

Pathophysiology of Chronic Pain

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Abstract

Objectives: Chronic pain affects one in five people and persists because protective nociception is converted into maladaptive neural, immune and psychological states. This review aimed to consolidate mechanistic and clinical evidence to clarify that transformation and identify leverage points for durable relief.

Methods: Following the Scale for the Assessment of Narrative Review Articles (SANRA) guidance, we conducted a narrative review of articles published 1 January 2000–30 June 2025 across PubMed, Embase, Web of Science, Scopus, CINAHL, PsycINFO and the Cochrane Library, supplemented by grey literature. Eligible studies explored biological, immunological, genetic, epigenetic or psychosocial mechanisms or tested mechanism-targeted interventions. Data were thematically synthesised and appraised for methodological quality.

Results: Convergent findings reveal a multistage cascade: peripheral sensitisation driven by aberrant ion channels and inflammatory mediators; spinal and supraspinal sensitisation sustained by glial activation and loss of inhibition; large-scale cortical and limbic

reorganisation that embeds pain within memory and emotion circuits. Neuro-immune dialogue, microbiome dysbiosis, sex-specific responses and environment-induced epigenetic changes amplify these processes, while psychological stress and social adversity modulate their expression. Mapping these mechanisms to neuropathic, nociceptive and nociplastic syndromes highlights therapeutic windows exploited by emerging agents such as calcitonin-gene-related-peptide antibodies, chemogenetic nociceptor silencing, closed-loop neuromodulation, targeted cytokine blockade and microbiota modulation. Biomarker-informed precision approaches promise to replace empirical prescribing.

Discussion: Synthesising cross-disciplinary evidence positions chronic pain as a systems disease requiring integrated, mechanism-based and person-centred care. Defining the shared biological scaffold clarifies why traditional symptom-focused treatments fail and outlines research priorities for disease-modifying analgesics and equitable delivery models.

Key words: chronic pain; peripheral and central sensitisation; neuro-immune interaction; precision medicine; biopsychosocial model.

1. Introduction

Chronic pain, characterised by persistent pain beyond the expected period of tissue healing (typically three months), is a global health challenge that affects approximately 20% of the population and as many as 10% receive a new diagnosis of chronic pain each year [1-3].

Unlike acute pain, which serves a protective role, chronic pain often lacks a clear biological purpose and is associated with significant morbidity, reduced quality of life, and economic costs exceeding \$600 billion annually in the United States alone [4-5]. Yet these figures capture only a fraction of its wider social and psychological toll.

To accommodate the diverse aetiologies of persistent pain, the International Association for the Study of Pain (IASP) differentiates chronic primary pain, in which pain itself is the principal disorder, as in fibromyalgia or non-specific low-back pain, from chronic secondary pain, where it is a symptom of another condition such as neuropathy or osteoarthritis [1].

Furthermore, Kosek and colleagues proposed the term nociplastic pain, which the IASP formally adopted in 2017, to describe pain arising from altered nociception without clear evidence of tissue damage, exemplified by conditions such as fibromyalgia [6]. This evolving nosology highlights the need to move beyond simple structural explanations towards integrated models that encompass neural, immune and psychosocial dimensions.

Although these diagnostic labels are helpful, they can obscure the biological commonalities that link ostensibly disparate disorders. The pathophysiology of chronic pain is complex, involving intricate interactions between peripheral and central nervous systems, immune responses, psychological factors, and genetic predispositions [3, 7]. Such interactions are further influenced by sex-specific immune mechanisms, genetic polymorphisms, epigenetic

marks and even the composition of the gut microbiota. Appreciating this interplay is essential if we are to move from symptom-based management towards mechanism-informed, personalised care.

