SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

# Histone Deacetylase 5 (HDAC5) in Major Depressive Disorder: Analyzing Current Gaps on Bridging Epigenetic Mechanisms to Clinical Translation

**By Christine Chen**

## AUTHOR BIOGRAPHY

Christine Chen is a senior at Hunter College High School. She enjoys drawing with graphite, listening to Shostakovich and Chappell Roan, and telling jokes to her friends. Her academic curiosity spans both the research world as well as the complexities of human health, reflected through her experience in shadowing, EMT work, and patient-centered volunteering. Outside of school, she volunteers at NYP hospital by talking to patients. Her motivation for research is driven by a desire to uncover the microscopic mechanisms that underlie behaviour and it's regarding mental health concerns.

## ABSTRACT

Major depressive disorder (MDD) is a widespread psychiatric disorder that affects over 163 million people globally. Current treatments for MDD include pharmacological agents, such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), electroconvulsive therapy (ECT), and more. Each treatment has the potential to provide symptom relief; however, they also have limitations. Recently there's been an interest in epigenetic regulators within the field of depression research; more specifically, researchers are focusing on histone deacetylases (HDACs) for their roles in regulating gene expression by modifying the structure of chromatin. Among the HDAC isoforms, one of the most intriguing is the class IIa isoform, HDAC5. HDAC5 overexpression increases stress vulnerability, linking HDAC5 to molecular signaling processes underlying depressive behaviors. Researchers do not yet fully understand the mechanistic pathways connecting HDAC5 to synaptic plasticity, the effects of HDAC5 modulation on brain penetration and potential off-target effects, and much more. To fill these gaps, future studies might wish to look into CRISPR-based gene editing for mapping HDAC5, PET imaging tracers, and more peripheral assays in vivo. Altogether these approaches will allow the field to work towards bridging preclinical and clinical findings. Bridging these translational gaps creates new opportunities to develop individualized therapies to treat depression, while addressing ongoing unmet needs in psychiatric medicine.

***Keywords:*** *Major Depressive Disorder, histone deacetylases, blood brain penetration, CRISPR gene editing, rodent models, psychiatric medicine, HDAC5, BDNF, c-Fos, post-mortem models, in vivo, epigenetic*

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

## INTRODUCTION

Major depressive disorder (MDD) is a pervasive psychiatric condition that affects over 163 million people worldwide, characterized by persistent low moods and cognitive impairments (Wu et al., 2022; Meng et al., 2023). The lifetime risk of developing MDD is estimated at around 15-20% in high-income countries, highlighting its substantial public health burden (Ganai et al. 2023). MDD is a multifactorial disorder, arising from the interplay of genetic predisposition, environmental stressors, and neurobiological dysregulation. Key neurobiological features include dysregulation of monoaminergic neurotransmission, altered stress hormone dynamics, impaired synaptic plasticity, and maladaptive epigenetic modifications (Nestler et al.,2016).

Current treatments for MDD include pharmacologic agents such as selective serotonin reuptake inhibitors (SSRIS), serotonin-nonrepinephrine reuptake inhibitors (SNRI), electroconvulsive therapy (ECT), and more recently, rapid-acting options like ketamine infusions (Karrouri et al., 2021). While these treatments can be effective, their use is limited by delayed onset of therapeutic action—typically 4-6 weeks for SSRIs—parital remission rates, and significant side effects (Machado-Vieira et al. 2009). Some effects may include sexual dysfunction, gastrointestinal disturbances, weight gain, sedation, and cardiovascular risk. Additionally treatment-resistant depression remains a substantial challenge, affecting approximately 30% of patients and prompting the need for novel mechanistic intervention (Łysik et al., 2025).

Recent research has turned toward an epigenetic understanding of depression, particularly in the role of histone deacetylases (HDACs), which regulate gene expression by removing acetyl groups from lysine residues on histone proteins, leading to chromatin condensation and transcriptional repression (Sun et al., 2012; Garayo-Larrea et al. 2024). HDAC activity affects neuroplasticity, stress responses, and behavioral outcomes in depression models (Nestler et al. 2016). Among the HDAC family, class IIa isoforms such as HDAC5 are highly expressed in the brain regions implicated in mood regulation, including the hippocampus, prefrontal cortex, and nucleus accumbens (Garayo-Larrea et al. 2024). HDAC5 is dynamically regulated by neuronal activity and stress, influencing transcriptional programs associated with synaptic remodeling and stress resilience (Li et al., 2024). Preclinical studies suggest that HDAC5 plays a pivotal role in mediating the efficacy of antidepressants. Chronic stress paradigms in rodents alters HDAC5 localization and activity, whereas HDAC5 nuclear export—a process by which HDAC5 exits the nucleus—correlates with enhanced antidepressant responses, indicating its role in facilitating the transcriptional plasticity of stress-responsive genes (Erburu et al., 2015). Key downstream targets include brain-derived neurotrophic factor (BDNF), glucocorticoid receptor-responsive genes, and immediate early genes involved in synaptic remodeling (Erburu et al., 2015).

