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EPIDRUGS FOR COGNITIVE DISORDERS: STATUS, CHALLENGES AND PROMISES

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Abstract:

Epigenetic regulation plays a crucial role in connecting genetic vulnerability and environmental factors in the development of cognitive disorders. Conditions such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), Alzheimer's disease (AD), and Parkinson's disease (PD) exhibit disrupted DNA methylation, histone modifications, and aberrant expression of non-coding RNAs, all of which have the potential to interfere with neuronal plasticity and cognitive functions. Since such epigenetic changes are reversible, they offer promising targets for therapy. Recent research has explored histone deacetylase inhibitors (HDACis), DNA methylation modulators, and nutritional cofactors such as folate and S-adenosylmethionine (SAM) to restore normal gene activity and improve neural health via modulation of epigenetic factors. The gut microbiome has also emerged as an important epigenetic factor, with microbiota-based treatments such as probiotics, prebiotics and microbiota transfer therapies showing potential benefits in ASD. However, challenges remain in achieving long-term effects, avoiding off-target impacts, and translating experimental success into clinical outcomes. Future progress will depend on integrating multi-omics data, advanced epigenetic mapping, and personalized medicine approaches. Understanding how epigenetic mechanisms shape brain function could eventually lead to innovative and effective treatments for cognitive disorders.

Keywords: *Cognitive disorders; Epigenetics; Epidrugs; Gut microbiome; Precision medicine*

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INTRODUCTION:

Cognitive disorders comprise a diverse group of conditions that disrupt the capacity of an individual to think, remember, and make decisions, ultimately impairing daily functioning [1]. These conditions encompass both developmental disorders, such as the autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD), as well as neurodegenerative conditions such as the Alzheimer's disease (AD) and Parkinson's disease (PD) [2]. Globally, the incidence of these disorders is rising, largely due to the interplay of genetic predispositions, environmental exposures, lifestyle-related risk factors, and epigenetic modifications [3]. Despite their distinct clinical features, these disorders commonly present with deficits in cognition, attention, memory, and executive functioning [4].

Each cognitive disorder poses unique challenges in diagnosis and management. For instance, ASD is mainly defined by impairments in social interaction and restricted, repetitive behavioral patterns, whereas ADHD is characterized by hyperactivity, impulsivity, and difficulties with sustained attention [5]. Conversely, progressive neurodegenerative conditions such as AD and PD show a gradual decline in memory, cognition, and motor abilities [6]. While genetic mutations have been identified in some cases, external factors such as stress, nutrition, and environmental toxins also play a significant role in the etiology of these disorders [7,8]. Recent studies have increasingly highlighted the contribution of epigenetic regulation in modulating the gene expression linked to these conditions, providing valuable insights into their pathophysiology and treatment prospects [9]. Epigenetic mechanisms act as a dynamic interface between the genetic makeup and environmental exposures, coordinating neurodevelopmental processes such as synaptic plasticity, learning and memory through modifications such as DNA methylation, histone acetylation, and non-coding RNA regulation [10,11]. Understanding these processes not only facilitates the identification of reliable molecular biomarkers for early detection, but also enable the design of targeted, reversible interventions capable of reprogramming aberrant gene expression patterns and improving cognitive outcomes [12,13]. A deeper understanding of such mechanisms holds promise for advancing targeted therapeutic strategies that address the underlying causes rather than merely mitigating the clinical symptoms [11].

Epigenetic alterations in cognitive disorders

Epigenetic regulation, encompassing DNA methylation, histone modification, chromatin remodeling, and non-coding RNA activity, plays a pivotal role in neurodevelopment and cognition. They act as a molecular interface between genetic predisposition and environmental exposure, fine-tuning neural circuits underlying cognition, memory, and behavior. Disruption of these processes has been consistently implicated in the pathophysiology of cognitive disorders. Moreover, these epigenetic changes may serve as biomarkers for early diagnosis and prognosis, as well as potential targets for novel therapeutic interventions.

