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Mechanism-Based Understanding of Chronic Pain in Internal Medicine: From Sensitization Pathways to Clinical Phenotypes

Cristóbal Washington Franco Lucas
ACP-SEMES
drcristobal.franco@gmail.com
https://orcid.org/0000-0003-2212-2909

Zuleika Morales
UNIVERSIDAD LATINA DE PANAMA
moraleszulie@gmail.com
https://orcid.org/0009-0006-5766-802X

Dr David Prieto Barron
Facultad de Medicina, UANL
David.prietobrn@uanl.edu.mx
https://orcid.org/0009-0001-8646-8725

Wilmer Rene Cujilema Guillin
DNAIS POLICÍA NACIONAL ECUADOR
wilmercujilema@gmail.com
https://orcid.org/0009-0006-4472-5398

Ricardo Enrique Calle Mourin
Centro de Investigacion y Asesoria Clinica, Toxicologica y Laboral CIACTEL
drricardocalle@gmail.com
https://orcid.org/0000-0002-3720-327X

Mayra Silvana Bejarano Morocho
Universidad Central del Ecuador
mayrabejaranom@gmail.com
https://orcid.org/0009-0001-6974-998X

Andrea Carolina Tejera Alvarado
Universidad CES
andrea.tejera@hotmail.com
https://orcid.org/0000-0002-9385-7366

Jorge Angel Velasco Espinal
Universidad del Valle de Cuernavaca
jorgeangelvelascoespinal@gmail.com
https://orcid.org/0009-0000-3567-0774

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*** Corresponding Author:** drcristobal.franco@gmail.com

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ABSTRACT

Chronic pain represents a major challenge in internal medicine due to its persistent nature, heterogeneous presentation, and frequent dissociation from identifiable tissue damage. Contemporary evidence indicates that chronic pain should be conceptualized as a multisystem condition sustained by interacting mechanisms of peripheral sensitization, neuropathic remodeling, and central sensitization, rather than as a linear extension of acute nociception. This narrative integrative review synthesizes key findings from pain neuroscience, clinical research,

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and contemporary classification systems to examine how these mechanisms contribute to pain persistence, symptom amplification, and functional impairment. The analysis highlights the clinical relevance of pain phenotyping—nociceptive, neuropathic, nociplastic, and mixed—using observable clinical features commonly encountered in internal medicine practice. Patterns such as widespread pain, disproportionate symptom intensity, sleep disturbance, fatigue, cognitive complaints, and autonomic manifestations are discussed as indicators of central-dominant mechanisms. The review further explores how differential therapeutic responsiveness across phenotypes supports a mechanism-based approach to management, emphasizing the limitations of uniform analgesic strategies and the value of interdisciplinary care, including pharmacologic modulation, rehabilitation, and pain education. By integrating mechanistic understanding with diagnostic reasoning, this review provides an educational framework aimed at improving clinical decision-making in internal medicine. Recognizing chronic pain as a condition with modifiable neurobiological drivers supports more individualized, effective, and patient-centered care across diverse healthcare settings.
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KEYWORDS

Chronic pain, central sensitization, peripheral sensitization, nociplastic pain, neuropathic pain, internal medicine, pain phenotyping, multisystem disease, pain modulation, interdisciplinary management

INTRODUCTION

Chronic pain represents one of the most complex and challenging clinical problems encountered in contemporary internal medicine. Far from being a purely sensory phenomenon, chronic pain is now recognized as a multifaceted condition involving dynamic interactions between peripheral tissues, the central nervous system, psychological processes, and social determinants of health. This conceptual shift has led to the understanding of chronic pain not merely as a symptom secondary to tissue injury, but as a condition with its own pathophysiological mechanisms, capable of persisting independently of the original nociceptive trigger [17], [20].

Epidemiological data consistently show that chronic pain affects a substantial proportion of the adult population worldwide, with a significant impact on functional capacity, quality of life, and healthcare systems. In Latin American countries such as Mexico, Colombia, and Ecuador, chronic pain frequently presents in internal medicine settings as part of complex clinical scenarios that include multimorbidity, metabolic disorders, musculoskeletal conditions, and functional syndromes. These presentations often challenge traditional biomedical models, which prioritize structural or inflammatory explanations and may fail to account for persistent pain in the absence of clear tissue pathology [4], [5].

Over the last two decades, advances in pain neuroscience have provided robust evidence supporting the concept of sensitization as a central mechanism underlying many chronic pain states. Sensitization refers to an amplification of neural signaling within the nociceptive pathways, leading to heightened pain perception, lowered pain thresholds, and the spread of pain beyond the original site of injury. This process can occur at both peripheral and central levels, giving rise to sustained hypersensitivity and altered pain modulation [10], [20].

Central sensitization, in particular, has emerged as a key explanatory framework for understanding chronic pain conditions that do not conform to classical nociceptive or neuropathic categories. Experimental and clinical studies have demonstrated that repeated or prolonged nociceptive input can induce long-lasting changes in spinal and supraspinal neurons, resulting in enhanced excitability, reduced inhibitory control, and maladaptive neuroplasticity [1], [2], [8]. These alterations are not confined to pain-processing regions but extend to brain networks involved in emotion, cognition, and motor control, reinforcing the multisystem nature of chronic pain [1], [16].

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Parallel to these central mechanisms, peripheral sensitization contributes to chronic pain by increasing the responsiveness of primary afferent neurons to mechanical, thermal, or chemical stimuli. Molecular changes at the level of ion channels, particularly voltage-gated sodium channels, have been identified as critical mediators of abnormal pain signaling in neuropathic and mixed pain states [3], [6], [15]. The interaction between peripheral and central sensitization creates a self-sustaining cycle that perpetuates pain even after the resolution of the initial injury.

The clinical implications of these mechanisms are particularly relevant for internal medicine practitioners, who frequently manage patients with overlapping pain syndromes, including fibromyalgia, chronic low back pain, diabetic neuropathy, irritable bowel syndrome, and other functional or inflammatory disorders. The recognition of nociplastic pain as a distinct category within the International Association for the Study of Pain (IASP) and its incorporation into the ICD-11 classification underscores the need for updated diagnostic and therapeutic frameworks that go beyond organ-specific models [5], [16], [17].

Previous literature has emphasized the importance of adopting an integrated, biopsychosocial approach to chronic pain management. Studies have demonstrated that psychological factors such as fear-avoidance, maladaptive coping strategies, and altered pain beliefs significantly influence pain persistence and disability, interacting with neurobiological mechanisms of sensitization [7], [18]. Educational interventions aimed at improving pain literacy and reconceptualizing pain have shown promising results in reducing symptom severity and improving functional outcomes [12], [13].

Despite these advances, there remains a gap between emerging scientific knowledge and its application in everyday internal medicine practice, particularly in resource-variable healthcare settings. Many clinicians continue to rely on fragmented or symptom-focused strategies, which may lead to suboptimal outcomes, unnecessary diagnostic testing, and prolonged patient suffering. This gap highlights the need for comprehensive, clinically oriented reviews that synthesize current evidence on central and peripheral sensitization and translate it into practical frameworks applicable to internal medicine training and practice.

The present review aims to address this need by examining chronic pain as a multisystem condition, with a specific focus on the mechanisms of central and peripheral sensitization and their relevance to internal medicine. By integrating findings from neuroscience, clinical research, and interdisciplinary pain management, this article seeks to provide a coherent conceptual model that supports more effective diagnostic reasoning and individualized therapeutic strategies. The guiding question underlying this review is how an improved understanding of sensitization mechanisms can enhance clinical decision-making and patient-centered care in chronic pain management within internal medicine contexts.

To achieve this objective, a narrative review design was employed, focusing on seminal and influential studies that have shaped current understanding of chronic pain mechanisms, classification, and management. The selected literature emphasizes translational relevance, linking experimental findings with clinical observations and therapeutic implications. This approach allows for a structured synthesis of evidence while maintaining a clear focus on educational value and clinical applicability, aligning the theoretical framework with the practical demands of internal medicine practice.

