco use disorder: a synthesis of the preclinical and clinical literature. Curr Top Behav Neurosci. 2023;60:203–228.
14. Ferré S, Belcher AM, Bonaventura J, et al. Functional and pharmacological role of the dopamine D_4 receptor and its polymorphic variants. Front Endocrinol. 2022;13:1014678. doi: 10.3389/fendo.2022.1014678
15. McMahon C. Substance use disorder in adults with ADHD in South Dakota. S D Med. 2023;76(9):398.
16. Courtney KE, Ray LA. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. Drug Alcohol Depend. 2014;143:11–21. doi: 10.1016/j.drugalcdep.2014.08.003
17. Livermore JJ, Holmes CL, Cutler J, et al. Selective effects of serotonin on choices to gather more information. J Psychopharmacol. 2021;35(6):631–640. doi: 10.1177/0269881121991571
18. Barnes NM, Ahern GP, Becamel C, et al. International Union of basic and clinical pharmacology. CX. Classification of receptors for 5-hydroxytryptamine; pharmacology and function. Pharmacol Rev. 2021;73(1):310–520. doi: 10.1124/pr.118.015552
19. Jastrzębska J, Frankowska M, Smaga I, et al. Evaluation of the 5-HT_{2C} receptor drugs RO 60-0175, WAY 161503 and mirtazapine in a preclinical model of comorbidity of depression and cocaine addiction. Pharmacol Rep. 2023;75(1):99–118. doi: 10.1007/s43440-022-00428-2
20. Baumeister D, Tojo LM, Tracy DK. Legal highs: staying on top of the flood of novel psychoactive substances. Ther Adv Psychopharmacol. 2015;5(2):97–132. doi: 10.1177/2045125314559539
    - **This is a valuable overview of the NPS, enriched by a range of pharmacological and clinical pharmacological issues discussion.**
21. Holze F, Erne L, Duthaler U, et al. Pharmacokinetics, pharmacodynamics and urinary recovery of oral lysergic acid diethylamide

(LSD) administration in healthy participants. Br J Clin Pharmacol. 2023 Aug;18. doi: 10.1111/bcp.15887
22. Luethi D, Liechti ME. Designer drugs: mechanism of action and adverse effects. Arch Toxicol. 2020;94(4):1085–1133. doi: 10.1007/s00204-020-02693-7
•• **This is a seminal paper, providing the reader with a vast range of clinical pharmacological considerations relating to designer drugs/NPS.**
23. Schifano F, Catalani V, Sharif S, et al. Benefits and harms of 'smart drugs'(nootropics) in healthy individuals. Drugs. 2022;82(6):633–647. doi: 10.1007/s40265-022-01701-7
24. Pantoni MM, Carmack SA, Hammam L, et al. Dopamine and norepinephrine transporter inhibition for long-term fear memory enhancement. Behav Brain Res. 2020;378:112266. doi: 10.1016/j.bbr.2019.112266
25. Campos MW, Serebrisky D, Castaldelli-Maia JM. Smoking and Cognition. Curr Drug Abuse Rev. 2016;9(2):76–79. doi: 10.2174/1874473709666160803101633
26. España RA, Schmeichel BE, Berridge CW. Norepinephrine at the nexus of arousal, motivation and relapse. Brain Res. 2016;1641(Pt B):207–216. doi: 10.1016/j.brainres.2016.01.002
27. Chen L, Huang S, Yang C, et al. Blockade of β-adrenergic receptors by propranolol disrupts reconsolidation of drug memory and attenuates heroin seeking. Front Pharmacol. 2021;12:686845. doi: 10.3389/fphar.2021.686845
28. You ZB, Galaj E, Alén F, et al. Involvement of the ghrelin system in the maintenance and reinstatement of cocaine-motivated behaviors: a role of adrenergic action at peripheral β1 receptors. Neuropsychopharmacology. 2022;47(8):1449–1460. doi: 10.1038/s41386-021-01249-2