Epigenetic alterations in ASD: ASD is strongly associated with epigenetic dysregulation affecting neurodevelopment and synaptic plasticity. Alterations in DNA methylation have been widely reported in ASD, particularly in genes crucial for neurodevelopment. Hypermethylation of *MECP2* gene, a key regulator of synaptic development and neuronal gene expression has been observed in individuals with ASD, potentially contributing to impaired synaptic plasticity and neurodevelopmental abnormalities [14]. Altered methylation of *CHD8* is associated with ASD [15]. Recent methylome studies have provided more concrete evidence of widespread DNA methylation differences in ASD and mapped new candidate genes. A study on peripheral blood methylome analysis has reported 853 differentially methylated CpG loci affecting 509 genes in children with ASD, identifying 64 genes previously annotated in the SFARI database (https://gene.sfari.org/). It was suggested that ASD involves broad epigenomic disruptions rather than isolated locus-specific changes [16,17,18].

Mechanistically, DNA methylation changes in ASD can reflect both genetic and environmental inputs. An individual-participant meta-analysis examined neonatal DNA methylation pattern in relation to polygenic risk scores (PGSs) for ASD. The study found that higher ASD polygenic burden is associated with specific methylation signatures at birth, supporting an "early origin" model in which the genetic risk is traceable via the epigenomic marks in neonates [19,20]. This finding bolsters the idea that certain epigenetic variations observed later in childhood may arise from developmental programming influenced by inherited risks.

Histone modifications also play a crucial role in ASD. Altered histone acetylation has been observed in genes involved in synaptic function, which can impair long-term potentiation (LTP) and contribute to learning and memory deficits in individuals with ASD. Studies in animal models have shown that inhibition of histone deacetylases (HDACs) can restore synaptic plasticity and improve social

behaviours, highlighting the relevance of histone acetylation in ASD pathophysiology [21,22,23]. Furthermore, altered expression of histone-modifying enzymes such as histone deacetylases (HDACs) has been identified in ASD models, suggesting that imbalanced acetylation/deacetylation disrupts neuronal plasticity.

Non-coding RNAs, particularly microRNAs (miRNAs), also contribute significantly to the pathogenesis of ASD. Dysregulation of miR-146a and miR-155 has been associated with immune dysfunction and neuroinflammation in ASD brain [24]. miRNA profiling studies have identified dysregulated levels of several miRNAs, including miR-132, miR-124, and miR-134 in ASD. These miRNAs regulate the expression of genes involved in synaptic growth, neuronal differentiation, and cortical signalling [25,26]. The findings from studies of various epigenetic factors suggest that ASD arises from an interplay of epigenetic disruptions that disturb neuronal connectivity and developmental trajectories.

Epigenetic alterations in ADHD: DNA methylation changes in the dopamine transporter (*SLC6A3*) and dopamine receptor (*DRD4*, *DRD5*) genes have been linked to attentional regulation and impulsivity. These modifications are thought to mediate the impact of environmental factors such as prenatal smoking exposure and early-life stress on ADHD risk [27,28,29,30].

Histone modification abnormalities have been observed in ADHD. Specifically, changes in histone H3 acetylation at dopaminergic gene promoters can alter transcriptional regulation, thereby contributing to the neurotransmitter imbalances associated with ADHD [31]. Altered expression patterns of non-coding RNAs have also been implicated in ADHD. Dysregulation of miR-34b and miR-129 has been shown to disrupt cortical maturation and synaptic signalling pathways, contributing to the neurodevelopmental abnormalities observed in ADHD [32,33,34].

However, a recent study using multiple epigenetic clocks to assess "epigenetic aging" in ADHD found no consistent evidence of accelerated epigenetic age in the corticostriatal brain regions or peripheral tissues after controlling for comorbidities and stimulant exposure [35]. The negative aging-clock result tampers the hypothesis that ADHD is characterized by global epigenetic age acceleration [35] and suggests that the epigenetic signatures in ADHD may be localized, dynamic, and context-dependent rather than reflecting a global aging phenotype.

Epigenetic alterations in AD: AD is heavily influenced by epigenetic dysregulation, particularly in genes associated with amyloid processing, tau phosphorylation, and neuroinflammation. Global DNA hypomethylation, coupled with site-specific hypermethylation, has been identified in AD brains, particularly at the promoters of memory-related genes [36]. Hypermethylation of the *APP* gene promoter disrupts amyloid precursor protein processing, thereby leading to increased amyloid-β accumulation. Similarly, altered methylation of the *MAPT* gene contributes to tau hyperphosphorylation and tangle formation [37]. Genome-wide studies have demonstrated global DNA hypomethylation with site-specific hypermethylation at memory and synaptic genes (e.g., *BDNF*, *SPINT1*), APOE-linked methylation shifts, and differential methylation at immune-related loci [38,39,40,41].

