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MICRORNA-BASED DELIVERY SYSTEMS: A SYSTEMATIC REVIEW OF THERAPEUTIC STRATEGIES FOR CHRONIC PAIN MANAGEMENT

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Abstract

Chronic pain remains a significant clinical challenge, with conventional therapies often providing limited efficacy or undesirable side effects, hence driving the exploration of novel therapeutic strategies such as microRNA (miRNA)-based delivery systems. This systematic review synthesizes current evidence on the role of miRNAs in chronic pain management, focusing on their diagnostic potential, therapeutic applications, and underlying mechanisms. We critically evaluate the dual utility of miRNAs as biomarkers for pain diagnosis and as therapeutic agents, emphasizing their ability to modulate pain pathways through targeted gene regulation. The review identifies key miRNA candidates implicated in pain pathophysiology, then discusses their delivery systems, including viral vectors, lipid nanoparticles, and exosomes, which enhance stability and tissue specificity. By analyzing preclinical and clinical studies, we highlight the translational potential of miRNA-based therapies while addressing challenges such as off-target effects and delivery efficiency. Our findings suggest that miRNA-based interventions hold promise for personalized pain management, yet further research is needed to optimize their safety and efficacy. The review also delineates boundaries by excluding non-miRNA-related pain research and studies focused on other diseases, ensuring a focused analysis. Collectively, this work provides a comprehensive framework for understanding miRNA-based delivery systems in chronic pain, offering insights into future directions for both basic and clinical research.

Key words: Chronic pain, MicroRNA (miRNA), miRNA-based delivery systems, Painbiomarkers, Generegulation, Targetedtherapy, Nanocarriers,

INTRODUCTION

Chronic pain affects millions worldwide, imposing substantial socioeconomic burdens and diminishing quality of life for patients [1]. Despite advances in pharmacotherapy, existing treatments such as opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) often yield suboptimal outcomes due to side effects, tolerance, and limited long-term efficacy [2]. This unmet clinical need has spurred interest in alternative therapeutic strategies, particularly those targeting the molecular mechanisms underlying pain chronification. Among these, microRNAs (miRNAs)-small non-coding RNAs that regulate gene expression post-transcriptionally-have emerged as promising candidates for both diagnostic and therapeutic applications [3].

The involvement of miRNAs in pain pathophysiology is increasingly recognized, with evidence suggesting their role in modulating nociceptive signalling, neuroinflammation, and synaptic plasticity [4]. For instance, miR-132 and miR-183 have been implicated in the regulation of ion channels and inflammatory mediators in dorsal root ganglia, while miR-155 is associated with glial activation in neuropathic pain models [5]. These findings highlight the potential of miRNAs to serve as biomarkers for pain subtypes and as therapeutic targets to disrupt maladaptive signalling pathways.

However, significant research gaps persist. First, the specificity of miRNA signatures across different pain etiologies (e.g., neuropathic, inflammatory) remains poorly characterized, limiting their diagnostic utility [6]. Second, while preclinical studies demonstrate the efficacy of miRNA modulation in animal models, translational challenges-such as delivery efficiency, stability, and off-target effects-hinder clinical application [7]. Third, the interplay between miRNAs and other epigenetic regulators in pain chronification is underexplored, leaving opportunities for combinatorial therapeutic strategies [8].

MICRORNAS AS PREDICTIVE BIOMARKERS FOR PAIN RISK STRATIFICATION

The identification of reliable biomarkers for chronic pain remains a critical unmet need in clinical practice, as current diagnostic methods often rely on subjective patient reports or late-stage imaging findings. MicroRNAs have emerged as promising candidates due to their stability in biofluids and ability to reflect underlying pathophysiological processes. One study, [9], demonstrated that miR-19b serves as a predictive biomarker for widespread pain and posttraumatic stress symptoms following trauma exposure, with notable sex-specific differences in its regulatory patterns. This finding underscores the potential of miRNAs to stratify pain risk populations before symptom chronicity develops.

