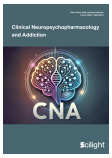
Scilight

Clinical Neuropsychopharmacology and Addiction
https://www.sciltp.com/journals/cna



Editorial

Check for updates

Epigenetic Mechanisms of Psychedelics in Addiction: Emerging Evidence and Therapeutic Potential

Antonio Inserra [1,2,3,*], Francesca Zoratto [1], Mauro Pettorruso [2,4,5] and Giovanni Martinotti [2,4,5,6]

[1] Centre for Behavioural Sciences and Mental Health, Istituto Superiore di Sanità, 00161 Rome, Italy
[2] Department of Neuroscience, Imaging and Clinical Sciences, G. d'Annunzio University of Chieti-Pescara, 66100 Chieti, Italy
[3] Behavioral Neuroscience Laboratory, University of Southern Santa Catarina, Santa Catarina 88705-755, Brazil
[4] Institute for Advanced Biomedical Technologies (ITAB), "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy
[5] Department of Mental Health, ASL 2 Lanciano-Vasto-Chieti, 66100 Chieti, Italy
[6] Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield AL10 9EU, UK
* Correspondence: antonio.inserra@iss.it
Received: 10 March 2026; Accepted: 30 March 2026; Published: 17 April 2026

How To Cite: Inserra, A.; Zoratto, F.; Pettorruso, M.; et al. Epigenetic Mechanisms of Psychedelics in Addiction: Emerging Evidence and Therapeutic Potential. *Clinical Neuropsychopharmacology and Addiction* **2026**, *2*(2), 6. https://doi.org/10.53941/cna.2026.100006

1. Potential Role of Psychedelics and Related Compounds as Modifiers of Epigenetic and Transcriptional Plasticity in Addiction

Substance use disorders (SUDs) are chronic, relapsing conditions characterized by maladaptive epigenetic remodeling, including histone acetylation, histone dopaminylation (a modification linking dopamine [DA] signaling to chromatin regulation), DNA methylation, and non-coding RNAs (ncRNAs) within reward-related circuits, particularly the mesocorticolimbic DA system [1–3]. These epigenetic changes lead to persistent gene expression changes that increase vulnerability to addiction and consolidate drug-associated memories, reinforcing compulsive substance seeking and relapse [1–3]. The reversibility of these epigenetic alterations provides a mechanistic foundation for pharmacological interventions capable of restoring adaptive gene expression, neurotrophic signaling, and structural plasticity, thereby reshaping maladaptive reward circuits and reducing relapse risk.

Psychedelics and related compounds such as ibogaine, psilocybin, ketamine, mescaline, 3,4-Methylenedioxymethamphetamine (MDMA), and the N,N-dimethyltryptamine (DMT)-containing Ayahuasca are emerging as a potential paradigm-shifting treatment of SUDs. Unlike conventional pharmacotherapies, psychedelic compounds have demonstrated the capacity to produce rapid and sustained reductions in substance use after only one or a few supervised sessions. For example, ibogaine demonstrates robust anti-addictive effects, particularly for opioids, stimulants, and poly-drug dependence, but clinical adoption remains constrained by cardiotoxicity [4], which is being addressed through the design of ibogaine analogues that retain anti-addictive and neuroplastic effects while eliminating cardiac risk [5–7]. Psilocybin-assisted psychotherapy similarly reduces alcohol and tobacco consumption after only one to three treatment sessions [8–11]. Accordingly, ketamine has shown efficacy across multiple SUDs when combined with structured behavioral therapy [12–15], and MDMA-assisted psychotherapy also shows preliminary promise for alcohol use disorder (AUD) [16,17]. Studies investigating naturalistic Ayahuasca users have unanimously reported lower AUD and SUDs rates among Ayahuasca drinkers, also in adolescent populations [18]. Similarly, naturalistic mescaline use has been associated with considerable SUD and AUD symptom reduction, or even complete abstinence [19–21].