Through examining the limited and often inconclusive human studies alongside the more robust but non-translational rodent data on HDAC5's role in depression, we can see that there is a critical gap in

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

connecting molecular mechanisms to clinically relevant outcomes, which is important because without bridging this gap, isoform-specific therapies that could target HDAC5 to improve treatment efficacy and reduce side effects will remain unrealized.

## HDAC IN ANIMAL MODELS AND HUMAN STUDIES

Rodent models of depression, including chronic unpredictable mild stress (CUMS), chronic social defeat stress (CSDS), and learned helplessness paradigms, serve as robust tools to study MDD pathophysiology (Markov et al. 2022). These models induce depression-like behaviors such as anhedonia, social avoidance, and reduced exploratory activity, which can be quantified using sucrose preference tests, social interaction assays, and open-field tasks (Markov, 2022). Manipulating HDAC5 expression or activity in these models provides insight into its causal role. For example, HDAC5 knockout mice exhibit enhanced stress resilience and heightened antidepressant responsiveness, whereas HDAC5 overexpression exacerbates stress susceptibility (Li et al. 2024). Pharmacologic inhibitions or gene knockdown of HDAC5 restores synaptic spine density and enhances BDNF expression in hippocampal and cortical neurons, linking epigenetic modulation to structural and functional neuroplasticity (Zeng et al., 2012).

Human studies remain limited but increasingly suggest the translational relevance of HDAC5. Postmortem analyses of individuals with MDD, reveal altered HDAC5 expression in the prefrontal cortex and limbic regions, supporting a role for isofrom-specific epigenetic dysregulation in depressive pathology (Schroeder et al., 2016). Peripheral blood and mRNA studies also indicate fluctuations in HDAC5 expression during depressive episodes, raising the potential for developing peripheral biomarkers to track disease progression or treatment response (Mariani et al. 2021). Unlike broad-spectrum HDAC inhibitors, which can lead to systemic toxicity and off-target effects, selective targeting of HDAC5 may provide a precision therapeutic approach (Nestler et al., 2016).

## COMPARISON OF HDAC ISOFORMS

HDACs comprise a family of 18 isoforms. They are classified into four groups (I-IV) based on their structure, function, and cellular localization (Seo et al., 2014). In neuropsychiatric research, HDAC2, HDAC5, and HDAC6, have been looked at. Each regulates neuroplasticity and stress responses differently, and clarifies why HDAC5 is a compelling target for (MDD).

### HDAC2 (class I)

HDAC2 is a nuclear isoform that broadly represses synaptic gene transcription. HDAC2 overexpression in rodent models decreases dendritic spine density, synaptic plasticity, and learning (Guan et al.,

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

2009). Human postmortem studies show increased HDAC2 expression in brains of people with cognitive impairment, indicating a role in decreased synaptic flexibility in depression and neurodegeneration (Garayo-Larrea et al. 2024). Pharmacologic inhibition of HDAC2 may improve cognition, but systemic inhibition of class I HDACs can produce toxicity (hepatotoxicity and hematopoietic dysfunction) through widespread transcriptional dysregulation of multiple housekeeping genes (Seto & Yoshida, 2014). To summarize, HDAC2 is highly relevant to cognition and synaptic plasticity, but, in addition to toxicity, there is a lack of mood-specific effects for therapeutic targeting.

**HDAC5 (Class IIa):**

HDAC5 is a signal-responsive isoform that dynamically moves between the nucleus and the cytoplasm relative to neuronal activity and stress exposure (Westlund et al., 2023). In contrast to HDAC2 that is continually nuclear, HDAC5's activity-dependent nuclear export allows it to function as a molecular switch for adaptive transcriptional responses (Yang et al., 2021). A rodent study showed chronic stress alters HDAC5 localization in the hippocampus and nucleus accumbens that correlated with depression-like behavior, whereas antidepressant treatment allowed for nuclear export of HDAC5 resulting in the transcription of neuroplasticity-related genes like BDNF and c-Fos (Wu et al., 2022; Wang et al. 2023). Knockdown of HDAC5 improved stress resilience and enhanced the efficacy of antidepressants suggesting HDAC5 is more directly regulating mood relevant neural circuitry than HDAC2 or HDAC6 (Erburu et al., 2015). Given the high levels of HDAC5 expression in stress-sensitive circuits, and the dynamic modulation of HDAC5 by pharmacological intervention, it is likely a more relevant target for MDD treatment.

**HDAC6 (Class IIb):**

HDAC6 is an isoform that is mainly cytoplasmic and has a different role than the nuclear isoforms. Importantly, HDAC6 does not only act on histones like other HDAC isoforms, but instead chiefly deacetylates various non-histone proteins, including α-tubulin and Hsp90, which all could impact processes such as axonal transport, protein degradation, and cellular stress responses on a broad range of processes (Seo et al., 2014). In psychiatric research, inhibition of HDAC6 has shown efficacy in depression and anxiety models by a mechanism that enhances synaptic transport and reduces maladaptive stress signaling (Misztak et al., 2017). More importantly, several small-molecule inhibitors of HDAC6 have reached the clinical trial phase for use in neurodegenerative diseases. Published preclinical evidence suggests, among other effects, an antidepressant-like and clinical indication for the treatment of Alzheimer's disease (Correia et al., 2021). Nevertheless, because HDAC6 targets a broad set of cytoplasmic processes, there are potential side effects associated with inhibition of HDAC6 which could impair proteostasis and promote immune dysfunction (Qu et al., 2025). HDAC6 is a compelling candidate to advance given its notable role in the regulation of stress adaptation, but it also carries more of a risk on the systemic level than HDAC5, as its actions are less circuit/glia specific (Qu et al., 2025).