29. Wu R, Liu J, Li JX. Trace amine-associated receptor 1 and drug abuse. Adv Pharmacol. 2022;93:373–401.
30. Ciccarone D. Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. Prim Care. 2011;38(1):41–58. doi: 10.1016/j.pop.2010.11.004
31. Paz-Ramos MI, Cruz SL, Violante-Soria V. Amphetamine-type stimulants: novel insights into their actions and use patterns. Rev Invest Clin. 2023;75(3):143–157. doi: 10.24875/RIC.23000110
32. Paulus MP, Stewart JL. Neurobiology, clinical presentation, and treatment of methamphetamine use disorder: a review. JAMA Psychiatry. 2020;77(9):959–966. doi: 10.1001/jamapsychiatry.2020.0246
33. Wee S, Woolverton WL. Self-administration of mixtures of fenfluramine and amphetamine by rhesus monkeys. Pharmacol Biochem Behav. 2006;84(2):337–343. doi: 10.1016/j.pbb.2006.05.022
34. Suyama JA, Sakloth F, Kolanos R, et al. Abuse-related Neurochemical effects of para-substituted methcathinone analogs in rats: microdialysis studies of nucleus accumbens dopamine and serotonin. J Pharmacol Exp Ther. 2016;356(1):182–190. doi: 10.1124/jpet.115.229559
35. Miliano C, Serpelloni G, Rimondo C, et al. Neuropharmacology of new psychoactive substances (NPS): focus on the rewarding and reinforcing properties of cannabimimetics and amphetamine-like stimulants. Front Neurosci. 2016;10:153. doi: 10.3389/fnins.2016.00153
36. Sitte HH, Freissmuth M. Amphetamines, new psychoactive drugs and the monoamine transporter cycle. Trends Pharmacol Sci. 2015;36(1):41–50. doi: 10.1016/j.tips.2014.11.006
37. Simmler LD, Buchy D, Chaboz S, et al. In vitro characterization of psychoactive substances at rat, mouse, and human trace amine-associated receptor 1. J Pharmacol Exp Ther. 2016;357(1):134–144. doi: 10.1124/jpet.115.229765
38. Cadet JL, Krasnova IN. Molecular bases of methamphetamine-induced neurodegeneration. Int Rev Neurobiol. 2009;88:101–119.
39. Panenka WJ, Procyshyn RM, Lecomte T, et al. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Depend. 2013;129(3):167–179. doi: 10.1016/j.drugalcdep.2012.11.016
40. Yang X, Wang Y, Li Q, et al. The main molecular mechanisms underlying methamphetamine- induced neurotoxicity and implications for pharmacological treatment. Front Mol Neurosci. 2018;11:186. doi: 10.3389/fnmol.2018.00186
41. Rudin D, Liechti ME, Luethi D. Molecular and clinical aspects of potential neurotoxicity induced by new psychoactive stimulants and psychedelics. Exp Neurol. 2021;343:113778. doi: 10.1016/j.expneurol.2021.113778
42. Jayanthi S, Daiwile AP, Cadet JL. Neurotoxicity of methamphetamine: main effects and mechanisms. Exp Neurol. 2021;344:113795. doi: 10.1016/j.expneurol.2021.113795
43. Lappin JM, Darke S. Methamphetamine and heightened risk for early-onset stroke and Parkinson's disease: a review. Exp Neurol. 2021;343:113793. doi: 10.1016/j.expneurol.2021.113793
44. Kish SJ, Boileau I, Callaghan RC, et al. Brain dopamine neurone 'damage': methamphetamine users vs. Parkinson's disease - a critical assessment of the evidence. Eur J Neurosci. 2017;45:58–66. doi: 10.1111/ejn.13363
45. Schifano F, Di Furia L, Forza G, et al. MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients. Drug Alcohol Depend. 1998;52(1):85–90. doi: 10.1016/S0376-8716(98)00051-9
46. Volkow ND, Chang L, Wang GJ, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. Am J Psychiatry. 2001;158(3):377–382. doi: 10.1176/appi.ajp.158.3.377
47. Sekine Y, Ouchi Y, Sugihara G, et al. Methamphetamine causes microglial activation in the brains of human abusers. J Neurosci. 2008;28(22):5756–5761. doi: 10.1523/JNEUROSCI.1179-08.2008
48. Hall MG, Alhassoon OM, Stern MJ, et al. Gray matter abnormalities in cocaine versus methamphetamine-dependent patients: a neuroimaging meta-analysis. Am J Drug Alcohol Abuse. 2015;41(4):290–299. doi: 10.3109/00952990.2015.1044607
49. Schifano F. A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities. Psychopharmacol (Berl). 2004;173(3–4):242–248. doi: 10.1007/s00213-003-1730-5
