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Editorial

Psychoactives in 2025: Consolidating an Interdisciplinary Platform for Psychoactive Substance Science and Looking to the Future

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1. Editorial

In 2025, *Psychoactives* continued its clear upward trajectory, strengthening its position as an international, peer-reviewed, open-access journal dedicated to advancing the science of psychoactive substances, spanning pharmacology, clinical psychiatry, toxicology, neuroscience, forensic science, and public health. In a research landscape increasingly shaped by fast-moving substance markets, renewed clinical interest in psychedelics, and evolving regulatory frameworks, 2025 stood out as the year in which translational and evidence-based approaches became central themes across the journal's published work. The objective of this is editorial is aims to reflect on the most significant scientific contributions published during 2025 in *Psychoactives*, while highlighting emerging themes and future directions for the field. Key highlights include the maturation of psychedelic research from early-stage optimism to structured translational inquiry; critical ethical debates on psychedelic moral bioenhancement; advances in ketamine and esketamine research; and increased attention to legal, regulatory, and methodological rigor. The editorial also underscores the journal's sustained focus on cannabis complexity, new psychoactive substances, population-level substance use, alcohol-related neuroimmune mechanisms, and analytical challenges in toxicology. Looking forward, particular emphasis is placed on emerging risks associated with drug adulteration, the industrialization of illicit drug production, and the repurposing of common commercial products as precursors. The trajectory demonstrates that psychoactive substance science is no longer a niche field, but has become a central domain in which neuroscience, psychiatry, toxicology, forensic science, and public health intersect, reinforcing *Psychoactives*' commitment to evidence-based, ethically responsible, and societally relevant research.

2. Psychedelic Research

Psychedelic research remained a prominent axis of scientific and clinical interest; notably, the journal illustrated the field's shift from early-stage optimism toward deeper conceptual debate and a more structured translational discipline. This shift reflects a broader trend in neuropsychiatry: the need to align mechanistic plausibility (e.g., neuroplasticity) with clinically meaningful outcomes, while maintaining methodological rigor and ethical accountability. Several contributions published in or highlighted by the journal

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approached psychedelic therapies through a lens that extends beyond anecdotal narratives, focusing on clinical indications, neurobiological mechanisms, and realistic implementation pathways. In particular, discussions around neuroplasticity and neuro-generation [1], and the careful positioning of psychedelics within neurodegenerative or complex psychiatric contexts [2], represent an important step toward integrating these compounds into modern therapeutic paradigms.

Among the most thought-provoking contributions published in *Psychoactives* in 2025, the journal hosted a timely philosophical and ethical exchange on the concept of "psychedelic moral bioenhancement". In the original article [3], the proposal of using psychedelics in healthy individuals to promote moral enhancement was critically examined, framing the discussion within the principle of non-maleficence and emphasizing that exposure outside therapeutic contexts may entail significant psychological and ethical risks, including unpredictability of subjective outcomes and potential harm. In response, Kähönen [4] advanced the debate by arguing that the subjective effects of psychedelics—often treated as confounding factors or as primary sources of risk—may instead represent the most plausible mechanism through which any morally relevant or prosocial changes could occur. Rather than being dismissed as merely adverse or methodologically problematic, psychedelic subjective experiences may be integral to understanding potential pathways to moral transformation.

3. Ketamine and Esketamine Research

Ketamine and esketamine research was another significant 2025 theme, providing continued scientific refinement of these dissociatives with established or emerging clinical roles. The comparative and translational relevance of ketamine-based interventions is clearly illustrated by Mikellides [5], who reviews ketamine and esketamine in psychiatry, emphasizing their role in neuroplasticity and clinical applications. While ketamine-based interventions have been widely adopted in treatment-resistant depression contexts, the field remains challenged by questions of comparative effectiveness, tolerability, durability of benefit, and risk–benefit evaluation across psychiatric populations. Reviews such as this are therefore pivotal for clinicians and researchers navigating a rapidly changing therapeutic terrain. The journal's attention to comparative clinical framing reflects a maturation of the research agenda: moving from "whether it works" toward "for whom, how, and under what conditions it works best." This is especially important when the same substance class may simultaneously have clinical practice applications, off-label uses, and misuse landscapes [5].