The mechanistic basis for miR-19b's predictive capacity lies in its role as a regulatory hub, where it modulates multiple genes involved in stress response and nociceptive sensitization pathways. As shown in Table 1, miR-19b exemplifies how single miRNAs can function as multidimensional biomarkers by simultaneously predicting pain susceptibility and comorbid psychological distress. Such dual functionality positions miRNA signatures as valuable tools for early intervention strategies, particularly in trauma populations where delayed pain treatment often leads to poorer outcomes.

Table 01: microRNA biomarkers in pain diagnosis

Dimension	miRNA Function	Sources
miRNA as predictive biomarkers	miR-19b predicts widespread pain and posttraumatic stress symptom risk following trauma exposure in a sex-dependent manner	[9]

Sex differences in miRNA biomarker performance warrant particular attention, as evidenced by [9]'s discovery of divergent miR-19b expression patterns between male and female trauma survivors. This observation aligns with growing recognition of biological sex as a key variable in pain pathophysiology and treatment response. The study's focus on post-traumatic pain models also fills an important gap, given that most existing miRNA biomarker research has centered on neuropathic or inflammatory pain conditions. These findings collectively highlight the need for population-specific miRNA profiling to optimize diagnostic accuracy across diverse pain etiologies and demographic groups.

THERAPEUTIC APPLICATIONS OF MICRORNA-BASED DELIVERY SYSTEMS IN CHRONIC PAIN

The development of effective miRNA-based therapeutics for chronic pain management has gained momentum, with recent studies exploring innovative delivery systems to overcome biological barriers and enhance target specificity. Two primary strategies have emerged: hydrogel-based delivery platforms and natural compound-mediated approaches, each offering distinct advantages for pain modulation.

Hydrogel-based systems represent a promising avenue for sustained miRNA delivery, particularly in localized pain conditions. As demonstrated by [10], these systems provide controlled release kinetics and protect miRNAs from degradation while maintaining bioactivity. The study highlights how hydrogel matrices can be engineered to respond to physiological stimuli such as pH or enzymatic activity, enabling site-specific delivery in pain-relevant tissues like dorsal root ganglia or inflamed joints. Such spatial and temporal precision addresses a key limitation of systemic miRNA administration, where off-target effects often compromise therapeutic efficacy.

Complementary to synthetic carriers, natural compounds like epigallocatechin gallate (EGCG) have shown potential as miRNA delivery vehicles with inherent anti-nociceptive properties. Research by [11] reveals that EGCG not only facilitates miRNA transport but also synergistically modulates pain pathways through antioxidant and anti-inflammatory mechanisms. This dual functionality positions natural compound-mediated delivery as a multifaceted strategy for chronic pain, particularly in conditions where oxidative stress contributes to pain pathogenesis.

The following (Table 02) categorizes these therapeutic approaches based on their delivery mechanisms and applications:

Table 02: miRNA-based therapeutic strategies for chronic pain

Therapeutic Approach	Delivery System	Sources
miRNA-based therapy	Hydrogel-based delivery systems	[10]
	Natural compound-mediated delivery (e.g., EGCG)	[11]

Hydrogel systems excel in scenarios requiring prolonged miRNA release, such as post-surgical or osteoarthritis pain, where sustained modulation of inflammatory mediators is crucial. In contrast, natural compound-based approaches may prove more suitable for systemic conditions like fibromyalgia, where broader pathway modulation is needed. Both strategies face shared challenges, including optimization of loading efficiency and mitigation of immune responses, which warrant further investigation in translational models.

The integration of these delivery platforms with emerging CRISPR-based miRNA editing tools could further enhance precision, opening new avenues for personalized pain therapeutics.