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

**Why HDAC5?**

Our comparison of the three isoforms shows the unique therapeutic positioning of HDAC5. Inhibition of HDAC2 shows that aspects of cognition can improve, but there is increased risk of an overall disruption of transcriptional control. HDAC6 inhibition can show an improvement in cellular resilience, but lack of ties to circuits regulating mood and off-target effects can make understanding behaviorally relevant consequences difficult. HDAC5, however, plays a role as a junction between environmental stress, the action of antidepressants, and neural plasticity, expressed in limbic areas consistent with MDD and appears to provide a combination of circuit specificity, activity dependence, and responsiveness to antidepressant therapeutics which makes it the most viable candidate for isoform selective intervention in depression (Yuan et al., 2023).

**Scientific Importance**

Understanding how environmental stress, neuronal stimulation, and antidepressant exposure converge at the molecular level, to regulate gene expression in mood circuitry ,relies on studying HDAC5. By defining cellular mechanisms of HDAC5 nuclear export and its impact on genes such as BDNF and additional related neuroplasticity targets, researchers can delineate pathways that contribute to resilience, adaptation to stress, and depressive phenotypes. Unifying results from rodent studies with human biology also produces a more integrated model of depression, contributing to the growing field of epigenetics and psychiatric disorders in particular.

**Clinical Importance**

Research into HDAC5 has direct relevance in the development of additional targeted and efficacious therapies for MDD. By understanding HDAC5's role in regulating stress-responsive transcription, we might design isoform-selective inhibitors to augment antidepressant efficacy and lower side effects that arise from systemic effects. This could potentially alleviate some limitations of current treatment, including time to onset, partial remission, and toxicity due to broad spectrum HDAC inhibitors or standard pharmacologic agents (Wang et al. 2023).

**Broader Importance**

HDAC5 research has systematic and public health consequences that extend beyond science and clinical practice. Depression affects millions of people worldwide, and is a significant financial, social, and emotional burden. Moving forward with the development of HDAC5-targeted therapies could help yield precision-based interventions that improve quality of life, better allocate healthcare costs, and provide hope for

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

many individuals with treatment-resistant depression. Further, it serves as an example of how mechanistic, molecular sciences can yield truly impactful solutions in the real world that represent a fusion of basic neuroscience and real human solutions.

## GAPS IN LITERATURE

However, it is important to consider the limitations and sometimes inconclusive findings of human studies on HDAC5's mechanism in depression in comparison to the strong but not translatable studies in rodents that show a role for HDAC5 (Garayo-Larrea et al., 2024). Collectively these studies highlight that there are gaps in the current scientific literature regarding the level of mechanistic understanding surrounding HDAC5 in MDD. It is important that these limits are addressed so that the gap can be bridged between molecular mechanisms and clinically relevant outcomes, which could provide potential avenues for isoform specific therapies to improve treatment efficacy while reducing unwanted side effects.

A major caveat in current studies is the use of rodent models, with very few studies performed in humans for cross collaboration. Explicitly, rodent studies using (CUMS), (CSDS), and learned helplessness models have provided an important means to explore the role of HDAC5 on the stress response and antidepressant response (Garayo-Larrea et al., 2024). Using these rodent models, researchers can focus on either manipulating HDAC5 expression or activity and detect the behavior and molecular response that occurs. For example, HDAC5 KO mice show a greater resilience to stress and an increased sensitivity to the efficacy of antidepressants; conversely, mice with increased HDAC5 overexpression are more susceptible to stress (Li et al., 2024). Collectively, these preclinical studies were essential in establishing the groundwork and understanding of HDAC5 as a modulator of neuroplasticity, especially of BDNF and other immediate early genes associated with synaptic remodeling.

However, rodent models have potential limitations in regards to translational relevance. Although they recreate some behaviors associated with depression, such as anhedonia and social avoidance, they fail to fully model the complex subjective experience of depression in humans. Human MDD, can involve a complex, biopsychosocial relationship, in which combinations of genetics, environment, psychosocial stressors, and multiple forms of individual variability can shape the presentation of symptoms. The limited number of postmortem studies and peripheral analysis of HDAC5 in human populations further complicates a direct comparison of the molecular mechanism underlying the actions of HDAC5 in rodent models and depression in humans (Garayo-Larrea et al., 2024). Postmortem studies are also limited to a single timepoint and do not reflect changes in HDAC5 across depressive episodes, treatment, or remission.

