

Epigenetic Consequences of $\Delta 9$ -THC Exposure on Neuroplasticity, Reward Homeostasis, and Intergenerational Health: Implications for Abstinence- Oriented Drug Policy



Executive Summary

Δ 9-tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, induces persistent epigenetic modifications — DNA methylation changes, histone post-translational modifications, and altered non-coding RNA expression — that disrupt mesolimbic reward circuitry, impair neuroplasticity, and elevate risks of addiction, cognitive decline, and psychosis.

Cannabidiol (CBD), while pharmacologically distinct and non-intoxicating, offers only limited mitigation of these effects under conditions of repeated co-exposure, and THC-driven neuroadaptations dominate the epigenetic landscape of the mesolimbic system.

Evidence from preclinical rodent models and human cohort studies converges on the conclusion that these molecular "imprints" are often long-lasting, sometimes intergenerational, and only partially reversible with abstinence, providing a strong evidentiary basis for prevention-oriented, abstinence-focused policy in vulnerable populations such as adolescents and pregnant women.

Epigenetics Fundamentals

EPIGENETICS REFERS TO HERITABLE CHANGES IN GENE EXPRESSION THAT OCCUR WITHOUT ALTERATION OF THE UNDERLYING DNA SEQUENCE, MEDIATED PRINCIPALLY BY DNA METHYLATION, POST-TRANSLATIONAL HISTONE MODIFICATIONS

Including acetylation and methylation at residues such as H3K9/14ac, H3K4me3, H3K9me2, and H3K9me3 and non-coding RNAs such as microRNAs and piRNAs.

These mechanisms regulate the accessibility of chromatin to transcriptional machinery and thereby govern the activity of genes involved in synaptic plasticity, neurodevelopment, and reward processing. The endocannabinoid system — comprising CB1 and CB2 receptors and endogenous ligands anandamide and 2-arachidonoylglycerol — is itself subject to epigenetic regulation and, when hijacked by exogenous cannabinoids like THC, becomes a conduit through which cannabis use reshapes gene expression in the brain's reward circuitry, including the ventral tegmental area (VTA) and nucleus accumbens (NAc).

Because DNA methylation marks can persist through cell division and, in some cases, through germ-cell maturation, they represent a plausible mechanistic bridge between an individual's drug-use history and both lifelong and cross-generational phenotypic outcomes

THC-Induced Epigenetic Alterations in Reward Circuitry

Rodent studies demonstrate that developmental and adolescent **THC** exposure produces enduring histone modifications at addiction-relevant gene loci. Prenatal **THC** exposure in rats decreases the transcriptionally permissive mark **H3K4me3** and increases the repressive mark **H3K9me2** at the **Drd2 (dopamine D2 receptor)** locus in the nucleus accumbens, together with reduced **RNA** polymerase II occupancy, producing persistently reduced **Drd2** expression that extends into adulthood in both rodents and humans. Adolescent **THC** exposure produces a parallel effect at the **Penk (proenkephalin)** locus, where persistent repressive **H3K9me2** and **H3K9me3** marks accompany enduring upregulation of **Penk mRNA** in the **NAC** shell, a change linked causally to heightened heroin-seeking behaviour in adulthood. These histone-level changes at **Drd2** and **Penk** — both central to dopaminergic reward signaling — indicate that **THC** exposure during sensitive developmental windows can permanently reprogram the transcriptional "set point" of reward circuitry, consistent with heightened vulnerability to substance dependence later in life. Beyond histone modification, human peripheral studies show that cannabis use is associated with increased **CpG** methylation at the **CNR1 (CB1 receptor)** gene promoter, inversely correlated with **CB1R mRNA** expression in blood lymphocytes, with methylation status tracking measures of cannabis craving and use severity. A genome-wide methylomic analysis of two first-episode psychosis cohorts identified a differentially methylated **CpG** site in the **CAVIN1** gene associated with current cannabis use, and a separate site in the **MCU** gene reaching array-wide significance specifically for high-potency (**THC greater than 10 percent**) cannabis use, with affected pathways implicating immune and mitochondrial function. Reporting consistent with these mechanistic findings, a widely discussed 2024 study covered by The BMJ found that high-potency cannabis (**THC greater than 10 percent**) leaves a distinct epigenetic mark on genes governing energy metabolism and immune function.