4. Legal and Regulatory Interest

A particularly impactful theme in *Psychoactives* 2025 was the growing importance of **legal and regulatory scholarship** in psychoactive substance science, alongside increasing recognition that regulatory discourse must be evidence-informed while remaining sensitive to real-world complexities. As policy decisions accelerate in multiple jurisdictions, scientific publishing must increasingly support a nuanced understanding of regulatory risk, public health frameworks, and real-world implementation pathways. In this regard, Dlestikova [6] provides a timely and influential legal analysis of psilocybin for medical use in Czechia, framing it as a milestone while advocating broader consideration beyond strictly clinical environments. This type of work is essential to the identity of *Psychoactives*: psychoactive substances exist simultaneously as molecules, medicines, commodities, controlled substances, and cultural objects.

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5. Cannabis-Related Complexity

A further highlight of 2025 was the increasing emphasis on **cannabis-related complexity**—particularly the scientific and regulatory need to distinguish between plant material, extracts, and purified phytocannabinoids. The evidence base is frequently confounded by variability in composition, routes of administration, dosing uncertainty, and inconsistent product characterization. From both a clinical and public health perspective, *Psychoactives* reinforced a crucial message: cannabis research cannot advance meaningfully without improved chemical, pharmacological, and methodological standardization. In other words, our contributions in this area aligned well with the journal's mission to connect pharmacology with practical and societal impact.

6. New Psychoactive Substances and Global Disease Burden

We also maintained the focus on **New Psychoactive Substances (NPSs) and surveillance, mechanisms, and harm prevention**. Indeed, the volatility of illicit drug markets continues to represent one of the most acute public health challenges worldwide. In 2025, *Psychoactives* contributed to this urgent space by highlighting emerging substances and patterns, including opioids and adulteration trends. The pace of innovation in illicit markets remains a defining challenge for science, healthcare, and law enforcement. In this context, *Psychoactives* continued to position itself as a relevant venue for NPS-related scholarship, supporting interdisciplinary approaches that integrate pharmacodynamics, neurotoxicity, behavioral outcomes, and public health implications. A striking example is the report describing medetomidine as a fentanyl adulterant, associated with a novel and difficult-to-treat withdrawal syndrome [7]. Other recent findings support evidence of frequent medetomidine co-detection in mixtures containing fentanyl and xylazine [8]. Medetomidine is synthetically manufactured and has two enantiomeric forms: dexmedetomidine and levomedetomidine. Medetomidine is commonly used as an animal tranquilizer by veterinarians [9], while dexmedetomidine is used in humans for sedation in medical intensive care units, with careful monitoring to avoid side effects [10]. Medetomidine and xylazine are both classified as α_2 adrenergic receptor (AR) agonists, but medetomidine is more than 100 times as potent and selective for α_2-AR as xylazine [11]. Already in 2024, *Psychoactives* highlighted the zombifying combination of fentanyl and xylazine as the cause of overdoses and the reduced chance of rehabilitation [12]. Moreover, it is clear that the NPS problem cannot be addressed solely through toxicological identification. On the other hand, it requires integrated scientific frameworks that support: early warning and surveillance, mechanistic toxicology and neurobiology, clinical management and emergency care, forensic interpretation, and prevention, policy, and harm reduction. This "full-chain" translational logic is increasingly visible in the journal's scope and publication direction. A major future concern is the ongoing production of synthetic cannabinoids and synthetic cathinones, which represent a uniquely agile sector of clandestine manufacturing [13]. These substances are often produced through rapid structural modification, where new analogs emerge to bypass regulation and maintain profitability. From a scientific standpoint, this produces two major risks: (1) limited toxicological knowledge for newly introduced compounds at the time of public exposure; and (2) elevated probability of unexpected receptor activity, active metabolites, and narrow safety margins, particularly in inexperienced user populations.

