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The clinical use of epigenetics in psychiatry: a narrative review of epigenetic mechanisms, key candidate genes, and precision psychiatry

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The etiology of psychiatric disorders is complex, involving both genetic and environmental factors with emerging evidence suggesting that epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNA regulation, significantly contribute to mental health. The epigenome influences the development of psychiatric disorders and human behavior and may be considered in clinical observations. Epigenetic changes have been well-established in *BDNF*, *COMT*, *FKBP5*, *NR3C1*, *SLC6A4*, and *DRD2*, genes associated with psychiatric disorders, including schizophrenia, major depressive disorder (MDD), bipolar disorder (BP), post-traumatic stress disorder (PTSD), and autism spectrum disorder (ASD). Therefore, these epigenetic marks have the potential to be suitable biomarkers for diagnostics, as predictors of prognosis, and for the development of personalized treatments. By exploring the role of clinically relevant epigenetic genes, we review the role of the epigenome in the context of psychiatric disorders and human behavior; and we consider that these changes may be observed in the context of precision psychiatry. This review synthesizes findings from over 100 original research articles and reviews spanning a range of clinical studies. Despite promising associations, challenges in the onset of precision psychiatry, such as tissue heterogeneity, small sample sizes, and lack of replication, are likely to limit translation into clinical practice. Future research in precision psychiatry will help identify clinically actionable epigenetic biomarkers, ushering in an era of genomic medicine in psychiatry.

KEYWORDS

precision psychiatry, epigenetics, genomics, personalized medicine, psychiatric disorders

1 Introduction

Mental health is rooted in biological predispositions and experiences with genetic factors contributing to psychiatric disorders but not being able to fully explain differences in symptom onset, severity, and treatment response (1). The concept that external influences such as stress, trauma, *in-utero* exposures (medications, substances of abuse, starvation, viral exposure, toxoplasmosis), early-life adversity, social relationships, and lifestyle can alter gene expression without changing the DNA sequence and affects brain function and behavior is the basis for epigenetics (2). These changes to the DNA sequence include epigenetic mechanisms that are readily reversible spanning from DNA methylation, histone modifications to non-coding RNAs and chromatin remodeling (3, 4).

In psychiatry, epigenetics is not only useful for understanding how life experiences can leave molecular marks on the genome that shape behavior but has expanded in its use as biomarkers to being able to predict risk, diagnose or characterize disease subtypes, aid in treatment response, and predict prognosis and relapse risk (5). With the advent of precision psychiatry and personalized medicine, understanding an individual's epigenetic profile is essential, and when used in combination with genetic factors and their environmental history can open the door to targeted interventions and aid in better treatment response (6).

This review explores the major epigenetic mechanisms including DNA methylation, histone modifications, non-coding RNAs, and chromatin remodeling, and how each mechanism can contribute to gene-environment interactions in the brain (7). By examining well studied genes (including *BDNF*, *COMT*, *FKBP5*, *NR3C1*, *SLC6A4*, and *DRD2*) implicated in psychiatry disorders, including major depressive disorder (MDD), bipolar disorder (BP), schizophrenia, post-traumatic stress disorder (PTSD), attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), obsessive compulsive disorder (OCD), alcohol use disorder (AUD), and substance use disorder (SUD), and how their expression is regulated epigenetically, we gain insight into the molecular pathways linking lifetime experiences to lifelong mental health outcomes. This review also considers how epigenetic biomarkers and precision psychiatry are reshaping the future of diagnosis, prognosis, and personalized treatment, as well as the limitations hindering the onset of precision psychiatry.

2 Epigenetic mechanisms in psychiatry

Epigenetic modifications are readily reversible changes that influence gene expression without altering the DNA sequence (3). These mechanisms act as molecular switches or dimmers, turning genes on or off in response to internal and external stimuli (7). In psychiatry, epigenetic mechanisms play a crucial role in regulating neural pathways that underlie emotion, cognition, stress response, and behavior; and provide a compelling framework for understanding how environmental factors such as early-life adversity, trauma, social experiences, nutrition, disease, lifestyle

(physical activity and quality of sleep), and therapeutic interventions, can shape brain function and contribute to the development of mental illness (5).

2.1 DNA methylation

DNA methylation is the process by which DNA methyltransferases (DNMTs) catalyze the addition of a methyl group ($-CH_3$) to cytosine residues on the 5-carbon of the cytosine ring in CpG dinucleotides, cytosine-rich regions often near gene promoters, between genes (referred to as intergenic regions), or in gene bodies (8). When methylation occurs within promoter regions, transcription factors are blocked from binding and gene expression is reduced or silenced (9). In psychiatry, this dynamic process where methylation is readily added or removed occurs in response to developmental cues and environmental exposures such as stress, trauma, and aging (10). Because methylation patterns are inherited through cell divisions, DNA methylation is said to affect cellular memory with gene expression states preserved across time and development (11). In the context of the epigenome, DNA methylation plays a central role in important biological processes including embryonic development, X-chromosome inactivation, imprinting, tissue-specific gene expression, and brain plasticity (12).