Developmental window	Exposure	Epigenetic mark	Affected gene/region	Behavioural/molecular outcome
In utero	THC	H3K4me3 (decreased), H3K9me2 (increased)	Drd2, NAc	Reduced dopamine D2 receptor expression into adulthood
Adolescence	THC	H3K9me2, H3K9me3	Penk, NAc shell	Enhanced heroin-seeking behaviour
Adolescence (parental germline)	THC	DNA methylation (Dlg4/PSD- 95 network)	NAc	Cross-generational increase in heroin self- administration
Adulthood	Cannabis (chronic)	CNR1 promoter hypermethylation	Blood lymphocytes	Correlates with craving, cannabis/nicotine dependence severity
Current use, high- potency	Cannabis (THC>10%)	CpG methylation	MCU, CAVIN1	Immune/mitochondrial pathway disruption

CBD-THC Interactions and Limits of Mitigation

Cannabidiol is pharmacologically distinct from THC, lacking intoxicating activity while exhibiting anti-inflammatory, neuroprotective, anxiolytic, and antipsychotic properties in some experimental contexts. However, the epigenetic literature indicates that CBD's mitigating potential is constrained.

Reviews of the endocannabinoid epigenome note that THC-driven chromatin remodelling in mesolimbic regions — particularly histone lysine methylation changes at *Drd2* and *Penk* — is the dominant epigenetic signature associated with cannabis exposure, with CBD's epigenetic influence comparatively under-characterized and not shown to reverse THC-induced neuroadaptations under repeated co-exposure.



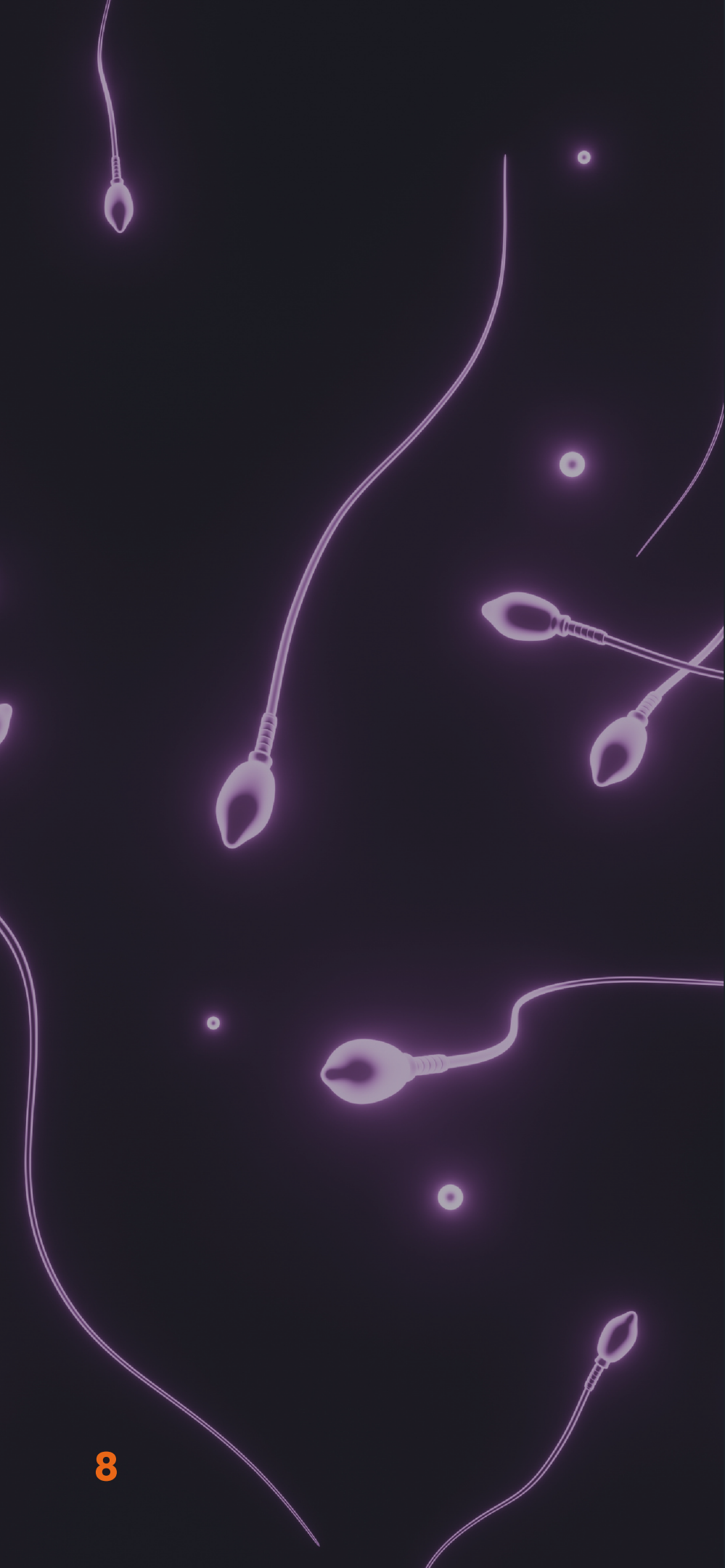
Contemporary cannabis products have also shifted dramatically toward higher THC-to-CBD ratios: confiscated cannabis samples averaged approximately 4 percent THC in 1996 versus 17.1 percent in 2017, while the THC-to-CBD ratio rose nearly tenfold, from roughly 12:1 in 2008 to 104:1 in 2017

