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NEW HORIZONS IN SUBSTANCE ABUSE DISORDER: A SYSTEMATIC REVIEW OF EPIGENETIC MECHANISMS AND MULTIDIMENSIONAL PERSPECTIVES (2023–2025)

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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 (hazzard 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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Introduction

Substance Use Disorders (SUDs) constitute a swiftly escalating global public health issue, characterized by a complicated origin, substantial co-occurrence with other conditions and considerable social and economic impacts [*Degenhardt L et al., 2019*]. Recent epidemiological studies indicate a rise in the prevalence of illicit drug consumption, overdose deaths, and treatment resistance - collectively highlighting the inadequacy of reductionist approaches previously employed in comprehending and addressing addictive disorders [*Volkow N et al., 2022*]. The complexity of SUDs - involving psychological, social, spiritual and legal aspects - necessitates a comprehensive conceptual model that enables the evaluation of these varied factors and their interrelations [*Koob G, Volkow N, 2016*].

Historically, research and clinical efforts were typically restricted to separate domains, concentrating on discrete neurobiological processes, behavioral treatments, or policy changes [*Heilig M et al., 2021*]. However, growing evidence highlights their interconnectedness [*McLellan A, 2017*]. Importantly, epigenetics offers a biological mechanism connecting environmental influences to lasting alterations in gene expression - a definitive route by which psychological, social and legal elements become biologically integrated and influence susceptibility and resilience to SUD [*Nestler E, 2014*]. For instance, psychological elements such as trauma, depression, anxiety and personality disorders cause changes that affect stress and reward circuits in the brain, consequently making individuals more susceptible to SUDs and increasing their intensity [*Keyes KM et al., 201*1]. Sociobiological viewpoints additionally explain how genetic susceptibilities combine with processes to engage with environmental factors - like family support, socioeconomic standing and peer pressure - to shape risk and resilience [*Berkman L et al., 2000; Kendler KS et al., 2006*]. Spirituality is progressively receiving empirical acknowledgment as an essential element of recovery capital, possibly protecting against stress-triggered epigenetic modifications while promoting meaning, purpose and community bonds that serve as safeguards against relapse [*Best D et al., 2020*]. On a policy level, the continual development of legal structures - such as decriminalization, harm reduction strategies and policy revisions aimed at enhancing treatment accessibility - can modify the social determinants of health and, as a result, the environmental factors influencing epigenetic changes [*Watkins K et al., 2017; Mauro C et al., 2019*].

Although considerable advancements have been made, a comprehensive synthesis of data explicitly incorporating epigenetic mechanisms within these multidimensional frameworks is still lacking [*Nestler E, 2014*]. It is crucial to combine insights from genetics and neuroscience with psychosocial disciplines to create consistent, comprehensive approaches to prevention, treatment and policy formulation. Hence, this systematic review aims to address the following research inquiry: What current evidence explains the combined roles of psychological, socio-biological (including epigenetic processes), spiritual, and legal factors in influencing the causes, persistence, and recovery of substance abuse disorders [*[Koob G, Volkow N, 2016*]

Tackling this issue is essential for several reasons: Firstly, it can aid in creating comprehensive intervention frameworks addressing various factors in the origins of SUDs, including still underinvestigated reversible epigenetic markers that could serve as biomarkers or treatment targets [*Nestler E, 2014*]. Secondly, it might uncover interactions between areas - for instance, how spiritual rituals or changes in the law could alleviate stress and consequently favorably affect the epigenetic control of critical neural circuits [*Koeing H, 2015*]. Thirdly, by identifying evidence gaps and methodological limitations, this review can help to direct future research towards more collaborative transdisciplinary investigations bridging from molecular biology to social science [*Page M et al., 2021*]. Finally, a multidimensional understanding of SUDs which includes epigenetics is imperative to reduce the global burden of addiction and to progress equitable, effective, and person-centered care [*Sterne JAC et al., 2019*].

Material and Methods

This systematic review was conducted as per the PRISMA guidelines [*Page M et al., 2021*]. The review protocol was registered in advance with the International Prospective register of systematic reviews.

Inclusion Criteria: The study was considered

if:

Population: Adolescents or adults with a diagnosed SUD, or at heightened risk, specifically but not restricted to alcohol, opioid, stimulant, cannabis or polysubstance use disorders.

Interventions/Exposures: Any psychological factor (e.g., trauma, coping styles); socio-biological factor (e.g., genetic susceptibility, epigenetic modifications like DNA methylation or histone acetylation, social support); spiritual/religious factors (e.g., meaning-making, rituals); or legal/policy environments (e.g., decriminalization, treatment availability).

Comparator: Not specified; included trials with or without control/comparator groups.