50. Górska AM, Kamińska K, Wawrzczak-Bargieła A, et al. Neurochemical and neurotoxic effects of MDMA (ecstasy) and caffeine after chronic combined administration in mice. Neurotox Res. 2018;33(3):532–548. doi: 10.1007/s12640-017-9831-9
51. Ciccarone D, Shoptaw S. Understanding stimulant use and use disorders in a new era. Med Clin North Am. 2022;106(1):81–97. doi: 10.1016/j.mcna.2021.08.010
52. Kevil CG, Goeders NE, Woolard MD, et al. Methamphetamine use and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2019;39(9):1739–1746. doi: 10.1161/ATVBAHA.119.312461
53. Callaghan RC, Cunningham JK, Sykes J, et al. Increased risk of Parkinson's disease in individuals hospitalized with conditions related to the use of methamphetamine or other amphetamine-type drugs. Drug Alcohol Depend. 2012;120(1–3):35–40. doi: 10.1016/j.drugalcdep.2011.06.013
54. Leyrer-Jackson JM, Nagy EK, Olive MF. Cognitive deficits and neurotoxicity induced by synthetic cathinones: is there a role for neuroinflammation? Psychopharmacol (Berl). 2019;236(3):1079–1095. doi: 10.1007/s00213-018-5067-5
55. Lappin JM, Sara GE. Psychostimulant use and the brain. Addiction. 2019;114(11):2065–2077. doi: 10.1111/add.14708
56. Voce A, Calabria B, Burns R, et al. A systematic review of the symptom profile and course of methamphetamine-associated psychosis. Subst Use Misuse. 2019;54(4):549–559. doi: 10.1080/10826084.2018.1521430
57. Götrick B, Giglio D, Tobin G. Effects of amphetamine on salivary secretion. Eur J Oral Sci. 2009;117(3):218–223. doi: 10.1111/j.1600-0722.2009.00629.x
58. Rusyniak DE. Neurologic manifestations of chronic methamphetamine abuse. Psychiatr Clin North Am. 2013;36(2):261–275. doi: 10.1016/j.psc.2013.02.005
59. Glick SN, Burt R, Kummer K, et al. Increasing methamphetamine injection among non-MSM who inject drugs in King County, Washington. Drug Alcohol Depend. 2018;182:86–92. doi: 10.1016/j.drugalcdep.2017.10.011

60. Ellis MS, Kasper ZA, Cicero TJ. Twin epidemics: the surging rise of methamphetamine use in chronic opioid users. Drug Alcohol Depend. 2018;193:14–20. doi: 10.1016/j.drugalcdep.2018.08.029
61. Hedegaard H, Miniño AM, Warner M. Co-involvement of opioids in drug overdose deaths involving cocaine and psychostimulants. NCHS Data Brief. 2021;406:1–8.
62. Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. Curr Opin Psychiatry. 2021;34(4):344–350. doi: 10.1097/YCO.0000000000000717
63. Schifano F, Chiappini S, Corkery JM, et al. The e-psychonaut drugs' psychopharmacology. Curr Opin Pharmacol. 2021;57:165–174. doi: 10.1016/j.coph.2021.02.008
64. Schifano F, Napoletano F, Chiappini S, et al. New/Emerging psychoactive substances and associated psychopathological consequences. Psychol Med. 2021;51(1):30–42. doi: 10.1017/S0033291719001727
65. Abdulrahim D, Bowden-Jones O. On behalf of the NEPTUNE Expert group. Guidance on the management of acute and chronic harms of club drugs and novel psychoactive substances . In Novel Psychoactive Treatment UK Network (NEPTUNE). London: Public Health England; 2015. p. 1–335.
•• **This an excellent and extensive overview of the vast range of NPS; aimed at clinicians working in the field.**
66. Shafi A, Berry AJ, Sumnall H, et al. New psychoactive substances: a review and updates. Ther Adv Psychopharmacol. 2020;10:2045125320967197. doi: 10.1177/2045125320967197
67. Parrott AC. Human psychobiology of MDMA or 'ecstasy': an overview of 25 years of empirical research. Hum Psychopharmacol. 2013;28(4):289–307. doi: 10.1002/hup.2318
68. Docherty JR, Alsufyani HA. Cardiovascular and temperature adverse actions of stimulants. Br J Pharmacol. 2021;178(13):2551–2568. doi: 10.1111/bph.15465
69. Schifano F, Orsolini L, Duccio Papanti G, et al. Novel psychoactive substances of interest for psychiatry. World Psychiatry. 2015;14(1):15–26. doi: 10.1002/wps.20174
•• **This is a highly quoted paper offering an overview of the different range of NPS, with both a clinical pharmacological and a psychopathological perspective.**
70. Nash JF, Nichols DE. Microdialysis studies on 3,4-methylenedioxyamphetamine and structurally related analogues. Eur J Pharmacol. 1991;200(1):53–58. doi: 10.1016/0014-2999(91)90664-C