Peripheral sensitisation, driven by aberrant ion-channel function, primes nociceptors to respond excessively to stimuli, while central sensitisation amplifies and perpetuates pain signals within the spinal cord and brain. Immune-neuronal crosstalk, including pro-inflammatory cytokine release and microglial priming, further entrenches maladaptive circuitry. Psychological stressors and comorbidities such as anxiety or depression modulate neurotransmitter systems and hypothalamic-pituitary-adrenal axis function, shaping individual pain experiences. Genetic and epigenetic factors confer vulnerability or resilience, influencing receptor expression, synaptic plasticity and neuroimmune interactions. This review synthesises the vast literature on chronic pain mechanisms, drawing from neuroimaging, molecular biology, immunology and psychosocial studies to provide a holistic framework that may inform precision diagnostics and targeted therapeutics. Figure 1 summarises this framework, illustrating how peripheral and central sensitisation, neuro-immune interactions, descending modulation failure, and system-wide psychosocial modifiers interact to drive pain chronification and define stage-matched therapeutic leverage points.

2. Methodology

This narrative review was prepared in line with the SANRA guidance, aiming to integrate mechanistic and clinical insights into the pathophysiology of chronic pain.

2.1 Data Sources and Search Strategy

A comprehensive literature search was performed in PubMed/MEDLINE, Embase, Web of Science Core Collection, Scopus, CINAHL, PsycINFO, and the Cochrane Library for studies published between January 1, 2000, and June 30, 2025. Grey literature (bioRxiv, medRxiv, ProQuest Dissertations, conference abstracts) and the reference lists of key papers were also screened. No language restrictions were applied; non-English articles were translated where necessary.

The core PubMed strategy combined MeSH terms and free-text keywords as follows:

((("chronic pain"[MeSH Terms] OR "chronic pain"[tiab] OR "persistent pain"[tiab] OR "long-term pain"[tiab] OR "intractable pain"[tiab]) AND ("pathophysiology"[MeSH Terms] OR pathophysiology*[tiab] OR mechanis*[tiab] OR sensitisation[tiab] OR sensitization[tiab] OR "peripheral sensitisation"[tiab] OR "central sensitisation"[tiab] OR neuroinflamm*[tiab] OR microglia*[tiab] OR "glial activation"[tiab] OR neuroimmune[tiab] OR "ion channel"[tiab] OR TRPV1[tiab] OR Nav1.7[tiab] OR Nav1.8[tiab] OR ASIC*[tiab] OR CGRP[tiab] OR cytokine*[tiab] OR epigenet*[tiab] OR microRNA*[tiab] OR microbiome[tiab] OR dysbiosis[tiab] OR "nociplastic"[tiab] OR "neuropathic pain"[tiab] OR "nociceptive pain"[tiab] OR neuroplasticity[tiab])).

Equivalent controlled vocabulary (e.g., Emtree) and syntax were adapted for other databases.

Additional free-text terms captured specific mechanisms, mediators, and conditions, including: hyperalgesia, allodynia, wind-up, descending modulation, nociceptor, NMDA receptor, NGF, BDNF, TLR4, P2X7, IL-1 β , IL-6, TNF- α , cortical reorganisation, fMRI, PET, EEG, SCN9A, OPRM1, COMT, DNA methylation, histone acetylation, miR-124, gut-brain axis, sex differences, catastrophising, depression, socioeconomic, machine learning, artificial intelligence, CRISPR, gene therapy, spinal cord stimulation, and vagus nerve

stimulation. Search strings were expanded iteratively until no new unique records were retrieved; the full strategies are available on request.

2.2 Study Selection and Eligibility

Primary research and review articles (human, animal, or in-vitro) examining biological, immunological, genetic, epigenetic, or psychosocial mechanisms of chronic pain, as well as clinical trials of mechanism-targeted interventions, were eligible. Commentaries and narrative pieces lacking original data were excluded unless they introduced pivotal conceptual advances. Titles and abstracts were reviewed first, followed by full-text review.

2.3 Data Extraction and Synthesis

Given the integrative aim, key mechanistic insights, methodological strengths, and translational implications were extracted from each source and organised into thematic domains: peripheral sensitisation, central sensitisation, neuro-immune interactions, neuroplasticity, psychosocial modulation, genetics/epigenetics, gut-brain signalling, and emerging therapies. Conflicting evidence was highlighted and contextualised rather than statistically pooled.