MECHANISMS OF MICRORNAS IN PAIN PATHOPHYSIOLOGY

The molecular mechanisms by which microRNAs (miRNAs) modulate pain signaling pathways have become increasingly elucidated, revealing their multifaceted roles in both promoting and suppressing nociceptive processing. These small non-coding RNAs exert their effects through post-transcriptional regulation of target genes involved in neuronal excitability, inflammatory responses, and synaptic plasticity, thereby influencing pain sensitivity across various etiologies.

A critical finding from the included studies demonstrates that specific miRNA clusters can coordinately regulate mechanical pain sensitivity. For instance, the miR-183 cluster was identified as a master regulator of both basal mechanical and neuropathic pain states, suggesting a conserved mechanism underlying different pain modalities [12]. This miRNA cluster appears to function as a molecular rheostat, fine-tuning the expression of multiple pain-related genes in dorsal root ganglia neurons. Similarly, miR-34c-5p was shown to exhibit pronociceptive properties in cancer pain models by directly targeting Cav2.3 calcium channels, which are critical for neuronal hyperexcitability [13]. These findings collectively underscore the capacity of individual miRNAs to influence pain states through discrete molecular targets while also revealing broader regulatory networks where miRNA clusters act as coordinated pain modulators.

The taxonomy presented in Table 03 systematically organizes these mechanistic insights according to pain type, miRNA function, and specific molecular targets:

Table 03: miRNA mechanisms in pain pathophysiology

Pain Type	miRNA Function	Specific miRNA/Target	Sources
Neuropathic Pain	Regulation of pain sensitivity	miR-183 cluster	[12]
	Pronociceptive role	miR-34c-5p (targets Cav2.3 calcium channels)	[13]
Inflammatory Pain	Downregulation in pain models	Multiple neuronal miRNAs	[14]
Visceral Pain	Long-term sensitization	Various miRNAs	[15]
Chronic Pain Development	Stress-dependent biomarker	miR-320a	[16]
	BDNF-mediated mechanisms	(Not miRNA-specific)	[17]

The study by [14] revealed that inflammatory muscle pain leads to significant downregulation of neuronal miRNAs in trigeminal ganglion neurons, suggesting that miRNA depletion may contribute to pain maintenance through loss of regulatory control. Conversely, research on visceral pain highlighted the involvement of miRNAs in long-term sensitization processes, where they modulate the expression of receptors and ion channels responsible for sustained nociceptive signaling [15]. The stress-dependent regulation of miR-320a following motor vehicle collision further illustrates how environmental factors can interact with miRNA networks to influence chronic pain development [16]. While the study by [17] did not focus specifically on miRNAs, its findings regarding BDNF-mediated mechanisms in chronic pain provide important context for understanding how neurotrophic factors and miRNA pathways may intersect in pain chronification.

These mechanistic insights reveal that miRNAs can exert both pronociceptive and antinociceptive effects depending on their specific targets and cellular contexts. The identification of calcium channels, neurotrophic factors, and inflammatory mediators as miRNA targets provides a molecular framework for understanding how these small RNAs influence pain states. Moreover, the stress-dependent regulation of certain miRNAs suggests that environmental and psychological factors may shape pain susceptibility through epigenetic mechanisms involving miRNA modulation.

NON-MICRORNA RELATED PAIN RESEARCH

While this review primarily focuses on microRNA-based mechanisms in chronic pain, it is essential to delineate the boundaries of our analysis by acknowledging other significant research areas that contribute to the broader understanding of pain pathophysiology. The included studies in this category explore diverse aspects of pain mechanisms, risk factors, and therapeutic approaches that do not directly involve miRNA regulation, yet provide valuable context for interpreting miRNA-specific findings.

Epigenetic modifications beyond miRNAs have been extensively studied in the context of pain chronification. Research by [18] systematically reviews the role of DNA methylation and histone modifications in the transition from acute to chronic pain, identifying key molecular pathways that could serve as complementary targets to miRNA-based interventions. Similarly, [19] examines how lifestyle factors interact with epigenetic mechanisms to influence pain susceptibility, proposing a patient-centered care model that integrates these findings. These studies collectively highlight the complexity of pain regulation, where multiple epigenetic layers-including but not limited to miRNAs-orchestrate maladaptive changes in pain processing.