This brings forth another major gap: there have not been longitudinal studies investigating HDAC5 expression in MDD patients. To date, no human studies have utilized longitudinal assessments of HDAC5, as

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

most rely on single time-point assessments from postmortem tissue or peripheral blood. We have knowledge of changes to HDAC5 in the prefrontal cortex or limbic regions in depressed subjects, and we can observe that the expression tends to be altered, but we cannot establish a temporal relationship with HDAC5 activity in relation to depressive symptoms and treatment response (Garayo-Larrea et al., 2024). Without longitudinal data, it will be impossible to determine if observed changes in HDAC5 are causative, compensatory, or correlational. For example, it will be important to determine if the nuclear export of HDAC5 occurs as a direct response to pharmacologic antidepressant intervention or if it is simply part of an adaptive or maladaptive stress-response. Longitudinal studies that measure HDAC5 expression or activity over time (ideally peripheral blood biomarkers or advanced imaging paradigms) are essential to understand these dynamic relationships.

An additional limitation in the literature is the limited understanding of the mechanistic processes that link HDAC5 to synaptic plasticity, regulation of BDNF, and other dynamics of hormone release in stress response. Although rodent studies have shown that nuclear export of HDAC5 promotes the transcription of neuroplasticity-related genes like BDNF, as well as modulating stress circuits, the actual molecular processes have not been defined (Ganai et al. 2016). It is not well understood how HDAC5 engages transcription factors, co-repressors, and chromatin-modifying complexes to regulate the changes in synaptic strength. It is also not well defined how HDAC5 may crosstalk with stress hormones, including glucocorticoid receptor pathways, due to limitations in human experimentation. These limitations hinder the translational capacity to implement targeted interventions, since modulating HDAC5 without understanding its downstream effects could have unintended and unpredictable effects in neural circuitry.

A further translational hurdle brought about by mechanistic uncertainty is the limited understanding of the isoform-specific crosstalk that exists between members of the HDAC family of enzymes. HDAC5 is a class IIa HDAC, but other class I (HDAC2) and IIb isoforms (i.e. HDAC6) have also been implicated in aspects of neural plasticity, cognition and regulation of stress. There is evidence that HDAC5 is especially responsive to neuronal activity and antidepressant treatment, but it remains unclear whether compensatory changes in activity and expression of other HDAC isoforms would occur when activity of HDAC5 is altered (Garayo-Larrea et al. 2024). If such crosstalk does occur, it could impact the outcome of ameliorative and mental health strategies that involve HDAC5 inhibition as a target. Isoform-specific crosstalk may also help explain the nuances of *in vivo* crosstalk and variability in response to antidepressants across individuals, emphasizing the necessity of mapping isoform-specific interactions in detail (Latcheva et al., 2018).

Another significant barrier in translational research is the absence of selective HDAC5 inhibitors in the clinical domain. Selective HDAC5 inhibitors are not currently used in clinical practice. Most clinical HDAC inhibitors under investigation or approved, are pan-HDAC inhibitors that target multiple isoforms. To date, most pan-HDAC inhibitors which have been shown to have antidepressant-like activity in preclinical studies carry considerable risk of systemic toxicity including hepatotoxicity, hematopoietic dysfunction, and off-target

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

neurotoxicity (Dai et al., 2024). The absence of selective HDAC5 inhibitors limits researchers' ability to assess its therapeutic value in humans, while hindering progress to isoform-specific interventions in the clinical space. To date, the selective modulation of HDAC5 without effects to other HDAC isoforms is a priority in neuropsychiatric pharmacology.

The BBB penetration and off-target effects of HDAC5-targeted therapies are also poorly studied. HDAC inhibitors are frequently large polar molecules that do not efficiently penetrate the BBB and cause CNS effects (Seo et al., 2014; Archie et al., 2021). Even if selective HDAC5 inhibitors are available, achieving the requisite concentrations in regions of interest (such as the hippocampus or nucleus accumbens) whilst avoiding peripheral tissue may be quite a challenge. Off-target interactions with other enzymes, transcription factors and signalling pathways have the potential to lessen therapeutic selectivity or lead to potential adverse effects. More research is needed to develop and investigate reliable delivery and formulation options (e.g., nanoparticles, prodrugs, structure guided BBB penetrant inhibitors, etc.) that may provide CNS specificity without affecting peripheral tissues.

Currently, there is a significant gap in peripherally measurable aspects of HDAC5 activity, e.g., in blood or cerebrospinal fluid (CSF). Existing methods of measurement of HDAC5 expression/activity are limited to postmortem tissue or rodent brain assays, which cannot be done in living and symptomatic human patients (Reddy et al., 2025). If peripheral biomarkers could be developed, examinable longitudinally to confirm HDAC5 dynamics, one could stratify patients based on HDAC5 activity and potentially also provide a means to measure early treatment response. Peripheral measures could also help validate clinical trials of selective inhibitors of HDAC5 by providing more integrated mechanistic readouts that could relate to eventual clinical outcome (Yang et al., 2021).

Ultimately, there are significant and complex gaps in the current literature about HDAC5 specifically, and in depression more widely, particularly considering the use of rodent models with limited validation in human state, a lack of longitudinal data, an unclear understanding of mechanistic pathways between HDAC5 and synaptic plasticity, stress hormones and with limited understanding of distinct isoform-specific crosstalk in real human symptoms, a lack of selective HDAC5 inhibitors, underexplored barrier and off-target inhibition implications and reliable peripheral biomarkers. Filling all these gaps may be needed before being able to translate encouraging findings in preclinical work into concrete clinic-ready therapeutics. If we can bridge this gap, we can develop isoform- and circuit-specific approaches to better the efficacy of antidepressants, reduce side effects, and improve overall MDD treatment outcomes. As it stands, HDAC5 may not achieve its therapeutic potential, and we might not achieve our goal of individualized treatment approaches for depression derived from epigenetics.