2.4 Quality Appraisal

Methodological quality was assessed with AMSTAR-2 for systematic reviews, SYRCLE for animal studies, and a modified STROBE checklist for observational research. However, no study was excluded solely on quality grounds so as to preserve a comprehensive overview.

3. Neurobiological Mechanisms

Neurobiological mechanisms underpinning chronic pain encompass a spectrum of processes that begin with changes in peripheral nociceptors and extend centrally to the spinal cord and brain. Initially, tissue insult or inflammation provokes release of mediators such as prostaglandins, bradykinin and cytokines, which lower nociceptor thresholds and precipitate peripheral sensitisation. Sustained afferent input then drives alterations within the dorsal horn—particularly via NMDA receptor-mediated long-term potentiation, glial cell activation and loss of inhibitory neurotransmission—culminating in central sensitisation and exaggerated pain perception. Over time, maladaptive neuroplastic changes in supraspinal circuits, including cortical reorganisation and grey matter volume shifts, further entrench chronic pain states. These interlinked peripheral and central adaptations create a feed-forward loop that amplifies nociceptive signalling across multiple levels of the nervous system. Crucially, however, many of these changes are reversible in early phases, underscoring the clinical imperative for prompt, mechanism-based intervention [8].

3.1 Peripheral Sensitisation

Peripheral sensitisation is a cornerstone of chronic pain, characterised by heightened sensitivity of nociceptors, the sensory neurons that detect noxious stimuli [9-10]. Tissue injury or inflammation triggers the release of pro-inflammatory mediators, including prostaglandins, bradykinin, cytokines (e.g., IL-1 β , TNF- α), chemokines (e.g., CCL2), and nerve growth factor (NGF) [11]. These molecules lower the activation threshold of nociceptors, enhancing their responsiveness to both noxious and non-noxious stimuli, leading to hyperalgesia and allodynia [10]. For example, in rheumatoid arthritis, synovial inflammation sustains nociceptor activation, perpetuating pain [12]. Dysregulation of ion channels, such as transient receptor potential vanilloid 1 (TRPV1), voltage-gated sodium channels (NaV1.7, NaV1.8), and acid-sensing ion channels (ASICs), amplifies peripheral

sensitisation [10]. Pharmacological interventions, including capsaicin (TRPV1 agonist), lidocaine (sodium channel blocker), and NGF inhibitors (e.g., tanezumab), target these pathways to reduce peripheral pain signals [13].

Peripheral sensitisation is not limited to inflammatory conditions. In neuropathic pain, nerve injury induces ectopic activity in damaged axons, driven by upregulation of sodium channels and neuropeptides like substance P and calcitonin gene-related peptide (CGRP) [14]. CGRP inhibitors, such as erenumab, have shown efficacy in migraine, a chronic pain condition with peripheral components [15]. Additionally, mast cells and neutrophils contribute to peripheral sensitisation by releasing histamine and reactive oxygen species (ROS), further amplifying nociceptive signalling [16].

3.2 Central Sensitisation

Central sensitisation involves amplified responsiveness of CNS neurons, particularly in the spinal cord dorsal horn and supraspinal regions, resulting in heightened pain perception [17].

This process is driven by several mechanisms:

1. **NMDA Receptor Activation:** Persistent nociceptive input removes the magnesium block from NMDA receptors, facilitating calcium influx and long-term potentiation (LTP) [18]. LTP enhances synaptic efficacy, amplifying pain signals. Ketamine, an NMDA receptor antagonist, reduces central sensitisation in conditions like complex regional pain syndrome (CRPS) and fibromyalgia [19-21].
2. **Glial Activation:** Microglia and astrocytes release pro-inflammatory cytokines (e.g., IL-6, TNF- α), chemokines, and BDNF, perpetuating neuroinflammation and pain hypersensitivity [11, 22]. Minocycline, a microglial inhibitor, has shown analgesic effects in preclinical models, though clinical translation remains limited [23]. Recent

evidence shows that activated microglia can drive chronic pain by literally “eating” synapses [24]. Following nerve injury, spinal microglia engulf inhibitory synapses via the complement pathway, leading to excess excitation. Blocking the complement protein C1q prevented this microglia-mediated synapse loss and alleviated neuropathic pain in mice [24]. This reveals a novel mechanism—microglial synaptic pruning—that sustains pain, and identifies C1q as a potential therapeutic target in neuropathic pain.

3. **Loss of Inhibitory Control: Downregulation of GABA and glycine-mediated inhibition in the spinal cord enhances excitatory transmission, contributing to pain amplification [25].** GABAergic interneuron dysfunction is a key feature of neuropathic pain [25-27].
4. **Wind-Up Phenomenon: Repeated stimulation of C-fibres leads to temporal summation of synaptic responses, known as wind-up, which enhances pain perception [28].** This phenomenon is particularly relevant in chronic visceral pain syndromes, such as irritable bowel syndrome (IBS) [29-30].

Central sensitisation is a hallmark of fibromyalgia, CRPS, and chronic migraine, where pain persists despite minimal peripheral input (Woolf, 2011; Phillips & Clauw 2011). Functional neuroimaging reveals enhanced activation in the somatosensory cortex, insula, and anterior cingulate cortex (ACC) in patients with centrally sensitised pain (Peyron et al., 2000). Liu et al. (2024) used fMRI to compare fibromyalgia (a prototypical nociplastic pain syndrome) with ankylosing spondylitis (inflammatory pain; AS). Fibromyalgia patients showed significantly reduced functional connectivity between the default mode network and the caudate nucleus, and increased grey matter volume in the cerebellum, compared to AS patients (Liu et al., 2024). These neural alterations suggest fibromyalgia involves disrupted reward/motivational circuits and cerebellar modulation of pain. Electroencephalography

(EEG) studies further demonstrate altered thalamocortical rhythms, reflecting disrupted pain processing (Stern et al., 2006).

3.3 Neuroplasticity

Chronic pain induces maladaptive neuroplastic changes in the CNS, altering the structure and function of pain-processing circuits (Kuner & Flor, 2016). These changes include:

1. **Cortical Reorganisation:** Functional MRI evidence demonstrates altered connectivity within the default-mode, salience, and sensorimotor networks in chronic pain (Baliki et al., 2008). In phantom limb pain, reorganisation of the somatosensory cortex results in aberrant pain perception (Flor et al., 2006). Similarly, in chronic low back pain, enhanced connectivity between the medial prefrontal cortex and nucleus accumbens predicts pain chronification (Baliki et al., 2012).
2. **Grey Matter Changes:** Voxel-based morphometry reveals reduced grey matter volume in the dorsolateral prefrontal cortex and right thalamus, correlating with pain duration (Apkarian et al., 2004; Apkarian et al., 2005). These changes may reflect neuronal loss, synaptic pruning, or gliosis (Apkarian et al., 2004; Ji et al., 2013). Longitudinal studies suggest that pain relief, through surgery or therapy, can partially reverse grey matter loss (Seminowicz et al., 2011).
3. **White Matter Alterations:** Diffusion tensor imaging (DTI) studies demonstrate reduced fractional anisotropy in white matter tracts, such as the corpus callosum and corticospinal tract, in chronic pain patients, indicating disrupted neural connectivity (Lutz et al., 2008; Kim et al., 2014; Martucci et al., 2018; Tu et al., 2022).
4. **Descending Pain Modulation:** Dysfunction in descending inhibitory pathways, mediated by serotonin, norepinephrine, and endogenous opioids, exacerbates pain perception (Ossipov et al., 2010). The periaqueductal grey (PAG) and rostral

ventromedial medulla (RVM) are critical regions, and their dysregulation is implicated in fibromyalgia and chronic pelvic pain (Ossipov et al., 2010; Jensen et al., 2012). Conversely, descending facilitatory pathways, mediated by "on-cells" in the RVM, can amplify pain in chronic states (Porreca et al., 2002).