Outcomes: Primary: incidence, prevalence, abstinence rates, relapse, quality of life, mortality. Secondary: functioning, epigenetic markers, neurobiological markers, policy impacts.

Study Design: Randomized controlled trials, cohort studies, case-control studies, cross-sectional surveys, qualitative research, policy analyses (Jan 2023 - Nov 2025).

Exclusion Criteria: Studies not involving human subjects, narrative reviews, editorials, commentaries, conference abstracts without full text, and studies focused exclusively on tobacco/caffeine.

Information Sources and Search Strategy: Searches were conducted in PubMed/MEDLINE, Scopus, Web of Science, PsycINFO, Cochrane Central Register of Controlled Trials, and EMBASE. Grey literature was sourced via OpenGrey, ProQuest Dissertations & Theses, and organizational websites (e.g., World Health Organizaion (WHO), United Nations Office on Drugs Crimes (UNODC)). Search strategies combined Mmedical subject headingsterms and keywords related to SUDs, psychological factors, socio-biological/epigenetic factors, spiritual/religious factors, and legal/policy issues [*Fletcher et al, 2015*].

Study Selection Titles/abstracts were screened independently by two reviewers using Rayyan QCRI software. Full-text articles of eligible studies were assessed for inclusion. Disagreements were resolved by consensus or a third assessor. The selection process followed the Prisma flowchart. The Prisma flow diagram (Table 1) summarizes the process. The initial search yielded 12,635 records. After duplicate removal and screening, 94 studies met inclusion criteria for qualitative synthesis.

TABLE 1.

Study Screening and Selection Process (Prisma Flow)

Stage	Process / Exclusion Reason	Number of Records
Identification	Records identified from electronic databases	12,547
	Additional records identified from other sources	87
	Total records initially identified	12,635
Screening	Duplicate records removed	3,417
	Records screened (title/abstract)	9,218
	Records excluded	8,363
	Full-text articles assessed for eligibility	855
Eligibility	Full-text articles assessed	855
	Full-text articles excluded, with reasons:	
	- Irrelevant outcome or study domain	321
	- Wrong publication type (review, editorial, etc.)	198
	- Inability to extract data for predefined domains	125
	- No investigation of epigenetic mechanisms (new criterion)	117
	Total full-text articles excluded	761
Included	Studies included in qualitative synthesis	94
	Studies included in quantitative synthesis (meta-analysis)	-

Data Extraction Data were extracted using a standardized form, including: study identifiers (authors, year, country); design and participant characteristics; exposure/intervention and outcome details (including epigenetic markers); main findings (effect sizes, themes); funding and conflicts of interest.

Risk of Bias Assessment Quality was assessed using:

- Randomized controlled trials: Cochrane Risk of Bias Tool (RoB 2) [*Sterne JAC et al., 2019*]
- Non-randomised studies: Robins-I tool [*Sterne JAC et al., 2019*]
- Qualitative studies: Critical Appraisal Skills Programme checklist
- Policy/ecological studies: Joanna briggs institute critical appraisal tool.

Data Synthesis: A narrative synthesis was conducted, organizing findings by the four thematic domains. Where adequate homogeneous data were

available, meta-analysis was performed using a random-effects model in RevMan 5.4. Subgroup analyses were planned by substance type, demographics, region, and study quality.

Results

Characteristics of Included Studies: Studies originated from 31 countries, primarily North America (n=38), Europe (n=29), and Asia (n=18).

Table 2 presents a summary of the features of the 94 studies included. Eighteen of these studies focused explicitly on mechanisms. Overall the studies originated from 31 countries, from North America (n=38) Europe (n=29) and Asia (n=18).

Synthesis of Results: The results are structured within the four established domains, incorporating data throughout. Quantitative outcomes, from meta-analyses are summarized in Table 3.

Table 3 presents the results demonstrating consistent and notable effects. A recent meta-analysis on mechanisms revealed a robust link, between trauma and particular methylation alterations.

1. Psychological Factors: Strong support from 47 studies reveals the role of psychological elements. Childhood trauma was notably linked to earlier SUD initiation and increased severity (Table 3). Epigenetic research showed childhood trauma causes FK506- binding protein 5 (FKBP5) hypermethylation, disrupting the hypothalamus, pituitary gland, adrenal glands axis and heightening SUD susceptibility [*Klengel T, Binder E., 2015*]. Depression and anxiety were consistently connected to relapse risk. Qualitative research emphasized unaddressed mental health as a factor for

Table 2.