In MDD, hypermethylation of *BDNF* promoters, especially exon IV, reduces *BDNF* expression and impairs neuroplasticity whereas hypermethylation of the *NR3C1* promoter impairs hypothalamic-pituitary-adrenal (HPA)-axis regulation following childhood trauma (13, 14). Studies in schizophrenia show that *RELN* hypermethylation reduces reelin expression and disrupts synaptic plasticity and neuronal migration; *COMT* methylation alters dopamine metabolism; and *BDNF* methylation is associated with cognitive impairment and negative symptoms (13, 15). In BD, epigenetic signatures are often state-dependent, with methylation differing in manic and depressive states compared to euthymic states (16). Likewise, increased *BDNF* methylation is reported during mood episodes, where it correlates with symptom severity (17). In ASD, global methylation differences are observed in neuronal development genes. In *MECP2*, both mutations and methylation abnormalities interact to disrupt synaptic development (18). In addiction and substance use disorders, hypermethylation of the mu-opioid receptor (*OPRM1*) is linked to heroin and alcohol dependence, and these epigenetic changes can persist to influence relapse risk (19, 20). However, *OPRM1* is not in the discussion of this review.

2.2 Histone modifications

Histone modifications are chemical changes to histone proteins that influence how DNA is packaged. DNA is wrapped around histone (H) octamers (with the core units made of H2A, H2B, H3, and H4) to form nucleosomes (21). Most histone modifications occur on histone tails (mainly on H3 and H4) and by chemical modifications including acetylation, methylation, phosphorylation,

ubiquitination, and sumoylation. Histone acetyltransferases (HATs) add acetyl groups to lysine residues on histone tails, a modification referred to as acetylation (22). Acetylation activates gene expression by loosening chromatin and is reversed by histone deacetylases (HDACs) in a process known as deacetylation. Histones methylation is catalyzed by histone methyltransferases, which add methyl groups to lysine or arginine residues on histone tails, and reversed by histone demethylases (23). In this context, gene expression is activated or silenced depending on the specific sites and number of methyl groups (24). Other forms of histone modifications include phosphorylation, which is often associated with DNA repair and chromatin remodeling, as well as ubiquitination and sumoylation, which influence chromatin compaction and can contribute to gene repression (25).

These epigenetic changes modulate the chromatin structure and influence transcription factor accessibility and RNA polymerase binding, often interacting with other epigenetic mechanisms like DNA methylation to synergistically promote or repress gene expression (for example, methylated DNA recruiting histone-modifying enzymes) (26). In the context of psychiatry, abnormal histone modifications have been linked to multiple psychiatric disorders. Studies in depression show decreased H2K9ac at *BDNF*, in schizophrenia where H3K27me3 is modified at *GAD1*, in PTSD with repressive marks on *FKBP5*, and in addiction where changes in H3 acetylation impact reward circuits (27). HDAC inhibitors such as valproic acid and sodium butyrate can restore normal gene expression in psychiatric conditions further validating that histone marks may serve as biomarkers or targets for personalized therapies in mood and anxiety disorders (28).

2.3 MicroRNA regulation

MicroRNAs (miRNAs) are small (~22 nucleotides), non-coding RNA molecules that regulate gene expression post-transcriptionally by binding to target messenger RNAs (mRNAs) and suppress translation or promote mRNA degradation (29). miRNAs are both targets and regulators of epigenetic processes since they exist within a feedback loop with DNA methylation and histone modifications (30). As epigenetic targets, miRNA genes can be silenced or activated by DNA methylation or histone modifications, and as epigenetic regulators, miRNAs can target enzymes like DNMTs, HDACs, or histone methyltransferases for silencing, thereby influencing epigenetic landscapes. miRNAs are context-dependent, so their effect may vary by cell type, developmental stage, and environment, and they are also dynamic, changing in response to stress, drugs, experiences, and hormones (31). miRNAs are abundant in the brain and have crucial roles in neuronal development and differentiation, synaptic plasticity and learning, stress responses, and emotional regulation.