Histone modifications are also reported in AD. Reduced histone acetylation at the promoters of synaptic plasticity-related genes, such as *BDNF*, impairs memory consolidation [42]. Overexpression of histone deacetylases, particularly HDAC2 and HDAC3, has been shown to suppress synaptic gene transcription, leading to impaired synaptic plasticity and accelerated cognitive decline in Alzheimer's disease [22,43,44].

Dysregulation of miRNAs has been observed in AD. Altered expression of miR-29a/b and miR-107 affect amyloid metabolism and tau phosphorylation pathways [45,46,47]. These findings underscore that the involvement of widespread epigenetic reprogramming in AD.

Epigenetic alterations in PD: Epigenetic alterations significantly influence the pathogenesis of PD, particularly through regulation of the *SNCA* gene, which encodes α-synuclein. Hypomethylation in intron 1 of *SNCA* has been consistently associated with α-synuclein overexpression, a central pathogenic event in PD [48]. Similar changes have been reported in genes involved in mitochondrial function and oxidative stress responses, suggesting that the epigenetic dysregulation contributes to neuronal vulnerability [49].

Histone modifications also contribute to PD pathology. Aberrant histone acetylation and methylation patterns have been reported in dopaminergic neurons, with evidence that altered histone H3K27 acetylation disrupts transcription of neuroprotective genes [50]. Additionally, non-coding RNAs regulate multiple aspects of PD

pathogenesis. Downregulation of miR-34b/c leads to mitochondrial dysfunction, while dysregulation of miR-7 and miR-153 alters *SNCA* expression [51]. These findings highlight the crucial role of epigenetic networks in modulating dopaminergic survival and disease progression.

Recent reviews compile evidence that DNA methyltransferases, histone acetylases/deacetylases, and non-coding RNAs regulate mitochondrial function, α-synuclein clearance, and the neuroinflammation-pathways directly relevant to dopaminergic vulnerability [52,53,54]. Preclinical studies suggest that selective modulation of specific HDAC isoforms and chromatin regulators can be neuroprotective in PD animal models, although translation to humans is still limited [55,54].

Epigenetic therapeutics in cognitive disorders

The reversibility of epigenetic modifications makes them highly attractive targets for therapeutic intervention in cognitive disorders. Unlike permanent genetic mutations, epigenetic changes such as DNA methylation, histone acetylation, and miRNA dysregulation can be dynamically modulated by small molecules, biologics, and environmental interventions. Emerging therapeutic approaches are aimed at correcting the dysregulated epigenetic landscapes.

Epigenetic therapeutics in ASD: ASD is associated with altered DNA methylation and histone modification. Several epigenetic therapeutic strategies have been explored, aimed at correcting these perturbations. One major approach is the use of histone deacetylase inhibitors (HDACi), which restore histone acetylation and improve synaptic plasticity. Valproic acid, an HDACi, has been shown in preclinical models to rescue synaptic deficits and improve social behaviors, although its teratogenic risks limit clinical application [21]. Although valproic acid itself can induce ASD-like features when administered during pregnancy, controlled postnatal exposure in animal studies has shown improvements in synaptic gene expression and cognitive flexibility [56,57,58]. Sodium butyrate, a short-chain fatty acid (SCFA) that inhibits HDACs, has demonstrated promising results in enhancing sociability and reducing repetitive behaviors in rodent ASD models [59,60]. Other HDACi, such as suberoylanilide hydroxamic acid (SAHA), are under investigation for their ability to normalize transcriptional dysregulation in ASD-related pathways [61].

Another promising therapeutic candidate is DNA methylation modulators. While direct pharmacological agents targeting methylation are not yet in clinical use for ASD, nutritional supplements influencing the methylation cycle such as folate, vitamin B12, and S-adenosylmethionine (SAM) have been evaluated. Clinical trials with folic acid supplementation have shown improvements in verbal communication among children with ASD [62]. Since hypomethylation of the *OXTR* gene has been linked to social deficits in ASD, strategies to correct the methylation status are being explored [63].