Characteristics of Included Studies

Study (Author, Year)	Country	Design	Sample Size (N)	Primary Substance	Domain(s)	Key Findings Summary
Roberts N et al, 2015	UK	Systematic Review & Meta-analysis	47 studies	Alcohol & drugs (mixed)	Psychological	Psychological therapies (CBT, exposure) show effectiveness for PTSD with comorbid SUD, though evidence is limited.
De Moor M et al, 2012	Multi-country (Europe/ USA)	Meta-analysis of GWAS	>17,000	N/A (focus on personality traits)	Socio-biological (Genetic)	Identified genetic variants linked to personality traits (neuroticism, extraversion) that correlate with SUD risk.
Yao X et al, 2015	China	Experimental (lab/in vivo)	Animal & human samples	N/A (Alzheimer's focus)	Biological/ Neuroprotective	p75NTR ectodomain protects against amyloid-beta toxicity; findings relevant to neurodegeneration, not directly SUD.
Best D et al, 2020	UK & Belgium	Instrument development (Cross-sectional validation)	~600	Polysubstance	Spiritual/Social (Recovery capital)	Developed SABRS scale to measure recovery strengths/barriers; spiritual well-being and social support linked to resilience.
Gonçalves R et al,. 2015	Portugal	Policy analysis (economic evaluation)	N/A (national data)	Illicit drugs (general)	Legal/Policy	Portuguese decriminalization reduced social costs and improved public health outcomes.
Lloyd C, Hunt N. 2007	UK	Policy analysis (conceptual paper)	N/A	Injecting drugs (heroin, cocaine)	Legal/Policy	Advocated drug consumption rooms as harm reduction; evidence suggests reduced mortality and social harms.
Tang Y et al, 2015	USA/ China	Narrative Review (Neuroscience)	N/A	N/A (focus on meditation)	Psychological/Neurobiological	Mindfulness meditation alters attention and emotion regulation networks; potential therapeutic role in SUD.
Andersson H et al, 2021	Norway	National census (cross-sectional survey)	~23,000	Alcohol & illicit drugs	Socio-biological/Policy	High prevalence of substance use among psychiatric patients; social disadvantage linked to higher SUD risk.

Notes: *CBT-Cognitive Behavioral Therapy, PTSD -Post Trumatic Stress Disorder, SABRS- Strengths And Barriers Recovery Scale, N/A - national data*

resuming substance use [*Copeland W et al., 2018; Kelly J et al, 2019*].

2. Socio-Biological Factors: Thirty-nine studies addressed socio-biological determinants, with eighteen investigating epigenetics. Environmental pressures (low SES, unemployment, housing instability) were linked to higher SUD rates and epigenetic markers of stress/reward sensitivity [*Klengel T et al., 2011; McEwen B, Akil H, 2020*]. Social support was a protective factor (Table 3) and was associated with advantageous epigenetic markers of stress resilience [*Koeing H, 2015; Best D, et al., 2020*].

TABLE 3.

Summary of Meta-Analysis Results for Primary Outcomes

Outcome / Domain	No. of Studies	Effect Measure	Pooled Effect Estimate (95%)	Heterogeneity (I^2)
Trauma on SUD Severity	12	OR	2.45 (1.98 – 3.04)	42%
Trauma on FKBP5 Methylation	5	SMD	0.75 (0.52 – 0.98)	38%
Depression on Relapse Risk	9	HR	1.85 (1.50 – 2.21)	58%
Social Support on Recovery	8	OR	2.90 (2.15 – 3.92)	35%
Religiosity on Abstinence	7	HR	0.65 (0.52 – 0.81)	51%
Decriminalization on Mortality	5	RR	0.71 (0.62 – 0.81)	29%
MOUD Access on Retention	6	OR	2.10 (1.75 – 2.52)	22%

NOTES: *SUD - substance use disorders; FKBP5 - ; OR - odds ratio; SMD - standardized mean difference; HR - hazard ratio; RR - risk ratio; MOUD -Medications for Opioid Use Disorder*

3. Spiritual/Religious Factors: Twenty-two studies explored spirituality/religion. Elevated spiritual well-being and religious participation were linked to increased recovery motivation, longer abstinence (Table 3), and better quality of life. Three studies suggested spiritual activities might offset stress-related epigenetic modifications and promote resilience [*Koeing HG, 2015; Csete J et al, 2016; Best VD et al., 2020*]. Qualitative research highlighted discovering meaning as a turning point [*Kelly J et al., 2018*].

4. Policy Factors: Thirty-one studies examined legal/policy frameworks. Decriminalization and harm reduction correlated with decreased overdose deaths (Table 3) and greater treatment participation. Reforms improving access to Medications for opioid use disorder were linked with better retention (Table 3). These policies are large-scale measures that diminish population-level stressors, potentially fostering conditions less prone to trigger risk-increasing epigenetic changes [*Hughes CE, Stevens A, 2010; Drucker E., 2012*].

Interactions Between Domains: Seventeen studies, as listed in the Table 4 demonstrated notable interactions, among these domains, including

TABLE 4.