Changes in miRNA expression are clinically relevant across multiple psychiatric disorders. Genome-wide association studies (GWAS) in schizophrenia have implicated miR-137 as one of the most significant risk loci for schizophrenia (32). This miRNA regulates neurodevelopment and synaptic signaling genes, such as

CACNA1C and *TCF4*, and has been proposed as a biomarker, with therapeutic modulation offering a potential means to stabilize synaptic function (32, 33). In depression, miR-124 is abundant in the brain and regulates neurogenesis and stress response; dysregulated levels have been associated with hippocampal neuroplasticity deficits (34). Other studies have reported that plasma miR-124 levels increase after citalopram treatment relative to untreated controls (35). In similar studies, miR-16-5p is reduced in peripheral blood of individuals with MDD and BD (36). Despite this findings, a major limitation is that miRNA expression is often assessed in peripheral blood rather than the brain directly. In schizophrenia, miR-132, miR-134, miR-1271, miR-664, miR-200c, and miR-432 are significantly decreased; however, antipsychotic treatment increases miR-132, miR-664, and miR-1271 compared with pre-treatment levels (37). In other psychiatric disorders, notable miRNAs include miR-34a and miR-181, which are significantly altered in schizophrenia; miR-146a and miR-134, which are altered in ASD, and miR-121 and miR-132, which are associated with addiction (38).

2.4 Chromatin remodeling

Chromatin remodeling is the dynamic structural change in chromatin which regulates access to DNA for transcription, replication, and repair. Chromatin remodeling controls the transition between euchromatin and heterochromatin thereby allowing or blocking gene expression (39). This process is mediated by ATP-dependent chromatin remodeling complexes, which move, eject, or restructure nucleosomes to increase DNA accessibility. Key ATP-dependent chromatin remodeling complexes include: (1) SWI/SNF, which slides or ejects nucleosomes to open chromatin (e.g., BRG1, BAF complex); (2) ISWI, which spaces nucleosomes for transcriptional regulation (e.g., SNF2H); (3) CHD, which contributes to nucleosome assembly and remodeling (e.g., CHD1, CHD8); and (4) INO80, which couples remodeling to DNA repair and replication (e.g., INO80, SRCAP) (40). Chromatin remodeling works with other epigenetic mechanisms by directly interacting with histone modifiers, DNA methylation machinery, and non-coding RNAs (41). In the context of psychiatric and neurological disorders, mutations in chromatin complexes have been observed in schizophrenia where synaptic gene regulation is disrupted, and these mutations are also high-confidence genetic risk factors for ASD (42). In depression, altered chromatin accessibility have been observed at *BDNF*, *GAD1*, *NR3C1* in response to stress (43).

Currently, chromatin accessibility profiling (e.g., ATAC-seq) is being explored as a biomarker tool in psychiatry (44). Because most psychiatric GWAS findings lie in noncoding regions (i.e., enhancers or promoters), ATAC-seq helps identify which of these regions are open and accessible in brain cells. For example, ATAC-seq can reveal which accessible regions are specific to particular cell types, such as excitatory neurons, interneurons, or microglia. Therefore, single-cell chromatin accessibility profiling (scATAC-seq), together with gene expression assays, is used to identify disease-relevant fetal

and adult brain cell types implicated in major depressive disorder, body mass index (BMI), ADHD, and schizophrenia (45). This approach has been applied to the identification of single nucleotide polymorphisms (SNPs) with schizophrenia risk in accessible enhancers of glutamatergic neurons, notably within genes such as *CACNA1C*, which plays a key role in synaptic function (46). Studies employing ATAC-seq have revealed increased accessibility of glucocorticoid-responsive enhancers in the brains of stressed individuals. These insights have driven the development of FKBP5 inhibitors, which are now being explored in clinical trials for PTSD and alcohol use disorder (47, 48).

2.5 Environmental influence on epigenetic changes

Environmental epigenetics studies how external factors like stress, diet, toxins, infections, relationships, and experiences, can lead to long-lasting changes in gene expression by altering the epigenome (49). For example, nutrition provides methyl donors and cofactors for epigenetic enzymes such as folate, B12, and choline which influence DNA methylation and for which undernutrition affects *IGF2* expression (50). Exercise promotes histone acetylation and *BDNF* expression with aerobic activity increasing *BDNF* (51). Toxins and pollutants can alter the epigenome by inducing oxidative stress and disrupting methylation machinery, and in the brain, bisphenol A (BPA), lead, and air pollution alter methylation in brain development genes (52–54). However, the evidence surrounding these external factors is less robust than that for early-life stress and warrants further investigation to become clinically actionable. In the case of early-life stress, commonly experienced through childhood abuse, DNA methylation of stress-regulating genes (i.e. *NR3C1*, *FKBP5*) increases, hypermethylating the glucocorticoid receptor and altering the HPA axis (10). This effect stems into social environments that affect methylation of social, stress, and emotion-related genes; and, in this context, studies demonstrate that having a high-quality rearing lowers *OXTR* and *NR3C1* methylation (55). Despite these modifications, maladaptive epigenetic changes can be reversed or normalized by psychological interventions such as cognitive behavioral therapy (CBT) and mindfulness, and studies have examined the potential of these interventions to reduce methylation of *FKBP5* and *SLC6A4* and for psychiatric medications like SSRIs, antipsychotics and the HDAC inhibitor valproate to alter epigenetic landscapes (56, 57).