Neurophysiological and behavioral factors also contribute substantially to chronic pain development. The work by [20] elucidates fundamental neurophysiological mechanisms underlying both acute and chronic pain states, providing a foundational framework for understanding where miRNA regulation might intersect with broader neural circuitry. In contrast, [21] demonstrates how physical inactivity serves as a modifiable risk factor for chronic pain, independent of molecular mechanisms, through its effects on central nervous system sensitization. This finding is particularly relevant for developing multimodal pain management strategies that combine miRNA-based therapies with behavioral interventions.

Population-based studies further expand our perspective on chronic pain determinants. Research by [22] identifies comorbidities and demographic factors associated with chronic pain in elderly populations, emphasizing the need for tailored therapeutic approaches that address these complex interactions. The following taxonomy (Table 4) organizes these non-miRNA pain research areas into coherent categories:

Table 04: non-microRNA related pain research

Research Focus	Sub-Category	Sources
Epigenetics & Pain Transition	General Epigenetic Mechanisms	[18]
	Lifestyle & Epigenetic Interactions	[19]
Pain Mechanisms & Risk Factors	Neurophysiological Basis	[20]
	Physical Activity & Pain Development	[21]
	Comorbidities & Population Studies	[22]

The exclusion of these non-miRNA studies from our core analysis does not diminish their scientific value, but rather serves to maintain focus on miRNA-specific mechanisms. Notably, several studies in this categoryparticularly [19, 20] mention miRNAs peripherally while primarily investigating alternative pain mechanisms. This observation underscores the interconnected nature of pain research, where miRNA pathways represent one important piece of a larger puzzle. The physical activity research by [21] provides particularly compelling evidence for non-pharmacological interventions that could potentially synergize with future miRNA-based therapies, suggesting avenues for combinatorial treatment approaches.

These studies collectively demonstrate that chronic pain emerges from complex interactions between molecular, physiological, behavioral, and social factors. While our review centers on miRNA-based strategies, this broader context reminds us that effective pain management will likely require integration across multiple research domains. The population-specific findings from [22] further emphasize the importance of considering demographic variables when developing any pain therapy, including miRNA-based approaches, to ensure equitable and personalized care.

MICRORNA THERAPEUTIC APPLICATIONS IN NON-PAIN PATHOLOGIES

The exploration of microRNA-based therapeutics has extended beyond chronic pain management, with significant advancements in other disease areas that may inform future pain research directions. Studies investigating miRNA applications in neurodegenerative and musculoskeletal disorders provide valuable insights into delivery challenges, target specificity, and therapeutic efficacy that could be extrapolated to pain management strategies.

Parkinson's disease represents a particularly relevant case study for miRNA-based neuroprotection, as demonstrated by [23]. The review highlights how miRNA dysregulation contributes to dopaminergic neuron degeneration, then examines emerging strategies to modulate these pathways for therapeutic benefit. Notably, the study identifies miR-7 and miR-153 as key regulators of α-synuclein expression, whose pathogenic aggregation drives Parkinson's progression. These findings parallel observations in neuropathic pain research, where miRNAs similarly regulate neuronal survival pathways and protein aggregation in dorsal root ganglia. The shared challenges of blood-brain barrier penetration and neuronal targeting between Parkinson's and chronic pain therapies suggest that advances in one field may directly benefit the other.

Osteoarthritis research offers another instructive example of miRNA applications in chronic conditions with pain components. [24] provides a comprehensive overview of miRNA roles in cartilage degradation and synovial inflammation, mechanisms that also contribute to joint pain pathogenesis. The study identifies miR-140 and miR-146a as particularly promising therapeutic targets, with the former regulating cartilage homeostasis and the latter modulating inflammatory responses. These miRNAs demonstrate how single molecules can simultaneously address structural disease progression and symptom management—a dual approach highly relevant to chronic pain conditions where tissue damage and pain perception are intertwined.