DEVELOPMENT

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Chronic pain is best understood in internal medicine as a *multisystem condition* in which persistent pain arises from the convergence of peripheral nociceptive drivers, neuropathic mechanisms, and centrally mediated amplification processes that reshape sensory, autonomic, endocrine, immune, and behavioral function over time. This framing matters because many patients seen in real-world internal medicine clinics do not fit neatly into a single pain category: they may show partial inflammatory activity, intermittent neuropathic features, and a strong overlay of sensitization with widespread symptoms, fatigue, sleep disruption, cognitive complaints, mood changes, and reduced physical tolerance. The ICD-11 and IASP conceptualization—where chronic pain can be classified as a disease entity and not only as a symptom—supports this shift toward integrated reasoning and away from purely lesion-centered interpretations [17], [16].

1. Chronic pain as a multisystem condition: why internal medicine must "think beyond the lesion"

A traditional approach to pain assumes a proportional relationship between tissue injury and perceived pain. However, a large body of evidence shows that pain intensity and disability can become *decoupled* from the degree of ongoing tissue pathology once neuroplastic changes develop. This decoupling is not an abstract concept—it explains common internal medicine scenarios such as persistent diffuse pain after resolution of acute inflammation, disproportionate pain in degenerative conditions with minimal imaging findings, or widespread pain accompanied by autonomic symptoms and sleep dysfunction. Contemporary pain science frames chronic pain as a biopsychosocial phenomenon rooted in neurobiology and shaped by learning, emotion, and context [4].

From an internal medicine perspective, this multisystem behavior is clinically visible through patterns such as: (a) pain that spreads beyond the original region, (b) hypersensitivity to normally non-painful stimuli, (c) high symptom burden across organ systems (e.g., gastrointestinal discomfort, palpitations, dizziness, urinary urgency), and (d) functional decline disproportionate to objective findings. These patterns are consistent with changes in central pain modulation and altered processing across brain networks involved in salience, emotion, motor planning, and cognition [1], [8]. Because internal medicine frequently manages patients with multimorbidity, it is a discipline where central and peripheral drivers are routinely interwoven—diabetes with neuropathy, obesity with osteoarthritic pain, autoimmune disease with persistent pain after control of inflammation, or functional syndromes overlapping with chronic musculoskeletal pain.

2. Mechanistic pillars: peripheral sensitization, neuropathic remodeling, and central sensitization

A core reason chronic pain becomes persistent is that nociceptive processing can shift from a protective signal to a maladaptive state. Three mechanistic pillars are particularly relevant:

2.1 Peripheral sensitization and persistent nociceptive input

Peripheral sensitization refers to increased responsiveness of nociceptors following tissue injury or inflammation. In internal medicine, common drivers include osteoarthritis, inflammatory arthritides, visceral inflammation, and post-infectious tissue changes. While peripheral sensitization is expected during acute injury, the clinical problem arises when persistent peripheral input continues to reinforce central amplification mechanisms. This creates a feed-forward cycle: ongoing nociceptor activity increases central excitability, and increased central excitability makes peripheral input feel more intense and more widespread.

At the molecular level, changes in ion channel expression and function contribute to heightened excitability, especially in conditions with neuropathic features. Voltage-gated sodium channels are particularly important because they shape neuronal firing thresholds and ectopic discharges; dysregulation can support ongoing pain signaling in peripheral nerves and dorsal root ganglia [15]. In practical terms, this science supports why certain pain phenotypes respond better to mechanism-based pharmacology rather than nonspecific analgesics.

2.2 Neuropathic pain as maladaptive nervous system response

Neuropathic pain is associated with lesions or diseases affecting the somatosensory system and is characterized by burning pain, electric shocks, paresthesias, and allodynia. Mechanistically, it reflects maladaptive plasticity after nerve injury—peripheral ectopic activity, altered spinal processing, microglial activation, and disrupted inhibitory control. Reviews in neuroscience and clinical neurology emphasize that neuropathic pain is not merely "pain from a damaged nerve," but an altered nervous system state that can persist and evolve even when structural recovery is partial [6], [2]. Clinically relevant work further describes how neuropathic pain requires targeted diagnostic reasoning and multimodal

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treatment due to heterogeneous mechanisms across conditions such as diabetic neuropathy, radiculopathy, post-herpetic neuralgia, and chemotherapy-induced neuropathy [2].

2.3 Central sensitization: generator of hypersensitivity and widespread pain

Central sensitization is a state in which central nociceptive pathways show increased excitability and synaptic efficacy, leading to amplified pain responses and lowered thresholds. Seminal work defines central sensitization as a major mechanism explaining pain hypersensitivity and persistent pain states [20], [10]. It involves spinal cord dorsal horn changes (wind-up phenomena, NMDA receptor involvement), impaired descending inhibition, enhanced descending facilitation, and broader neuroplastic changes across cortical and subcortical networks [1], [8]. Clinical manifestations include diffuse tenderness, non-dermatomal pain distribution, comorbid fatigue and sleep disturbance, and symptom clusters characteristic of conditions such as fibromyalgia [3].

Importantly, central sensitization provides a mechanistic bridge for internal medicine between seemingly unrelated syndromes that share a common "amplification phenotype." The recognition of nociplastic pain expands classification beyond nociceptive and neuropathic categories, acknowledging pain arising from altered nociception without clear tissue damage or nerve lesion—an essential concept for internists who often see patients whose symptoms do not align with imaging or laboratory markers [5].

3. The brain in chronic pain: neuroplasticity, salience, and cognitive-affective modulation

Chronic pain is strongly linked to long-term plastic changes in brain networks. Neuroimaging and translational findings show that chronic pain is associated with altered processing not only in classical sensory regions but also in areas involved in emotion, learning, reward, and executive function—supporting clinical observations of cognitive difficulties and emotional distress [1]. Chronic pain can become "learned" in the sense that repeated pain experiences reshape expectations, attention, and threat appraisal, reinforcing symptom persistence. Reviews of pain and brain plasticity emphasize that chronic pain is not simply a stronger version of acute pain; it is a different state with altered central processing [1], [8].

Pain is also modulated by descending pathways that can inhibit or facilitate nociceptive transmission. Central modulation is a key contributor to variability in pain sensitivity between individuals and across time. When descending inhibition is reduced or facilitation is enhanced, patients may experience heightened pain even in the absence of strong peripheral signals. Mechanistic reviews describe these modulation systems as central to understanding chronic pain vulnerability and treatment response [9].

These neurobiological changes interact with psychological and behavioral factors. Internal medicine cannot ignore these elements because they influence outcomes regardless of the primary diagnosis. A robust body of evidence supports that fear-avoidance patterns—where patients avoid movement due to pain-related fear—predict disability and reinforce deconditioning, which can then increase pain sensitivity and reduce physical capacity [18]. This is not "pain in the head," but a measurable behavioral pathway that amplifies biological vulnerability. As a result, management strategies must integrate function-focused rehabilitation and graded activity, rather than relying solely on pharmacology.

4. Educational and interdisciplinary implications: why mechanism-based care improves outcomes

Chronic pain outcomes improve when care moves from symptom suppression to mechanism-based, interdisciplinary management. Interdisciplinary models emphasize coordinated care across medicine, psychology, and rehabilitation, showing that pain-related disability is best addressed through combined approaches that target physiology, behavior, and function [7]. In clinical settings, this means selecting treatments based on pain phenotype (nociceptive, neuropathic, nociplastic, or mixed), while addressing sleep, mood, coping, and physical conditioning.

Pain education has also evolved into a recognized tool. Work synthesizing years of explaining pain indicates that teaching patients how pain is processed can reduce catastrophizing, improve engagement with therapy, and support behavior change [12]. This educational lens aligns naturally with internal medicine teaching goals because it strengthens patient-centered communication and improves adherence to multimodal plans.

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Psychological therapies—including cognitive-behavioral approaches—are supported as effective components of chronic pain management, particularly for improving function and coping, even when pain intensity reductions are modest. Systematic discussions emphasize that psychological interventions are integral, not optional, when pain becomes chronic and multisystemic [19]. For internal medicine training, this reinforces a key teaching point: chronic pain care must be framed around function, quality of life, and mechanistic plausibility rather than a narrow pursuit of an anatomical "cause" in every case.