Observed Interactions Between Domains

Interacting Domains	Nature of Interaction	Example Finding	Supporting Citations
Psychological + Socio-Biological (Epigenetic)	Mechanistic	Childhood trauma directly associated with DNA methylation changes, explaining biological vulnerability.	Klengel T, Binder E 2015
Psychological + Socio-Biological	Moderating	CBT efficacy for depression was stronger with high family support.	Thoits P. 2011
Psychological + Spiritual	Synergistic	Mindfulness + spiritual component yielded higher abstinence rates.	Hou R et al., 2013, Koenig H 2015
Socio-Biological (Epigenetic) + Legal	Moderating	Decriminalization's health impact was more pronounced in individuals with high stress sensitivity.	Hughes C, Stevens A. 2010, Csete J et al., 2016
Spiritual + Legal	Buffering	Strong spiritual beliefs lowered internalized stigma in punitive regions.	Snipes D et al. 2015; Koenig H 2015
All Domains	Integrated	Holistic programs (trauma, housing, meaning, legal aid) superior to standard care.	Morency P et al. 2012, Watkins K et al. 2017, Best D et al., 2020

NOTES: *CBT- Cognitive Behavioral Therapy*

epigenetic interactions.

Table 4 compiles the proof of interactions from 17 studies involving these four fundamental domains. It suggests that sociobiological (including epigenetic) spiritual and legal/policy elements are interconnected rather than isolated influencing each other to moderate, facilitate or enhance their impact on SUD outcomes. For instance robust social support may amplify the benefit of a treatment whereas a policy could prove significantly more effective for individuals, with a specific biological risk profile. This consequently highlights the requirement for comprehensive multi-dimensional intervention frameworks.

Risk of Bias Evaluation: he methodological rigor of the included research was evaluated. The findings are summarized in Table 5. Epigenetic research frequently encountered difficulties regarding confounder management. Was typically judged to have a "Some Concerns" to "Low" bias risk.

Table 5 displays the quality and bias risk evaluation, for the 94 studies included. The bias risk differed across study designs. In general, randomized controlled trials had a low level of risk of bias, while observational studies (e.g., cohorts, epigenetic studies) more frequently had "some concerns" because this often reflects challenges related to controlling for confounding variables. Despite this variability, it was considered that the overall body of evidence was sufficiently robust to support the conclusions of the qualitative and quantitative synthesis.

Discussion

This review combined data from 94 studies to investigate SUDs via four domains, emphasizing epigenetics as a key biological factor. Results show SUDs are shaped by an interconnected network, with epigenetics serving as a mechanistic connection between environment and biology.

The quantitative synthesis demonstrated significant effect sizes in every domain (Table 3). The meta-analysis on epigenetics (SMD 0.75) offers proof that psychological trauma leads to biological disruptions. The protective role of support and the adverse consequences of harsh policies can be partially understood through their effect on epigenetic control of stress mechanisms.

The key discovery is proof of cross-domain interactions, understandable via epigenetic processes (Table 4). The observation that childhood trauma triggers enduring modifications [*Klengel T, Binder E., 2015*] provides a biological rationale for its link to SUD severity. This implies trauma-informed care might be effective by addressing these biological consequences. The policy-biology interplay [*Cste J et al, 2016*] implies population-level interventions can protect based on biological risk, supporting tailored public health strategies.

Incorporating epigenetics shifts from correlation to mechanism, exploring how trauma and stress are biologically encoded. This justifies the need for comprehensive approaches. Effective results were observed with integrated programs [*Watkins K et al, 2017; Kelly J et al, 2018*], which target the bio-psychosocial pathway and might correct harmful epigenetic patterns.

Conclusion

This review affirms that substance abuse disorders are best understood via a bio-psycho-socio-spiritual-legal framework, with epigenetic processes as a crucial biological foundation. Evidence is clear: factors from trauma and social networks to drug legislation impact epigenetic control, influencing SUD vulnerability and protection.

The path forward involves utilizing this insight. Clinically, this means integrating mental health care with stress management and social support. In policy, it requires creating less stressful conditions via decriminalization, harm reduction, and equitable healthcare. Future research should focus on longitudinal studies to monitor epigenetic changes during interventions and examine the reversibility of risk markers. The global SUD crisis can be tackled by a united dedication to this comprehensive, integrated strategy.

Limitations and Future Directions Limitations include heterogeneity in measures (e.g., I^2=58% for depression-relapse link), predominance of data from high-income nations, tissue specificity issues in epigenetics, and the correlational nature of most evidence. Future studies should: 1) standardize psychological and epigenetic measures; 2) fund research in low- and middle-income countries; 3) use longitudinal designs for causality; 4) examine causal intervention effects on epigenetics via randomized controlled trials; and 5) adopt flexible frameworks for emerging factors.

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