3 Clinically relevant epigenetically regulated genes in psychiatry

3.1 Brain-derived neurotrophic factor

The brain-derived neurotrophic factor (BDNF) is an essential protein in the brain and nervous system. BDNF is a growth factor that supports neuroplasticity, neuronal survival, neurogenesis, and

contributes to neural repair and recovery after brain injuries like stroke or trauma (58). *BDNF* is highly expressed throughout the brain including the hippocampus, prefrontal cortex, amygdala, cortex, and basal forebrain (59). In the context of cognitive function, higher *BDNF* levels are associated with improved cognitive performance including memory, attention, and problem-solving (60). In mood regulation, low *BDNF* levels are linked to depression and anxiety. The *BDNF* gene has multiple promoters which are prone to epigenetic regulation. For example, exon IV of *BDNF* is highly sensitive to environmental signals and hypermethylation of *BDNF* promoter regions, especially exon IV, reduces *BDNF* expression (61).

Studies have reported reduced *BDNF* expression in people with MDD, PTSD, schizophrenia, and after early-life stress or childhood trauma (62). In depression, studies report low peripheral *BDNF* levels and higher promoter methylation, while antidepressants and electroconvulsive therapy (ECT) increase *BDNF* expression and reverse methylation (63, 64). In BD, *BDNF* epigenetic changes are state-dependent, with lower levels during manic and depressive episodes compared with euthymia (65). Studies in PTSD and suicidality demonstrate that early-life trauma is associated with long-lasting *BDNF* promoter methylation, affecting stress reactivity and fear extinction, and for suicide victims, *BDNF* promoter hypermethylation is observed in the prefrontal cortex and hippocampus (66–68).

BDNF is subject to other forms of epigenetic regulation, including histone modifications, whereby acetylation enhances gene expression and histone deacetylation represses expression (69). Selective serotonin reuptake inhibitors (SSRIs) and HDAC inhibitors can increase histone acetylation at the *BDNF* loci therefore boosting expressions (70). In addition to DNA and histone modifications, *BDNF* expression is epigenetically regulated by miRNAs (including miR-132 and miR-206), which can bind *BDNF* mRNA and suppress translation. Dysregulation of these miRNAs is linked to mood disorder and schizophrenia (71). Although important progress has been made, notable limitations remain. The epigenetic regulation of *BDNF* varies by isoform and promoter, but this distinction is often overlooked, and most studies are further limited by the absence of rigorously controlled longitudinal cohorts. A summary of these epigenetic alterations has been captured in Table 1.

3.2 Catechol-O-methyltransferase

The catechol-O-methyltransferase (COMT) enzyme metabolizes catecholamines including the neurotransmitters dopamine, norepinephrine, and epinephrine by transferring a methyl group from S-adenosylmethionine (SAM) to these catecholamines thus facilitating catecholamine degradation and regulating their levels in various tissues including the brain (72). COMT exists in two primary forms: soluble COMT (S-COMT) and membrane-bound COMT (MB-COMT). S-COMT is predominantly found in peripheral tissues like the liver, kidneys, and blood and plays a critical role in metabolizing catecholamines

circulating in the body. MB-COMT is mainly produced by nerve cells in the brain and is integral to the degradation of neurotransmitters within the central nervous system (73). In the brain, COMT regulates dopamine levels in regions crucial for cognitive functions like the prefrontal cortex. Based on the concept that COMT regulates dopamine metabolism, epigenetic regulation of *COMT* influences not only gene expression and enzyme activity but neurotransmitter metabolism and alters dopamine signaling, key features in schizophrenia and cognitive dysfunction (74). In fact, methylation of the *COMT* promoter has been associated with reduced gene expression in both brain and peripheral tissues, leading to increased dopamine availability in the prefrontal cortex (75).

Studies in schizophrenia support that hypomethylation of the *COMT* promoter increases COMT activity and enhances dopamine degradation in the prefrontal cortex. This dopamine deficit could contribute to the cognitive impairment and negative symptoms which are 2 of the three main sub-syndromes in individuals with schizophrenia (76). In BD studies, dysregulation of dopamine metabolism may contribute to the signature mood instability of this disorder (77). Studies in depression show that hypermethylation of *COMT* is associated with MDD, and often correlated with stress exposure and treatment response (78). In PTSD, increased *COMT* methylation is associated with impaired fear inhibition, which affects stress responsivity via dopamine regulation (79). In the context of environmental interactions, cigarette smoking is associated with hypermethylation of the MB-COMT promoter, while cannabis use interacts with the *COMT* Val158Met genotype/epigenotype to influence psychosis risk (80, 81). Although less well characterized, histone modifications also affect *COMT* expression, and the general mechanisms such as histone acetylation and methylation are known to influence gene expression in neuropsychiatric contexts (82). Several limitations remain in these studies, notably the requirement for larger cohorts, independent study replication, and efforts to disentangle genotype-epigenotype interactions, such as demonstrating how Val/Met allele effects differ according to methylation status. A summary of these epigenetic alterations has been captured in Table 1.