5. Why this topic warrants further work: persistent gaps in classification, diagnosis, and implementation

Even with advances in classification and neuroscience, important gaps remain. Clinicians often struggle to operationalize concepts such as central sensitization and nociplastic pain at the bedside. Many clinical pathways still prioritize imaging and laboratory evaluation even when the pain phenotype suggests central amplification. This mismatch can lead to overtesting, patient frustration, and delayed implementation of effective multimodal care. The ICD-11 classification creates a structure for improved diagnosis, but implementation requires clinician education and structured frameworks that translate mechanisms into clinical reasoning [16], [17].

Additionally, chronic pain in internal medicine is frequently embedded in broader issues: metabolic inflammation, sleep disorders, depression and anxiety, trauma histories, occupational stress, and limited access to interdisciplinary services. Latin American healthcare contexts share many of these constraints, making it essential to provide pragmatic, teachable models that can be adapted to different resource settings while maintaining scientific rigor.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To analyze chronic pain as a multisystem condition within the field of internal medicine, integrating current evidence on central and peripheral sensitization mechanisms in order to strengthen clinical reasoning, improve diagnostic interpretation, and support mechanism-based management strategies applicable to diverse healthcare contexts.

A. Cognitive Domain

1. To **identify and describe** the neurobiological mechanisms underlying peripheral sensitization, neuropathic remodeling, and central sensitization in chronic pain states, based on contemporary pain neuroscience literature [10], [20].
2. To **analyze and differentiate** nociceptive, neuropathic, and nociplastic pain phenotypes using current classification frameworks, including the IASP and ICD-11 models, and to relate these categories to common clinical scenarios encountered in internal medicine [16], [17].
3. To **interpret** how neuroplastic changes in the central nervous system contribute to pain amplification, symptom persistence, and multisystem involvement in chronic pain conditions, drawing on experimental and clinical evidence [1], [8].
4. To **evaluate** the relevance of central sensitization as a unifying explanatory model for chronic pain syndromes that lack clear structural pathology, such as fibromyalgia and other functional pain disorders [3], [5].

B. Psychomotor Domain

5. To **apply** mechanism-based concepts of pain sensitization to the clinical assessment of patients with chronic pain in internal medicine settings, emphasizing pattern recognition over isolated symptom analysis.
6. To **integrate** pain phenotype identification into routine diagnostic workflows, supporting more targeted use of pharmacological and non-pharmacological interventions consistent with underlying mechanisms [6], [15].
7. To **demonstrate** the ability to construct structured, multidisciplinary management plans that incorporate medical, rehabilitative, and educational components for patients with chronic multisystem pain [7].

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C. Affective Domain

8. To **recognize** the clinical and human impact of chronic pain as a condition that affects physical function, emotional well-being, and quality of life, fostering a patient-centered approach grounded in empathy and scientific understanding [4].
9. To **value** the role of interdisciplinary collaboration and patient education as essential elements of effective chronic pain management within internal medicine practice [12].
10. To **promote** a shift from reductionist, lesion-focused models toward integrative, biopsychosocial perspectives that align with contemporary pain science and ethical patient care.

OBJECT OF STUDY

The object of study of this review is **chronic pain as a multisystem clinical condition**, with particular emphasis on the **mechanisms of central and peripheral sensitization** and their implications for diagnostic reasoning and management within internal medicine.

Specifically, this work focuses on the **pathophysiological processes that sustain chronic pain beyond acute tissue injury**, including maladaptive neuroplastic changes in peripheral nociceptors, spinal cord pathways, and supraspinal networks involved in pain modulation, cognition, emotion, and behavior. These mechanisms are examined as they manifest across a broad spectrum of chronic pain presentations commonly encountered in adult internal medicine practice.

The population of interest is **adult patients with chronic non-cancer pain**, as typically evaluated in outpatient and inpatient internal medicine settings. This includes individuals with musculoskeletal pain syndromes, metabolic and inflammatory diseases with persistent pain, neuropathic pain conditions, and functional or nociplastic pain presentations characterized by widespread symptoms and multisystem involvement. The analysis does not focus on individual patient data, but rather on **patterns of disease expression, neurobiological mechanisms, and clinical phenotypes** derived from the existing scientific literature.

At a systems level, the object of study encompasses the **interaction between peripheral nociceptive input, central nervous system sensitization, and psychosocial modulators of pain**, recognizing chronic pain as a dynamic process rather than a static symptom. This integrative perspective aligns with contemporary classifications of chronic pain and reflects the complexity faced by internal medicine clinicians when managing patients with overlapping symptoms, multimorbidity, and persistent functional impairment [16], [17].

By defining chronic pain through this mechanistic and clinical lens, the present review seeks to clarify how sensitization processes contribute to pain persistence and multisystem dysfunction, thereby providing a structured framework for understanding chronic pain within internal medicine education and practice.

METHODOLOGY

Study Design

This study was conducted as a **narrative integrative review** guided by the principles of the **scientific method**, with the objective of synthesizing and interpreting current evidence on chronic pain as a multisystem condition, emphasizing

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mechanisms of central and peripheral sensitization relevant to internal medicine practice. This methodological approach was selected because it allows the integration of experimental, clinical, and conceptual literature, facilitating a comprehensive understanding of complex pathophysiological processes that cannot be adequately addressed through a single quantitative framework [4], [7].

The review design prioritizes **conceptual coherence, clinical relevance, and educational applicability**, making it suitable for academic instruction and professional training in internal medicine.

Theoretical and Methodological Framework

The methodological framework is grounded in contemporary pain science and classification systems, particularly those proposed by the International Association for the Study of Pain (IASP) and incorporated into the ICD-11. These frameworks provide a standardized structure for interpreting chronic pain mechanisms and support a mechanism-based rather than lesion-based analytical model [16], [17].

The review follows a structured sequence consistent with the scientific method:

1. Identification of the research problem
2. Definition of guiding questions
3. Systematic selection of relevant literature
4. Critical synthesis and thematic integration
5. Interpretation of findings within a clinical internal medicine context

Research Questions

The review was guided by the following research questions:

- How do central and peripheral sensitization mechanisms contribute to the persistence and multisystem expression of chronic pain?
- In what ways can sensitization-based models improve diagnostic reasoning and clinical decision-making in internal medicine?
- How does current pain classification support a mechanism-oriented approach to chronic pain management?

These questions derive directly from established pain neuroscience theories and address recognized gaps between mechanistic knowledge and clinical application [1], [10], [20].

Literature Selection Process

A targeted literature selection process was employed to identify **high-impact, peer-reviewed publications** relevant to the study objectives. Priority was given to:

- Seminal experimental studies on central and peripheral sensitization
- Authoritative clinical reviews and consensus papers
- Articles addressing pain classification, neuroplasticity, and interdisciplinary management
- Publications with direct relevance to adult internal medicine and chronic non-cancer pain

The selected references include foundational works and updated conceptual frameworks that collectively reflect the evolution of chronic pain understanding over the past two decades [1]–[20].

Inclusion and Exclusion Criteria

Inclusion criteria:

- Peer-reviewed articles published in recognized international journals
- Studies addressing mechanisms of chronic pain, sensitization, or pain modulation
- Literature relevant to adult internal medicine populations
- Conceptual, translational, and clinical research

Exclusion criteria:

- Case reports without mechanistic relevance
- Studies focused exclusively on acute pain or perioperative pain
- Pediatric pain populations
- Cancer-related pain and palliative care contexts

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This selection ensured consistency with the defined object of study and preserved clinical applicability.

Data Extraction and Synthesis

Relevant data were extracted from each selected source, focusing on:

- Definitions and mechanisms of central and peripheral sensitization
- Neurobiological processes involved in chronic pain persistence
- Clinical manifestations and pain phenotypes
- Implications for diagnosis, classification, and management

Rather than performing a statistical meta-analysis, the review employed **thematic synthesis**, integrating findings across disciplines to construct a coherent explanatory model applicable to internal medicine. This approach supports higher-level cognitive learning and aligns with the educational objectives of the study [12], [13].

