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Neuroepigenetic Effects of Non-Pharmacological Pain Treatments: A Narrative Review

Dawood Hossaini [1], Ahmad Wali Ataye [2,3], *Murtaza Haidary [1,4], Naseer Ahmad Durrani [2], Mohammad Baryalai Barya [5]

1. *Department of Paraclinical Sciences and Laboratory Management, Faculty of Medical Laboratory Technology, Khatam Al-Nabieen University, Kabul, Afghanistan*
2. *Department of Public Health, Faculty of Medicine, Afghan International Islamic University of Kabul, Afghanistan*
3. *Department of Clinical Sciences, Faculty of Medical Laboratory Technology, Khatam Al-Nabieen University, Kabul, Afghanistan*
4. *Medical Research and Technology Center, Khatam Al-Nabieen University, Kabul, Afghanistan.*
5. *Kabul University of Medical Science, Kabul, Afghanistan*

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*Corresponding Author:
Murtaza Haidary

E-mail address:
sadramurtaza@gmail.com
murtaza.haidary@knu.edu.af

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ABSTRACT

Background: Chronic pain is increasingly recognized as a multidimensional condition shaped by biological, psychological, and environmental factors. Conventional pharmacological treatments, including opioids and non-steroidal anti-inflammatory drugs (NSAIDs), are limited by side effects, tolerance, and poor long-term efficacy, highlighting the need for alternative therapeutic strategies. We aimed to summarize evidence on epigenetic mechanisms underlying chronic pain and to evaluate how non-pharmacological interventions contribute to pain modulation through epigenetic remodeling.

Methods: A narrative review of experimental and clinical studies was conducted, focusing on epigenetic changes associated with chronic pain and the effects of non-pharmacological interventions, including exercise, cognitive behavioral therapy (CBT), mindfulness, neuromodulation techniques, acupuncture, sleep, and dietary modulation.

Results: Chronic pain involves widespread epigenetic remodeling across spinal and supraspinal regions, contributing to central sensitization, neuroinflammation, and maladaptive neuroplasticity. Non-pharmacological interventions converge on shared epigenetic mechanisms: exercise enhances histone acetylation and brain-derived neurotrophic factor (BDNF) expression; CBT and mindfulness normalize stress-related DNA methylation and microRNA profiles; neuromodulation techniques (transcutaneous electrical nerve stimulation, repetitive transcranial magnetic stimulation, transcranial direct current stimulation, and deep brain stimulation) influence histone acetylation and opioid receptor gene methylation; acupuncture regulates DNA methylation and histone acetylation in pain-related neural circuits; and lifestyle factors such as sleep and diet modulate circadian and inflammatory gene expression.

Conclusion: Non-pharmacological pain therapies exert clinically meaningful effects through epigenetic remodeling of nociceptive pathways, positioning them as promising adjunctive or alternative approaches to pharmacological treatment. Future research should prioritize longitudinal multi-omics studies and biomarker-driven precision strategies to optimize therapeutic selection and efficacy.

Keywords: Chronic pain; Epigenetics; DNA methylation; Histone modification; microRNAs; non-pharmacological therapy; Neuromodulation

Introduction

Pain is now widely acknowledged as a complex phenomenon involving multiple dimensions shaped by biological, psychological, and environmental factors. Acute pain generally subsides once tissue repair occurs, but in some individuals, dysfunctional neural adaptations lead to chronic pain, marked by heightened pain sensitivity (hyperalgesia) and pain from normally non-painful stimuli (allodynia) [1, 2]. In addition to encoding stimulus features such as location, duration, and intensity, pain engages complex responses, including involuntary reflexes and autonomic processes.

The global prevalence of pain, standardized for age and gender, varies widely, with a weighted average of 27.5%, ranging from 9.9% to 50.3% across populations. Chronic pain represents a major public health burden in regions such as the United States and Europe due to its high prevalence and associated socioeconomic costs [3].

Despite advances in medicine, current pharmacological treatments face several limitations that affect both their effectiveness and safety. Many options provide only temporary relief, typically lasting 4 to 6 hours, requiring multiple doses throughout the day. This can be inconvenient and may prevent patients from achieving adequate pain control [4]. Moreover, common treatments, such as opioids and nonsteroidal anti-inflammatory drugs (NSAIDs), are associated with substantial adverse effects, including gastrointestinal complications, cardiovascular risks, and organ toxicity, which can limit their long-term use and effectiveness [5]. While opioids are effective for pain relief, they carry a high risk of addiction [6] and tolerance, leading to increased dosages over time and potential misuse [7]. The development of tolerance can also result in opioid-induced hyperalgesia, where patients become more sensitive to pain, counteracting the intended analgesic effects [8]. These limitations underscore the pressing need to identify alternative mechanisms and therapeutic targets.

The neural substrates of pain involve a distributed network, including the anterior cingulate cortex (ACC), insular cortex, amygdala, hippocampus, periaqueductal gray (PAG), and rostral ventromedial medulla (RVM). Dysregulation within these cortical-limbic and brainstem circuits contributes to central sensitization and the persistence of chronic pain [9]. Epigenetic remodeling within these regions has been increasingly implicated in the maladaptive plasticity underlying pain chronification. Epigenetics is defined as heritable yet reversible changes in gene expression that occur without alterations in the DNA sequence, primarily through mechanisms such as DNA methylation/hydroxymethylation, histone modifications, and non-coding RNAs [10]. These mechanisms enable cells to adapt transcriptional programs to environmental and physiological signals, thereby linking external stimuli to long-term changes in neural function. Changes in DNA methylation, histone modifications, and microRNA (miRNA) expression regulate transcriptional programs in pain-related circuits, contributing to central sensitization, maladaptive neuroplasticity, and pain persistence [1,11,12].