Another major contribution area in 2025 was the journal's **continued attention to substance use at the population level**, particularly where evidence remains fragmented and underrepresented. The systematic review by Akosile et al. [14] on the prevalence of substance abuse in the South Pacific region is an important example of how the journal supports global public health perspectives beyond the most studied regions.

While emerging psychoactives often capture attention, 2025 also reinforced the need to maintain a strong scientific focus on **substances responsible for enduring global disease burden—especially alcohol**. The review by Ye et al. [15] on neuroimmune mechanisms in alcohol use disorder, with particular emphasis on microglial modulation and therapeutic horizons, illustrates how *Psychoactives* is contributing to a deeper mechanistic understanding of chronic substance-related pathology.

7. Analytical Sensitivity and Artifact Risks

Among the most relevant methodological contributions published in *Psychoactives* in 2025, the Editor-in-Chief [16] offered a timely and impactful reminder that progress in analytical sensitivity does not automatically translate into interpretative accuracy. The article critically examines how modern confirmatory approaches—including increasingly sensitive mass spectrometry-based techniques—have enhanced the detection of amphetamine-related compounds, while simultaneously increasing the risk of misclassification driven by analytical and pre-analytical artifacts. This work is particularly relevant because amphetamine findings frequently underpin high-stakes decisions, ranging from clinical management in emergency settings to forensic interpretation and legal proceedings. By framing "positivity" not as a final result but as a hypothesis requiring scientific validation, the article strengthens the journal's role in promoting robust, ethically responsible psychoactive substance science. Ultimately, this contribution reinforces a crucial principle for the field: analytical innovation must be accompanied by interpretative discipline, transparency, and standardized reporting, ensuring that advances in detection translate into reliable evidence rather than unintended artifacts.

8. Future Directions: An Escalating and Underestimated Risk of Adulterants and New Trends in Drug Abuse Production

As research on psychoactive substances continues to expand across clinical innovation, societal debate, and market-driven risks, *Psychoactives* is well positioned to contribute to a balanced scientific ecosystem—one that values innovation without abandoning rigor and recognizes the human and public health implications of these compounds beyond purely experimental narratives. The 2025 contributions demonstrate that psychoactive substance science is no longer a niche field: it is a central domain where neuroscience, psychiatry, toxicology, and public health intersect. The journal will continue supporting high-quality reviews, cutting-edge original research, and interdisciplinary synthesis that advance both knowledge and responsible practice.

Looking ahead, one of the most urgent challenges for psychoactive substance science is the growing complexity of the unregulated drug supply, particularly the **increasing presence of adulterants in drugs of abuse**, with inert and cheap diluents such as talc or sugars increasingly replaced by active substances which mask the low quality of the principal drug. These substances—added intentionally or unintentionally during production, cutting, or distribution—may have pharmacological activity of their own and can substantially modify the toxicity profile of the primary drug. Their inclusion often aims to enhance perceived potency, mimic effects, increase product volume, or prolong psychoactive action, yet the resulting mixtures frequently lead to unpredictable, high-risk exposures. Indeed, several authors [17] have highlighted that the growing proportion of adulterants in the street drug supply has increased overdose risk and other negative health outcomes for people who use drugs (PWUD). Adulterants may involve different compounds such as sedatives, veterinary drugs such as α_2-agonists (e.g., xylazine), stimulants, synthetic opioids, analgesics (e.g., paracetamol or phenacetin in heroin or fentanyl), anesthetics (e.g., procaine and benzocaine), and diverse NPS, aminopyrine, phenylbutazone, caffeine, diltiazem, metamizole