— a trend that reduces any protective buffering CBD might theoretically offer in naturally occurring cannabis products. This pharmacological imbalance is compounded by the fact that CBD and THC share overlapping drug-metabolizing pathways (notably CYP2C9, CYP2C19, and CYP3A4), meaning co-administration can alter, rather than reliably attenuate, systemic THC exposure and its downstream epigenetic consequences.

Epigenetic Aging and Cognitive/Psychiatric Consequences

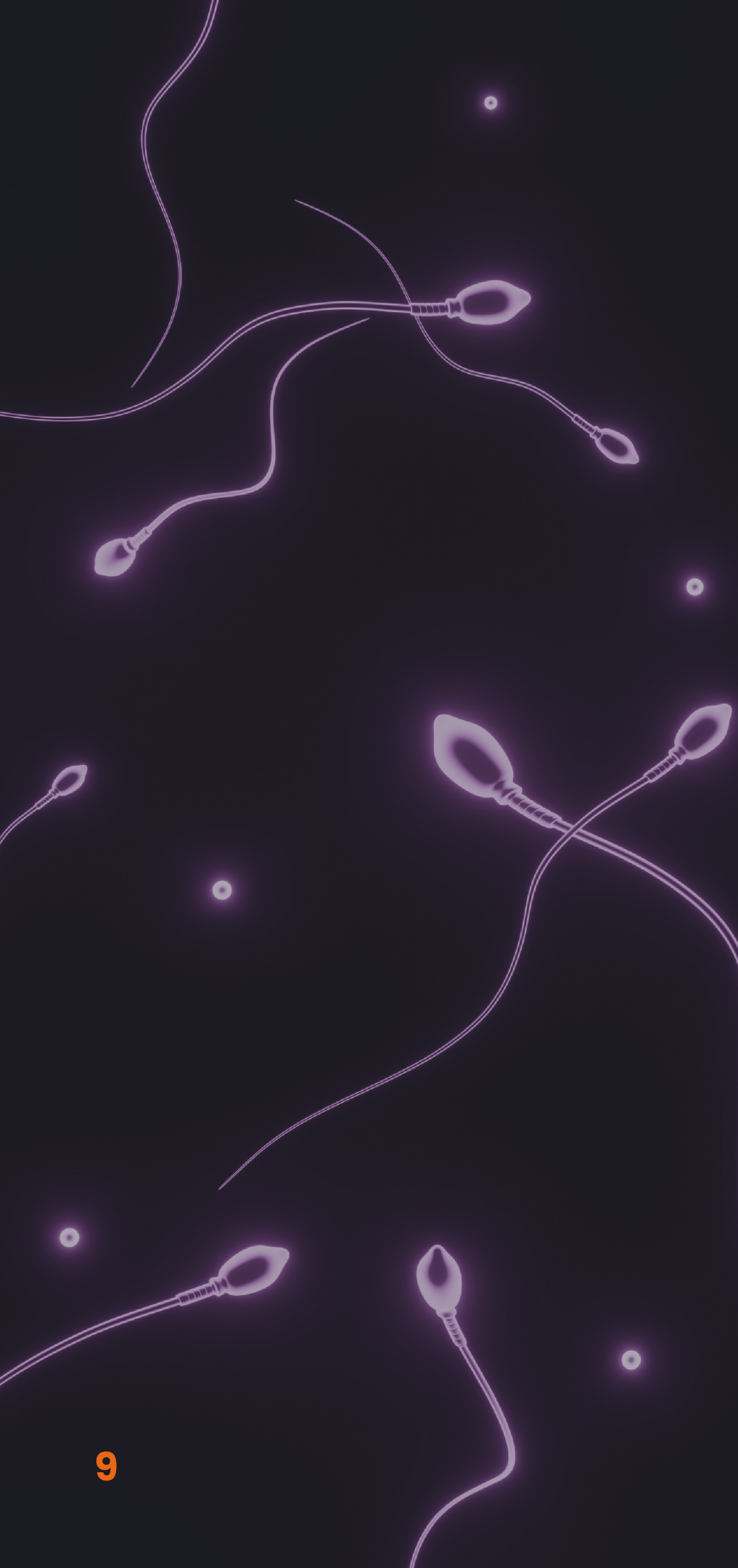
A 17-year prospective study following 154 participants from age 13 to 30 found that lifetime marijuana use significantly predicted accelerated epigenetic aging on two independent clocks (**DNAmGrimAge** and **DunedinPoAm**), with effects of similar magnitude to cigarette smoking and persisting after controlling for smoking history, demographic factors, and psychiatric symptoms. A clear dose-response relationship was observed among users, and effects were most strongly linked to recent rather than distal use, with mediation analysis indicating that roughly a third of the epigenetic aging effect operated through **hypomethylation** at the **AHRR-linked site cg05575921** — a mark also associated with **hydrocarbon/particulate inhalation**. This finding suggests that at least part of cannabis's epigenetic aging signature may be attributable to smoke inhalation rather than **THC** pharmacology alone, and that some effects may partially revert with reduced or discontinued use, though this reversibility appears incomplete and use-dependent rather than guaranteed.