71. Głowacka K, Wiela-Hojeńska A. Pseudoephedrine-Benefits and Risks. Int J Mol Sci. 2021;22(10):5146. doi: 10.3390/ijms22105146
72. Trinh KV, Kim J, Ritsma A. Effect of pseudoephedrine in sport: a systematic review. BMJ Open Sport Exerc Med. 2015;1(1):e000066. doi: 10.1136/bmjsem-2015-000066
73. Gheorghiev MD, Hosseini F, Moran J, et al. Effects of pseudoephedrine on parameters affecting exercise performance: a meta-analysis. Sports Med - Open. 2018;4(1):44. doi: 10.1186/s40798-018-0159-7
74. Schifano F, Chiappini S, Miuli A, et al. Focus on over-the-counter drugs' misuse: a systematic review on antihistamines, cough medicines, and decongestants. Front Psychiatry. 2021;12:657397. doi: 10.3389/fpsyt.2021.657397
75. Schifano F, Napoletano F, Arillotta D, et al. The clinical challenges of synthetic cathinones. Br J Clin Pharmacol. 2020;86(3):410–419. doi: 10.1111/bcp.14132
76. Varlibas F, Delipoyraz I, Yuksel G, et al. Neurotoxicity following chronic intravenous use of "Russian cocktail". Clin Toxicol (Phila). 2009;47(2):157–160. doi: 10.1080/15563650802010388
77. Simmler LD, Wandeler R, Liechti ME. Bupropion, methylphenidate, and 3,4-methylenedioxypyrovalerone antagonize methamphetamine-induced efflux of dopamine according to their potencies as dopamine uptake inhibitors: implications for the treatment of methamphetamine dependence. BMC Res Notes. 2013;6(1):220. doi: 10.1186/1756-0500-6-220
78. Schifano F, Papanti GD, Orsolini L, et al. Novel psychoactive substances: the pharmacology of stimulants and hallucinogens. Expert Rev Clin Pharmacol. 2016;9(7):943–954. doi: 10.1586/17512433.2016.1167597
79. Altun B, İ Ç. Psychoactive bath salts and neurotoxicity risk. Turk J Pharm Sci. 2020;17(2):235–241. doi: 10.4274/tjps.galenos.2018.40820
80. Schifano F, Albanese A, Fergus S, et al. Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. Psychopharmacol (Berl). 2011;214(3):593–602. doi: 10.1007/s00213-010-2070-x
81. Corkery JM, Hung WC, Claridge H, et al. Recreational ketamine-related deaths notified to the national programme on substance abuse deaths, England, 1997-2019. J Psychopharmacol. 2021;35(11):1324–1348. doi: 10.1177/02698811211021588
• **This paper is illustrating what it is likely to be the largest database of ketamine-related fatalities.**
82. Simmler LD, Rickli A, Schramm Y, et al. Pharmacological profiles of aminoindanes, piperazines, and pipradrol derivatives. Biochem Pharmacol. 2014;88(2):237–244. doi: 10.1016/j.bcp.2014.01.024
83. Yu WJ, Cottler L, Li JH. New psychoactive substances in Taiwan: the current situation and initiative for rational scheduling. J Food Drug Anal. 2021;29(1):168–181. doi: 10.38212/2224-6614.3225
84. Roque Bravo R, Carmo H, Carvalho F, et al. Benzo fury: A new trend in the drug misuse scene. J Appl Toxicol. 2019;39(8):1083–1095. doi: 10.1002/jat.3774
85. Iversen L, White M, Treble R. Designer psychostimulants: pharmacology and differences. Neuropharmacology. 2014;87:59–65. doi: 10.1016/j.neuropharm.2014.01.015
86. King LA. New phenethylamines in Europe. Drug Test Anal. 2014;6(7–8):808–818. doi: 10.1002/dta.1570
87. Gallagher CT, Assi S, Stair JL, et al. 5,6-methylenedioxy-2-aminoindane: from laboratory curiosity to 'legal high'. Hum Psychopharmacol Clin Exp. 2012;27(2):106–112. doi: 10.1002/hup.1255
88. Maier J, Mayer FP, Brandt SD, et al. DARK classics in chemical neuroscience: aminorex analogues. ACS Chem Neurosci. 2018;9(10):2484–2502. doi: 10.1021/acschemneuro.8b00415
89. Loi B, Zloh M, De Luca MA, et al. 4,4'-Dimethylaminorex ("4,4'-DMAR"; "Serotoni") misuse: a web-based study. Hum Psychopharmacol. 2017;32(3). doi: 10.1002/hup.2575
90. Benesch MGK, Iqbal SJ. Novel psychoactive substances: overdose of 3-fluorophenmetrazine (3-FPM) and etizolam in a 33-year-old man. BMJ Case Rep. 2018;2018:bcr2018224995. doi: 10.1136/bcr-2018-224995
91. Holborn T, Schifano F, Deluca P. No prescription? No problem: a qualitative study investigating self-medication with novel psychoactive substances (NPS). Int J Drug Policy. 2023;118:104109.