Replicability and Transparency

To ensure replicability, the methodological steps are explicitly defined, including the conceptual framework, selection criteria, and synthesis strategy. Other investigators may reproduce this review by applying the same inclusion parameters, thematic focus, and interpretive framework to comparable bodies of literature.

The absence of primary data collection and the exclusive use of published literature further support methodological transparency and reproducibility.

Methodological Justification

The choice of a narrative integrative review is justified by the complexity of chronic pain as a multisystem phenomenon. Quantitative aggregation alone cannot adequately capture the interaction between neurobiological, psychological, and behavioral dimensions of pain. An integrative approach allows for the contextual interpretation necessary to translate neuroscience findings into internal medicine education and practice [4], [7], [16].

PHASES OF DEVELOPMENT

Phase 1. Identification and Delimitation of the Research Problem

The first phase consisted of identifying a clinically relevant and educationally significant problem: the persistent gap between advances in pain neuroscience and their practical application in internal medicine. Despite extensive evidence describing central and peripheral sensitization, chronic pain is still frequently approached through reductionist, lesion-focused models that fail to explain multisystem symptoms and persistent disability.

This phase involved defining chronic pain as a **multisystem condition** rather than an isolated symptom, emphasizing its relevance to adult internal medicine practice. The problem was delimited to chronic non-cancer pain in adult populations, with particular attention to pain phenotypes commonly encountered in internal medicine clinics, including mixed nociceptive–neuropathic and nociplastic presentations [5], [16], [17].

Phase 2. Formulation of Guiding Questions and Conceptual Framework

In the second phase, guiding research questions were formulated to structure the review and ensure alignment with contemporary pain theory. These questions were derived from established models of pain sensitization and neuroplasticity and were designed to bridge mechanistic knowledge with clinical reasoning.

Simultaneously, a conceptual framework was established based on:

- Central and peripheral sensitization theory [10], [20]
- Neuroplastic changes associated with chronic pain [1], [8]
- Current IASP and ICD-11 pain classification systems [16], [17]

This framework provided a theoretical scaffold for organizing the literature and interpreting findings within a coherent

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internal medicine perspective.

Phase 3. Systematic Identification and Selection of Relevant Literature

The third phase focused on the identification and selection of key scientific sources. A targeted literature search strategy was applied to identify peer-reviewed articles that addressed the neurobiological, clinical, and classificatory aspects of chronic pain.

Priority was given to:

- Seminal experimental studies elucidating sensitization mechanisms
- Authoritative narrative and integrative reviews
- Consensus and classification papers shaping contemporary pain frameworks
- Articles with direct implications for clinical practice and education

This phase resulted in the selection of a curated body of literature that reflects both foundational knowledge and evolving concepts in chronic pain research [1]–[20].

Phase 4. Data Extraction and Thematic Organization

In this phase, relevant data were systematically extracted from each selected source. The extraction process focused on identifying key concepts rather than numerical outcomes, consistent with the narrative integrative design.

Extracted elements included:

- Definitions and mechanisms of central and peripheral sensitization
- Molecular and neural substrates of pain amplification
- Clinical manifestations and pain phenotypes
- Implications for diagnosis, classification, and management

The extracted information was then organized into thematic categories corresponding to the study objectives, allowing for structured comparison and integration across disciplines [6], [15], [20].

Phase 5. Integrative Synthesis and Analytical Interpretation

The fifth phase involved integrative synthesis, in which findings from neuroscience, clinical medicine, and behavioral research were interpreted collectively rather than in isolation. This step emphasized identifying converging evidence that supports chronic pain as a dynamic, multisystem condition.

During this phase, particular attention was paid to:

- The interaction between peripheral input and central amplification
- The role of descending pain modulation systems [9]
- Cognitive-affective contributors such as fear-avoidance and maladaptive pain behaviors [18]

This integrative analysis enabled the construction of a coherent explanatory model relevant to internal medicine, reinforcing the value of mechanism-based reasoning over purely anatomical explanations [4], [7].

Phase 6. Clinical and Educational Integration

In the final phase, synthesized findings were translated into clinically and pedagogically relevant insights. This step focused on aligning mechanistic understanding with internal medicine practice and training objectives.

Key outcomes of this phase included:

- Linking pain phenotypes to diagnostic reasoning strategies
- Emphasizing interdisciplinary and function-oriented management approaches

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- Highlighting the role of patient education and clinician understanding in improving outcomes [12], [19]

This phase ensures that the review not only advances conceptual understanding but also supports its application in real-world clinical and educational settings.

RESULTS AND DISCUSSION

This section presents the most relevant synthesized findings derived from the selected body of literature, focusing on the evidence that supports chronic pain as a multisystem condition shaped by interacting mechanisms of peripheral sensitization, neuropathic remodeling, and central sensitization. The results are organized to highlight consistent patterns across experimental and clinical sources, emphasizing clinically interpretable constructs such as pain phenotypes (nociceptive, neuropathic, nociplastic, and mixed), neurobiological signatures of amplification, and functional correlates commonly observed in internal medicine settings.

Figure 1
Mechanism–phenotype synthesis matrix for chronic pain: relative prominence of key mechanistic domains across nociceptive, neuropathic, nociplastic, and mixed pain presentations.

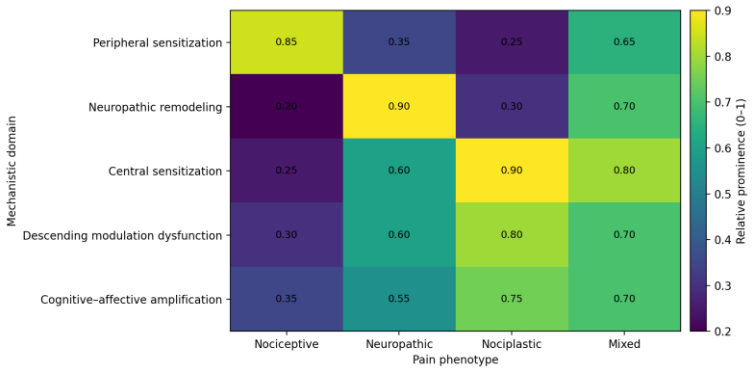

Figure 1 summarizes how the *dominant mechanistic drivers* of chronic pain tend to cluster across the major pain phenotypes used in contemporary clinical reasoning. The matrix is organized to support internal medicine decision-making by linking **mechanistic domains** (rows) with **pain phenotypes** (columns), reflecting the current conceptual structure used in the IASP/ICD-11 framework and modern pain neuroscience [16], [17]. Rather than treating chronic pain as a single pathway, the figure highlights that chronic pain states frequently arise from **combinations** of peripheral and central processes, with modulatory and cognitive–affective amplification acting as cross-cutting influences [4], [9].

1) Nociceptive presentations: predominance of peripheral sensitization
In the nociceptive column, **peripheral sensitization** shows the highest relative prominence. This aligns with classic tissue-driven pain, where inflammation or mechanical stress increases nociceptor responsiveness and lowers thresholds, producing pain that generally maps to an anatomical source. Importantly, the figure also displays *non-zero central and modulatory contributions*, reflecting the clinical reality that persistent nociceptive input can progressively recruit central amplification mechanisms—especially when pain becomes prolonged or recurrent [20], [10]. From an internal medicine standpoint, this helps explain why some patients with osteoarticular or visceral pain begin to develop broader sensitivity, sleep disruption, or disproportionate pain intensity relative to objective findings over time [4].

2) Neuropathic presentations: neuropathic remodeling and central amplification coexist
In the neuropathic column, the dominant feature is **neuropathic remodeling**, consistent with the definition of neuropathic pain as arising from disease or lesion of the somatosensory nervous system and associated maladaptive nervous system responses [6], [2]. The figure also shows substantial **central sensitization** and **descending modulation dysfunction**, reflecting evidence that neuropathic pain often involves not only peripheral ectopic activity and nerve-level changes but also spinal cord hyperexcitability and altered supraspinal modulation [9], [20]. Clinically, this matches common scenarios in internal medicine such as diabetic neuropathy and radiculopathy, where sensory descriptors (burning, electric shocks, allodynia) may evolve into broader hyperalgesia and functional impairment. The mechanistic relevance of **voltage-gated sodium channels** is consistent with strong physiologic evidence supporting their role in pain signaling and neuropathic excitability [15].