Separately, genome-wide association with schizophrenia risk has implicated **COMT gene methylation** status interacting with the **Val158Met polymorphism**: adolescents with the Met/Met genotype combined with high **COMT promoter methylation** were less likely to be frequent cannabis users, underscoring a bidirectional gene-epigenome-behavior relationship relevant to psychosis vulnerability. High-potency cannabis use has been associated with elevated psychosis risk in multiple cohort studies, with one analysis estimating that as many as one in four new psychosis cases in a London catchment area were attributable to **high-THC "skunk"** cannabis use, consistent with a dose-response relationship between **THC** exposure, potency, and psychiatric outcomes.



Sperm Epigenome and Intergenerational Risk

The most direct evidence for heritable, intergenerational harm comes from studies of the sperm epigenome. In a paired human-rodent investigation, researchers found 3,979 differentially methylated CpG sites in the sperm of cannabis users compared to non-user controls, with approximately 78 percent showing decreased methylation, and 183 individual CpG sites across 177 genes exhibiting a dose-response relationship between urinary THC concentration and methylation level. Affected genes clustered in KEGG pathways including Hippo signalling, MAPK signalling, and cancer-related pathways, with substantial overlap between human and rat datasets despite limited overlap at the level of individual genes, suggesting pathway-level rather than strictly gene-specific vulnerability. In a parallel rat model, paternal THC exposure prior to mating altered DNA methylation at more than 600 genes in sperm and produced corresponding methylation and behavioral changes in unexposed adult offspring, including increased heroin self-administration, altered synaptic plasticity in the striatum, and disrupted glutamatergic and dopaminergic gene expression, centered on a *Dlg4* (PSD-95)-associated interaction network in the nucleus accumbens.

An illustration of several sperm cells on a dark purple background. The sperm cells are depicted with glowing yellow heads and long, thin, wavy tails. Some tails are long and curved, while others are shorter. There are also small, glowing yellow dots scattered around the sperm cells.

A follow-up study focused on the autism-candidate gene DLGAP2 found 17 differentially methylated CpG sites in sperm of cannabis-using men, with confirmed hypomethylation validated by bisulphite pyrosequencing; parallel rat experiments demonstrated the same locus was hypomethylated in both THC-exposed paternal sperm and the nucleus accumbens of offspring, offering direct mechanistic support for germline-to-brain transmission of an epigenetic mark. Cannabis use is also independently associated with reduced sperm concentration and impaired spermatogenesis via disruption of endocannabinoid signalling in testicular tissue, compounding fertility and offspring-health concerns. Reprogramming of DNA methylation occurs at two waves during human development — in primordial germ cells and immediately post-fertilization — yet a subset of marks, including those at imprinted loci and thousands of additional genomic regions, resist this resetting, providing a plausible mechanism by which paternal preconception cannabis exposure could transmit altered gene-regulatory information to offspring.