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

## FUTURE RESEARCH DIRECTIONS

The ongoing complexity in our understanding of HDAC5 in (MDD) highlights a number of highlighted areas of urgent research interest. Using current molecular approaches and translational approaches to connect rodent models and molecular observations to real clinical studies in humans, we can begin to build a bridge between what we observe preclinically in rodent models to the human clinical space. Below are six potential research directions.

### CRISPR-based gene editing to get at HDAC5 regulatory circuits

CRISPR-Cas9 technologies for genetic and epigenetic manipulation of HDAC5 could provide unprecedented specificity. CRISPR provides a unique avenue for gene disruption with site-specific knockouts, knock-ins, and base edits. For example, CRISPR studies manipulating epigenetic regulators of neuronal plasticity in rodent model systems have shown that it is possible to map a causal pathway between chromatin remodeling and behavioral outcomes (Kolanu, 2024). These technologies can be applied to HDAC5 to understand whether its activity directly or indirectly modulates brain-derived neurotrophic factor (BDNF) expression, in the context of one or more intermediate transcription factors. Finally, if we pair CRISPR perturbations with next generation sequencing (e.g., ATAC-seq, ChIP-seq), the mapping would create a comprehensive atlas of HDAC5 genome binding sites in neurons in response to stress and antidepressant treatments (Weekley et al., 2025).

### Cell-type–specific knock-in/out models in rodents

A limitation of current rodent studies is that most studies examine either global or regionally located HDAC5, which means some contributions of select populations cannot be extracted. However, depression and antidepressant responses rely on a vast array of interacting excitatory neurons, inhibitory interneurons, and glia. If researchers could create conditional knock-in/out models with either Cre-loxP technology or a Cre non-recombinase method, they could manipulate HDAC5 in a specific population with more confidence (Patzke et al., 2016). For instance, Cre-loxP technology could be used in a defined population such as excitatory (glutamatergic) pyramidal neurons in the medial prefrontal cortex or dopamine neurons in the ventral tegmental area (Jeong et al., 2024). The importance of varying more than the measurements in preclinical work emphasizes the ability to vary the cellular resolution. With cell-type–specific tools, we could demonstrate whether HDAC5 acts decisively in the circuits of the excitatory, inhibitory circuits, or additional systems to support its use for drug development that avoids unintended systemic effects in the long run.

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

**Creating selective HDAC5 inhibitors with better BBB penetrance**

Although pan-histone deacetylase wide (HDACi) drugs are available in the clinic (e.g. vorinostat (SAHA) and valproate), none selectively target HDAC5 as their primary mechanism of action and also do not have as much potential for CNS penetrance (Seo et al., 2014). The potential toxicity of current HDAC inhibitors can include SD in both cardiac and immune systems, making them poor candidates for chronic exposure in vulnerable psychiatric patients (Hull et al., 2016). Prior works in medicinal or organic chemistry have uncovered promising scaffolds that have the potential to overcome the BBB. (Wu et al., 2023). However, these studies primarily examine pan-HDAC activity or HDAC isoform(s), such as HDAC6. An HDAC5 specific inhibitor with optimal lipophilicity, molecular weight, penetration, and efflux transport avoidance would signify revolutionary progress in translational approaches. Computational modeling or docking, structure-guided design, and high-throughput screening in combination, could produce a new class of compounds with both isoform specificity and penetrability into the CNS.

**PET imaging tracers for monitoring HDAC5 activity in vivo**

Another critical gap is tracking HDAC5 activity longitudinally in the living human brain. There are currently epigenetic regulators PET imaging tracers under development for HDAC isoforms, but not yet ones with enough specificity to target HDAC5 (Yeh et al., 2014). If radioligands were designed to selectively bind to HDAC5, longitudinal imaging studies could be conducted while measuring its expression in MDD patients before, during, and after antidepressant treatment. Their preliminary PET imaging data would function as imaging biomarkers of the research hypothesis set forth by rodent studies, i.e., whether HDAC5 nuclear export in the human brain is associated with antidepressant effects. The identified HDAC-targeting compound using PET imaging could also help stratify patients in HDAC-targeted compounds in clinical trials and as a direct mechanistic readout of drug engagement.

**Peripheral assays of HDAC5 overall expression or acetylation states**

Due to the invasiveness of brain sampling for HDAC5, peripheral assays represent a biologically relevant and major translation bridge. Any peripheral assays that were able to identify blood based or CSF biomarker readouts of HDAC5 expression, activity or downstream acetylation states could serve as valuable and accessible biomarkers of diagnosis and treatment monitoring. Preliminary study results have demonstrated that select HDAC isoform mRNA levels can be identified peripherally and correspond to depressive states (Garayo-Larrea et al., 2024). Although these results show the potential linkage of future findings to HDAC5 changes from current literature, there are inconsistencies and most of the work is small sample sizes. Increasing assay sensitivity to test if it was possible to monitor HDAC5 activity via droplet digital PCR, next generation sequencing or a mass-spectrometry based proteomics assay could produce sufficient monitoring HDAC5

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

activity. Some ideas, using peripheral markers would be particularly valuable to relate mechanisms to clinical endpoints in the real-world population, as invasive sampling would not be possible.