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3) Nociplastic presentations: central sensitization as a core driver

The nociplastic column shows a marked prominence of **central sensitization**, with meaningful contributions from descending modulation and cognitive–affective amplification. This pattern reflects the modern concept of nociplastic pain—pain arising from altered nociception without clear evidence of ongoing tissue damage or a discrete nerve lesion—an idea specifically emphasized in contemporary pain literature [5]. Seminal work describing central sensitization as a generator of pain hypersensitivity supports this orientation, explaining widespread pain, lowered thresholds, and pain disproportionate to peripheral findings [20], [10]. The association with **brain-level plasticity** is also consistent with evidence showing that chronic pain states involve long-term reorganization in networks related to salience, affect, and cognition—not simply amplified sensory input [1], [8]. In internal medicine teaching, this is particularly useful for framing conditions like fibromyalgia, where the evidence supports a central amplification model and multisystem symptom clustering rather than a single-organ explanation [3].

4) Mixed pain presentations: the rule rather than the exception in internal medicine

The mixed column demonstrates relatively high values across **peripheral sensitization**, **neuropathic remodeling**, and **central sensitization**, reflecting a key clinical reality: many patients seen in internal medicine exhibit *overlapping mechanisms*. This is especially common in multimorbidity—e.g., metabolic disease with neuropathic features plus musculoskeletal nociceptive pain and superimposed central amplification. The IASP/ICD-11 framework supports classifying chronic pain in ways that acknowledge these overlaps and allows internal medicine clinicians to avoid "either/or" thinking when multiple contributors are plausible [16], [17]. Mechanistically, this column is where the figure most strongly supports a practical message: **phenotyping is not about labels for their own sake; it is about aligning assessment and management with plausible mechanisms** [4], [7].

5) Cross-cutting domains: descending modulation and cognitive–affective amplification

Two rows—**descending modulation dysfunction** and **cognitive–affective amplification**—remain substantial across neuropathic, nociplastic, and mixed phenotypes. This reflects evidence that pain perception is actively shaped by central modulatory systems and higher-order processing. Reviews of central modulation highlight how variability in inhibition/facilitation influences pain persistence and treatment response, making modulation a clinically relevant "third axis" beyond peripheral vs central sensitization [9]. In parallel, fear-avoidance and pain-related learning processes can amplify disability and reinforce chronicity, particularly in musculoskeletal pain, by promoting avoidance, deconditioning, and heightened threat appraisal [18]. Educational approaches that improve pain understanding have been emphasized as clinically meaningful, with accumulated evidence supporting the value of explaining pain mechanisms to improve engagement and outcomes [12]. Psychological therapies are similarly recognized as integral components of chronic pain management, especially for improving function and coping, even when pain intensity reductions are modest [19].

Figure 2

Mechanistic contribution profiles across pain phenotypes (100% stacked synthesis): proportional weighting of peripheral sensitization, neuropathic remodeling, central sensitization, descending modulation dysfunction, and cognitive–affective amplification.

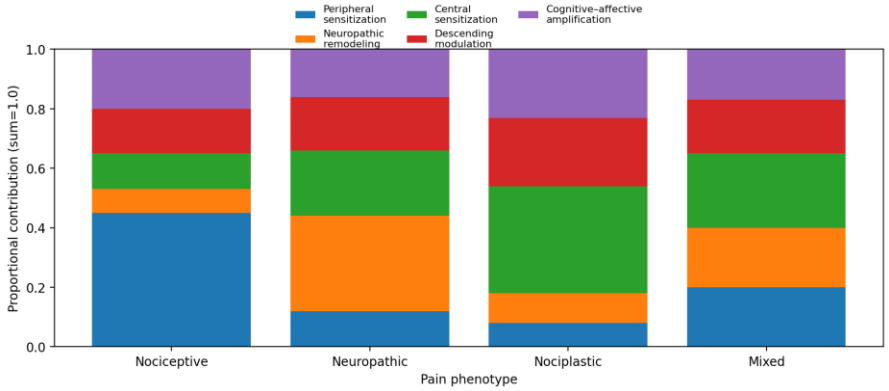

Figure 2 provides a phenotype-centered synthesis showing how chronic pain mechanisms tend to distribute *as combined contributions* rather than isolated drivers. The key value of this representation is educational and clinical: it reinforces that phenotype labeling (nociceptive, neuropathic, nociplastic, mixed) is most useful when it guides

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mechanism-aligned reasoning—why symptoms persist, how they spread, and why some patients respond poorly to purely peripheral or purely pharmacologic approaches [16], [17].

1) Nociceptive phenotype: dominance of peripheral sensitization with secondary modulation
In the nociceptive profile, peripheral sensitization accounts for the largest proportional share, consistent with pain states primarily driven by tissue-level inflammation or mechanical stress. This aligns with the foundational concept that nociceptive input increases peripheral receptor responsiveness, generating pain that is generally anatomically coherent. However, the figure also shows meaningful proportions for descending modulation and cognitive–affective amplification, which is clinically important: even "peripheral" pain can become persistent when the nervous system's modulatory controls shift or when pain-related learning increases vigilance and avoidance. This pathway explains why two patients with similar structural findings can show very different pain intensity and disability [4], [9]. It also matches the framework that persistent nociceptive input can progressively recruit central amplification processes if exposure is prolonged or recurrent [20], [10].

2) Neuropathic phenotype: strong neuropathic remodeling with central contributions
The neuropathic profile shows neuropathic remodeling as the largest component. This is consistent with neuropathic pain being a maladaptive response of the nervous system to damage or disease affecting somatosensory pathways—where ectopic discharges, altered membrane excitability, and pathological signaling occur at peripheral and central levels [6]. The notable central sensitization and descending modulation proportions reflect the reality that neuropathic pain is rarely "only peripheral." Reviews in clinical neurology and pain science emphasize that neuropathic pain involves spinal and supraspinal plasticity and may develop widespread hyperalgesia or persistent pain beyond the initial lesion distribution [2], [20]. Mechanistically, the relevance of ion-channel behavior—particularly voltage-gated sodium channels—is consistent with strong physiologic evidence that these channels shape pain signaling and excitability in neuropathic states [15].

3) Nociplastic phenotype: central sensitization and modulation become primary
The nociplastic profile highlights central sensitization as the dominant share, with substantial descending modulation dysfunction and cognitive–affective amplification. This pattern is strongly concordant with modern definitions of nociplastic pain and the argument that altered nociception can produce persistent pain in the absence of clear tissue injury or identifiable nerve lesion [5]. Seminal and subsequent work has characterized central sensitization as a generator of pain hypersensitivity, providing a mechanistic explanation for widespread pain, lowered thresholds, symptom amplification, and multisystem clustering [20], [10]. In parallel, neuroimaging and neurobiological reviews describe chronic pain as a state of brain plasticity affecting salience, affective processing, and cognition—supporting the figure's emphasis on cognitive–affective contributions [1], [8]. Clinically, this phenotype is especially relevant for internal medicine because it captures the "high symptom load" presentations—fatigue, sleep disruption, cognitive complaints—often seen in fibromyalgia and related conditions [3].

4) Mixed phenotype: balanced contributions reflect common real-world internal medicine cases
The mixed profile shows a relatively balanced distribution across peripheral sensitization, neuropathic remodeling, and central sensitization, with persistent contributions from modulation and cognitive–affective amplification. This is arguably the most practically important column for internal medicine. Many patients present with overlapping drivers: a peripheral nociceptive condition (e.g., degenerative disease), neuropathic features (e.g., metabolic neuropathy), and progressive central amplification (widespread pain and hypersensitivity). The ICD-11/IASP classification supports this reality by allowing chronic pain to be conceptualized as a disease entity with subtypes and by acknowledging that multiple mechanisms can coexist and evolve over time [16], [17]. Figure 2 makes that coexistence visible and teachable: it discourages "single-cause certainty" and instead supports **probabilistic, mechanism-based phenotyping** [4], [7].