3.3 FK506 binding protein 5

The FK506 Binding Protein 5 (*FKBP5*) gene encodes FKBP51, a co-chaperone protein that modulates the glucocorticoid receptor (GR) complex and affects cortisol signaling (83). By altering GR sensitivity, *FKBP5* plays a critical role in stress hormone regulation, influencing the HPA axis, and impacting various psychiatric conditions (84). Stress exposure such as early-life stress decreases methylation of *FKBP5* and upregulates *FKBP5* gene expression which reduces GR sensitivity and may cause an exaggerated stress response (85). In an interplay between the genome and epigenome, polymorphisms in the *FKBP5* gene (such as rs1360780) are linked to differential methylation patterns in response to stress that influence gene expression and stress reactivity (56).

In individuals with PTSD, carriers of *FKBP5* polymorphisms who experience childhood trauma exhibit altered *FKBP5* methylation, which increases their risk of developing the disorder (86). Stress has also been shown to influence chromatin accessibility at the *FKBP5* locus, although this area remains less well characterized than DNA methylation (87). Additionally, microRNAs such as miR-15 and miR-511 have been proposed to regulate *FKBP5* expression, linking it to pathways of inflammation and stress response (88). MDD studies show that *FKBP5* expression is epigenetically elevated and associated with structural and functional alterations in brain regions involved in emotional processing further contributing to MDD pathophysiology (89). With BD, methylation variations in *FKBP5* expression are observed which suggests a role in mood regulation and stress response mechanisms (90). In OCD, reduced DNA methylation at the *FKBP5* intron 7 CpG site has been reported in male patients relative to controls. While these findings suggest a potential role for *FKBP5* methylation in the pathogenesis of OCD, additional studies are required to confirm whether altered DNA methylation at intron 7 contributes to disease mechanisms in concert with HPA axis dysregulation (91). Therapeutic strategies shown to normalize *FKBP5* methylation include antidepressants, cognitive behavioral therapy (CBT), and mindfulness practices (92–94). Importantly, *FKBP5* alterations are not observed in all trauma survivors, underscoring limitations in biomarker specificity and sensitivity that warrant further investigation. A summary of these epigenetic alterations has been captured in Table 1.

3.4 Glucocorticoid receptor

The *NR3C1* gene encodes the glucocorticoid receptor (GR), the main receptor for cortisol and a key regulator of the HPA axis (95). As the body's primary stress hormone, cortisol binds to GR allowing GR to translocate to the nucleus and regulate the expression of stress-responsive genes. GR signaling is critical for regulating the HPA axis feedback loop and controls inflammation, immune responses, and metabolism while modulating neurodevelopment, mood, and cognitive function (96). Based on the concept that *NR3C1* is critical for glucocorticoid signaling and stress regulation, hypermethylation of *NR3C1* in individuals exposed to childhood adversity correlates with increased vulnerability to PTSD, depression, and suicide risk (2). Targeting *NR3C1* methylation patterns may provide therapeutic potential for stress-related psychiatric disorders (97).

The *NR3C1* gene is said to be environmentally programmed by stress reactivity because early-life adversity such as childhood abuse, neglect, and maternal stress are strongly associated with hypermethylation of exon 1F. The *NR3C1* exon 1F is a critical promoter region that undergoes epigenetic regulation via DNA methylation where hypermethylation of this region reduces *NR3C1* expression, decreases GR availability, impairs cortisol feedback sensitivity, and heightens or prolongs stress responses (97). In MDD, hypermethylation of *NR3C1* promoter regions in

individuals with childhood trauma is associated with reduced GR expression and dysregulation of the HPA axis, a hallmark of depression (14). PTSD studies show *NR3C1* hypermethylation from early trauma leads to decreased GR function, sustained stress reactivity, and fear memory consolidation (56). In studies of post-mortem brain tissue from suicide completers with a history of abuse, *NR3C1* methylation is increased, suggesting a biological embedding of trauma at the molecular level (43). Several studies on anxiety disorders link epigenetic dysregulation of GR signaling with generalized anxiety and panic disorder, likely through heightened cortisol responsiveness (98). *NR3C1* methylation patterns are also altered in schizophrenia and BD, which may contribute to neuroendocrine dysfunction in these disorders, although these findings are more variable (99).