While the available evidence remains mostly limited to proof-of-concept, naturalistic, and retrospective studies, converging evidence suggests that psychedelics may counteract the maladaptive epigenetic and transcriptional changes in the nucleus accumbens (NAc), prefrontal cortex (PFC), and ventral tegmental area (VTA) underlying SUDs, thus facilitating recovery from addiction [3,22–30]. Understanding how psychedelics modulate the epigenetic landscape governing reward- and neurotrophic-related gene expression in SUDs in relevant brain circuits may thus inform future strategies for relapse prevention, circuit restoration, and sustained

recovery. The preliminary yet converging evidence provides a compelling rationale for continued investigation and careful, yet timely translation into clinical practice.

2. Mechanistic Foundations: Epigenetic and Neuroplastic Remodeling

Psychedelics act primarily via modulation of brain-derived neurotrophic factor (BDNF) signaling and agonism at the serotonin 2A receptor (5-hydroxytryptamine 2A receptor; 5-HT2A), activating intracellular signaling pathways including the mitogen-activated protein kinase/extracellular signal-regulated kinase cascade (MAPK/ERK) and the cyclic adenosine monophosphate response element-binding protein pathway (cAMP response element-binding protein; CREB), resulting in upregulation of neurotrophic and plasticity-related genes such as BDNF, FosB (FBJ murine osteosarcoma viral oncogene homolog B; FosB-including the addiction-relevant splice variant ΔFosB-), and glial cell line-derived neurotrophic factor (GDNF) [24,27,31–34]. Preclinical studies demonstrate that psychedelics increase histone acetylation at plasticity-related gene promoters and induce prolonged epigenomic alterations at enhancer regions controlling synaptic assembly, changes that persist after acute exposure [25,30,32]. These epigenetic modifications facilitate dendritic spine growth, synaptic remodeling in prefrontal cortex and nucleus accumbens, potentially contributing to the restoration of reward circuitry function disrupted by SUDs [25,30,32,35]. Emerging evidence also suggests that psychedelics may modulate ncRNA networks involved in synaptic plasticity and inflammatory signaling, though systematic profiling in addiction models remains limited. Ketamine operates through N-methyl-D-aspartate (NMDA) receptor antagonism, acutely increasing synaptogenesis and dendritic spine density via BDNF- and mechanistic target of rapamycin (mTOR)-dependent, epigenetic-mediated pathways [32,36]. Preclinical evidence suggests that ibogaine induces GDNF upregulation in VTA and NAc, promoting dopaminergic recovery and functional restoration [37,38]. However, molecular evidence linking ibogaine's anti-addictive potential to epigenetics also remains lacking. Lastly, psychedelics and related compounds may transiently reopen critical-period-like states of heightened plasticity, facilitating therapeutic remodeling when paired with structured psychotherapy [39].

3. Critical Knowledge Gaps and Future Directions

Despite compelling preliminary evidence, substantial knowledge gaps remain. Most clinical trials are small, open-label, or single-site studies with heterogeneous designs, limited long-term follow-up, and lack of epigenetic-related outcomes [4,40,41]. The majority of mechanistic epigenetic data derive from rodent models examining bulk tissue, leaving cell-type-specific effects on distinct neuronal and glial populations largely unexplored, such as dopamine 1 receptor (D1)- versus D2-expressing medium spiny neurons in the NAc and layer V pyramidal neurons in the PFC [32]. Direct demonstration of psychedelic-induced epigenetic remodeling in human populations with SUDs is lacking, representing a critical translational gap. Blinding remains problematic in psychedelic trials due to distinctive subjective effects, potentially introducing expectancy bias. Most studies exclude participants with severe psychiatric or medical comorbidities, limiting generalizability. The relative contributions of subjective psychedelic experience versus molecular neuroplastic effects remain unclear, as does the potential for non-psychedelic analogues to reproduce therapeutic benefits while reducing safety concerns or enhancing scalability.