This shift has driven interest in exploring non-pharmacological interventions—such as exercise, diet, environmental enrichment, and neuromodulation—which not only modulate pain perception but may also exert beneficial effects by remodeling epigenetic marks [13, 14]. These interventions are thought to influence pain through mechanisms such as modulation of the hypothalamic–pituitary–adrenal (HPA) axis, enhancement of neurotrophic factors like BDNF, regulation of immune and inflammatory pathways, and alterations in circadian and met-

abolic processes [15-17]. Despite the extent to which non-pharmacological treatments exert their effects via epigenetic mechanisms remains underexplored.

In this context, we aimed to synthesize current evidence on how non-pharmacological therapies induce epigenetic modifications and neural plasticity to modulate pain perception. The review highlights fundamental concepts, controversies, and knowledge gaps while outlining future directions for precision, mechanism-based pain management.

Methods

This narrative review was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) criteria [18] to ensure methodological rigor, transparency, and balanced synthesis. A comprehensive literature search was performed through PubMed, Scopus, and Web of Science databases between January 2000 and June 2025 to identify studies investigating epigenetic mechanisms associated with non-pharmacological interventions for pain. The search strategy combined controlled vocabulary and free-text terms, including chronic pain, neuropathic pain, nociplastic pain, epigenetics, DNA methylation, histone modification, microRNA, exercise, cognitive-behavioral therapy, mindfulness, neuromodulation (TENS, rTMS, tDCS, DBS), acupuncture, and lifestyle interventions (diet, sleep).

A total of 680 records were identified through database searching and manual reference screening. After removal of 126 duplicate records, 554 articles remained for title and abstract screening. Of these, 421 records were excluded based on irrelevance to the review topic. The full texts of 133 potentially eligible articles were then assessed in detail. Following full-text evaluation, 54 articles were excluded because they did not meet the inclusion criteria, primarily due to insufficient focus on epigenetic mechanisms or exclusive emphasis on pharmacological interventions. Ultimately, 79 studies were included in the final narrative synthesis.

Only peer-reviewed English-language articles were considered if they examined preclinical or clinical models linking non-pharmacological treatments with molecular or epigenetic changes relevant to pain modulation; studies focusing exclusively on pharmacological or genetic mechanisms were excluded. Reference lists of key reviews and primary studies were manually screened to capture additional relevant publications. Extracted information encompassed study design, species or population, intervention characteristics, targeted neural regions, and identified epigenetic markers such as DNA methylation, histone acetylation, or non-coding RNA regulation. Evidence was synthesized narratively using a thematic and integrative approach to identify convergent molecular pathways—including BDNF signaling, stress-axis gene methylation, and inflammatory microRNA modulation—and to connect mechanistic findings with translational and clinical implications. The review emphasized completeness of evidence, scientific reasoning, and critical balance in line with SANRA recommendations. As this review is based on previously published studies, ethical approval was not required.

Results

Neurobiology of Pain

Pain arises from specialized nociceptors, including peptidergic and non-peptidergic C-fibers and Aδ fibers, which detect mechanical, thermal, and chemical threats [19]. These neurons transduce noxious stimuli via TRP channels (TRPV1, TRPA1, TRPM8) and voltage-gated sodium channels (NaV1.7, NaV1.8), while mediators like bradykinin, prostaglandins, NGF, ATP, and protons produce peripheral sensitization, lowering activation thresholds and causing localized hyperalgesia [20-22] Activated nociceptors release glutamate, substance P, and CGRP onto dorsal horn neurons, where

AMPA and NMDA receptors mediate fast excitatory transmission and neuropeptides drive slower modulatory responses, contributing to central sensitization and long-term plasticity [23, 24]. Ascending nociceptive signals reach thalamus, brainstem, and cortical areas (somatosensory cortices, insula, anterior cingulate), integrating sensory, affective, and cognitive dimensions, while descending pathways from PAG and RVM modulate spinal processing [25, 26]. Neuro-immune interactions, including cytokines and glial-derived factors like IL-1β and BDNF, further maintain chronic pain independently of tissue damage [27, 28]. These mechanisms underscore the importance of multimodal therapies targeting peripheral sensitization, spinal plasticity, descending modulation, and psychosocial factors [19].

Epigenetic Mechanisms in Pain

Epigenetic mechanisms play a fundamental role in the development and persistence of chronic and neuropathic pain by modulating gene expression without altering the underlying DNA sequence [30, 31]. These mechanisms shape pain sensitivity arising from inflammation, tissue damage, or nerve injury through the regulation of ion channels and neurotransmitter receptors in sensory neurons of the dorsal root ganglion, spinal cord, and brain [32-34]. Among the major epigenetic modifications involved are histone modifications, DNA methylation, and non-coding RNAs. Histone acetylation, methylation, and other covalent changes—controlled by "writer, reader, and eraser" proteins—drive the expression of pro-nociceptive genes, while histone deacetylase (HDAC) inhibitors have been shown to attenuate pain hypersensitivity [31, 34, 35]. Likewise, DNA methylation of specific promoters such as TRPA1 is closely associated with pain sensitivity [33, 36]. In parallel, non-coding RNAs, including miRNAs and lncRNAs, fine-tune the expression of pain-related genes and contribute to the maintenance of neuropathic pain [30, 32]. Collectively, these epigenetic modifications enhance excitatory signaling through glutamate and NMDA receptors, α2δ-1, and growth factors, while downregulating inhibitory pathways such as mu opioid receptors and potassium channels [31, 34, 37]. Moreover, the expression of calcitonin gene-related peptide (CGRP), a key mediator of migraine and inflammatory pain, is epigenetically regulated through DNA methylation, histone modifications, and non-coding RNAs [38].