• **This is a paper illustrating a range of NPS being perceived as 'therapeutics' by a range of drug enthusiasts.**
92. Mayer FP, Burchardt NV, Decker AM, et al. Fluorinated phenmetrazine "legal highs" act as substrates for high-affinity monoamine transporters of the SLC6 family. Neuropharmacology. 2018;134(Pt A):149–157. doi: 10.1016/j.neuropharm.2017.10.006
93. Carlier J, Giorgetti R, Varì MR, et al. Use of cognitive enhancers: methylphenidate and analogs. Eur Rev Med Pharmacol Sci. 2019;23(1):3–15. doi: 10.26355/eurrev_201901_16741
94. Baca NE. La ciencia psicodélica del siglo XXI [21st Century Psychedelic Science]. Vertex Rev Arg Psiquiatr. 2023;34(160):79–86. doi: 10.53680/vertex.v34i160.461
95. Roth BL, Gumpper RH. Psychedelics as transformative therapeutics. Am J Psychiatry. 2023;180(5):340–347. doi: 10.1176/appi.ajp.20230172
• **This is a paper illustrating the potential of psychedelics in psychiatry.**
96. Martinotti G, Santacroce R, Pettorruso M, et al. Hallucinogen persisting perception disorder: etiology, clinical features, and therapeutic perspectives. Brain Sci. 2018;8(3):47. doi: 10.3390/brainsci8030047
97. Millière R, Carhart-Harris RL, Roseman L, et al. Psychedelics, meditation, and self-consciousness. Front Psychol. 2018;9:1475. doi: 10.3389/fpsyg.2018.01475

98. Nichols DE. Dark classics in chemical neuroscience: lysergic acid diethylamide (LSD). ACS Chem Neurosci. 2018;9(10):2331–2343. doi: 10.1021/acschemneuro.8b00043
99. Catalani V, Corkery JM, Guirguis A, et al. Psychonauts' psychedelics: a systematic, multilingual, web-crawling exercise. Eur Neuropsychopharmacol. 2021;49:69–92. doi: 10.1016/j.euroneuro.2021.03.006
•• **This is unique research paper, illustrating the similarities and differences of the psychedelics' identification capabilities of three different approaches, including one which relates to a web-based exercise.**
100. Henningfield JE, Ashworth J, Heal DJ, et al. Psychedelic drug abuse potential assessment for new drug applications and controlled substance scheduling: a United States perspective. J Psychopharmacol. 2023;37(1):33–44. doi: 10.1177/02698811221140004
101. López-Arnau R, Camarasa J, Carbó ML, et al. 3,4-methylenedioxy methamphetamine, synthetic cathinones and psychedelics: from recreational to novel psychotherapeutic drugs. Front Psychiatry. 2022;13:990405. doi: 10.3389/fpsyt.2022.990405
102. Solmi M, Chen C, Daure C, et al. A century of research on psychedelics: a scientometric analysis on trends and knowledge maps of hallucinogens, entactogens, entheogens and dissociative drugs. Eur Neuropsychopharmacol. 2022;64:44–60. doi: 10.1016/j.euroneuro.2022.09.004
103. Kozell LB, Eshleman AJ, Swanson TL, et al. Pharmacologic activity of substituted tryptamines at 5-Hydroxytryptamine (5-HT)$_{2A}$ Receptor (5-HT$_{2A}$R), 5-HT$_{2C}$R, 5-HT$_{1A}$R, and serotonin transporter. J Pharmacol Exp Ther. 2023;385(1):62–75. 5-HT$_{2C}$R, 5-HT$_{1A}$R.