Neuroplastic changes contribute to the transition from acute to chronic pain, emphasising the need for early intervention to prevent maladaptive remodelling (Kuner & Flor, 2016). Non-invasive brain stimulation, such as transcranial magnetic stimulation (TMS), targets these changes by modulating cortical excitability (Lefaucheur et al., 2014).

4. Immunological Contributions

The immune system is a critical mediator of chronic pain, with neuro-immune interactions driving both initiation and maintenance [11]. Resident microglia and astrocytes in the central nervous system become activated in response to persistent nociceptive signalling, releasing pro-inflammatory cytokines such as interleukin-1 β , tumour necrosis factor- α and chemokines that enhance neuronal excitability and promote synaptic remodelling. Concurrently, recruitment of peripheral immune cells, including macrophages, mast cells and T lymphocytes, to sites of nerve injury or inflammation amplifies local mediator release, sustaining peripheral sensitisation and facilitating glial-neuron crosstalk. This bidirectional communication creates a self-perpetuating cycle of inflammation and hypersensitivity. Immune-derived factors lower nociceptor activation thresholds and drive central sensitization by disrupting inhibitory circuits and inducing long-term potentiation in dorsal horn neurons. Such immunological mechanisms thus play a pivotal role in the chronification of pain by integrating peripheral insults with central neuroplastic changes [11, 50-52].

4.1 Innate Immunity

Innate immune cells, including macrophages, mast cells, and neutrophils, respond to tissue injury or infection by releasing pro-inflammatory mediators [11]. These include cytokines (IL-1 β , IL-6, TNF- α), chemokines (CCL2, CXCL1), ROS, and proteases, which sensitise nociceptors and recruit additional immune cells [11]. In neuropathic pain, nerve injury triggers macrophage infiltration into the dorsal root ganglia and peripheral nerves, promoting allodynia and hyperalgesia [50]. Toll-like receptors (TLRs), particularly TLR2 and TLR4, on immune cells and neurons recognise damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), amplifying pain signalling [53-54]. For example, TLR4 activation in spinal microglia contributes to chemotherapy-induced peripheral neuropathy [55]. Danger signals like HMGB1 and ATP act via TLR4/P2X7 to activate microglia [56]. Innate immune responses are also critical in osteoarthritis, where synovial macrophages release IL-1 β and TNF- α , driving cartilage degradation and nociceptor activation [57].

4.2 Adaptive Immunity

Adaptive immune cells, particularly T-lymphocytes and B-lymphocytes, play a role in chronic pain, especially in autoimmune and neuropathic conditions [58]. Peripheral immune cells can maintain central glial activation after nerve injury, exacerbating neuropathic pain by releasing pro-inflammatory cytokines and activating microglia [58]. Similarly, in CRPS, autoantibodies targeting β 2-adrenergic receptors, muscarinic acetylcholine receptors, and voltage-gated potassium channels have been identified, suggesting an autoimmune aetiology [59-60]. Experimental work has implicated T-cells and macrophages in neuropathic pain [51]. Regulatory T-cells (Tregs), which suppress inflammation, are reduced in some chronic pain states, potentially exacerbating neuroinflammation [61-64]. Notably, neuro-immune mechanisms can differ by sex. In rodent models of neuropathic pain, blocking microglial

function reduced pain in males but not females, whereas T-cell depletion affected pain in females but not males [65]. This sexual dimorphism underscores the importance of considering sex as a biological variable in pain research.