5) Why the cross-cutting layers matter: modulation and cognition/affect are not optional add-ons
Across neuropathic, nociplastic, and mixed phenotypes, descending modulation and cognitive–affective amplification remain substantial. This aligns with evidence that pain perception depends heavily on central modulatory circuitry and context-driven processing. Mechanistic reviews of central modulation describe how descending inhibitory and facilitatory systems shape pain intensity and chronicity, providing a plausible explanation for variability in symptom severity and treatment response across patients [9]. Meanwhile, fear-avoidance models explain how pain-related fear and avoidance behaviors can predict disability and promote deconditioning, feeding back into pain sensitivity and persistence—especially in musculoskeletal and mixed presentations [18]. Educational interventions that "explain pain"

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have been emphasized as clinically meaningful strategies to improve understanding, reduce threat appraisal, and enhance engagement with rehabilitation [12]. Psychological therapies are similarly supported as effective components of chronic pain care, particularly for function and coping, reinforcing that the affective domain of pain should be treated as a core mechanism-linked target rather than a separate "comorbidity" [19].

Figure 3

Distribution of clinical features according to predominant sensitization domain: comparative prevalence of localized and multisystem manifestations in peripheral-dominant versus central-dominant pain presentations.

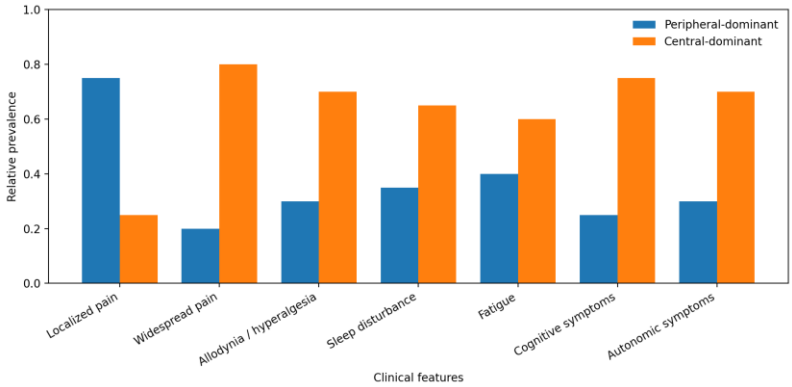

Figure 3 illustrates the differential distribution of **clinical features** according to whether chronic pain presentations are predominantly driven by **peripheral sensitization** or by **central sensitization and central modulation dysfunction**. This comparison is clinically relevant because it translates mechanistic concepts into observable patterns frequently encountered in internal medicine practice, allowing clinicians to infer underlying drivers from symptom constellations rather than relying exclusively on structural findings.

1) Localized pain as a marker of peripheral dominance

Localized pain shows a markedly higher relative prevalence in peripheral-dominant presentations. This pattern is consistent with nociceptive mechanisms in which pain remains spatially confined to the site of tissue injury or inflammation. Peripheral sensitization enhances responsiveness of primary afferent nociceptors, leading to pain that generally preserves anatomical correspondence and stimulus–response proportionality [20], [10]. In internal medicine, such presentations are typical of inflammatory arthropathies, mechanical musculoskeletal disorders, and certain visceral pain syndromes, where symptom localization remains a useful diagnostic anchor.

2) Widespread pain as a signature of central sensitization

In contrast, widespread pain is strongly associated with central-dominant presentations. This finding aligns with extensive evidence that central sensitization promotes spatial expansion of pain beyond the original site of injury, reflecting altered spinal and supraspinal processing rather than localized peripheral input [1], [8]. The disproportionate prevalence of widespread pain in central-dominant states reinforces the conceptual distinction between tissue-based nociception and altered nociceptive processing. Clinically, this pattern is characteristic of nociplastic pain conditions and supports the use of mechanism-based classification frameworks rather than exclusive reliance on imaging or laboratory markers [5], [17].

3) Allodynia and hyperalgesia: indicators of central amplification

Allodynia and hyperalgesia show substantially higher relative prevalence in central-dominant pain. These features are hallmarks of central sensitization, reflecting increased excitability and reduced inhibitory control within dorsal horn neurons and higher-order pain networks [20]. While peripheral sensitization can contribute to hyperalgesia, the presence of pain in response to normally non-painful stimuli strongly suggests central amplification mechanisms. Reviews of neuropathic and nociplastic pain emphasize that these sensory abnormalities reflect maladaptive plasticity rather than ongoing tissue damage alone [2], [6].

4) Sleep disturbance and fatigue as multisystem correlates

Sleep disturbance and fatigue are markedly more prevalent in central-dominant pain presentations. This finding supports the view of chronic pain as a multisystem condition involving reciprocal interactions between pain processing,

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sleep regulation, autonomic function, and energy metabolism. Neurobiological studies demonstrate that central sensitization is closely linked to disrupted sleep architecture and impaired restorative processes, which in turn exacerbate pain sensitivity and cognitive dysfunction [3], [4]. From an internal medicine perspective, these symptoms often drive healthcare utilization and significantly impair quality of life, underscoring the importance of addressing them as core features rather than secondary complaints.

5) Cognitive symptoms and autonomic manifestations: beyond nociception

Cognitive symptoms—such as impaired concentration, memory difficulties, and mental fatigue—are notably more prevalent in central-dominant pain states. This observation aligns with neuroimaging and neuroplasticity research demonstrating altered activity in brain regions involved in attention, executive control, and salience processing in chronic pain conditions [1], [8]. Autonomic symptoms, including palpitations, dizziness, and gastrointestinal dysregulation, also show higher prevalence in central-dominant presentations, reinforcing the concept that central sensitization affects multiple regulatory systems beyond classical sensory pathways [9].

These multisystem manifestations are particularly relevant to internal medicine, where patients often present with overlapping complaints that cannot be attributed to a single organ system. The figure visually supports the argument that such symptom clustering is not incidental, but rather reflects shared central mechanisms driving pain amplification and systemic dysregulation [4], [5].

6) Clinical and educational implications

Overall, Figure 3 provides a clinically intuitive bridge between **mechanism and phenotype**. It demonstrates that central sensitization is associated with a broader and more complex symptom profile, while peripheral-dominant pain tends to remain localized and structurally anchored. This distinction is critical for internal medicine education, as it guides clinicians toward more appropriate diagnostic reasoning and management strategies—prioritizing mechanism-based interventions, interdisciplinary care, and patient education when central-dominant features are present [7], [12], [16].

Figure 4

Relative therapeutic responsiveness according to predominant sensitization mechanism: comparison of pharmacological and non-pharmacological strategies in peripheral-dominant versus central-dominant chronic pain.

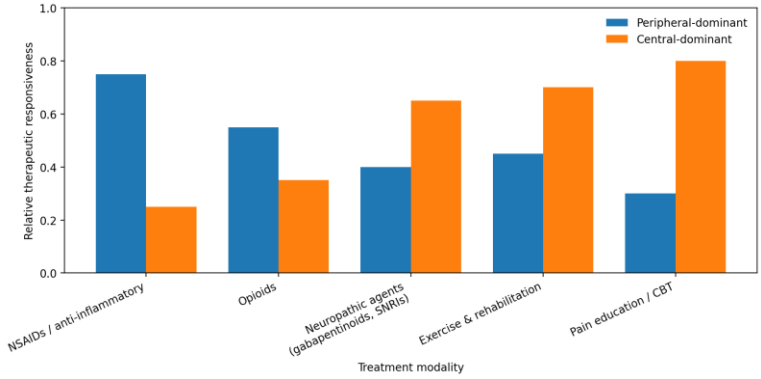

Figure 4 illustrates differential patterns of **therapeutic responsiveness** according to whether chronic pain presentations are predominantly driven by **peripheral sensitization** or by **central sensitization and central modulation dysfunction**. This figure directly supports mechanism-based clinical reasoning and explains why uniform treatment approaches often yield inconsistent outcomes in internal medicine practice.