Emerging evidence suggests that the gut microbiome exerts significant epigenetic influence on neurodevelopment and behavior, positioning it as a key factor in the pathophysiology of ASD. The bidirectional gut–brain axis enables microbial metabolites, such SCFAs (e.g., butyrate, propionate), to modulate DNA methylation and histone acetylation in neuronal cells, thereby affecting gene expression associated with synaptic plasticity and neuroinflammation [26]. Dysbiosis, defined as an imbalance in gut microbial composition, has been consistently reported in ASD, with altered levels of *Bacteroides*, *Clostridium*, and *Desulfovibrio* species correlating with gastrointestinal symptoms and behavioral severity [64,65,66].

Microbiota-targeted therapies have therefore gained attention as potential epigenetic interventions. Probiotic supplementation, particularly with *Lactobacillus* and *Bifidobacterium* strains, has demonstrated improvement in social behaviors and reduced anxiety-like symptoms in ASD animal models and small clinical cohorts [67,68,69]. Prebiotics such as galactooligosaccharides and fructooligosaccharides have shown the ability to enhance beneficial microbial population and modulate SCFA levels, influencing the histone acetylation patterns relevant to neuroplasticity [70,71,72,73]. Dietary interventions rich in fiber and polyphenols are also being evaluated for their microbiota-mediated epigenetic effects on brain function. More advanced approaches like fecal microbiota transplantation (FMT) and microbiota transfer therapy (MTT) have produced encouraging outcome. Long-term follow-up studies indicate sustained improvements in gastrointestinal health and ASD-related behaviors following MTT [74]. Taken together, these findings suggest that modulation of the gut microbiome is a promising and minimally invasive epigenetic therapeutic strategy for ASD, capable of restoring microbial and molecular homeostasis along the gut–brain axis.

miRNA-based therapies are also being explored. Experimental therapies using antagomirs (miRNA inhibitors) or miRNA mimics hold potential, though

clinical translation is still in the preclinical stages. Environmental and behavioral interventions that have epigenetic effects are receiving increasing attention. Studies suggest that early behavioral interventions and environmental enrichment can partially reverse epigenetic abnormalities by modulating activity-dependent gene expression [75,76,77]. Thus, integrating pharmacological and non-pharmacological strategies may provide synergistic therapeutic benefits for ASD.

Beyond pharmacological interventions, nutraceutical and lifestyle approaches targeting epigenetic modifications are also being explored. Nutrients such as folate, choline, and betaine are essential for one-carbon metabolism and DNA methylation, and supplementation during pregnancy has been associated with reduced ASD risk [78,79,80]. More recently, research has examined polyphenols such as resveratrol and curcumin, which modulate histone acetylation and miRNA expression, showing potential for reducing neuroinflammation and improving behavioral outcomes in ASD animal models [81,82,83].

Overall, while clinical translation remains limited, the ongoing identification of ASD-specific epigenetic signatures provides opportunities to design personalized interventions. Advances in targeted delivery of epigenetic modulators, such as nanoparticle-based systems, are expected to accelerate the therapeutic solution for ASD [18,84,85].

Epigenetic therapeutics in ADHD: Epigenetic therapies for ADHD target DNA methylation, histone modifications, and non-coding RNAs, all of which influence dopaminergic and noradrenergic pathways central to the disorder. In comparison to ASD, the investigation of epigenetic therapies in ADHD remains scarce; however, there is a growing focus as emerging evidence underscores the significance of DNA methylation and histone modifications in genes related to dopaminergic functions and neurodevelopment.

DNA methylation-targeted interventions have been proposed for ADHD, given the abnormal methylation in *SLC6A3* and *DRD4* genes [27,28,86]. Nutritional and metabolic interventions such as omega-3 fatty acids, zinc, and methyl donors like SAM and folate may indirectly restore methylation balance [87]. Clinical studies show that children with ADHD benefit from combined dietary supplementation, which has measurable effects on behavior and attention, possibly through epigenetic modulation.