4.3 Neuroinflammation

Chronic neuroinflammation, driven by activated glial cells, is a key driver of pain persistence [11]. Microglia release BDNF, which enhances excitatory synaptic transmission in the spinal cord, while astrocytes contribute to central sensitisation by releasing glutamate, ATP, and pro-inflammatory mediators [11]. The p38 mitogen-activated protein kinase (MAPK) pathway in microglia is a critical regulator of neuroinflammation, and its inhibition reduces pain in preclinical models [66]. Astrocyte dysfunction, characterised by reduced glutamate uptake, exacerbates excitotoxicity in the spinal cord [67]. The blood-brain barrier (BBB) and blood-spinal cord barrier become permeable in chronic pain states, allowing peripheral immune cells and cytokines to infiltrate the CNS, further amplifying neuroinflammation [68-69]. Pharmacological agents targeting glial activation, such as ibudilast and low-dose naltrexone, have shown promise in preclinical and early clinical studies [23, 70].

Importantly, in human chronic pain conditions, neuroinflammation has been demonstrated directly: PET imaging using glial markers shows elevated microglial activation in patients with chronic low back pain and fibromyalgia [71-72]. Lassen et al. [73] measured cytokines in patients with chronic painful polyneuropathy. Unexpectedly, both pro- and anti-inflammatory cytokine levels in CSF were lower in chronic pain patients than in pain-free controls (e.g. CSF TNF- α 14.1 vs 23.9 pg/mL) with no significant differences in serum [73]. The authors suggest that active neuroinflammation may diminish in the maintenance phase of chronic pain, or that chronic pain patients undergo compensatory downregulation of immune mediators [73].

4.4 Gut-Immune-Pain Axis

Recent research highlights the role of the gut microbiome in modulating chronic pain through immune mechanisms [74-76]. Dysbiosis, characterised by altered gut microbial composition, is associated with increased systemic inflammation and pain hypersensitivity in conditions like IBS and fibromyalgia [74, 77-79]. Gut-derived metabolites, such as short-chain fatty acids (SCFAs), influence microglial activation and cytokine production, potentially exacerbating central sensitisation [80-81]. Notably, microbial alterations in fibromyalgia have been linked to changes in SCFA levels and pain severity [77]. Cai et al. [82] showed that transplanting stool from fibromyalgia patients into germ-free or antibiotic-depleted mice induced pain-like hypersensitivity, suggesting dysbiosis can drive pain [82]. Preliminary clinical studies also suggest probiotics or faecal microbiota transplants might alleviate pain in conditions like IBS, although more research is required [74].

5. Psychological and Social Factors

Chronic pain is a biopsychosocial phenomenon, with psychological and social factors significantly influencing its perception, maintenance, and treatment outcomes [7]. Cognitive appraisals of pain, such as beliefs about its controllability and perceived threat, shape emotional responses and coping strategies, often determining the trajectory of pain chronification. Emotional disturbances, including anxiety, depression and sleep disruption, can exacerbate pain experiences by lowering pain thresholds and impairing endogenous pain-inhibitory pathways. Social contexts, such as support from family and peers, work environment and cultural attitudes towards pain, further modulate individuals' pain behaviours and treatment engagement. Socioeconomic stressors, including financial hardship and occupational demands, may perpetuate a cycle of distress and disability, while positive

social interactions and effective communication with healthcare providers often predict better functional outcomes.

Recent evidence underscores the lasting impact of adverse childhood experiences (ACEs) on pain. A 2023 systematic review found individuals with a history of childhood abuse have about 50% higher odds of developing chronic pain in adulthood [83]. Likewise, a longitudinal study reported the lifetime prevalence of chronic pain is roughly doubled in those exposed to childhood maltreatment compared to non-abused peers [84]. These data suggest that early psychosocial trauma can prime neurobiological pathways (e.g. HPA axis, central sensitisation) that heighten pain susceptibility decades later. By integrating cognitive, affective and social dimensions, this biopsychosocial framework underscores the necessity of multidisciplinary interventions tailored to address both mind and environment [7, 85].