Future research priorities include mechanistic trials integrating longitudinal neuroimaging, single-cell RNA sequencing, chromatin accessibility assays (i.e., ATAC-seq), 3D chromatin architecture, sex differences in epigenetic response, immune-epigenetic alterations (i.e., microglia), and cell-type-specific epigenetic profiling to directly link epigenetic remodeling with clinical outcomes such as sustained abstinence and relapse prevention. Large-scale, multi-site randomized trials employing standardized psychotherapy protocols, diverse patient populations, and harmonized epigenetic endpoints are essential to robustly evaluate the epigenetic effects of psychedelics for SUDs. Development and testing of safer analogues—particularly for ibogaine—may expand therapeutic access while minimizing cardiovascular and psychiatric risks. Integration of ethnobotanical knowledge from traditional psychedelic use (Ayahuasca in South America, iboga in West Africa) should inform culturally sensitive approaches that respect indigenous practices while advancing modern clinical translation.

4. Conclusions

Psychedelics represent a mechanistically novel approach to addiction treatment, with the potential to reset maladaptive transcriptional programs through epigenetic remodeling while facilitating enduring behavioral change within structured psychotherapeutic frameworks. By targeting the molecular substrates of addiction—altered chromatin states, dysregulated neurotrophic signaling, and impaired circuit plasticity— in addiction-related brain circuits, these compounds may directly counteract the epigenetic and transcriptional imprints that sustain

compulsive substance use. The convergence of molecular, structural, and behavioral effects—often producing rapid and sustained benefits after limited dosing—distinguishes psychedelics from conventional pharmacotherapies and positions them as potentially disease-modifying interventions for SUDs.

Yet the evidence base remains preliminary. Most clinical studies are small, open-label, methodologically heterogeneous, and with limited follow-up. Although meaningful clinical signals have been observed across alcohol, tobacco, cocaine, opioid, and polysubstance use disorders, careful translation is essential. Safety considerations—particularly for compounds such as ibogaine—standardization of psychotherapeutic protocols, and improved patient selection strategies must be prioritized. Large-scale, multi-site randomized controlled trials integrating epigenetic biomarkers, longitudinal follow-up, and diverse patient populations will be necessary to improve the mechanistic understanding, and establish efficacy, durability, and safety. In parallel, the development of non-psychedelic analogues that preserve neuroplastic and epigenetic benefits while minimizing psychiatric and cardiovascular risks may expand accessibility and enhance clinical feasibility. Together, continued investigation grounded in scientific rigor and ethical responsibility is essential to determine whether psychedelic-assisted therapies can fulfill their promise as durable, mechanism-informed, epigenetics-mediated treatments for addiction.

If validated through mechanistic and clinical investigation, psychedelic-assisted interventions may represent the first class of addiction treatments designed not merely to suppress symptoms, but to reprogram the epigenetic and transcriptional architecture sustaining compulsive drug use.

Conflicts of Interest

The authors declare that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest. Given the role as the Editor-in-Chief, Giovanni Martinotti had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Funding

This work was funded by the European Union – NextGenerationEU – within the Italian National Recovery and Resilience Plan–PNRR M6C2–Investment 2.1 "Valorisation and strengthening of biomedical research in the National Health Service" (project title: Advancing PRecise Interventions for resistant DEpression: rebalancing brain networks and investigating the trajectories of antidepressant effect with non-psychedelic psilocybin and personalized neuromodulation (PRIDE); project code PNRR-MCNT2-2023-12377068 to FZ and GM).

Use of AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT to improve the language and correct typos and grammatical errors. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Abbreviations

5-HT2A	5-hydroxytryptamine 2A receptor
AUD	alcohol use disorder
BDNF	brain-derived neurotrophic factor
CREB	cyclic adenosine monophosphate response element-binding protein
DA	dopamine
DMT	N,N-dimethyltryptamine
ERK	extracellular signal-regulated kinase
GDNF	glial cell line-derived neurotrophic factor
LSD	lysergic acid diethylamide
MAPK	mitogen-activated protein kinase
MDMA	3,4-methylenedioxymethamphetamine
NAc	nucleus accumbens
ncRNA	non-coding RNA
NMDA	N-methyl-D-aspartate