Histone modification-based therapies are also being explored as potential interventions. Preclinical studies indicate that HDAC inhibitors (HDACi) can improve behavioral and cognitive deficits, while these are not yet widely tested in ADHD, they represent a potential therapeutic strategy [88,42,89]. One of the most promising directions is the use of HDACi to normalize histone acetylation in prefrontal cortex circuits that regulate attention and impulse control [22]. Animal studies suggest that SAHA and sodium butyrate can improve working memory and reduce hyperactivity by modulating the synaptic plasticity genes [90,91]. Human trials in this direction are yet to be conducted.

miRNA-based intervention is another promising strategy. Although no clinical trials currently target miRNAs in ADHD, future therapies may involve synthetic miRNA mimics or inhibitors delivered to affected neural circuits.

Non-pharmacological epigenetic interventions, such as dietary supplementation with methyl donors (e.g., folate, vitamin B12, S-adenosylmethionine), are under investigation as adjuncts to stimulant medications. Mindfulness-based interventions have been shown to alter miRNA profiles associated with stress regulation, though their role in ADHD remains exploratory [92,93,94,95].

An additional dimension is the role of psychosocial and environmental interventions. Evidence suggests that behavioral therapies and exercise can exert epigenetic effects by modifying DNA methylation patterns in stress-related and dopamine genes [96]. Thus, a multimodal strategy combining pharmacological, nutritional, and behavioral interventions may offer an excellent comprehensive epigenetic therapeutic approach for ADHD.

Overall, while ADHD lags behind ASD, AD, and PD in terms of epigenetic therapeutics, the increasing recognition of methylation biomarkers and histone dynamics offers potential pathways for personalized treatment strategies.

Epigenetic therapeutics in AD: AD represents the most advanced field of epigenetic therapeutic research among cognitive disorders. Several strategies are being explored to counteract abnormal DNA methylation and histone modification patterns observed in AD brains.

Preclinical studies demonstrate that HDACi such as vorinostat and sodium butyrate enhance synaptic plasticity, restore memory deficits, and upregulate neuroprotective genes in AD models [42]. Vorinostat and Entinostat have demonstrated

improvements in cognitive performance and synaptic density in AD mouse models [97,98,99]. Notably, recent studies highlight the therapeutic potential of class I HDACi in restoring acetylation of histone H4 at genes regulating synaptic plasticity, suggesting a mechanism for long-term memory rescue. The inhibition of HDAC2 relieves transcriptional repression of synaptic genes, improving cognitive performance in mouse models. While clinical translation is ongoing, concerns about off-target effects and systemic toxicity remain [97,100,22].

DNA methyltransferase (DNMT) inhibitors such as 5-azacytidine and RG108 have been reported to restore synaptic plasticity in animal models [101,11]. However, their use in humans is limited due to toxicity concerns. Newer and more selective DNMTi are being investigated.

miRNA-targeted therapies are actively being explored in AD. Restoration of miR-29a/b expression, which regulate *BACE1* expression (crucial for amyloid-β generation), has been shown to reduce amyloid pathology [47,45,102]. Replacement therapies using miRNA mimics have shown reduction of amyloid plaque burden in mouse models [103,104,105]. Similarly, modulation of miR-107 can impact tau phosphorylation pathways. Novel delivery systems such as lipid nanoparticles are being designed to facilitate miRNA-based therapies in the brain.

In addition to pharmacological interventions, nutraceutical and lifestyle approaches play an epigenetic role in AD. Compounds such as resveratrol, curcumin, and sulforaphane act as natural epigenetic modulators, influencing histone acetylation and DNA methylation pathways to exert neuroprotective effects [106,107,38]. Physical exercise and cognitive training have also been shown to induce beneficial epigenetic changes in AD-related pathways [108,109,110].

Overall, AD remains the most promising candidate for translation of epigenetic therapeutics into clinical practice, with several compounds advancing toward early-phase clinical trials.

Epigenetic therapeutics in PD: In PD, epigenetic therapeutics aim to regulate α-synuclein expression, protect dopaminergic neurons, and reduce neuroinflammation.

DNA methylation-based therapies are particularly relevant for PD, given the hypomethylation of the *SNCA* gene promoter leading to α-synuclein overexpression. While direct pharmacological modulation of *SNCA* methylation has not yet been achieved, experimental studies are testing DNMT activators that could restore normal methylation levels [48]. Targeted methylation editing utilizing CRISPR-dCas9 tools is currently being investigated to reinstate methylation levels and mitigate α-synuclein pathology [111]. Nutritional approaches involving methyl donors like folate and vitamin B may also indirectly influence methylation pathways [49].