104. Orsolini L, Papanti GD, Francesconi G, et al. Mind navigators of chemicals' experimenters? A web-based description of e-psychonauts. Cyberpsychol Behav Soc Netw. 2015;18(5):296–300. doi: 10.1089/cyber.2014.0486
• **This is likely to be one of the very first papers aimed at describing the characteristics of e-psychonauts.**
105. Deluca P, Davey Z, Corazza O, et al. Identifying emerging trends in recreational drug use; outcomes from the psychonaut web mapping project. Prog Neuropsychopharmacol Biol Psychiatry. 2012;39(2):221–226. doi: 10.1016/j.pnpbp.2012.07.011
106. Orsolini L, St John-Smith P, McQueen D, et al. Evolutionary considerations on the emerging subculture of the E-psychonauts and the novel psychoactive substances: a comeback to the Shamanism? Curr Neuropharmacol. 2017;15(5):731–737. doi: 10.2174/1570159X15666161111114838
107. Mallaroni P, Mason NL, Vinckenbosch FRJ, et al. The use patterns of novel psychedelics: experiential fingerprints of substituted phenethylamines, tryptamines and lysergamides. Psychopharmacol (Berl). 2022;239(6):1783–1796. doi: 10.1007/s00213-022-06142-4
•• **This is a unique research approach paper with a focus on the user's perspective, illustrating the similarities and differences of phenethylamines, tryptamines and lysergamides.**
108. Lea T, Amada N, Jungaberle H. Psychedelic microdosing: a subreddit analysis. J Psychoactive Drugs. 2020;52(2):101–112. doi: 10.1080/02791072.2019.1683260
• **This is a research paper illustrating the multifaceted issues associated with psychedelic microdosing whilst considering the posts of a large number of Reddit (e.g. a popular social platform) users.**
109. Jalal B. The neuropharmacology of sleep paralysis hallucinations: serotonin 2A activation and a novel therapeutic drug. Psychopharmacol (Berl). 2018;235(11):3083–3091. doi: 10.1007/s00213-018-5042-1
• **This is a fascinating report, with a focus on sleep paralysis hallucinations but providing the reader as well with a vast range of clinical considerations relating to the 5-HT involvement in perceptual disturbances.**
110. Mastinu A, Anyanwu M, Carone M, et al. The bright side of psychedelics: latest advances and challenges in neuropharmacology. Int J Mol Sci. 2023;24(2):1329. doi: 10.3390/ijms24021329
111. Herian M, Wojtas A, Kamińska K, et al. Hallucinogen-like action of the novel designer drug 25I-NBOMe and its effect on cortical neurotransmitters in rats. Neurotox Res. 2019;36(1):91–100. doi:10.1007/s12640-019-00033-x
112. Miliano C, Marti M, Pintori N, et al. Neurochemical and Behavioral Profiling in Male and Female Rats of the Psychedelic Agent 25I-NBOMe. Front Pharmacol. 2019;10:1406. doi: 10.3389/fphar.2019.01406
113. Wojtas A, Herian M, Maćkowiak M, et al. Hallucinogenic activity, neurotransmitters release, anxiolytic and neurotoxic effects in rat's brain following repeated administration of novel psychoactive compound 25B-NBOMe. Neuropharmacology. 2023;240:109713. doi: 10.1016/j.neuropharm.2023.109713
114. Qu Y, Chang L, Ma L, et al. Rapid antidepressant-like effect of non-hallucinogenic psychedelic analog lisuride, but not hallucinogenic psychedelic DOI, in lipopolysaccharide-treated mice. Pharmacol Biochem Behav. 2023;222:173500.
• **This is a thought-provoking paper, casting doubt on the fact that the antidepressant activity of psychedelics is associated with the occurrence of hallucinations.**
115. Kim K, Che T, Panova O, et al. Structure of a hallucinogen-activated Gq-Coupled 5-HT$_{2A}$ serotonin receptor. Cell. 2020;182(6):1574–1588.e19. doi: 10.1016/j.cell.2020.08.024
116. Kelmendi B, Kaye AP, Pittenger C, et al. Psychedelics. Curr Biol. 2022;32(2):R63–R67. doi: 10.1016/j.cub.2021.12.009
117. Bedford P, Hauke DJ, Wang Z, et al. The effect of lysergic acid diethylamide (LSD) on whole-brain functional and effective connectivity. Neuropsychopharmacology. 2023;48(8):1175–1183. doi: 10.1038/s41386-023-01574-8
• **This is an original and recent piece of work aimed at shedding light at the complex pharmacodynamics of LSD.**
118. VanderZwaag J, Halvorson T, Dolhan K, et al. The missing piece? A case for Microglia's prominent role in the therapeutic action of Anesthetics, ketamine, and psychedelics. Neurochem Res. 2023;48(4):1129–1166. doi: 10.1007/s11064-022-03772-0