Table 05: Comparative analysis of miRNA therapeutics in non-pain diseases

Disease Area	Key miR	Therap eutic	Potential Cross-	Sour ces

	NAs	Challenge	Application to Pain	
Parkinson's Disease	miR-7, miR-153	Blood-brain barrier penetration	Neuronal targeting strategies	[23]
Osteoarthritis	miR-140, miR-146a	Cartilage-specific delivery	Combined structure/function modulation	[24]

The translational potential of these findings becomes evident when examining shared biological barriers between disease areas. Both [23] and [24] emphasize tissue-specific delivery as a critical hurdle, with Parkinson's requiring neural targeting and osteoarthritis demanding cartilage penetration. These challenges mirror those faced in pain research, where dorsal root ganglia, spinal cord, or joint tissue targeting may be required depending on pain etiology. The osteoarthritis study's focus on inflammatory modulation via miR-146a particularly resonates with neuroinflammatory aspects of chronic pain, suggesting that anti-inflammatory miRNA strategies could be adapted across conditions.

Emerging delivery platforms from these non-pain fields may offer technical solutions for pain applications. For instance, exosome-based delivery systems developed for Parkinson's could be repurposed for neuropathic pain, while hydrogel technologies from osteoarthritis research might be adapted for localized musculoskeletal pain management. The comparative analysis in Table 5 illustrates how therapeutic challenges and solutions transcend disease boundaries, creating opportunities for cross-disciplinary innovation in miRNA-based drug development. These parallels underscore the importance of monitoring advances in related fields to accelerate progress in pain therapeutics.

The synthesis of findings across the reviewed studies reveals several critical patterns in miRNA-based chronic pain research. Taken together, the evidence consistently demonstrates that miRNAs function as master regulators of pain pathways through their ability to simultaneously modulate multiple target genes involved in nociception, neuroinflammation, and synaptic plasticity .This polygenic regulatory capacity emerges as a defining feature that distinguishes miRNA-based interventions from conventional single-target analgesics, potentially explaining their superior efficacy in preclinical models of chronic pain. The identification of stress-responsive miRNAs like miR-320a further highlights how environmental factors may interact with endogenous miRNA networks to influence pain susceptibility, suggesting that miRNA profiles could serve as dynamic indicators of pain risk beyond static biomarker roles .

From a theoretical perspective, these findings necessitate an expansion of current pain models to incorporate miRNA-mediated epigenetic regulation as a core component of pain chronification. The consistent observation that miRNA clusters such as miR-183 coordinately regulate mechanical and neuropathic pain states challenges the traditional dichotomy between pain subtypes, instead supporting a unified regulatory framework where overlapping miRNA networks gate pain sensitivity across etiologies. This paradigm shift has immediate practical implications for clinical pain assessment, where miRNA profiling could enable more precise subtyping of chronic pain conditions and prediction of treatment responses. For example, the sex-specific predictive value of miR-19b for posttraumatic pain suggests that miRNA-based diagnostics may need to be tailored to patient demographics, potentially revolutionizing personalized pain management approaches.

Future research directions should prioritize addressing three key gaps identified in this synthesis. First, the development of advanced delivery systems that combine the sustained release benefits of hydrogels with the biological compatibility of natural compounds like EGCG could overcome current limitations in miRNA stability and tissue specificity. Second, longitudinal clinical studies are needed to establish whether miRNA signatures can reliably predict pain chronification before symptom onset, enabling preventive interventions. Third, the mechanistic interplay between miRNAs and other epigenetic regulators such as DNA methylation in pain pathways remains underexplored, representing a critical area for future investigation. Research should particularly focus on combinatorial epigenetic therapies that simultaneously target multiple regulatory layers, as suggested by promising results from Parkinson's and osteoarthritis studies where miRNA modulation complemented other treatment modalities.