HDACi such as sodium butyrate and trichostatin A have demonstrated neuroprotective effects by enhancing histone acetylation, reducing dopaminergic neuron loss, and improving motor performance in PD models [112,113,114]. By enhancing histone acetylation, these agents reactivate neuroprotective gene transcription. Newly developed class-specific HDAC inhibitors are being created to minimize systemic toxicity and enhance central nervous system (CNS) penetration [115,116].

Restoration of miR-34b/c expression has been shown to rescue mitochondrial dysfunction and neuronal survival [117,118,32]. miR-7 and miR-153 negatively regulate *SNCA* expression, and their mimics have reduced α-synuclein accumulation in cell and mouse models [119,120,121]. Other miRNAs, such as miR-124, are being targeted to promote neurogenesis and reduce neuroinflammation in PD.

Natural compounds with epigenetic activity, such as polyphenols and caffeine, are being studied for their neuroprotective potential. These agents influence histone acetylation and DNA methylation, potentially offering safe long-term interventions for PD patients [122,123,124]. Moreover, natural compounds like curcumin and green tea polyphenols are being explored for their dual antioxidant and epigenetic modulatory effects. Small molecules that modulate epigenetic regulators, such as sirtuin activators, can enhance mitochondrial function and protect against oxidative stress in PD models [125,126].

Overall, PD epigenetic therapeutics are rapidly advancing, with increasing focus on precision epigenetic editing tools and combinatorial therapies integrating pharmacological and lifestyle approaches.

Epigenetic therapies for cognitive disorders: Approved drugs and clinical candidates

Autism spectrum disorders: As of now, there are no U.S. Food and Drug Administration (FDA)-approved epigenetic drugs for ASD. The FDA has

approved only behavioral and antipsychotic interventions (e.g., risperidone, aripiprazole) to manage ASD symptoms.

Commercial and clinical interest in epigenetic approaches for ASD is growing, but remains in an early stage. The current approaches prioritize CNS-optimized and isoform-selective compounds (e.g., selective inhibitors of specific histone methyltransferases or HDAC isoforms) and non-small-molecule approaches (e.g., miRNA modulators, targeted epigenome editors) that promise greater specificity and tolerability [127,128,129,130].

In terms of clinical trials, active interventional studies of conventional epidrugs for core ASD symptoms are scarce. Instead, the emphasis is on biomarker discovery based on large-scale methylome profiling and peripheral miRNA panels to stratify the patients and identify the subgroups most likely to benefit from epigenetic modulation [131,132]. Preclinical research in ADHD-relevant animal models continues to highlight the therapeutic potential of targeting epigenetic regulators. Alterations in histone modifications, particularly via inhibition of the G9a or EHMT family of histone methyltransferases, have been shown to improve attention, impulsivity, and hyperactivity-related behaviours. For example, inhibition of EHMT 1 or 2 (G9a or GLP) rescued social and cognitive deficits in rodent models of neurodevelopmental dysfunction, while modulation of the same pathway reduced anxiety-like and hyperactivity-related behaviours [133,134]. These findings provide crucial guidance for selecting epigenetic targets in future first-in-human trials for ADHD. Pediatric specific safety data, careful demonstration of CNS target engagement, and strategies to avoid developmental off-target effects need to be considered while developing therapies for ASD. Consequently, the upcoming research on epidrugs for ASD is expected to include biomarker-driven, small-scale, meticulously controlled early-phase trials instead of extensive efficacy studies [135,136,137].

Attention-deficit/hyperactivity disorder: To date, no pharmaceutical company has progressed an epigenetic drug candidate for ADHD into clinical trials. Accumulating evidence points toward dopaminergic pathway methylation changes and histone modification dysregulation in ADHD [138,30,139]. These insights have encouraged research into epidrug approaches, though the translation to clinical therapies is not yet attained.

Alzheimer's disease: AD presents the greatest potential for the application of epigenetic therapies in clinical trials. The market for AD therapeutics is large and rapidly expanding, driven by the aging population and unmet clinical needs.