Neural Circuits Affected by Epigenetic Remodeling

Epigenetic mechanisms critically shape neural circuits involved in pain perception, modulation, and chronification. By persistently altering gene expression, these modifications influence neuronal excitability, synaptic plasticity, and communication across peripheral and central circuits, ultimately shaping both sensory and affective components of pain.

Peripheral Sensory Neurons and Spinal Cord

In primary sensory neurons of the dorsal root ganglia (DRG), MBD1, an epigenetic repressor, has emerged as a key mediator of acute and neuropathic pain. Mo et al. (39) demonstrated that MBD1 deficiency in DRG neurons reduces responses to mechanical, thermal, and chemical stimuli, and blunts nerve injury-induced hypersensitivity. Conversely, MBD1 overexpression induces spontaneous and evoked pain, highlighting its sufficiency in promoting pain phenotypes. Mechanistically, MBD1 recruits DNA methyltransferase 3a (DNMT3a) to the promoters of the μ-opioid receptor (Oprm1) and the voltage-gated potassium channel Kv1.2 (Kcna2), leading to DNA methylation and transcriptional silencing. Downregulation of Kcna2 diminishes potassium currents, increases DRG excitability, and contributes to hyperalgesia and allodynia, while suppression of Oprm1 reduces opioid analgesic efficacy. Notably, MBD1 knockdown restores Oprm1 and Kcna2 expression, normalizes neuronal excitability, and en-

hances morphine-induced analgesia in neuropathic models [39]. At the spinal level, epigenetic modifications continue to modulate nociceptive processing. Increased histone deacetylase (HDAC) activity reduces histone acetylation at inhibitory neurotransmitter genes, including GABAergic markers, leading to decreased inhibitory tone and dorsal horn hyperexcitability—a hallmark of central sensitization. Pharmacological HDAC inhibition restores histone acetylation, enhances inhibitory gene expression, and attenuates pain hypersensitivity [40, 41]. Together, these peripheral and spinal mechanisms illustrate how epigenetic silencing and chromatin remodeling heighten nociceptive signaling and reduce analgesic responsiveness.

Brainstem and Descending Modulation Cortical and Limbic Regions

Pain perception is further shaped by epigenetic regulation in cortical and limbic circuits. The prefrontal cortex (PFC) exerts top-down inhibitory control over spinal and limbic circuits, but DNA methylation and histone modifications of pain- and plasticity-related genes can disrupt this regulation, facilitating the transition from acute to chronic pain [42]. In the amygdala, stress-sensitive epigenetic changes enhance excitatory synaptic signaling, amplifying the affective and aversive aspects of pain [43]. The hippocampus shows dysregulated microRNA expression (e.g., upregulation of miR-132, downregulation of miR-124) and histone modifications that impair synaptic plasticity, reinforce maladaptive pain memory, and contribute to cognitive deficits [44, 45].

Chronic pain leads to significant epigenetic modifications in the spinal dorsal horn, a critical region for processing nociceptive (pain) signals. One key event is the increased DNA methylation at the promoter region of the μ-opioid receptor (Oprm1) gene. This methylation is associated with the recruitment of MeCP2 (Methyl-CpG-binding protein 2) and HDAC1 (Histone Deacetylase 1) to the Oprm1 promoter. MeCP2 binding to methylated DNA recruits HDAC1, leading to histone deacetylation and chromatin condensation, thereby suppressing gene transcription. Consequently, the expression of MOR is reduced in primary sensory neurons of the dorsal root ganglia (DRG), diminishing the efficacy of opioid analgesics like morphine. Importantly, experimental knockdown of MeCP2 restores MOR expression and enhances the analgesic effects of morphine in neuropathic pain models, suggesting that targeting this epigenetic pathway could improve opioid efficacy in chronic pain management [46].

Chronic pain induces significant epigenetic modifications in the spinal cord, particularly in the promoters of inflammatory genes such as chemokines. These modifications include increased histone acetylation at lysine 9 (H3K9ac) and trimethylation at lysine 4 (H3K4me3), which are associated with active transcription. This epigenetic remodeling leads to the upregulation of pro-inflammatory cytokines and chemokines, contributing to neuroinflammation and the persistence of pain hypersensitivity. Conversely, pharmacological inhibition of histone deacetylases (HDACs) can suppress this inflammatory response. HDAC inhibitors, such as trichostatin A and sodium butyrate, have been shown to reduce histone deacetylation, thereby normalizing gene expression and attenuating pain hypersensitivity in neuropathic models. These findings underscore the therapeutic potential of targeting chromatin remodeling pathways to manage chronic pain [42].

Chronic pain conditions induce epigenetic alterations in the PAG that affect opioid receptor expression. Increased DNA methylation and histone modifications at the promoter regions of opioid receptor genes can lead to their downregulation [46]. This downregulation impairs the PAG's ability to modulate pain effectively, contributing to the persistence of chronic pain states [42, 47]. Conversely, interventions that reverse these epigenetic modifications, such as

histone deacetylase inhibitors, can restore opioid receptor expression in the PAG [46]. This restoration enhances descending inhibitory control over pain, highlighting a potential therapeutic strategy for chronic pain management [46]. While detailed mapping of epigenetic changes in the PAG is still emerging, current evidence underscores the significance of epigenetic regulation in this region and its implications for chronic pain [42, 47].