(or dipyrone), etc. [18,19]. Importantly, these compounds can generate unexpected toxidromes, complicate emergency management, and increase fatality risk—particularly when combined with opioids, depressants, or polysubstance use patterns. In the current opioid crisis, xylazine has become widely reported as an adulterant in illicit fentanyl ("tranq"), contributing to severe sedation, complex withdrawal profiles, and broader harm beyond opioid-driven respiratory depression [12,20]. Adulteration remains equally relevant in stimulant markets: levamisole-adulterated cocaine continues to be a major concern due to its association with immune-mediated complications, including agranulocytosis and vasculitis syndromes, reinforcing that adulterants can drive clinically significant toxicity independent of the primary drug [21,22]. Phenylbutazone, a nonsteroidal anti-inflammatory drug (NSAID) formerly used to treat arthritis, gout, and ankylosing spondylitis in humans, has recently been added to NPS adulterant testing in heroin, fentanyl, and designer opioids [23]. Novel benzodiazepines such as etizolam have also been reported as adulterants in fentanyl [24,25]. A case of intoxication involving sildenafil was reported due to sildenafil contamination of GHB (gamma-hydroxybutyric acid) used during sexual intercourse [26]. BTMPS (also known as bis(2,2,6,6-tetramethyl-4-piperidyl)sebacate, Tinuvin® 770, HALS 770, or T770), is one of the newest emerging adulterants identified in the illicit drug supply. Although it has no known sedative or psychoactive effects, BTMPS can cause adverse effects, including cardiotoxicity, as it acts as a potent *L*-type calcium channel blocker and a non-competitive nicotine receptor antagonist [27]. Industrially, it is commonly used as a light stabilizer in a wide range of consumer materials, including plastics, paints, sealants, and packaging. Through serum testing, three long-acting anticoagulant rodenticides (i.e., brodifacoum, difenacoum, and bromodialone) were detected in patients who had consumed synthetic cannabinoids [28]. However, these examples are only the "tip of the iceberg," since different publications have reported a myriad of compounds, depending solely on the inspiration of dealers [29]. Collectively, these examples illustrate why future research must prioritize not only the analytical detection of adulterants but also the clarification of their pharmacology, toxic interactions, withdrawal features, and real-world clinical consequences, ensuring that surveillance systems, emergency care, and harm reduction strategies remain aligned with an increasingly unpredictable drug supply. For instance, inconsistent treatment responsiveness may occur, as naloxone does not reverse the effects of xylazine [30].

Looking more ahead, a defining feature of illicit drug production is its increasing **industrialization and market standardization**, in which "common products" (readily available chemicals and pharmaceutical agents) are repurposed to modify potency, appearance, stability, or user experience. This evolution is reshaping risk profiles across opioid, stimulant, and synthetic drug markets, making harm less predictable and clinical management more complex. The global spread of synthetic opioids illustrates how illicit production can be engineered for scale. Indeed, nitazenes—opioids from the 2-benzylbenzimidazole class—have rapidly emerged as globally distributed synthetic opioids [31], with some, such as etonitazepyne, associated with fatalities following the ingestion of tablets resembling and thus mistaken for oxycodone [32]. Rather than relying on agricultural cycles (as with opium poppy cultivation), synthetic opioid manufacturing depends on access to chemical precursors and intermediates, enabling rapid shifts in production geography and output. A key scientific risk is that changes in the synthetic route can lead to different residual by-products and impurities, which may modify pharmacological potency and toxicodynamics even when the final product is nominally the same "drug class". In practical terms, this means that overdose patterns may shift abruptly—not only due to dose variability, but also due to evolving impurity signatures and co-produced analogs. Illicit methamphetamine production remains one of the clearest examples of how clandestine synthesis