**Linking biomarkers to treatment response**

Ultimately, the maximum value of any putative biomarker is its predictive ability to link molecular changes to clinical outcomes. The next major step for HDAC5 would be to develop studies that include molecular biomarkers, neuroimaging biomarkers and depression treatments. For example, whether baseline blood HDAC5 expression levels, or baseline PET counts or binding in HDAC-identified brain regions predict response to selective serotonin reuptake inhibitors, ketamine or electroconvulsive therapy, or instead that HDAC5 can be boot strapped longitudinally to see if changes in HDAC5 expression has predictive validity for the early return of symptoms (relapse), or maintenance of symptom remission over time. In linking these biomarkers to clinical trajectories, not only would HDAC5 be validated as a mechanistic target, but also, we could develop stratified treatment protocol designs to move psychiatry to precise medicine.

## CONCLUSION

As stated before, MDD remains a significant burden on individuals and society, affecting millions of people worldwide, even with many treatments available. We have described the major limitations of today's pharmacologic treatments for depression, including a slow onset of antidepressant response, inconsistency in response to treatment, and adverse side effects of antidepressant drugs that make treatment more desirable than ever. A novel approach to investigate potential molecular and structural mechanisms underlying depression is through epigenetic regulation, such as HDAC5. Because HDAC5 affects gene expression changes related to neuroplasticity and stress, HDAC5 serves as an important drug target for antidepressant development.

The surveyed data demonstrates both the promise and limitations of current understandings. Models in rodents have greatly clarified the behavioral and neurobiological functions of HDAC5, demonstrating the effect of its nuclear export on antidepressant efficacy and resilience to stress. However, studies pertaining specifically to people are few, sporadic, and mostly—if not entirely—cross-sectional. We do not yet have a robust longitudinal study to link the pattern of HDAC5 expression to treatment response, or the trajectory of depressive symptoms. The study of human subjects is further limited because there are currently no isoform-selective HDAC5 inhibitors available, nor a complete understanding of its permeability across the blood-brain barrier (BBB), leaving us unable to translate from bench to bedside.

Future directions for research provide a path forward for tangible solutions. CRISPR-based editing can use cell-type-specific models to map the intricate regulatory network associated with HDAC5. Positron emission tomography (PET) tracers could be used to visualize its function in vivo. Selective inhibitors with greater BBB

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

penetration could provide safer, faster-acting antidepressants. Development of biomarker measures of HDAC5 expression or acetylation states in a peripheral tissue could change the way we diagnose and monitor treatment, moving us towards precision psychiatry based on a mechanistic understanding of psychological symptoms.

If the field goes on to conquer the divide between mechanistic understanding and clinical practice of HDAC5—then we would significantly change the treatment for depression, and extend outwards to the neuropsychiatry field itself. By unlocking the molecular aspect of HDAC5, we might finally enter an era in which antidepressant treatment is science, specificity and personalized—not a series of trial and error.

## REFERENCES

Archie, S. R., Al Shoyaib, A., & Cucullo, L. (2021). Blood-Brain Barrier Dysfunction in CNS Disorders and Putative Therapeutic Targets: An Overview. Pharmaceutics, 13(11), 1779. https://doi.org/10.3390/pharmaceutics13111779

A. Garayo-Larrea, A. Azqueta, R.M. Tordera, Role of histone deacetylases in neuroplasticity impairments and inflammation in major depression, Neuroscience Applied, Volume 3, 2024, 104081, ISSN 2772-4085. https://doi.org/10.1016/j.nsa.2024.104081

Correia, A. S., & Vale, N. (2021). Antidepressants in Alzheimer's Disease: A Focus on the Role of Mirtazapine. Pharmaceuticals (Basel, Switzerland), 14(9), 930. https://doi.org/10.3390/ph14090930

Dai, W., Qiao, X., Fang, Y., Guo, R., Bai, P., Liu, S., Li, T., Jiang, Y., Wei, S., Na, Z., Xiao, X., & Li, D. (2024). Epigenetics-targeted drugs: Current paradigms and future challenges. Signal Transduction and Targeted Therapy, 9(1), 332. https://doi.org/10.1038/s41392-024-02039-0

Erburu, M., Muñoz-Cobo, I., Domínguez-Andrés, J., Beltran, E., Suzuki, T., Mai, A., Valente, S., Puerta, E., & Tordera, R. M. (2015). Chronic stress and antidepressant induced changes in Hdac5 and Sirt2 affect synaptic plasticity. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, 25(11), 2036–2048. https://doi.org/10.1016/j.euroneuro.2015.08.016