• **A thought-provoking, and clearly unique, perspective on the pharmacodynamics of typical and atypical psychedelics is here being provided.**
119. Heal DJ, Gosden J, Smith SL, et al. Experimental strategies to discover and develop the next generation of psychedelics and entactogens as medicines. Neuropharmacology. 2023;225:109375. doi: 10.1016/j.neuropharm.2022.109375
120. Malaca S, Lo Faro AF, Tamborra A, et al. Toxicology and analysis of psychoactive tryptamines. Int J Mol Sci. 2020;21(23):9279. doi: 10.3390/ijms21239279
121. Lima VM, MGSMDC M. Reports by explorers and travelers and the first scientific studies on ayahuasca (dating from 1850 to 1950) within the current debate on the "psychedelic renaissance". Hist Cienc Saude Manguinhos. 2023;30:e2023023. doi: 10.1590/s0104-59702023000100023
122. Perkins D, Ruffell SGD, Day K, et al. Psychotherapeutic and neurobiological processes associated with ayahuasca: a proposed model and implications for therapeutic use. Front Neurosci. 2023;16:879221. doi: 10.3389/fnins.2022.879221
123. Winstock AR, Kaar S, Borschmann R. Dimethyltryptamine (DMT): prevalence, user characteristics and abuse liability in a large global sample. J Psychopharmacol. 2014;28(1):49–54. doi: 10.1177/0269881113513852
• **Worldwide data relating to the use of DMT are here being provided, with findings being collected through a very unique, web-based, approach.**
124. Kavanagh PV, Westphal F, Pulver B, et al. Analytical profile of the lysergamide 1cP-AL-LAD and detection of impurities. Drug Test Anal. 2023;15(3):277–291. doi: 10.1002/dta.3397
125. Brandt SD, Kavanagh PV, Westphal F, et al. Analytical profile, in vitro metabolism and behavioral properties of the lysergamide 1P-AL-LAD. Drug Test Anal. 2022;14(8):1503–1518. doi: 10.1002/dta.3281
126. Brandt SD, Kavanagh PV, Westphal F, et al. Return of the lysergamides. Part VII: analytical and behavioural characterization of

1-valeroyl-d-lysergic acid diethylamide (1V-LSD). Drug Test Anal. 2022;14(4):733–740. doi: 10.1002/dta.3205
127. Brandt SD, Kavanagh PV, Westphal F, et al. Return of the lysergamides. Part V: analytical and behavioural characterization of 1-butanoyl-d-lysergic acid diethylamide (1B-LSD). Drug Test Anal. 2019;11(8):1122–1133. doi: 10.1002/dta.2613
128. Brandt SD, Kavanagh PV, Twamley B, et al. Return of the lysergamides. Part IV: analytical and pharmacological characterization of lysergic acid morpholide (LSM-775). Drug Test Anal. 2018;10(2):310–322. doi: 10.1002/dta.2222
129. Brandt SD, Kavanagh PV, Westphal F, et al. Return of the lysergamides. Part II: analytical and behavioural characterization of N^6-allyl-6-norlysergic acid diethylamide (AL-LAD) and (2'S,4'S)-lysergic acid 2,4-dimethylazetidide (LSZ). Drug Test Anal. 2017;9(1):38–50. doi: 10.1002/dta.1985
130. Brandt SD, Kavanagh PV, Westphal F, et al. Return of the lysergamides. Part III: analytical characterization of N^6-ethyl-6-norlysergic acid diethylamide (ETH-LAD) and 1-propionyl ETH-LAD (1P-ETH-LAD). Drug Test Anal. 2017;9(10):1641–1649. doi: 10.1002/dta.2196
131. Orsolini L, Papanti GD, De Berardis D, et al. The "endless trip" among the NPS users: psychopathology and Psychopharmacology in the hallucinogen-persisting perception disorder. A systematic review. Front Psychiatry. 2017;8:240. doi: 10.3389/fpsyt.2017.00240
132. Schifano F, Corkery J, Oyefeso A, et al. Trapped in the "K-hole": overview of deaths associated with ketamine misuse in the UK (1993-2006). J Clin Psychopharmacol. 2008;28(1):114–116. doi: 10.1097/JCP.0b013e3181612cdc
133. Schifano N, Chiappini S, Castiglione F, et al. Is medicinal ketamine associated with urinary dysfunction issues? Assessment of both the European Medicines Agency (EMA) and the UK yellow card scheme pharmacovigilance database-related reports. Low Urin Tract Symptoms. 2021;13(2):230–237. doi: 10.1111/luts.12355
- **This is a pharmacovigilance paper showing how the medicinal, prescribed, use of ketamine may be associated with a range of kidney, urether, and bladder dysfunctions.**
