

DOI: <https://doi.org/10.56936/18290825-2026.20v.2-82>**NEW HORIZONS IN SUBSTANCE ABUSE DISORDER: A SYSTEMATIC REVIEW OF EPIGENETIC MECHANISMS AND MULTIDIMENSIONAL PERSPECTIVES (2023–2025)****ESMAELZADEH M.^{1,2*}, ASHTEARI MEHRJARDI A.³, MOHAMMADINIA O.⁴, MOHAMMADPOUR S.⁵, HOKMABADI M.E.^{6*}, AMINI F.⁷, AZIZI T.⁸, VAKILI AHRARI RODI M.⁹**

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ABSTRACT

Introduction: Substance use disorders represent a critical global challenge, characterized by multifaceted etiologies often studied in isolation. Epigenetics provides a mechanism linking environmental exposures to biological susceptibility. This review synthesizes the most recent evidence (2023-2025) to analyze substance use disorders complexity through a holistic lens integrating epigenetic, psychological, socio-biological, spiritual, and legal perspectives.

Material and Methods: Following PRISMA guidelines, a comprehensive search of databases (PubMed, Scopus, Web of Science, PsycINFO, EMBASE, Cochrane) was conducted. Ninety-four studies meeting inclusion criteria were analyzed. Data were extracted, and random-effects meta-analyses were performed where feasible.

Results: Quantitative synthesis revealed significant effect sizes across all domains. Key findings include a strong association between trauma and substance use disorder severity (OR 2.45) and a novel meta-analytic link between trauma and specific epigenetic aberrations (standardized mean differences 0.75). Social support (OR 2.90), religiosity (hazard ratio 0.65), decriminalization (RR 0.71), and improved access to Medication for opioid use disorder (OR 2.10) emerged as protective factors. Epigenetic studies demonstrated how adversity becomes biologically embedded. Significant cross-domain interactions were identified, with epigenetics acting as a central mediator between environmental experiences and biological outcomes.

Conclusion: Evidence supports a holistic, integrated model of substance use disorders where epigenetic processes mediate the biological embedding of risk and resilience. Effective intervention requires breaking down disciplinary silos to simultaneously address psychological trauma, socio-environmental stressors, and their epigenetic influences. Future research must employ longitudinal designs to investigate the reversibility of epigenetic markers and evaluate multilevel interventions incorporating this biological perspective.

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