Converging human imaging/post-mortem and animal studies show that both the insula and ACC undergo epigenetic alterations in conditions such as chronic pain, stress-related disorders, depression and addiction, and that manipulating these epigenetic marks changes neural function and behavior [48, 49]. DNA methylation and hydroxymethylation (5mC/5hmC) exhibit region- and locus-specific alterations in cortical genes regulating synaptic function, inflammation, and neuroplasticity. Such epigenetic modifications have been associated with structural and functional changes in key brain regions, including the insula and ACC, detected through both epigenome-wide association studies and targeted analyses [50]. Histone acetylation in cortical neurons enhances chromatin accessibility and promotes the transcription of plasticity genes, crucial for synaptic remodeling and cognitive processes. In contrast, histone deacetylation, mediated by HDACs, condenses chromatin and represses gene expression. Inhibition of HDAC activity has reversed maladaptive behaviors in animal models, suggesting that HDAC inhibitors may offer therapeutic potential in treating disorders associated with impaired neuronal plasticity [49, 51]. miRNA expression in cortical tissue (including ACC) modulates synaptic and inflammatory pathways relevant to pain and mood disorders; altered miRNA profiles are repeatedly reported in patient tissue and animal models [52].

Imaging-guided methylation studies have correlated DNA methylation signatures with insular cortical morphology (e.g., right insular surface area) and related behavioral/trait measures — indicating epigenetic variation maps onto insular structure/function in humans [48]. recent experiments manipulating epigenetic enzymes (e.g., HDACs) or locus-specific chromatin states in the anterior insular cortex change behaviors relevant to addiction, impulsivity and decision-making, showing the insula is epigenetically plastic and behaviorally consequential [53].

The ACC shows epigenetic regulation in stress, anxiety, depression and chronic pain models. Reviews and experimental studies report DNA methylation and histone modification changes in ACC that correlate with altered pain sensitivity, emotional processing and antidepressant responses [51]. Human post-mortem and patient tissue studies identify altered methylation/miRNA patterns in ACC from depressed or stressed individuals, linking molecular chromatin changes to psychiatric phenotypes [52]. Epigenetic changes alter expression of neurotransmitter receptors, neurotrophic factors and synaptic proteins — shifting excitability and synaptic strength in insula/ACC circuits. This can promote pain chronification, negative affect, or compulsive drug-seeking [49, 50].

Epigenetic Mechanisms of Non-Pharmacological Pain Treatments

Exercise and Physical Activity

Exercise is among the most studied non-pharmacological interventions for pain, with evidence showing its ability to reduce hyperalgesia by modulating both peripheral and central inflammatory processes [54, 55]. Regular aerobic and resistance training attenuate stress reactivity and normalize HPA axis activity, reducing glucocorticoid-driven sensitization of nociceptive circuits [14, 56]. At the molecular level, exercise induces histone acetylation in the hippocampus and spinal cord, facilitating expression of plasticity-related genes such as *BDNF* and *c-Fos* that contribute to analgesic effects [57, 58]. Chronic pain has been associated with

accelerated epigenetic aging, which may influence the persistence and severity of pain conditions. For instance, individuals experiencing high-impact pain show significant differences in epigenetic aging markers compared to those without pain, suggesting that pain may drive epigenetic changes that affect overall health and function [59].

Furthermore, physical activity enhances DNA methylation turnover in immune cells, down-regulating pro-inflammatory genes (e.g., TNF-α, IL-6) while upregulating anti-inflammatory mediators [60, 61]. The epigenetic changes resulting from exercise, particularly H3K9ac enrichment and promoter demethylation of BDNF, are considered essential for the sustained hypoalgesic effects of regular physical activity [62, 63]. Exercise can influence the expression of miRNAs, which are involved in pain pathways. For example, studies on mice have shown that both resistance and aerobic exercises can down-regulate miRNA-155, leading to increased pain thresholds and potentially providing therapeutic benefits for conditions like multiple sclerosis [64]. These modifications contribute to a long-lasting reduction in pain sensitivity, highlighting the importance of exercise as a therapeutic strategy in pain management.

Cognitive-Behavioral Therapy (CBT)

CBT has emerged as a leading non-pharmacological intervention for chronic pain, alleviating symptoms through cognitive reappraisal, reduction of catastrophizing, and improved coping strategies that modulate affective-motivational circuits of pain [65, 66]. While direct studies connecting CBT-induced epigenetic changes with pain outcomes are still limited, converging evidence from both pain epigenetics and psychotherapeutic epigenetic modulation provides a compelling theoretical foundation for exploring how CBT may alleviate chronic pain through epigenetic pathways [1, 67, 68]. Neuroimaging studies indicate that CBT normalizes connectivity in brain regions involved in pain perception, particularly within the prefrontal and limbic systems, thereby enhancing cognitive control over pain and emotional responses [69-71]. These changes suggest enhanced cognitive control over pain and emotional responses. Psychological stress and maladaptive cognition can lead to alterations in DNA methylation patterns in stress-responsive genes, such as Nuclear Receptor Subfamily 3 Group C Member 1 (NR3C1) and FKBP5, which are linked to pain vulnerability. CBT may counteract these effects by restoring balanced methylation and reducing histone deacetylation, thereby potentially reversing the epigenetic changes associated with chronic pain [72-74]. CBT may counteract these effects by restoring balanced methylation and reducing histone deacetylation in prefrontal–limbic networks, thereby potentially reversing maladaptive epigenetic signatures associated with pain chronification [75]. Supporting this view, preliminary data suggest that CBT can reduce peripheral expression of pro-inflammatory miRNAs such as miR-155 and miR-132, providing an additional epigenetic mechanism for its clinical efficacy [76, 77].