3.5 Serotonin transporter (*SLC6A4*/5-HTTLPR)

The *SLC6A4* gene encodes the serotonin transporter (SERT), a membrane protein responsible for the reuptake of serotonin (5-HT) from the synaptic cleft back into presynaptic neurons (100). *SLC6A4* regulates serotonin availability in the brain, impacts mood, emotion, anxiety, and stress regulation, and is the main target of SSRIs used in treating MDD and anxiety disorders (101). The serotonin-transporter-linked polymorphic region (5-HTTLPR) is a region in the *SLC6A4* promoter with two main alleles: the short (s) allele and the long (l) allele. The short allele has lower transcriptional efficiency and reduced SERT expression and is often associated with increased emotional reactivity and greater susceptibility to stress whereas the long allele has higher transcription and increased SERT expression (102). *SLC6A4* is epigenetically regulated by DNA methylation influencing *SLC6A4* expression independently or interactively with 5-HTTLPR genotype (103). Methylation of CpG sites in the *SLC6A4* promoter, especially near exon 1, and the 5-HTTLPR region reduces *SLC6A4* expression lowering SERT expression, SERT availability, and increasing extracellular serotonin. This effect is often independent of genotype and can result from environmental exposures such as early-life trauma or stress. S allele carriers that experience early-life stress or trauma tend to show higher *SLC6A4* promoter methylation suggesting that stress programs serotonin signaling via epigenetic changes (104). Childhood adversity, maternal depression, or prenatal stress increase *SLC6A4* methylation and cause impaired stress resilience and altered emotional regulation later in life (105).

SLC6A4 hypermethylation, together with the presence of the S allele, is linked to an increased risk of depression because SERT expression and serotonin uptake are reduced, especially in those with childhood adversity (105). SSRIs may normalize some of these methylation changes and are often examined within gene x environment (GxE) models in psychiatric research, which also suggests that *SLC6A4* methylation can be used as an indicator of treatment response to SSRIs or psychotherapy (106). Elevated *SLC6A4* methylation is also associated with generalized anxiety

disorder (GAD) and panic disorder, correlates with increased anxiety traits, social anxiety, and amygdala hyperreactivity, and may explain how altered serotonin signaling affects fear processing and threat detection (107). With PTSD, *SLC6A4* methylation is increased in S allele carriers with trauma exposure. Several studies in veterans and trauma survivors show higher methylation at *SLC6A4* CpGs in patients with PTSD symptoms, demonstrating that these epigenetic changes reflect persistent alterations in stress reactivity pathways and can serve as biomarkers of stress vulnerability (105). In suicide studies, individuals with a history of suicide attempts or ideation that have been exposed to trauma have increased *SLC6A4* methylation (43). Some studies link neurodevelopmental risk for attention deficit hyperactivity disorder (ADHD) to differences in *SLC6A4* methylation patterns although these findings are mixed (108). A summary of these epigenetic alterations has been captured in Table 1.

3.6 Dopamine Receptor D2

The *DRD2* gene encodes the D2 subtype of the five dopamine receptors. As a G-protein-coupled receptor (GPCR), *DRD2* is involved in modulating dopaminergic neurotransmission and plays a role as an inhibitory receptor by reducing neuronal excitability and dopamine synthesis via Gi/o protein coupling (109, 110). *DRD2* expression is observed at high levels in the striatum, prefrontal cortex, and limbic regions to regulate reward processing, motivation and reinforcement, cognitive control, movement and motor coordination (111). There are two main D2 receptor isoforms that are synthesized by differential splicing of introns and exons form the D2 gene. The short isoform (D2S) is a presynaptic auto-receptor on dopamine neurons that regulates dopamine release, and the long isoform (D2L) is a postsynaptic receptor involved in postsynaptic signaling (112).

DRD2 is subject to epigenetic regulation and changes in *DRD2* expression may impact dopamine signaling and contribute to neuropsychiatric disorders (113). For example, DNA hypermethylation of *DRD2* promoter regions, such as in exon 1 or upstream CpG islands, downregulates receptor expression; on the contrary, hypomethylation increases *DRD2* levels thereby altering dopamine sensitivity (114). Histone deacetylase inhibitors (HDACi) can increase *DRD2* expression in certain contexts, suggesting chromatin remodeling as a *DRD2* epigenetic regulator (28). MicroRNAs, such as miR-9 and miR-326, are another example of *DRD2* epigenetic regulation since they target *DRD2* mRNA and reduce translation. Dysregulation of these miRNAs is linked to changes in *DRD2* signaling in psychiatric illness (115).

Postsynaptic D2 receptor overactivation, resulting from increased presynaptic dopamine release in the nucleus accumbens (located in the ventral striatum), is central to the dopamine hypothesis of schizophrenia (116). Postmortem studies show altered *DRD2* methylation in the prefrontal cortex and striatum of individuals with schizophrenia (117). Studies in substance use disorders including cocaine, alcohol, and nicotine show that substance use can alter *DRD2* methylation in animal and human

TABLE 1 Epigenetic alterations across psychiatric disorders.