Genetic–Epigenetic Interplay and Pharmacogenomics

THC is metabolized primarily via **CYP2C9** (accounting for an estimated 70 percent of phase I metabolism), with lesser contributions from **CYP2C19** and **CYP3A4/5**, while **CBD** is metabolized chiefly through **CYP2C9**, **CYP2C19**, and **CYP3A4** to its active metabolites **7-OH-CBD** and **7-COOH-CBD**. Reduced-function **CYP2C92** and 3 alleles elevate and prolong plasma concentrations of **THC** and its active metabolite **11-hydroxy-THC**, increasing risk of adverse psychoactive effects, while phase II glucuronidation of **THC** and **CBD** metabolites by **UGT1A9** and **UGT2B7** provides an additional layer of interindividual pharmacokinetic variability. The transporter gene **ABCB1**, encoding **P-glycoprotein**, modulates brain disposition of **THC**, and a specific **ABCB1** variant (**rs1045642, 3435C>T**) has been associated with elevated cannabis dependence risk.

Neurobiologically, the **AKT1 rs2494732** variant is one of the most replicated pharmacogenomic findings in this field, substantially increasing odds of acute **THC**-induced psychotomimetic effects, a relationship compounded by concurrent methylation changes at neurodevelopmental genes. The **COMT Val158Met polymorphism** similarly interacts with cannabis exposure to influence executive function, memory, and psychosis susceptibility, with genotype-methylation interactions shown to moderate frequency of use in adolescents. A 2025 review characterizes **CYP2C9/THC** and **AKT1/psychotomimetic**-risk associations as areas of "implementation maturity" for pharmacogenomic-guided dosing, while flagging multigenic analgesic response signals as requiring further replication. Collectively, these gene-drug interactions indicate that epigenetic risk is not uniform across the population: individuals carrying reduced-metabolism **CYP2C9** alleles or risk variants in **AKT1** face compounded vulnerability to both acute psychotomimetic effects and the persistent epigenetic changes reviewed above.

Long-Term and Generational Harms

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The weight of evidence indicates that cannabis-induced epigenetic changes fall along a spectrum of reversibility.

Sperm-based DNA methylation marks appear more responsive to cessation of use, consistent with the ongoing turnover of germ cells, whereas methylation and histone marks established in the brain during critical prenatal or adolescent developmental windows — such as those at *Drd2* and *Penk* in the nucleus accumbens — appear substantially more durable and, in some cases, effectively permanent once established.

This asymmetry is central to the policy argument that abstinence, rather than moderated or "harm-reduced" use, offers the most robust protection against neurodevelopmental and intergenerational harm, since the brain's epigenetic imprint may not fully normalize even after drug discontinuation.



Epigenetic age acceleration associated with lifetime marijuana use correlates with broader indicators of physiological deterioration and is linked in the literature to cognitive decline, though the specific study on epigenetic aging found effects were substantially recency-dependent and potentially attributable in part to smoke inhalation rather than THC alone, an important nuance for policy framing that should not be elided. Prenatal cannabis exposure has additionally been associated in epidemiological studies with increased likelihood of NICU admission, lower birth weight, and neurodevelopmental and autism-spectrum-related outcomes, with one ecological analysis projecting a substantial rise in autism diagnoses in U.S. states with legalized cannabis relative to non-legal states by 2030, although such ecological correlations cannot establish causation independent of epigenetic confirmation.

Recommendations for Policy and Clinical Practice



The convergence of preclinical and human epigenetic evidence supports several concrete practice and policy implications. Pharmacogenomic testing — particularly for CYP2C9 variants affecting THC clearance and AKT1 variants affecting psychotomimetic risk — should be integrated into any clinical decision framework for medical cannabis to enable individualized dose titration and risk stratification. Given documented drug-drug interaction potential across CYP2C9, CYP2C19, CYP3A4, and UGT1A9/2B7 pathways shared by THC and CBD with numerous co-administered medications, clinicians should systematically screen for interacting drugs and titrate cannabinoid doses conservatively, starting low and monitoring closely.

Because the epigenetic evidence indicates THC-driven neuroadaptations in reward circuitry are established preferentially during prenatal and adolescent developmental windows and show limited reversibility, and because CBD does not reliably counteract these THC-driven changes under repeated co-exposure, public health messaging and clinical guidance should prioritize abstinence during adolescence and gestation over harm-reduction or moderated-use frameworks for these populations. Policy development should explicitly account for the escalating THC potency of contemporary cannabis products and the corresponding decline in THC-to-CBD ratios, which amplify epigenetic and psychiatric risk relative to historical cannabis preparations. Finally, given the demonstrated potential for germline transmission of cannabis-associated methylation changes, preconception cannabis use by either parent warrants specific inclusion in reproductive health counselling, an area of research and policy that remains substantially underdeveloped relative to the attention given to prenatal maternal exposure.