Mindfulness and Meditation

Mindfulness-based interventions (MBIs), including mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT), have demonstrated efficacy in reducing pain intensity, improving coping, and enhancing emotional regulation in chronic pain populations [78, 79]. Neuroimaging studies show that mindfulness practice modulates activity and connectivity within prefrontal, insular, and anterior cingulate cortices—regions central to the affective and sensory dimensions of pain [80, 81]. These brain regions are also sites of epigenetic remodeling in chronic pain, suggesting that mindfulness may exert therapeutic effects through molecular plasticity. Indeed, psychological stress and sustained nega-

tive affect are linked to maladaptive DNA methylation patterns in stress-related genes such as NR3C1 and FKBP5, which contribute to pain vulnerability [68, 72]. Emerging evidence indicates that mindfulness practices can reverse such effects: participation in MBSR has been associated with changes in global DNA methylation and altered methylation of genes regulating stress reactivity, immune function, and neuroplasticity, including BDNF and SLC6A4 [82, 83]. In addition to their effects on stress-related gene pathways, MBIs have been reported to influence histone deacetylase (HDAC) expression, thereby shifting the chromatin landscape toward a more transcriptionally permissive state. For example, a single intensive meditation session (8 h) was shown to significantly downregulate the expression of HDAC2, HDAC3, and HDAC9 in peripheral blood mononuclear cells, accompanied by alterations in histone H4 acetylation and H3K4 trimethylation, both of which are associated with open chromatin and active transcription [82]. Moreover, mindfulness training alters miRNA expression patterns, such as downregulation of pro-inflammatory miR-21 and upregulation of miR-124, which is anti-inflammatory and neuroprotective [84]. Meditation exerts its analgesic effects not only via psychological mechanisms but also through enduring epigenetic reprogramming of stress and immune pathways [85].

Neuromodulation (TENS, rTMS, tDCS, DBS)

Neuromodulatory techniques have emerged as significant interventions for pain management, leveraging their ability to induce neuroplastic changes within the nervous system. These techniques include transcutaneous electrical nerve stimulation (TENS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS), each contributing to pain relief through distinct mechanisms. TENS reduces hyperalgesia by modulating spinal dorsal horn excitability, which is crucial for pain management. It operates through mechanisms that involve the inhibition of nociceptive transmission in the central nervous system, providing symptomatic relief for various pain conditions [86]. Experimental models of neuropathic pain have shown that electrostimulation reduces spinal expression of pro-inflammatory cytokines and glial activation, effects that are accompanied by increased histone acetylation [87].

Both rTMS and transcranial direct current stimulation (tDCS) enhance cortical excitability, particularly in regions associated with pain modulation, such as the prefrontal and motor areas. These techniques indirectly influence descending pain inhibition, contributing to pain relief and improved functional outcomes in chronic pain conditions [88, 89]. DBS, particularly when targeting areas like the PAG or anterior cingulate cortex, has demonstrated long-term analgesic effects. These effects are linked to epigenetic changes, including alterations in histone acetylation and DNA methylation of genes associated with pain modulation, such as opioid receptors [90, 91]. Neuromodulation techniques have been shown to enhance histone acetylation at promoters of neurotrophic factors like BDNF and c-Fos, while reducing DNA methylation of opioid receptor genes. This epigenetic remodeling is a critical pathway through which these interventions exert their effects on pain and neuroplasticity [92, 93]. Preclinical evidence indicates that neuromodulation enhances histone acetylation at promoters of *BDNF* and *c-Fos*, while reducing DNA methylation of opioid receptor genes (*Oprm1*), restoring endogenous analgesic tone [94]. In parallel, rTMS has been associated with altered expression of miRNAs such as miR-132 and miR-134, known regulators of synaptic plasticity and cortical excitability [95]. These findings highlight epigenetic remodeling as a convergent pathway for neuromodulatory interventions.

Acupuncture and Related Somatic Therapies

Acupuncture has emerged as a potent non-pharmacological analgesic approach with epigenetic underpinnings. Studies demonstrate that electroacupuncture decreases global DNA methylation and expression of DNA methyltransferases, suggesting a mechanism through which electroacupuncture may reverse nerve injury-induced DNA hypermethylation and restore μ-opioid receptor expression [96]. Acupuncture promotes angiogenesis and neuroprotection through the regulation of histone acetylation, particularly at the VEGF gene. This modulation is associated with increased expression of angiogenic factors and a reduction in inflammatory responses [97]. The increase in H3K9 acetylation specifically has been linked to enhanced gene expression related to neuroprotection and inflammation [98]. Additionally, Research indicates that miR-214 plays a significant role in modulating neuroinflammation and pain responses. Specifically, the downregulation of miR-214 enhances the expression of colony-stimulating factor-1 (CSF1), associated with increased neuroinflammation and pain behaviors. Conversely, restoring miR-214 levels can alleviate these effects, suggesting its potential as a therapeutic target in neuropathic pain management [99]. Similarly, miR-339 has influenced neuropathic pain through its effects on microglial activation and inflammatory responses. The administration of miR-339 can alleviate pain behaviors by suppressing the expression of pro-inflammatory cytokines, thereby mitigating the inflammatory response associated with neuropathic pain [100]. The modulation of histone acetylation by acupuncture leads to significant changes in the expression of inflammatory cytokines. For instance, acupuncture has been observed to reduce levels of pro-inflammatory cytokines such as TNF-α and IL-1β while promoting anti-inflammatory cytokines, thereby facilitating a balanced immune response [101]. The effects of acupuncture on glial activation are particularly noteworthy. By increasing histone acetylation, acupuncture not only downregulates pro-inflammatory gene expression but also enhances the neuroprotective functions of microglia. This is achieved through reduced nitric oxide release and increased phagocytic activity, which are crucial for clearing debris and promoting recovery after spinal cord injury [102]. These findings provide strong evidence that acupuncture exerts its analgesic effect through coordinated epigenetic remodeling in both spinal and supraspinal circuits.