PFC	prefrontal cortex
SUD	substance use disorder
VTA	ventral tegmental area
ΔFosB	addiction-relevant splice variant of FosB

References

1. Hamilton, P.J.; Nestler, E.J. Epigenetics and addiction. *Curr. Opin. Neurobiol.* **2019**, *59*, 128–136. https://doi.org/10.1016/j.conb.2019.05.005.
2. Koijam, A.S.; Singh, K.D.; Nameirakpam, B.S.; et al. Drug addiction and treatment: An epigenetic perspective. *Biomed. Pharmacother.* **2024**, *170*, 115951.
3. Lepack, A.E.; Werner, C.T.; Stewart, A.F.; et al. Dopaminylation of histone H3 in ventral tegmental area regulates cocaine seeking. *Science* **2020**, *368*, 197–201. https://doi.org/10.1126/science.aaw8806.
4. Köck, P.; Froelich, K.; Walter, M.; et al. A systematic literature review of clinical trials and therapeutic applications of ibogaine. *J. Subst. Abuse Treat.* **2022**, *138*, 108717. https://doi.org/10.1016/j.jsat.2021.108717.
5. Heinsbroek, J.A.; Giannotti, G.; Bonilla, J.; et al. Tabernanthalog reduces motivation for heroin and alcohol in a polydrug use model. *Psychedelic Med.* **2023**, *1*, 111–119.
6. Cameron, L.P.; Tombari, R.J.; Lu, J.; et al. A non-hallucinogenic psychedelic analogue with therapeutic potential. *Nature* **2021**, *589*, 474–479.
7. Havel, V.; Kruegel, A.C.; Bechand, B.; et al. Oxa-Iboga alkaloids lack cardiac risk and disrupt opioid use in animal models. *Nat. Commun.* **2024**, *15*, 8118. https://doi.org/10.1038/s41467-024-51856-y.
8. Bogenschutz, M.P.; Ross, S.; Bhatt, S.; et al. Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* **2022**, *79*, 953–962. https://doi.org/10.1001/jamapsychiatry.2022.2096.
9. Johnson, M.W.; Garcia-Romeu, A.; Cosimano, M.P.; et al. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *J. Psychopharmacol.* **2014**, *28*, 983–992.
10. Johnson, M.W.; Garcia-Romeu, A.; Griffiths, R.R. Long-term follow-up of psilocybin-facilitated smoking cessation. *Am. J. Drug Alcohol Abus.* **2017**, *43*, 55–60.
11. Luquiens, A.; Belahda, D.; Graux, C.; et al. Psilocybin in alcohol use disorder and comorbid depressive symptoms: Results from a feasibility randomized clinical trial. *Addiction* **2025**. https://doi.org/10.1111/add.70152.
12. Grabski, M.; McAndrew, A.; Lawn, W.; et al. Adjunctive Ketamine With Relapse Prevention-Based Psychological Therapy in the Treatment of Alcohol Use Disorder. *Am. J. Psychiatry* **2022**, *179*, 152–162. https://doi.org/10.1176/appi.ajp.2021.21030277.
13. Dakwar, E.; Nunes Edward, V.; Hart Carl, L.; et al. A Single Ketamine Infusion Combined With Mindfulness-Based Behavioral Modification to Treat Cocaine Dependence: A Randomized Clinical Trial. *Am. J. Psychiatry* **2019**, *176*, 923–930. https://doi.org/10.1176/appi.ajp.2019.18101123.
14. Janssen-Aguilar, R.; Meshkat, S.; Demchenko, I.; et al. Role of ketamine in the treatment of substance use disorders: A systematic review. *J. Subst. Use Addict. Treat.* **2025**, *175*, 209705. https://doi.org/10.1016/j.josat.2025.209705.
15. Martinotti, G.; Chiappini, S.; Pettorruso, M.; et al. Therapeutic Potentials of Ketamine and Esketamine in Obsessive–Compulsive Disorder (OCD), Substance Use Disorders (SUD) and Eating Disorders (ED): A Review of the Current Literature. *Brain Sci.* **2021**, *11*, 856. https://doi.org/10.3390/brainsci11070856.
16. Sessa, B.; Higbed, L.; O'Brien, S.; et al. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. *J. Psychopharmacol.* **2021**, *35*, 375–383. https://doi.org/10.1177/0269881121991792.
17. Thurgur, H.; Sessa, B.; Higbed, L.; et al. MDMA-assisted psychotherapy for AUD: Bayesian analysis of WHO drinking risk level and exploratory analysis of drinking behavior and psychosocial functioning at 3 months follow-up. *Alcohol. Alcohol.* **2025**, *60*, agaf031. https://doi.org/10.1093/alcalc/agaf031.
18. Richard, J.; Garcia-Romeu, A. Psychedelics in the Treatment of Substance Use Disorders and Addictive Behaviors: A Scoping Review. *Curr. Addict. Rep.* **2025**, *12*, 15. https://doi.org/10.1007/s40429-025-00629-8.
19. Agin-Liebes, G.; Haas, T.F.; Lancelotta, R.; et al. Naturalistic use of mescaline is associated with self-reported psychiatric improvements and enduring positive life changes. *ACS Pharmacol. Transl. Sci.* **2021**, *4*, 543–552.
20. Uthaug, M.V.; Davis, A.K.; Haas, T.F.; et al. The epidemiology of mescaline use: Pattern of use, motivations for consumption, and perceived consequences, benefits, and acute and enduring subjective effects. *J. Psychopharmacol.* **2022**, *36*, 309–320.