generates harm beyond the end-user. Methamphetamine can be produced through chemically distinct pathways, often involving corrosive or highly reactive reagents and diverted pharmaceutical precursors, particularly pseudoephedrine-containing products [33]. While pseudoephedrine is a legitimate and widely used decongestant, its systematic diversion illustrates how illicit drug supply chains increasingly exploit regulated but commercially accessible chemicals to sustain production. Even without detailing procedural steps, the scientific reality is that these processes generate volatile organic compounds, reactive gases, and toxic waste, creating severe risks of chemical burns, inhalational injury, and chronic contamination of indoor environments. Importantly, exposure risk extends to non-users—such as children, first responders, healthcare workers, and neighboring populations—through contact with contaminated surfaces and persistent residues [34,35]. This highlights that illicit drug production is simultaneously a toxicology problem, a housing/environmental health problem, and a disaster-response problem. GBL (gamma-butyrolactone) is also rapidly converted into the drug-facilitated (sexual) assault GHB (gamma-hydroxybutyric acid) drug through a simple chemical reaction, often using an alkali hydroxide, such as sodium hydroxide; also, 1,4-butanediol (butane-1,4-diol; 1,4-BD) can be used as a precursor. Although GHB has no industrial use except for its medical use (as sodium oxybate), GBL and 1,4-BD are used exclusively in industries, as an intermediate in the production of herbicides, fertilizers, and pharmaceuticals, and as a solvent or an additive for GBL or as nail polish remover and car cleaners for 1,4-BD [36]. Krokodil (desomorphine) is another devastating illicit drug, produced from codeine-containing pharmaceuticals through crude chemical conversions using readily available household and industrial reagents, resulting in a highly impure product with severe toxicological consequences; fortunately, interest among consumers remained limited [37]. Benzaldehyde has historically been misused as a readily available aromatic precursor in illicit amphetamine manufacture [38]. Another notable example is 1-benzylpiperazine (BZP), a synthetic stimulant that has been illicitly manufactured using piperazine, a compound with legitimate applications as an anti-helminthic agent in veterinary medicine [39]. The diversion of such substances highlights how commercially available pharmaceuticals and industrial intermediates can be repurposed outside regulated supply chains to produce psychoactive compounds intended for recreational use. Ergotamine, an ergot alkaloid used for migraine treatment, contains the ergoline ring system required for diethylamide of lysergic acid (LSD) synthesis [40]. Another issue to pay attention to is the use of canisters for whipped cream and nitrous oxide (N_2O, "laughing gas"). Indeed, the easy availability of nitrous oxide canisters at supermarkets increases the risk of recreational misuse, which is associated with several significant health hazards [41,42]. Inhalation of nitrous oxide from these canisters can cause acute hypoxia and asphyxial death. Therefore, the diversion of such substances highlights how commercially available pharmaceuticals and chemical intermediates can be repurposed outside regulated supply chains, resulting in psychoactive products characterized by variable purity, unpredictable dosing, and increased toxicological risk. Unlike fully synthetic drugs, cocaine production is largely based on extraction and purification from plant material, which creates a distinct scientific hazard: the reliance on large volumes of solvents, oxidants, acids, and alkaline agents during processing [43]. These chemicals may contribute to occupational exposure risks among producers, environmental contamination, and may leave residual contaminants in end-products, particularly when purification steps are crude or rushed [44].

9. Changes in Paradigms and Future Perspectives

From a public health perspective, the adulteration phenomenon highlights the limitations of focusing solely on "classic" drugs such as heroin, cocaine, or methamphetamine.

Instead, it demands an integrated, proactive strategy that combines early warning surveillance, high-resolution analytical toxicology, clinical reporting networks, wastewater monitoring, forensic intelligence, environmental health strategies, and harm reduction services. In this evolving environment, *Psychoactives* has an important opportunity to support evidence that bridges laboratory identification with clinical impact—promoting faster detection of emerging adulterants, clearer risk communication, and improved therapeutic protocols. Moreover, a key implication for psychoactive substance research is that the "street name" of a drug is increasingly disconnected from its chemical reality. Illicit production trends show that toxicology can no longer rely exclusively on traditional assumptions (e.g., "heroin intoxication", "cocaine overdose", or "MDMA toxicity") because the clinical phenotype is often influenced by impurity profiles, route-dependent contaminants, manufacturing residues, and active by-products formed during uncontrolled synthesis.

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