Ganai, S. A., Ramadoss, M., & Mahadevan, V. (2016). Histone Deacetylase (HDAC) Inhibitors - emerging roles in neuronal memory, learning, synaptic plasticity and neural regeneration. Current neuropharmacology, 14(1), 55–71. https://doi.org/10.2174/1570159x13666151021111609

Garayo-Larrea, A., Azqueta, A., & Tordera, R. M. (2024). Role of histone deacetylases in neuroplasticity impairments and inflammation in major depression. Neuroscience applied, 3, 104081. https://doi.org/10.1016/j.nsa.2024.104081

Guan, J. S., Haggarty, S. J., Giacometti, E., Dannenberg, J. H., Joseph, N., Gao, J., Nieland, T. J., Zhou, Y., Wang, X., Mazitschek, R., Bradner, J. E., DePinho, R. A., Jaenisch, R., & Tsai, L. H. (2009). HDAC2 negatively regulates memory formation and synaptic plasticity. Nature, 459(7243), 55–60. https://doi.org/10.1038/nature07925

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

Hanson, J. E., Deng, L., Hackos, D. H., Lo, S. C., Lauffer, B. E., Steiner, P., & Zhou, Q. (2013). Histone deacetylase 2 cell autonomously suppresses excitatory and enhances inhibitory synaptic function in CA1 pyramidal neurons. The Journal of neuroscience : the official journal of the Society for Neuroscience, 33(14), 5924–5929. https://doi.org/10.1523/JNEUROSCI.3162-12.2013

Jeong, M., Choi, J.-H., Jang, H., Sohn, D. H., Wang, Q., Lee, J., Yao, L., Lee, E. J., Fan, J., Pratelli, M., Wang, E. H., Snyder, C. N., Wang, X. Y., Shin, S., Gittis, A. H., Sung, T. C., Spitzer, N. C., & Lim, B. K. (2024). Viral vector-mediated transgene delivery with novel recombinase systems for targeting neuronal populations defined by multiple features. Neuron, 112(1), 56-72.e4. https://doi.org/10.1016/j.neuron.2023.09.038

Karakatsani, M. E., Ji, R., Murillo, M. F., Kugelman, T., Kwon, N., Lao, Y. H., Liu, K., Pouliopoulos, A. N., Honig, L. S., Duff, K. E., & Konofagou, E. E. (2023). Focused ultrasound mitigates pathology and improves spatial memory in Alzheimer's mice and patients. Theranostics, 13(12), 4102–4120. https://doi.org/10.7150/thno.79898

Karrouri, R., Hammani, Z., Benjelloun, R., & Otheman, Y. (2021). Major depressive disorder: Validated treatments and future challenges. World journal of clinical cases, 9(31), 9350–9367. https://doi.org/10.12998/wjcc.v9.i31.9350

Kolanu N. D. (2024). CRISPR-Cas9 Gene Editing: Curing Genetic Diseases by Inherited Epigenetic Modifications. Global medical genetics, 11(1), 113–122. https://doi.org/10.1055/s-0044-1785234

Latcheva, N. K., Viveiros, J. M., Waddell, E. A., Nguyen, P. T. T., Liebl, F. L. W., & Marenda, D. R. (2018). Epigenetic crosstalk: Pharmacological inhibition of HDACs can rescue defective synaptic morphology and neurotransmission phenotypes associated with loss of the chromatin reader Kismet. Molecular and cellular neurosciences, 87, 77–85. https://doi.org/10.1016/j.mcn.2017.11.007

Li, N., Liu, T., Wang, Y. Y., Xu, T., Shi, H. J., Chang, L., & Zhu, L. J. (2024). Hippocampal HDAC5-mediated histone acetylation underlies stress susceptibility in mice exposed to chronic social defeat stress. Neuroscience, 557, 89–99. https://doi.org/10.1016/j.neuroscience.2024.08.010

Łysik, A., Logoń, K., Szczygieł, A., Wołoszczak, J., Wrześniewska, M., & Leszek, J. (2025). Innovative approaches in the treatment-resistant depression: exploring different therapeutic pathways. GeroScience, 47(4), 5543–5558. https://doi.org/10.1007/s11357-025-01615-8

Machado-Vieira, R., Salvadore, G., Luckenbaugh, D. A., Manji, H. K., & Zarate, C. A., Jr (2008). Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depressive disorder. The Journal of clinical psychiatry, 69(6), 946–958. https://doi.org/10.4088/jcp.v69n0610

Mariani, N., Cattane, N., Pariante, C., & Cattaneo, A. (2021). Gene expression studies in Depression development and treatment: an overview of the underlying molecular mechanisms and biological processes to identify biomarkers. Translational psychiatry, 11(1), 354. https://doi.org/10.1038/s41398-021-01469-6

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

Markov, D. D., & Novosadova, E. V. (2022). Chronic Unpredictable Mild Stress Model of Depression: Possible Sources of Poor Reproducibility and Latent Variables. Biology, 11(11), 1621. https://doi.org/10.3390/biology11111621

Markov D. D. (2022). Sucrose Preference Test as a Measure of Anhedonic Behavior in a Chronic Unpredictable Mild Stress Model of Depression: Outstanding Issues. Brain sciences, 12(10), 1287. https://doi.org/10.3390/brainsci12101287