No epigenetic drug has yet received FDA approval for AD. Strong mechanistic has motivated multiple early-phase clinical programs and repurposing attempts of oncology epidrugs [42,140,38]. The AD drug development pipeline identifies epigenetic regulators as an emerging subgroup within disease modifying therapies (DMTs), highlighting continued interest in chromatin remodelling, transcriptional regulation, and gene expression control as therapeutic approaches. Importantly these candidates are primarily categorized as disease modifying interventions supporting the concept that epigenetic therapies may target pathogenetic mechanisms upstream of amyloid deposition, tau pathology, synaptic dysfunction, and neuroinflammation [141].

A brain-penetrant HDACi, EVP-0334/FRM-0334, progressed to early human trials aimed at evaluating safety, pharmacokinetics, and biomarker effects for related dementias. These trials not only confirmed feasibility, but also highlighted the necessity for isoform selectivity and favorable CNS exposure [142]. Repurposed pan-HDACi such as vorinostat were evaluated in small safety and tolerability studies; however, they encountered dose-limiting systemic toxicities that resulted in fatigue and gastrointestinal distress, which hindered chronic use in elderly AD patients at effective CNS exposures [44,97]. Consequently, current commercial and academic efforts prioritize next-generation epidrugs that include HDAC isoform-selective inhibitors with improved blood-brain barrier penetration (especially HDAC2/3 selectivity), BET bromodomain inhibitors adapted for CNS use, miRNA-based therapeutics (BACE1-targeting miRNA mimics), and targeted epigenome editors that could regulate disease-relevant loci without global transcriptional disruption [143,144,145,146,136]. Another compound, FRM-0334, which was designed to enhance progranulin expression through epigenetic modulation, commenced Phase I trials for frontotemporal dementia and was also evaluated for AD; however, it was ultimately discontinued due to insufficient efficacy.

In preclinical models, selective HDAC2 inhibitors, DNMT inhibitors, and BET inhibitors have shown promise in restoring memory function and synaptic plasticity. Natural compounds such as curcumin and resveratrol, which exert epigenetic effects, are being

tested in small-scale human studies for cognitive benefits [143,147,148,149,150].

Parkinson's disease: PD epigenetic programs have significantly advanced to the preclinical stage. Several interventions such as isoform-selective HDAC6 inhibitors, miRNA mimics/antagomirs, and epigenetic editing constructs are in the preclinical stage. Human trials of classic epidrugs in PD have been limited or inconclusive [26,151]. Valproic acid, a broad HDACi, has been explored off-label in PD, but with inconsistent outcomes and safety issues. More targeted epidrugs, such as isoform-selective HDACi and DNMT inhibitors, are under preclinical investigation for neuroprotection and α-synuclein clearance.

Regulatory and market strategies for PD emphasize two key aspects- safe/chronic dosing in older adults, and locus-specificity. Consequently, the focus is on targeted oligonucleotide therapies, such as antisense oligonucleotides (ASOs) or miRNA modulators, or locus-directed epigenome editors delivered via optimized CNS vectors or non-viral nanoparticles. These approaches are paired with biomarkers of target engagement, including cerebrospinal fluid (CSF) α-synuclein levels and DNA methylation status, as well as neuroprotection endpoints [152,153,154,155,129].

How long does the effect of epigenetic therapy last?

The duration of the therapeutic effects of epigenetic interventions largely depends on the type of agent, target mechanism, and disease context. Unlike conventional drugs that act directly on neurotransmitters or receptors, epigenetic therapies modify the transcriptional landscape, leading to changes that may persist long after treatment discontinuation [156,157]. These long-lasting effects arise since epigenetic modifications can influence gene regulation across cell divisions, especially in the neural cells with relatively stable epigenomes [44].

The persistence of these effects, however, varies. HDACi such as valproic acid and sodium butyrate have shown reversible gene expression changes that subside over time after drug withdrawal [158,159,160]. In contrast, DNA methylation–targeting agents can induce long-lasting effects since methylation marks are stably propagated during DNA replication [156]. In neurodegenerative diseases like AD and PD, where the neuronal turnover is low, sustained therapeutic benefits depend on maintaining epigenetic homeostasis rather than transient modification [44,161,162].