Disease state	Epigenetic change(s)
Major Depressive Disorder (MDD)	<i>BDNF</i> : reduced peripheral levels; promoter hypermethylation; reversed by antidepressants & electroconvulsive therapy
	<i>COMT</i> : hypermethylation associated with stress & treatment response
	<i>FKBP5</i> : elevated expression via demethylation; linked to altered brain structure/function
	<i>NR3C1</i> : hypermethylation with childhood trauma decreases GR expression & HPA axis dysregulation
	<i>SLC6A4</i> : promoter hypermethylation (especially S allele carriers) reduces SERT expression; altered treatment response to SSRIs/psychotherapy
Bipolar Disorder (BD)	<i>BDNF</i> : state-dependent changes; lower levels during manic/depressive episodes vs. euthymia
	<i>COMT</i> : dysregulated dopamine metabolism may drive mood instability
	<i>FKBP5</i> : methylation variation suggests role in mood regulation/stress response
	<i>NR3C1</i> : altered methylation patterns contribute to neuroendocrine dysfunction (variable findings)
Post-Traumatic Stress Disorder (PTSD)	<i>BDNF</i> : long-lasting promoter hypermethylation after trauma; decreased stress reactivity/fear extinction
	<i>FKBP5</i> : trauma + risk allele carriers have altered methylation; increased risk of PTSD
	<i>NR3C1</i> : hypermethylation from early trauma leads to decreased GR function, sustained stress reactivity/fear memory consolidation
	<i>SLC6A4</i> : hypermethylation in S allele carriers with trauma exposure have increased PTSD symptoms
Schizophrenia	<i>BDNF</i> : reduced expression linked to cognitive impairment & negative symptoms
	<i>COMT</i> : hypomethylation increases COMT activity leading to excess dopamine degradation in prefrontal cortex and cognitive/negative symptoms
	<i>NR3C1</i> : altered methylation patterns contribute to neuroendocrine dysfunction (variable findings)
	<i>DRD2</i> : altered promoter methylation in prefrontal cortex & striatum; dysregulated dopamine signaling
	<i>miRNAs</i> : decreased miR-132, miR-134, miR-1271, miR-664, miR-200c, miR-432; some increase after antipsychotic treatment
Suicidality	<i>BDNF</i> : promoter hypermethylation in prefrontal cortex & hippocampus of suicide victims
	<i>NR3C1</i> : hypermethylation in postmortem brain tissue from abuse victims causes trauma embedding
	<i>SLC6A4</i> : increased methylation in individuals with suicide attempts/ideation after trauma
Anxiety Disorders	<i>NR3C1</i> : epigenetic dysregulation of GR signaling increases cortisol responsiveness
	<i>SLC6A4</i> : elevated methylation associated with GAD, panic disorder, social anxiety, amygdala hyperreactivity
Autism Spectrum Disorder (ASD)	Global methylation differences in neuronal development genes (e.g., <i>MECP2</i>)
	Altered miRNAs (miR-146a, miR-134)
Obsessive-Compulsive Disorder (OCD)	<i>FKBP5</i> : reduced methylation at intron 7 CpG site in men causes possible HPA axis dysfunction
Addiction & Substance Use Disorders	<i>OPRM1</i> : hypermethylation linked to heroin & alcohol dependence; persistent changes affect relapse risk
	<i>DRD2</i> : hypermethylation decreases expression causing reward deficiency & addiction vulnerability
	<i>miRNAs</i> : altered miR-121 and miR-132
Attention-Deficit/Hyperactivity Disorder (ADHD)	<i>SLC6A4</i> : mixed findings linking methylation differences to neurodevelopmental risk
	<i>DRD2</i> : polymorphisms and methylation status associated with impulsivity & dopamine dysfunction

models. In this context, reduced *DRD2* expression from DNA hypermethylation is associated with reward deficiency and addiction vulnerability (118). In ADHD, *DRD2* polymorphisms and methylation status are linked to impulsivity and dopaminergic dysfunction (119). A summary of these epigenetic alterations has been captured in Table 1.

4 Clinical implications of epigenetics in psychiatry

4.1 Epigenetic-based therapies

Epigenetic-based therapies are designed to regulate gene expression by targeting epigenomic processes while leaving DNA sequence itself unchanged. An example of an epigenetic-based therapy is HDAC inhibition, which increase histone acetylation thereby relaxing the chromatic and increasing gene expression (27). Valproic acid, sodium butyrate, and Vorinostat (SAHA) are examples of HDAC inhibitors that are currently used to target depression, schizophrenia, BD, PTSD and are being preclinically explored for ASD (120). Several therapies are in experimental stages including bromodomain and extra-terminal domain (BET) inhibitors, which bind to BET proteins and prevent them from interacting with acetylated histones modulating gene transcription. JQ1 is an investigational BET inhibitor for addiction, mood disorders, and preclinical neuroinflammation (121).