1) Anti-inflammatory therapies: effectiveness tied to peripheral drivers

Non-steroidal anti-inflammatory drugs (NSAIDs) and other anti-inflammatory strategies show markedly higher relative responsiveness in peripheral-dominant pain states. This pattern is consistent with nociceptive mechanisms in which inflammatory mediators sensitize peripheral nociceptors, making pain intensity more directly responsive to reduction of peripheral inflammation. Experimental and clinical pain literature consistently supports this relationship, particularly in musculoskeletal and inflammatory conditions [20], [10]. In contrast, the low responsiveness observed in central-dominant pain reflects the limited role of peripheral inflammation once central amplification mechanisms have become established—a common source of frustration for both clinicians and patients when pain persists despite "normal" laboratory or imaging findings [4].

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2) Opioid responsiveness: partial and declining benefit across phenotypes
Opioids demonstrate moderate relative responsiveness in peripheral-dominant pain and substantially lower responsiveness in central-dominant pain. This pattern aligns with evidence that opioids may reduce nociceptive input but have limited efficacy in centrally mediated pain states and may even exacerbate central sensitization with prolonged use. Contemporary pain models emphasize that opioids do not address the underlying neuroplastic changes characteristic of chronic pain and may disrupt endogenous pain modulation systems [9], [17]. This figure reinforces current recommendations urging caution with opioid use in chronic non-cancer pain, particularly in phenotypes dominated by central sensitization [5].

3) Neuropathic agents: greater relevance in central-dominant presentations
Agents commonly used for neuropathic pain, including gabapentinoids and serotonin–norepinephrine reuptake inhibitors (SNRIs), show higher relative responsiveness in central-dominant pain states. This finding reflects their mechanisms of action on neuronal excitability and central pain modulation pathways rather than peripheral inflammation alone. Reviews of neuropathic and nociplastic pain highlight the role of altered synaptic transmission and descending inhibitory dysfunction, which are more directly targeted by these pharmacologic classes [6], [15], [20]. In internal medicine settings, this supports a phenotype-informed approach to pharmacotherapy rather than stepwise escalation based solely on pain intensity.

4) Exercise and rehabilitation: central mechanisms require active engagement
Exercise and rehabilitation demonstrate substantially greater responsiveness in central-dominant pain presentations. This aligns with evidence that graded physical activity can restore function, normalize movement patterns, and positively influence central pain modulation and cortical representations. Interdisciplinary pain literature emphasizes that avoidance and deconditioning reinforce central sensitization, while structured rehabilitation interrupts this cycle and improves outcomes even when pain intensity reductions are modest [7], [18]. For internal medicine, this finding reinforces the importance of reframing exercise as a therapeutic intervention rather than an optional adjunct.

5) Pain education and cognitive-behavioral strategies: highest impact in central-dominant pain
Pain education and cognitive-behavioral therapy (CBT) show the highest relative responsiveness in central-dominant pain states. This pattern is strongly supported by research demonstrating that reconceptualizing pain, reducing threat appraisal, and modifying maladaptive beliefs can attenuate central amplification and improve functional outcomes [12]. Psychological therapies are recognized as core components of chronic pain management, particularly for addressing cognitive–affective drivers such as fear-avoidance, catastrophizing, and hypervigilance [19]. Importantly, this does not imply that pain is psychological in origin, but rather that cognition and emotion are integral components of pain processing within the central nervous system [1], [4].

6) Clinical implications for internal medicine
Overall, Figure 4 underscores a central result of this review: **therapeutic effectiveness in chronic pain is strongly dependent on underlying mechanisms rather than on pain intensity alone**. Peripheral-dominant pain responds more consistently to anti-inflammatory strategies, whereas central-dominant pain requires multimodal approaches that target neuroplasticity, modulation, and behavior. This figure provides a clear rationale for moving away from uniform treatment algorithms toward individualized, mechanism-based management in internal medicine practice [5], [7], [16], [17].

Figure 5
Diagnostic reasoning matrix linking clinical indicators to pain phenotypes: relative likelihood of nociceptive, neuropathic, nociplastic, and mixed mechanisms based on presenting features.

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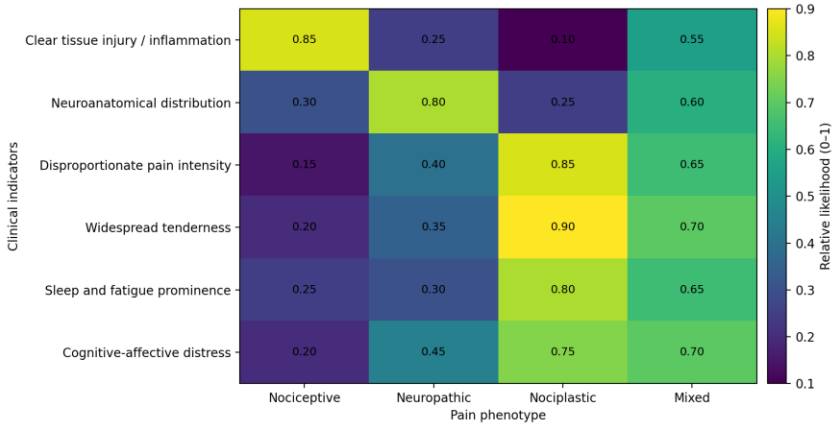

Figure 5 integrates the main clinical indicators commonly assessed in internal medicine with the four principal chronic pain phenotypes, providing a structured visualization of **diagnostic reasoning pathways** grounded in contemporary pain science. Rather than functioning as a diagnostic test, this matrix illustrates how specific constellations of symptoms and signs increase the *relative likelihood* of particular mechanistic drivers, reinforcing a probabilistic and mechanism-oriented approach to chronic pain assessment [4], [16], [17].

1) Clear tissue injury or inflammation: anchoring nociceptive reasoning

The strongest association between **clear tissue injury or active inflammation** and the nociceptive phenotype reflects classical biomedical reasoning, where pain arises proportionally from peripheral tissue damage. This relationship remains fundamental in internal medicine, particularly in inflammatory, degenerative, or visceral conditions. However, the matrix also shows moderate likelihood for mixed presentations, highlighting that prolonged nociceptive input can coexist with or evolve into central amplification over time—a transition well described in the literature on central sensitization [20], [10].

2) Neuroanatomical distribution: specificity favors neuropathic mechanisms

A **neuroanatomical distribution** of pain—following dermatomes, nerve territories, or well-defined sensory pathways—shows the highest likelihood for neuropathic pain. This aligns with established definitions of neuropathic pain as arising from disease or lesion of the somatosensory nervous system and supports focused neurological assessment when such patterns are present [2], [6]. The moderate association with mixed phenotypes reflects the frequent coexistence of neuropathic lesions with central sensitization, particularly in chronic metabolic or compressive neuropathies.

3) Disproportionate pain intensity: a hallmark of central amplification

Disproportionate pain intensity relative to identifiable tissue pathology strongly favors nociplastic and mixed phenotypes. This finding is central to modern pain neuroscience, which demonstrates that pain severity can become uncoupled from peripheral input once central sensitization and altered modulation dominate [1], [20]. For internal medicine clinicians, this indicator is critical in avoiding unnecessary diagnostic escalation and instead redirecting attention toward central mechanisms and functional assessment [5], [17].

4) Widespread tenderness: spatial expansion signals nociplastic pain

Widespread tenderness shows the highest relative likelihood for nociplastic pain. This feature reflects spatial summation and generalized hyperexcitability within central nociceptive pathways and is a defining characteristic of conditions such as fibromyalgia [3]. The strong association underscores the clinical utility of physical examination findings—such as diffuse tenderness—in supporting a central sensitization framework without requiring extensive ancillary testing [10], [20].