Furthermore, animal studies indicate that early-life epigenetic interventions may confer durable behavioral and cognitive benefits, suggesting the possibility of developmental "windows of plasticity" where interventions can yield long-term outcomes [163,164,165]. Despite promising results, long-term clinical evidence in humans remains limited. Therefore, ongoing trials are focusing on optimizing dosage, treatment duration, and combination strategies to achieve stable yet controllable epigenetic reprogramming.

Limitations of epigenetic therapy

Although epigenetic therapy offers a revolutionary approach to cognitive and neurodegenerative disorders, several limitations constrain its clinical translation. A major challenge pertains to the specificity. Most epigenetic drugs, such as HDACi and DNA methyltransferase inhibitors act globally across the genome, affecting both disease-relevant and unrelated genes [166,167]. This lack of target selectivity can result in off-target effects, including unwanted gene activation or silencing, cytotoxicity, and systemic toxicity [168,169,170].

Another limitation is the context-dependent nature of epigenetic regulation. The same modification may exert different effects depending on the cell type or developmental stage. For instance, while HDAC inhibition can enhance neuronal plasticity in some contexts, it may also disrupt normal gene expression and induce aberrant neuronal activity in others [44]. Moreover, most current epigenetic drugs were originally developed for oncology, and their pharmacokinetics, dosing, and toxicity profiles may not suit long-term neurological use [171,172].

Blood–brain barrier (BBB) penetration poses an additional hurdle for CNS disorders. Many epigenetic modulators, including nucleoside analog DNMT inhibitors, exhibit poor brain bioavailability [173,174,175]. Furthermore, epigenetic heterogeneity across patients adds complexity. Variations in baseline methylation or histone patterns influence therapeutic response, necessitating precision-medicine approaches [176,177,178].

Ultimately, ethical and safety issues continue to exist concerning the possibility of heritable or unintended transgenerational impacts resulting from epigenetic modification [179,180,181]. While no clinical evidence currently supports germline transmission of drug-induced epigenetic changes, the theoretical possibility underscores the need for rigorous long-term monitoring and ethical oversight in clinical applications.

Future Directions

Future investigations into epigenetic therapies for cognitive disorders are progressing towards precision, combination, and personalized medicine. Recent developments in high-throughput sequencing and single-cell epigenomics enable the precise mapping of disease-specific epigenetic signatures [156]. These insights pave the way for targeted epigenetic editing using CRISPR/dCas9-based tools fused with epigenetic modifiers, enabling locus-specific control of methylation or acetylation without altering the DNA sequence [182,183].

Combination therapies that integrate epigenetic modulators with neuroprotective, anti-inflammatory, or neurotrophic agents are gaining attention. For example, co-administration of HDACi with BDNF-enhancing compounds or anti-oxidants has shown synergistic neurorestorative effects in AD and PD [184,185,186].

The gut–brain–epigenome axis represents another emerging area, where microbiota-targeted interventions modulate host epigenetic states through microbial metabolites such as short-chain fatty acids [187,188,189]. Personalized microbiome-based epigenetic modulation may offer novel, low-risk interventions for neurodevelopmental disorders.

Furthermore, machine learning–driven epigenomic analysis is expected to identify predictive biomarkers for therapy response and disease progression, accelerating drug discovery [190,191,192]. Ultimately, the integration of multi-omics, artificial intelligence (AI), and patient-derived organoid models has the potential to revolutionize epigenetic therapy, evolving it into a personalized and adaptive treatment framework.

CONCLUSION:

Epigenetic mechanisms are central to the pathophysiology of cognitive disorders. Over the past decade, evidence has revealed that DNA methylation, histone modification, and non-coding RNAs coordinate complex regulatory networks underlying neuronal development, synaptic plasticity, and cognitive function. The therapeutic potential of modulating these mechanisms through HDACi, DNMT inhibitors, miRNA regulators, and microbiota-targeted approaches has opened new horizons in neuroscience.

Nevertheless, challenges such as off-target effects, limited BBB penetration, and patient-specific variability must be addressed before these therapies achieve clinical proficiency. The integration of precision epigenetics, advanced delivery systems, and biomarker-guided trials will be essential for translating preclinical success into effective human therapies. As the field advances, epigenetic therapeutics hold the promise of not merely alleviating symptoms but fundamentally restoring the molecular equilibrium that sustains healthy cognition and behaviour.

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