Meng, Y., Du, J., Liu, N., Qiang, Y., Xiao, L., Lan, X., Ma, L., Yang, J., Yu, J., & Lu, G. (2023). Epigenetic modulation: Research progress on histone acetylation levels in major depressive disorders. Journal of Drug Targeting, 31(2), 142–151. https://doi.org/10.1080/1061186X.2022.2125978

Misztak, P., Pańczyszyn-Trzewik, P., & Sowa-Kućma, M. (2018). Histone deacetylases (HDACs) as therapeutic target for depressive disorders. Pharmacological Reports, 70(2), 398–408. https://doi.org/10.1016/j.pharep.2017.08.001

Nestler, E. J., Peña, C. J., Kundakovic, M., Mitchell, A., & Akbarian, S. (2016). Epigenetic Basis of Mental Illness. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry, 22(5), 447–463. https://doi.org/10.1177/1073858415608147

Patzke, C., & Südhof, T. C. (2016). The conditional KO approach: Cre/Lox technology in human neurons. Rare diseases (Austin, Tex.), 4(1), e1131884. https://doi.org/10.1080/21675511.2015.1131884

Sun, H., Kennedy, P. J., & Nestler, E. J. (2013). Epigenetics of the depressed brain: role of histone acetylation and methylation. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology, 38(1), 124–137. https://doi.org/10.1038/npp.2012.73

Schroeder, F. A., Gilbert, T. M., Feng, N., Taillon, B. D., Volkow, N. D., Innis, R. B., Hooker, J. M., & Lipska, B. K. (2017). Expression of HDAC2 but not HDAC1 transcript is reduced in dorsolateral prefrontal cortex of patients with schizophrenia. ACS Chemical Neuroscience, 8(3), 662–668. https://doi.org/10.1021/acschemneuro.6b00372

Seo, Y. J., Kang, Y., Muench, L., Reid, A., Caesar, S., Jean, L., Wagner, F., Holson, E., Haggarty, S. J., Weiss, P., King, P., Carter, P., Volkow, N. D., Fowler, J. S., Hooker, J. M., & Kim, S. W. (2014). Image-guided synthesis reveals potent blood-brain barrier permeable histone deacetylase inhibitors. ACS chemical neuroscience, 5(7), 588–596. https://doi.org/10.1021/cn500021p

Voineskos, D., Daskalakis, Z. J., & Blumberger, D. M. (2020). Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatric disease and treatment, 16, 221–234. https://doi.org/10.2147/NDT.S198774

Wang, H. K., Su, Y. T., Ho, Y. C., Lee, Y. K., Chu, T. H., Chen, K. T., & Wu, C. C. (2023). HDAC1 is Involved in Neuroinflammation and Blood-Brain Barrier Damage in Stroke Pathogenesis. Journal of inflammation research, 16, 4103–4116. https://doi.org/10.2147/JIR.S416239

Westlund, K. N., Montera, M., Goins, A. E., Shilling, M. W., Afaghpour-Becklund, M., Alles, S. R. A., & Hui, S. E. (2024). Epigenetic HDAC5 inhibitor reverses craniofacial neuropathic pain in mice. Journal of Pain, 25(2), 428–450. https://doi.org/10.1016/j.jpain.2023.09.015

SCHOLARLY REVIEW JOURNAL

*E-ISSN: 2996-8380*
*Published by Leadership & Innovation Lab*

**WINTER 2025/2026**

Wu, M.-S., Li, X.-J., Liu, C.-Y., Xu, Q., Huang, J.-Q., Gu, S., & Chen, J.-X. (2022). Effects of histone modification in major depressive disorder. Current Neuropharmacology, 20(7), 1261–1277. https://doi.org/10.2174/1570159X19666210922150043

Yuan, M., Yang, B., Rothschild, G., Mann, J. J., Sanford, L. D., Tang, X., Huang, C., Wang, C., & Zhang, W. (2023). Epigenetic regulation in major depression and other stress-related disorders: molecular mechanisms, clinical relevance and therapeutic potential. Signal transduction and targeted therapy, 8(1), 309. https://doi.org/10.1038/s41392-023-01519-z

Zeng, Y., Tan, M., Kohyama, J., Sneddon, M., Watson, J. B., Sun, Y. E., & Xie, C. W. (2011). Epigenetic enhancement of BDNF signaling rescues synaptic plasticity in aging. The Journal of neuroscience : the official journal of the Society for Neuroscience, 31(49), 17800–17810. https://doi.org/10.1523/JNEUROSCI.3878-11.2011 (Retraction published J Neurosci. 2013 Dec 11;33(50):19735. doi: 10.1523/JNEUROSCI.4832-13.2013.)

Zhang, J. P., Yang, Z. X., Zhang, F., Fu, Y. W., Dai, X. Y., Wen, W., Zhang, B., Choi, H., Chen, W., Brown, M., Baylink, D., Zhang, L., Qiu, H., Wang, C., Cheng, T., & Zhang, X. B. (2021). HDAC inhibitors improve CRISPR-mediated HDR editing efficiency in iPSCs. *Science China. Life sciences*, *64*(9), 1449–1462. https://doi.org/10.1007/s11427-020-1855-4