21. Blum, K.; Futterman, S.F.L.; Pascarosa, P. Peyote, a potential ethnopharmacologic agent for alcoholism and other drug dependencies: Possible biochemical rationale. *Clin. Toxicol.* **1977**, *11*, 459–472.
22. Ruffell, S.G.D.; Netzband, N.; Tsang, W.; et al. Ceremonial Ayahuasca in Amazonian Retreats—Mental Health and Epigenetic Outcomes From a Six-Month Naturalistic Study. *Front. Psychiatry* **2021**, *12*, 687615. https://doi.org/10.3389/fpsyt.2021.687615.
23. Inserra, A. Hypothesis: The Psychedelic Ayahuasca Heals Traumatic Memories via a Sigma 1 Receptor-Mediated Epigenetic-Mnemonic Process. *Front. Pharmacol.* **2018**, *9*, 330. https://doi.org/10.3389/fphar.2018.00330.
24. Inserra, A.; Campanale, A.; Cheishvili, D.; et al. Modulation of DNA methylation and protein expression in the prefrontal cortex by repeated administration of D-lysergic acid diethylamide (LSD): Impact on neurotropic, neurotrophic, and neuroplasticity signaling. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2022**, *119*, 110594. https://doi.org/10.1016/j.pnpbp.2022.110594.
25. de la Fuente Revenga, M.; Zhu, B.; Guevara, C.A.; et al. Prolonged epigenomic and synaptic plasticity alterations following single exposure to a psychedelic in mice. *Cell Rep.* **2021**, *37*, 109836. https://doi.org/10.1016/j.celrep.2021.109836.
26. Ly, C.; Greb, A.C.; Cameron, L.P.; et al. Psychedelics promote structural and functional neural plasticity. *Cell Rep.* **2018**, *23*, 3170–3182.
27. De Gregorio, D.; Inserra, A.; Enns, J.P.; et al. Repeated lysergic acid diethylamide (LSD) reverses stress-induced anxiety-like behavior, cortical synaptogenesis deficits and serotonergic neurotransmission decline. *Neuropsychopharmacology* **2022**, *47*, 1188–1198. https://doi.org/10.1038/s41386-022-01301-9.
28. De Gregorio, D.; Popic, J.; Enns Justine, P.; et al. Lysergic acid diethylamide (LSD) promotes social behavior through mTORC1 in the excitatory neurotransmission. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2020705118. https://doi.org/10.1073/pnas.2020705118.
29. Richardson, B.; Inserra, A.; Pileggi, M.; et al. Differential effects of psilocybin and lisuride on serotonin and dopamine neuronal activity and behavior. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2025**, *142*, 111522. https://doi.org/10.1016/j.pnpbp.2025.111522.
30. Jaster, A.M.; Hadlock, T.M.; Buzzi, B.; et al. Sex-specific role of the 5-HT2A receptor in psilocybin-induced extinction of opioid reward. *Nat. Commun.* **2025**, *16*, 10206. https://doi.org/10.1038/s41467-025-64887-w.