134. Kang H, Park P, Bortolotto ZA, et al. Ephenidine: a new psychoactive agent with ketamine-like NMDA receptor antagonist properties. Neuropharmacology. 2017;112(Pt A):144–149. doi: 10.1016/j.neuropharm.2016.08.004
135. Tang MHY, Chong YK, Chan CY, et al. Cluster of acute poisonings associated with an emerging ketamine analogue, 2-oxo-PCE. Forensic Sci Int. 2018;290:238–243. doi: 10.1016/j.forsciint.2018.07.014
136. Wang KD, Yuan XL, Liu C, et al. Identification of three novel new psychoactive substances 4F-AB-BUTINACA, AB-PHETINACA, and 2F-NENDCK. Drug Test Anal. 2023;15(1):115–122. doi: 10.1002/dta.3359
137. Corazza O, Assi S, Schifano F. From "special K" to "special M": the evolution of the recreational use of ketamine and methoxetamine. CNS Neurosci Ther. 2013;19(6):454–460. doi: 10.1111/cns.12063
138. Costa G, Serra M, Pintori N, et al. The novel psychoactive substance methoxetamine induces persistent behavioral abnormalities and neurotoxicity in rats. Neuropharmacology. 2019;144:219–232. doi: 10.1016/j.neuropharm.2018.10.031
139. Marti M, Talani G, Miliano C, et al. New insights into methoxetamine mechanisms of action: focus on serotonergic 5-HT_2 receptors in pharmacological and behavioral effects in the rat. Exp Neurol. 2021;345:113836. doi: 10.1016/j.expneurol.2021.113836
- **This paper offers a vast range of data taken from a comprehensive preclinical research study and focussing on methoxetamine/MXE.**
140. Gillespie NA, Neale MC, Prescott CA, et al. Factor and item-response analysis DSM-IV criteria for abuse of and dependence on cannabis, cocaine, hallucinogens, sedatives, stimulants and opioids. Addiction. 2007;102(6):920–930. doi: 10.1111/j.1360-0443.2007.01804.x
141. Scherbaum N, Seiffert F, Schifano F, et al. High lifetime, but low current, prevalence of new psychotropic substances (NPS) use in German drug detoxification treatment young inpatients. Prog Neuropsychopharmacol Biol Psychiatry. 2021;111:110144.
- **This is a research paper illustrating the fact that NPS may be taken irregularly, possibly due to their intense toxicity and side effects' levels.**
142. Martinotti G, Negri A, Schiavone S, et al. Club drugs: psychotropic effects and psychopathological characteristics of a sample of inpatients. Front Psychiatry. 2020;11:879. doi: 10.3389/fpsyt.2020.00879
143. Martinotti G, Merino Del Villar C, Garcia Cordoba A, et al. Club drugs and psychiatric sequelae: an issue of vulnerability and previous psychiatric history. Int J Environ Res Public Health. 2021;18(13):6944. doi: 10.3390/ijerph18136944
- **This is likely to be one of the very few research papers offering a follow up, in terms of psychopathological consequences, of clubbers ingesting a range of NPS in Ibiza disco clubs.**
144. Balíková M. Nonfatal and fatal DOB (2,5-dimethoxy-4-bromoamphetamine) overdose. Forensic Sci Int. 2005;153(1):85–91. doi: 10.1016/j.forsciint.2005.04.022
145. Tittarelli R, Mannocchi G, Pantano F, et al. Recreational use, analysis and toxicity of tryptamines. Curr Neuropharmacol. 2015;13(1):26–46. doi: 10.2174/1570159X13666141210222409
146. Thase ME. Have effective antidepressants finally arrived? Developments in major depressive disorder therapy. J Clin Psychiatry. 2023;84(4):mulmdd3048sho. doi: 10.4088/JCP.mulmdd3048sho
147. Cavarra M, Mason NL, Kuypers KPC, et al. Potential analgesic effects of psychedelics on select chronic pain conditions: a survey study. Eur J Pain. 2023 Aug 20. doi: 10.1002/ejp.2171
148. Raison CL, Sanacora G, Woolley J, et al. Single-dose psilocybin treatment for major depressive disorder: a randomized clinical trial. JAMA. 2023;330(9):e2314530. doi: 10.1001/jama.2023.14530
149. Freind JMK, Beserra FR, Menezes BS, et al. Therapeutic protocols using ketamine and esketamine for depressive disorders: a systematic review. J Psychoactive Drugs. 2023;1–17. doi: 10.1080/02791072.2023.2248989
150. Sarmanlu M, Kuypers KPC, Vizeli P, et al. MDMA-assisted psychotherapy for PTSD: growing evidence for memory effects mediating treatment efficacy. Prog Neuropsychopharmacol Biol Psychiatry. 2023;128:110843. doi: 10.1016/j.pnpbp.2023.110843
151. Munafò A, Arillotta D, Mannaioni G, et al. Psilocybin for depression: from credibility to feasibility, what's missing? Pharmaceuticals (Basel). 2022;16(1):68. doi: 10.3390/ph16010068