Lifestyle and Sleep-Based Interventions

Lifestyle factors such as diet and sleep regulation significantly influence pain states via epigenetic pathways. Sleep deprivation has been shown to induce hypermethylation in circadian genes, such as CLOCK and PER1, which disrupts circadian rhythms and enhances inflammatory gene expression, contributing to hyperalgesia (pain sensitivity) [103]. Conversely, restorative sleep can normalize DNA methylation at these loci, restoring homeostasis in the HPA axis and reducing nociceptive sensitivity [104]. Nutrition-based interventions also modulate epigenetic regulation: omega-3 fatty acids inhibit HDAC activity and increase histone acetylation in pain-related circuits, while polyphenols such as curcumin and resveratrol modulate DNA methylation of anti-inflammatory genes, attenuating neuroinflammation and nociceptive signaling [105]. Collectively, these findings highlight sleep and diet as modifiable behavioral factors with the capacity to reverse maladaptive epigenetic changes associated with chronic pain.

Integration and Convergence Across Modalities

Despite their methodological differences, exercise, CBT, mindfulness, neuromodulation, acupuncture, and lifestyle interventions converge on shared epigenetic pathways. Firstly, the regulation of brain-derived neurotrophic factor

(BDNF) expression is a critical aspect of these therapies. BDNF is essential for neuroplasticity and plays a significant role in modulating pain perception. Changes in BDNF expression have been linked to the efficacy of these therapies in managing pain [106]. Secondly, the modulation of opioid receptor gene methylation is another important mechanism. Epigenetic modifications, particularly DNA methylation, can significantly affect the expression of opioid receptors, which are crucial for pain modulation. This suggests that non-pharmacological interventions may enhance the efficacy of existing pain management strategies by modifying these pathways [107]. Additionally, these therapies have been shown to suppress the expression of inflammatory cytokines such as IL-6 and TNF-α, involved in pain and inflammatory responses. This suppression is part of the broader anti-inflammatory effects of these interventions, contributing to their overall effectiveness in pain management [108]. Furthermore, the normalization of miRNA networks is another significant outcome of these therapies. miRNAs play a crucial role in regulating gene expression related to synaptic plasticity and glial activity. Non-pharmacological therapies may help normalize these networks, thereby enhancing pain resilience and recovery [109].

Music therapy / Art therapy

Music therapy has affected both the neural and epigenetic responses to stress. Engaging in music therapy can lead to changes in gene expression involved in the stress response, such as those related to corticotropin-releasing factor (CRF) and glucocorticoid receptors. This can result in the modulation of the hypothalamic-pituitary-adrenal (HPA) axis, which plays a key role in the body's response to stress. Music therapy may also impact histone modification and DNA methylation, potentially influence neuroplasticity and enhance emotional resilience [110]. Similarly, art therapy has been linked to changes in epigenetic regulation, particularly in relation to genes involved in emotional regulation and stress resilience. Engaging in creative processes such as painting or drawing can activate brain regions involved in emotion regulation, and studies have suggested that these activities may modulate DNA methylation patterns associated with neuroinflammation and neurotransmitter systems. These modifications might contribute to enhanced coping mechanisms and a reduction in symptoms of anxiety and depression [111].

Clinical and Translational Implications

Human studies increasingly show that DNA methylation and circulating small RNAs differ between people with chronic pain and controls, and in some cases track severity or prognosis, positioning them as candidate diagnostic/monitoring biomarkers. For example, whole-blood BDNF promoter methylation is altered in patients with chronic musculoskeletal pain and relates to biopsychosocial status, supporting translational use as a minimally invasive readout of central plasticity [112]. Clinical evidence also links pain states to the peripheral methylome across conditions (e.g., low back pain, fibromyalgia), with systematic reviews highlighting reproducible methylation signals in immune, neurotrophic, and stress-axis genes [50]. Parallel efforts in circulating miRNAs show disease-associated profiles in fibromyalgia and low back pain, and new pilot work suggests that miRNAs can help classify nociceptive vs. nociplastic pain—a key clinical distinction for treatment selection [113, 114]. Epigenetic variation in stress-axis regulators (FKBP5, NR3C1) and serotonergic genes (SLC6A4) is measurable in blood and has been linked to symptom severity and treatment response in human cohorts, suggesting that baseline or therapy-induced methylation could stratify patients toward cognitive-behavioral, mindfulness, or graded-activity approaches that normalize HPA-axis tone [115, 116]. Beyond psychiatric populations, FKBP5 methylation patterns in

people with chronic pain have been reported to index a neuropathic component, raising the prospect that epigenetic fingerprints could guide choices between centrally acting non-pharmacological therapies (CBT/mindfulness, rTMS/tDCS) versus peripherally focused strategies (exercise, TENS) [115]. Presurgical circulating miRNA panels have also predicted 1-year postsurgical pain reduction after spine procedures, illustrating how pre-intervention liquid-biopsy profiles might forecast who benefits from specific treatments and intensity of follow-up [117]. Because non-pharmacological interventions can reprogram pain networks, their biomarker-guided deployment may spare opioids while targeting underlying drivers. Human studies show that structured exercise programs reshape the blood methylome (including cardiometabolic and inflammatory pathways), consistent with clinical benefits in pain and function, and providing a mechanistic basis for durable analgesia without pharmacotherapy [118].