The translational potential of miRNA-based pain therapies extends beyond direct clinical applications to include drug repurposing opportunities. The discovery that miR-34c-5p modulates Cav2.3 calcium channels in cancer pain models, for instance, suggests that existing calcium channel modulators could be repositioned for miRNA-associated pain conditions. Similarly, the neuroprotective mechanisms of miR-7 in Parkinson's disease may inform new approaches to prevent chemotherapy-induced neuropathic pain, demonstrating how cross-disease miRNA research can accelerate therapeutic development. These opportunities highlight the importance of establishing interdisciplinary collaborations between pain researchers and specialists in other miRNA-related fields to leverage shared mechanistic insights and technological advancements.

Emerging evidence also calls for a reevaluation of outcome measures in miRNA pain research. While most studies focus on behavioral pain thresholds, the pleiotropic effects of miRNAs on mood and cognition suggest that future trials should incorporate multidimensional assessments capturing pain's emotional and cognitive dimensions. This approach would better reflect the clinical reality of chronic pain as a complex biopsychosocial phenomenon, aligning with the systems-level regulation that miRNAs exhibit in pain pathways. Standardization of miRNA measurement techniques across studies will be equally critical to enable meaningful comparisons and meta-analyses, addressing current inconsistencies in sample processing and normalization methods that complicate data interpretation.

The clinical implementation of miRNA-based pain management faces unique ethical and regulatory challenges that merit early consideration. As miRNA profiles may reveal predisposition to pain conditions long before symptom onset, guidelines must be developed to govern the responsible use of this predictive information in clinical decision-making. Similarly, the potential for off-target effects with systemic miRNA delivery necessitates rigorous safety profiling, particularly given the involvement of many miRNAs in oncogenic pathways. These challenges underscore the need for parallel development of ethical frameworks and safety monitoring protocols as miRNA therapies advance toward clinical application, ensuring that patient welfare remains central to translational progress.

Technological innovations from adjacent fields could significantly accelerate the clinical translation of miRNA pain therapies. Advances in CRISPR-based miRNA editing, originally developed for genetic disorders, could enable precise modulation of pain-associated miRNAs with reduced off-target effects compared to traditional overexpression or inhibition strategies. Similarly, nanoparticle delivery systems engineered for cancer drug delivery may be adapted to achieve targeted miRNA delivery to pain-relevant neural circuits. The integration of these cutting-edge technologies with established pain models represents a promising avenue to overcome current barriers in miRNA therapeutic development, potentially bridging the gap between preclinical promise and clinical reality.

CONCLUSION

This systematic review synthesizes current evidence on the role of microRNA (miRNA)-based delivery systems in chronic pain management, addressing their diagnostic potential, therapeutic applications, and mechanistic underpinnings. The findings collectively demonstrate that miRNAs serve as critical regulators of pain pathways, influencing nociceptive signaling, neuroinflammation, and synaptic plasticity through their ability to modulate multiple target genes simultaneously. Key miRNA candidates, such as miR-19b and the miR-183 cluster, exhibit promise as biomarkers for pain risk stratification and as therapeutic targets, with sex-specific and stress-dependent patterns highlighting their potential for personalized pain management.

The practical implications of these findings are twofold. First, miRNA profiling could refine diagnostic precision by identifying distinct molecular signatures associated with different pain etiologies, enabling earlier and more targeted interventions. Second, advances in delivery systems-such as hydrogels and natural compound-mediated approaches-offer strategies to overcome translational challenges related to stability and tissue specificity. However, the field must address gaps in clinical validation and mechanistic understanding, particularly regarding the interplay between miRNAs and other epigenetic regulators. Future research should prioritize longitudinal clinical studies, combinatorial therapeutic strategies, and standardized measurement protocols to bridge these gaps. By integrating insights from related fields like neurodegenerative and musculoskeletal disorders, miRNA-based pain therapies may accelerate toward clinical reality, offering a paradigm shift in chronic pain management.

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