31. Siegel, J.S.; Liston, C.; Nicol, G.E.; et al. The science of psychedelic medicine. *Nat. Med.* **2026**, *32*, 449–462. https://doi.org/10.1038/s41591-025-04194-5.
32. Inserra, A.; Campanale, A.; Rezai, T.; et al. Epigenetic mechanisms of rapid-acting antidepressants. *Transl. Psychiatry* **2024**, *14*, 359. https://doi.org/10.1038/s41398-024-03055-y.
33. de Camargo, R.W.; Joaquim, L.; Machado, R.S.; et al. Ayahuasca Pretreatment Prevents Sepsis-Induced Anxiety-Like Behavior, Neuroinflammation, and Oxidative Stress, and Increases Brain-Derived Neurotrophic Factor. *Mol. Neurobiol.* **2025**, *62*, 5695–5719. https://doi.org/10.1007/s12035-024-04597-4.
34. Inserra, A.; De Gregorio, D.; Gobbi, G. Psychedelics in Psychiatry: Neuroplastic, Immunomodulatory, and Neurotransmitter Mechanisms. *Pharmacol. Rev.* **2021**, *73*, 202–277. https://doi.org/10.1124/pharmrev.120.000056.
35. Floris, G.; Dabrowski, K.R.; Zanda, M.T.; et al. Psilocybin reduces heroin seeking behavior and modulates inflammatory gene expression in the nucleus accumbens and prefrontal cortex of male rats. *Mol. Psychiatry* **2025**, *30*, 1801–1816. https://doi.org/10.1038/s41380-024-02788-y.
36. Leccisotti, I.; Moretti, M.C.; Altamura, M.; et al. The epigenetic mechanisms of ketamine in the treatment of depression: A systematic review. *Epigenomics* **2025**, *17*, 1641–1658. https://doi.org/10.1080/17501911.2025.2583892.
37. Carnicella, S.; Kharazia, V.; Jeanblanc, J.; et al. GDNF is a fast-acting potent inhibitor of alcohol consumption and relapse. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 8114–8119. https://doi.org/10.1073/pnas.0711755105.
38. Marton, S.; González, B.; Rodríguez, S.; et al. Ibogaine Modifies GDNF, BDNF and NGF Expression in Brain Regions Involved in Mesocorticolimbic and Nigral Dopaminergic Circuits. *ChemRxiv* **2018**. https://doi.org/10.26434/chemrxiv.7261559.v1.
39. Nardou, R.; Sawyer, E.; Song, Y.J.; et al. Psychedelics reopen the social reward learning critical period. *Nature* **2023**, *618*, 790–798. https://doi.org/10.1038/s41586-023-06204-3.
40. Meshkat, S.; Malik, G.; Zeifman, R.J.; et al. Efficacy and safety of psilocybin for the treatment of substance use disorders: A systematic review. *Neurosci. Biobehav. Rev.* **2025**, *173*, 106163. https://doi.org/10.1016/j.neubiorev.2025.106163.
41. Rathore, B.S.; Singh, S.; Gupta, M.; et al. Safety and efficacy of ketamine for the treatment of patients with alcohol use disorder: A systematic review. *Am. J. Drug Alcohol Abus.* **2025**, *51*, 563–576.