In parallel, clinical tDCS trials in pain disorders (e.g., knee osteoarthritis) report pain reductions alongside BDNF changes, aligning with epigenetic/neurotrophic mechanisms seen in preclinical work and supporting the idea that brain-stimulation–evoked plasticity can serve as an opioid-sparing adjunct [119]. At the systems level, chronic pain has been associated with accelerated epigenetic aging, underscoring the potential for lifestyle-anchored, epigenetically active therapies (sleep restoration, activity, mindfulness) to improve both pain and biological aging trajectories [60].

Evidence syntheses of human chronic pain methylomes now permit identification of replicable loci and analytic pipelines suitable for clinical assay development, but multicenter validation, standardization of sample handling, and assay harmonization remain essential before regulatory adoption [50]. For miRNAs, contemporary reviews and recent clinical studies emphasize feasibility (qPCR-based detection in serum/plasma) and suggest that confined panels could be moved into CLIA-style workflows, provided prospective studies confirm stability, confounder robustness (age, sex, medications), and responsiveness to treatment [120]. Histone acetylation is highly dynamic and attractive for short-horizon monitoring, whereas DNA methylation can be more persistent—useful for prognosis but slower to change, complicating early response assessment [12]. Specificity is another hurdle: interventions that globally alter chromatin could affect off-target gene networks; hence, composite biomarker panels (e.g., “BDNF-inflammation-stress axis” signatures) may maximize signal-to-noise while limiting individual-locus artifacts [34]. Finally, ethical considerations include privacy of methylome/miRNA data (which may reveal comorbidity risks), potential stigmatization via “biological risk” labels, and informed consent for longitudinal molecular tracking, all of which require governance frameworks akin to those adopted for genomics [121]. In the near term, the most actionable path is hybrid clinical trials that pair guideline-based non-pharmacological therapies (exercise, CBT/mindfulness, neuromodulation) with pre/post epigenetic profiling, using validated loci (e.g., *BDNF* methylation, FKBP5/NR3C1/SLC6A4 methylation, small miRNA panels) to (i) refine patient selection, (ii) titrate dose/intensity, and (iii) justify opioid dose reduction when molecular and clinical endpoints align [112, 115].

Future Directions

The future of research on epigenetic pathways in non-pharmacological pain management requires a shift toward longitudinal and mechanistic studies. Current evidence is largely cross-sectional or derived from preclinical models, leaving uncertainty about causality. Longitudinal trials are needed to directly link specific interventions (e.g., mindfulness, exercise, or neuromodulation) to measurable epigenetic out-

comes such as DNA methylation dynamics, histone modifications, or miRNA signatures, and to determine whether these molecular changes persist over time and correlate with long-term analgesia and improved quality of life [82]. For instance, a recent trial on fibromyalgia patients receiving an 8-week mindfulness program reported sustained decreases in stress-related gene methylation (NR3C1, FKBP5) and corresponding reductions in pain severity, but longer follow-up is essential to confirm durability [122]. The integration of multi-omics approaches—including epigenomics, transcriptomics, proteomics, metabolomics, and neuroimaging—represents a promising direction for understanding the complex biological mechanisms underlying pain perception and modulation. This systems-level strategy can elucidate how epigenetic alterations translate into functional changes in brain networks involved in pain processing. For instance, coupling methylome-wide association studies (MWAS) with functional magnetic resonance imaging (fMRI) could clarify whether exercise-induced demethylation of the BDNF promoter correlates with increased activity in descending inhibitory circuits, such as the PAG to the RVM pathways.

Recent studies have highlighted the potential of multi-omics approaches to uncover novel biomarkers and therapeutic targets for pain-related conditions. For example, a comprehensive review emphasized the significance of integrating various omics data to reveal interaction networks among molecules at different biological levels, thereby overcoming the limitations of single-omics approaches [123]. Furthermore, advancements in high-resolution methodologies, such as single-cell and spatial omics techniques, enhance the ability to dissect molecular complexities within pain-related pathways [124]. Furthermore, there is significant potential in combined multimodal therapies, where behavioral and neuromodulatory interventions are applied synergistically. CBT may normalize stress-related epigenetic changes in limbic regions, while neuromodulation techniques such as rTMS or tDCS can enhance neuroplasticity through histone acetylation and BDNF signaling. Pilot studies suggest that such combinations can lead to greater clinical improvement than monotherapies, but systematic epigenetic assessments in these contexts remain limited [125]. Similarly, lifestyle-based interventions such as sleep restoration or anti-inflammatory diets may act additively with CBT or exercise to stabilize epigenetic networks regulating the HPA axis and inflammatory cytokines, potentially amplifying analgesic outcomes [126]. Finally, synergies between epigenetic drugs and behavioral interventions represent a cutting-edge frontier. Histone deacetylase inhibitors, which enhance histone acetylation and neuroplasticity, are being explored in animal pain models. When paired with environmental enrichment or behavioral training, these agents show amplified and longer-lasting analgesic effects compared to either approach alone [127].