References

- Allen, R. M., Vassoler, F. M., Fabien, N. K., Byrnes, E. M., & Byrnes, J. J. (2020). Cannabis use and the sperm epigenome: A budding concern? *Environmental Epigenetics*, 6(1), dvaa002. <https://doi.org/10.1093/eep/dvaa002>[pubmed.ncbi.nlm.nih](https://pubmed.ncbi.nlm.nih.gov/32811111/)
- Ellul, P., Melki, C., Baglin, A., Lenglet, T., & Mouren, M. C. (2024, October 17). The impact of high-potency cannabis on DNA and psychosis: A groundbreaking epigenetic insight [Rapid response]. *The BMJ*, 387, q1702. <https://www.bmj.com/content/387/bmj.q1702/rr-0>[pmc.ncbi.nlm.nih](https://pubmed.ncbi.nlm.nih.gov/41465160/)
- Grover, S., & Kukreti, R. (2025). Medical marijuana and treatment personalization: The role of genetics and epigenetics in response to THC and CBD. [Journal name pending]. <https://pubmed.ncbi.nlm.nih.gov/41465160/>
- Hutchison, K. E., Bidwell, L. C., & Ellingson, J. M. (2024). Methylomic signature of current cannabis use in two first-episode psychosis cohorts. *Molecular Psychiatry*. <https://doi.org/10.1038/s41380-024-02689-0>[nature](https://www.nature.com/articles/s41380-024-02689-0)
- Osborn, M. P., Zaenglein, C. R., & Petrenko, C. L. M. (2022). Cannabinoids and drug metabolizing enzymes: Potential for drug-drug interactions and implications for drug safety and efficacy. *Expert Opinion on Drug Metabolism & Toxicology*, 18(12), 1–15. <https://doi.org/10.1080/17512433.2022.2148655>[tandfonline](https://www.tandfonline.com/doi/full/10.1080/17512433.2022.2148655)

Rong, C., Carmona, N. E., Lee, Y. L., Ragguett, R.-M., Pan, Z., Rosenblat, J. D., Subramaniapillai, M., Shekotikhina, M., Almatham, F., Alageel, A., Mansur, R., Ho, R. C., & McIntyre, R. S. (2018). Drug-drug interactions as a result of co-administering Δ^9 -THC and CBD with other psychotropic agents: A systematic review. *Expert Opinion on Drug Safety*, 17(1), 51–54.
<https://doi.org/10.1080/14740338.2018.1553618>scielo

Sherva, R., Wilhelmsen, K., Pomerleau, C. S., Chasse, S. A., Rice, J. P., Snedecor, S. M., Bierut, L. J., Neuman, R. J., & Pomerleau, O. F. (2017). Pharmacogenetics of cannabinoids. PMC, PMC5794848.
<https://pmc.ncbi.nlm.nih.gov/articles/PMC5794848/>pmc.ncbi.nlm.nih

Skene, K., & Murray, R. M. (2015, March 3). High potency cannabis [Rapid response]. *The BMJ*, 350, h1205.
<https://www.bmj.com/content/350/bmj.h1205/rapid-responses>

Szutorisz, H., & Hurd, Y. L. (2018). High times for cannabis: Epigenetic imprint and its legacy on brain and behavior. *Neuroscience & Biobehavioral Reviews*, 85, 93–101. <https://pmc.ncbi.nlm.nih.gov/articles/PMC5682234/>bmj

omas-Roig, J., & Havemann-Reinecke, U. (2016). Epigenetic effects of cannabis exposure. *Biological Psychiatry*, 79(7), 613–619.
<https://pmc.ncbi.nlm.nih.gov/articles/PMC4789113/>pubmed.ncbi.nlm.nih

Watson, C. W.-M., Campbell, L. M., Sun-Suslow, N., Hong, S., Umlauf, A., Ellis, R. J., Iudicello, J. E., & Letendre, S. L. (2022). Lifetime marijuana use and epigenetic age acceleration: A 17-year prospective examination. *Drug and Alcohol Dependence*, 233, 109363. <https://pmc.ncbi.nlm.nih.gov/articles/PMC8982677/>bmj



Note: two entries above (Grover & Kukreti; Skene & Murray) list partial bibliographic detail because full author/journal metadata was not retrievable from the source pages during research; verify these against the original database records (PubMed ID 41465160 and BMJ 350:h1205) before final submission.