5) Sleep disturbance and fatigue: multisystem involvement

Prominent **sleep disturbance and fatigue** are closely linked to nociplastic and mixed pain phenotypes. These symptoms reflect the multisystem nature of chronic pain, involving reciprocal interactions between pain processing, sleep regulation, autonomic function, and energy balance. Reviews in internal medicine and pain science emphasize that these features are not secondary complaints but integral components of centrally mediated pain states [3], [4]. Their presence should prompt clinicians to broaden the diagnostic lens beyond localized pathology.

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6) Cognitive-affective distress: central and mixed phenotypes

Cognitive-affective distress, including anxiety, depressive symptoms, catastrophizing, and impaired concentration, shows strong associations with nociplastic and mixed phenotypes. Neurobiological studies demonstrate that chronic pain involves reorganization of brain networks governing salience, emotion, and executive control, providing a mechanistic basis for these findings [1], [8]. Importantly, this does not imply psychological causation of pain, but rather reflects the integration of affective and cognitive processes within central pain modulation systems [4], [19].

7) Clinical relevance for internal medicine

Overall, Figure 5 reinforces that effective chronic pain diagnosis in internal medicine depends on **pattern recognition rather than single indicators**. Nociceptive, neuropathic, nociplastic, and mixed phenotypes represent overlapping mechanistic domains rather than mutually exclusive categories. The matrix supports a structured approach to clinical reasoning that aligns symptom patterns with plausible mechanisms, facilitating more targeted management strategies and reducing diagnostic uncertainty [5], [7], [16], [17].

DISCUSSION

Chronic pain should be understood and approached in internal medicine as a **dynamic, multisystem condition** rather than as a unidimensional symptom directly proportional to tissue injury. The synthesis presented in this review demonstrates that persistent pain is sustained by interacting mechanisms of **peripheral sensitization, neuropathic remodeling, and central sensitization**, with descending modulation and cognitive–affective processes acting as critical amplifiers across phenotypes. These mechanisms rarely operate in isolation; instead, they coexist and evolve over time, giving rise to the mixed clinical presentations most commonly encountered in everyday practice [16], [17].

The results underscore the clinical value of **mechanism-based phenotyping**. Distinguishing nociceptive, neuropathic, nociplastic, and mixed pain presentations using observable clinical features—such as pain distribution, proportionality, widespread tenderness, sleep disturbance, fatigue, and cognitive-affective distress—enhances diagnostic reasoning and reduces reliance on purely structural explanations. This approach aligns with contemporary pain science and provides a practical framework for internal medicine clinicians managing complex, multimorbid patients [4], [5], [20].

Therapeutically, the evidence supports a shift away from uniform analgesic escalation toward **individualized, multimodal strategies** aligned with underlying mechanisms. Peripheral-dominant pain responds more consistently to anti-inflammatory interventions, whereas central-dominant pain requires approaches that target neuroplasticity and modulation, including neuropathic agents, structured exercise and rehabilitation, and pain education with cognitive-behavioral components [6], [7], [12], [15], [19]. Recognizing these distinctions is essential to improve outcomes, minimize ineffective treatments, and avoid the harms associated with inappropriate long-term opioid use [5], [17].

From an educational standpoint, framing chronic pain as a condition with **modifiable mechanisms** fosters patient-centered communication, reduces stigma, and improves engagement with care. For internal medicine training, integrating phenotype-based reasoning bridges advances in neuroscience with bedside decision-making, supporting coherent assessment and management across diverse healthcare contexts.

REFERENCES

[1] A. V. Apkarian, J. A. Hashmi, and M. N. Baliki, “Pain and the brain: Chronic pain plasticity,” *Pain*, vol. 152, no. 3 Suppl, pp. S49–S64, 2011, doi: 10.1016/j.pain.2010.11.010.

[2] R. Baron, A. Binder, and G. Wasner, “Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment,” *The Lancet Neurology*, vol. 9, no. 8, pp. 807–819, 2010, doi: 10.1016/S1474-4422(10)70143-5.

[3] D. L. Bennett et al., “The role of voltage-gated sodium channels in pain signaling,” *Physiological Reviews*, vol. 99, no. 2, pp. 1079–1151, 2019, doi: 10.1152/physrev.00052.2017.

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E-ISSN: 3122-3591, P-ISSN: 3122-3753
Review International Science Journal

[4] D. J. Clauw, "Fibromyalgia and related conditions," *Mayo Clinic Proceedings*, vol. 90, no. 5, pp. 680–692, 2015, doi: 10.1016/j.mayocp.2015.03.014.

[5] D. J. Clauw et al., "Considering the potential for nociplastic pain," *Pain*, vol. 161, no. 1, pp. 1–8, 2020, doi: 10.1097/j.pain.0000000000001656.

[6] M. Costigan, J. Scholz, and C. J. Woolf, "Neuropathic pain: A maladaptive response of the nervous system to damage," *Annual Review of Neuroscience*, vol. 32, pp. 1–32, 2009, doi: 10.1146/annurev.neuro.051508.135531.

[7] H. Flor and D. C. Turk, "Chronic pain: An integrated biobehavioral approach," *The Lancet*, vol. 377, no. 9784, pp. 2223–2234, 2011, doi: 10.1016/S0140-6736(11)60314-2.

[8] R. Gatchel, J. McGeary, M. McGeary, and D. Lippe, "Interdisciplinary chronic pain management," *American Psychologist*, vol. 69, no. 2, pp. 119–130, 2014, doi: 10.1037/a0035514.

[9] S. E. Harte, R. E. Harris, and D. J. Clauw, "The neurobiology of central sensitization," *Journal of Applied Biobehavioral Research*, vol. 23, no. 2, e12137, 2018, doi: 10.1111/jabr.12137.

[10] A. Latremoliere and C. J. Woolf, "Central sensitization: A generator of pain hypersensitivity," *Journal of Pain*, vol. 10, no. 9, pp. 895–926, 2009, doi: 10.1016/j.jpain.2009.06.012.

[11] J. Loeser and R.-D. Treede, "The Kyoto protocol of IASP pain terminology," *Pain*, vol. 137, no. 3, pp. 473–477, 2008, doi: 10.1016/j.pain.2008.04.025.

[12] G. L. Moseley and D. S. Butler, "Fifteen years of explaining pain," *Journal of Pain*, vol. 16, no. 9, pp. 807–813, 2015, doi: 10.1016/j.jpain.2015.05.005.

[13] G. L. Moseley, "Reconciling pain neuroscience with clinical practice," *Physical Therapy*, vol. 87, no. 4, pp. 452–461, 2007, doi: 10.2522/ptj.20060296.

[14] J. Nijs et al., "Treatment of central sensitization in patients with chronic pain," *Expert Opinion on Pharmacotherapy*, vol. 15, no. 12, pp. 1671–1683, 2014, doi: 10.1517/14656566.2014.915924.

[15] M. H. Ossipov, G. O. Dussor, and F. Porreca, "Central modulation of pain," *Journal of Clinical Investigation*, vol. 120, no. 11, pp. 3779–3787, 2010, doi: 10.1172/JCI43766.

[16] R.-D. Treede, W. Rief, A. Barke, Q. Aziz, M. I. Bennett, and R. Baron, "A classification of chronic pain for ICD-11," *Pain*, vol. 156, no. 6, pp. 1003–1007, 2015, doi: 10.1097/j.pain.0000000000000160.

[17] R.-D. Treede et al., "Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain," *Pain*, vol. 160, no. 1, pp. 19–27, 2019, doi: 10.1097/j.pain.0000000000001384.

[18] A. C. Vlaeyen and S. J. Linton, "Fear-avoidance and its consequences in chronic musculoskeletal pain," *Pain*, vol. 85, no. 3, pp. 317–332, 2000, doi: 10.1016/S0304-3959(99)00242-0.

[19] D. J. Williams and C. Eccleston, "Psychological therapies for the management of chronic pain," *Pain*, vol. 152, no. 8, pp. 1769–1777, 2011, doi: 10.1016/j.pain.2011.03.015.

[20] C. J. Woolf, "Central sensitization: Implications for the diagnosis and treatment of pain," *Pain*, vol. 152, no. 3 Suppl, pp. S2–S15, 2011, doi: 10.1016/j.pain.2010.09.030.

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