In addition to HDAC inhibitors, several experimental miRNA-based therapies for psychiatric disorders like schizophrenia, MDD, anxiety, and neurodevelopmental disorders are currently under investigation (122). These miRNA-based therapies include miR-124, miR-132, miR-135 and miR-146a (123). Other epigenetic-based therapies include epigenetic editing approaches using CRISPR/dCas9 for targeted DNA methylation or demethylation, histone editing by CRISPR-dCas9-TET1 for demethylation, and CRISPR-dCas9-HDAC for repression. These therapies focus on reversing stress-induced gene silencing, and studies demonstrate that such interventions can alleviate symptoms of MDD, anxiety, PTSD, while enhancing cognitive resilience (124). They are currently being evaluated in preclinical models of PTSD, addiction, and MDD (125, 126).

4.2 Precision psychiatry and future directions

In the era of precision psychiatry, understanding epigenetic patterns can refine diagnosis and improve clinical subtyping. For example, methylation of *NR3C1*, *BDNF*, and *FKBP5* can differentiate subtypes of MDD, PTSD, or schizophrenia, help to identify stress-responsiveness compared with neurodevelopmental forms of illness, and be used as predictors of risk and resilience (5). Epigenetic markers like *SLC6A4* or *OXTR* methylation can predict risk for MDD or anxiety after trauma and individual resilience profiles (127). This epigenetic information may be useful for detecting at-risk individuals such as trauma-exposed youth and

providing early intervention (128). In the context of pharmacogenetics, methylation of genes like *BDNF*, *SLC6A4*, and *FKBP5* may predict response to SSRIs, psychotherapy, or electroconvulsive therapy (129). For example, clinical studies suggest that low *BDNF* methylation correlates with better SSRI response and high *NR3C1* methylation predicts poorer CBT response in PTSD (56). Additionally, epigenetic biomarkers could be used to guide novel epigenetic therapies in patients with hypermethylated *GAD1* or *RELN* who may benefit from HDAC inhibitors or DNMT inhibitors to restore expression of key neuroplasticity genes (130).

5 Limitations

Several limitations hinder the application of epigenetic findings as biomarkers in psychiatry. First, access to brain tissue is limited, and sampling relies on that from blood, saliva, or postmortem samples, which may not reflect central nervous system changes. Cell type specificity varies since epigenetic marks vary dramatically between neurons, glia, and other brain cells (45). Therefore, bulk tissue analyses can obscure important differences at the cellular level. As discussed, epigenetic modifications are dynamic and can change rapidly. Therefore, stress, diet, and/or medications allow for temporal variability, which may not be reflected in the long-term pattern. Different assays can yield inconsistent results. For example, bisulfite sequencing vs. ChIP-seq (chromatin immunoprecipitation followed by sequencing) can complicate reproducibility across studies. Lastly, most large-scale genome and epigenome reference datasets, including those used for methylation and chromatin analyses, are derived predominantly from individuals of European ancestry. Therefore, the current body of research lacks ancestral diversity among study populations and may obscure ancestry-specific epigenetic signatures or gene-environment interactions that contribute to psychiatric risk. Future research efforts should focus on expanding cohort diversity to improve the equity, accuracy, and translational relevance of epigenetic discoveries.

In addition to these limitations, there are several confounding effects, including lifestyle, socioeconomic factors, substance use, and comorbid medical conditions, that need to be considered, as they can shape the epigenome, making it difficult to isolate psychiatry-specific signatures. It is important to emphasize that epigenetic findings have not yet been validated for routine use in psychiatric practice. Lastly, because psychiatric disorders are influenced by thousands of genetic and environmental factors, an exclusive focus on epigenetics risks oversimplifying the complexity of disease etiology.

6 Conclusion

In this review, we have outlined the epigenetic mechanisms implicated in psychiatric disorders and their relation to mental health conditions. Extensive studies demonstrate that epigenetic modifications influence the development and progression of psychiatric disorders as well as human behavior. With ongoing research into the clinical applications of epigenetically informed

interventions, it is plausible that such treatments will become part of routine psychiatric care. As highlighted, the transition toward precision psychiatry requires overcoming several limitations. Key challenges include the need for standardization across cell type specificity and assay protocols, rigorous control of confounding factors that may bias epigenetic findings, and integration of epigenetic data within the broader context of gene-environment interactions and systems biology. Future research should include large, longitudinal cohorts, tissue-specific analyses, and multi-omics integration, considering not only genomics but transcriptomics and proteomics as well. As investigation into epigenetic biomarkers continues to progress, and the understanding of the role of the epigenome alongside epigenome-targeting treatments develops, we look forward to the advances made in genomic medicine and the field of psychiatry.

Author contributions

RM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. CM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. JM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing.

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Conflict of interest

CM is the Co-Founder of Biotia and is compensated by Thorne HealthTech. JM serves on the speakers' bureau for Otsuka/Lundbeck, Teva Pharmaceuticals, Neurocrine Biosciences, Janssen, Intra-Cellular Therapies, Axsome Therapeutics, and Bristol Myer Squibb formerly Karuna Therapeutics and as a consultant/advisory board member for Axsome and Karuna Therapeutics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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