Translating this concept clinically could open a new era of combined pharmacological–behavioral therapy for refractory chronic pain, though safety, specificity, and ethical challenges remain. Taken together, future research must aim for precision pain medicine, where epigenetic signatures guide patient selection, therapy optimization, and monitoring of treatment efficacy. With robust longitudinal designs, multi-omics integration, and innovative combination strategies, the field has the potential to revolutionize non-pharmacological pain treatment and reduce dependency on opioid-based regimens.

Discussion

The emerging field of pain epigenetics provides a unifying framework to explain how environmental, psychological, and behavioral interventions exert long-lasting effects on nociceptive processing. Epigenetic mechanisms like DNA

methylation, histone modifications, and non-coding RNAs have been implicated in neural and inflammatory gene regulation, linking experiences to durable molecular and neural changes [1]. Despite this rapid progress, several controversies and challenges remain. First, findings across human epigenetic studies are inconsistent: while some cohorts show reproducible methylation changes in genes involved in pain modulation and inflammation (e.g., *BDNF, HDAC4, IL-17, TNFRSF13B, PRKG1*), others fail to detect robust signals or yield conflicting results [128]. This variability reflects methodological heterogeneity, such as differences in tissue sources (e.g., blood vs. brain), small sample sizes, and cross-sectional designs that limit causal inference [128, 129]. Second, the causal role of epigenetic modifications remains under debate. Animal studies provide compelling evidence that DNA methylation and histone modifications can drive chronic pain behaviors—for instance, promoter methylation of Oprm1 and Kcna2 or hypomethylation of CXCR3 and GPR151 in dorsal root ganglia and spinal cord are linked to neuropathic pain in rodents [31, 130]. However, human data remain largely correlational due to the ethical and technical challenges of acquiring neural tissue and performing longitudinal interventional studies [50, 128]. Third, although non-pharmacological interventions consistently influence stress, inflammation, and neural plasticity, their direct links to epigenetic remodeling are still underexplored. While mechanistic links exist from exercise and lifestyle interventions to epigenetic change in cognition and general brain plasticity. modality-specific evidence—especially for CBT, mindfulness, or acupuncture—remains sparse, limiting our understanding of molecular underpinnings in clinical contexts.

Fundamental challenges also include translating molecular findings into clinically actionable biomarkers. Epigenetic assays face issues of specificity, stability, and accessibility; for example, blood-based DNA methylation patterns may not reflect central nervous system status, and lack standardization across laboratories limits reproducibility and validation [128, 129]. Moreover, ethical considerations—such as the privacy of methylome or miRNA data—must be addressed before large-scale application, drawing from broader concerns in precision health data governance. The need for longitudinal studies tracking epigenetic changes before, during, and after non-pharmacological interventions to distinguish causation from correlation and observe temporal dynamics [128]. Integration of multi-omics approaches (e.g., epigenomics, transcriptomics, proteomics, neuroimaging) to capture interplay across molecular, cellular, and network levels—this integrated strategy may yield deeper mechanistic insights than epigenetic measures alone [50]. The development of causal models that link specific molecular signatures to pain chronification and treatment response, potentially including intervention trials combined with epigenetic monitoring. Potential developments lie in biomarker-guided personalized medicine—where baseline epigenetic profiles help stratify patients toward the most effective non-pharmacological therapy. For instance, methylation signatures in stress or inflammation-related genes could guide whether a patient might benefit more from mindfulness vs. exercise-based interventions. Additionally, combining behavioral interventions with neuromodulation—or, in experimental settings, with epigenetic agents (e.g., HDAC inhibitors)—may open new therapeutic avenues by synergistically modulating gene expression and neuroplasticity, although clinical translation remains nascent [11]. Ultimately, advancing precision pain medicine will require bridging molecular neuroscience with behavioral and systems-level interventions, moving from mechanistic insights to clinically actionable, individualized treatments.

Conclusion

Emerging evidence highlights that epigenetic mechanisms DNA methylation, histone modifications, and miRNA regulation—are central to these processes, influencing nociceptive transmission, neuroinflammation, and cortical–limbic plasticity. Non-pharmacological interventions, including cognitive-behavioral therapy, mindfulness, exercise, acupuncture and electroacupuncture, neuromodulation, and lifestyle modifications, exert therapeutic benefits not only by reshaping cognition, emotion, and coping but also by inducing epigenetic remodeling across spinal and supraspinal networks. These interventions have been shown to normalize prefrontal–limbic connectivity, reduce stress-related methylation of genes such as *NR3C1* and *FKBP5*, enhance neuroplasticity via BDNF promoter activity, and downregulate pro-inflammatory miRNAs such as miR-155, thereby providing a molecular explanation for their sustained analgesic effects. Importantly, peripheral DNA methylation patterns and circulating miRNAs are emerging as candidate biomarkers of treatment response, offering opportunities for precision medicine approaches that tailor interventions to individual epigenetic profiles. Despite promising findings, the current literature is limited by small sample sizes, heterogeneity in study designs, and a lack of longitudinal and causal evidence linking specific epigenetic modifications to clinical outcomes. Future work integrating multi-omics, neuroimaging, and behavioral data will be critical to unravel the complex interactions between psychosocial factors, neural circuits, and epigenetic mechanisms in chronic pain. By bridging molecular neuroscience with behavioral science, this integrative framework positions non-pharmacological treatments as not only symptomatic interventions but also as epigenetic modulators capable of promoting long-term resilience, reducing dependence on pharmacological therapies, and advancing personalized pain medicine.

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Conflict of Interest

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