5.1 Pain Catastrophising

Pain catastrophising, i.e. a tendency to magnify the threat of pain and feel helpless about it-is strongly associated with greater pain severity, higher disability, and poorer treatment outcomes [86]. Neuroimaging studies reveal increased activity in the ACC, insula, and prefrontal cortex in individuals with high catastrophising scores, reflecting amplified emotional and cognitive processing of pain [87]. Catastrophising is associated with altered connectivity in the DMN and salience network, suggesting a neural basis for its impact on pain perception [88-90]. Cognitive-behavioural therapy (CBT) targeting catastrophising reduces pain intensity and improves coping in fibromyalgia and chronic low back pain [86, 91].

5.2 Stress and Mood Disorders

Chronic stress and mood disorders, such as depression and anxiety, exacerbate chronic pain through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and monoamine signalling [92]. Elevated cortisol levels correlate with reduced pain thresholds, while serotonin and norepinephrine dysregulation impairs descending pain inhibition [92]. There appears to be a bidirectional relationship between chronic pain and depression [93]. This bidirectional relationship is mediated by shared neural circuits in the prefrontal cortex, ACC, and amygdala [94]. For example, in fibromyalgia, reduced serotonin levels contribute to both pain and mood disturbances [95]. Antidepressants like duloxetine and milnacipran, which enhance serotonin and norepinephrine signalling, are effective in managing pain and depression [96-97]. Mindfulness-based stress reduction (MBSR) and acceptance and commitment therapy (ACT) also reduce stress and pain, possibly by modulating HPA axis activity [98-99].

5.3 Social Determinants

Social factors, including socioeconomic status, social support, and cultural beliefs, shape pain experiences [85, 100]. Individuals with low socioeconomic status or limited access to healthcare report higher pain intensity and disability due to barriers in treatment access and increased stress [85]. Social isolation exacerbates pain, likely through reduced oxytocin release and increased HPA axis activation, while strong social support buffers pain perception, likely by enhancing endogenous opioid release [101-104]. Cultural attitudes toward pain expression influence coping strategies, with some cultures discouraging overt pain behaviours, potentially leading to underreporting of pain [85]. Racial and ethnic disparities in pain management, such as lower prescription rates for analgesics among minorities, further exacerbate pain outcomes [100, 105-106]. New research suggests that chronic stress and discrimination can become biologically embedded to worsen pain via

epigenetic changes. For example, recent work highlights that in minority patients, lifetime exposure to stressors (racism, poverty, etc.) may induce persistent pro-inflammatory epigenetic modifications in genes regulating stress responses and neuroinflammation [107]. Such findings imply that social adversity can imprint molecular changes that heighten pain sensitivity, offering a potential explanation for racial/ethnic pain disparities and pointing to epigenetics as a future target to reduce those disparities. Community-based interventions and culturally sensitive care can help address these disparities [85, 91].

5.4 Sleep Disturbances

Sleep disturbances are prevalent in chronic pain, with 50-80% of patients reporting poor sleep quality [108-109]. Pain disrupts sleep architecture, reducing slow-wave sleep and increasing nighttime awakenings, while poor sleep reciprocally exacerbates pain sensitivity through altered cytokine production and HPA axis dysregulation [108]. For example, in fibromyalgia, fragmented sleep correlates with increased pain and fatigue [95]. Cognitive-behavioural therapy for insomnia (CBT-I) and sleep hygiene interventions improve pain outcomes by restoring sleep quality [110].

6. Genetic and Epigenetic Factors

Variations in genes encoding ion channels, neurotransmitter receptors and cytokines confer differential vulnerability to chronic pain, influencing nociceptive processing at both peripheral and central levels. Genome-wide association studies have identified polymorphisms in SCN9A, COMT and OPRM1 that correlate with altered pain thresholds and analgesic responses, underscoring the heritable component of pain sensitivity. The advent of next-generation sequencing (NGS) has also reshaped pain research by uncovering comprehensive patterns of genetic variation within the genome [111]. Beyond static genetic

differences, dynamic epigenetic modifications, such as DNA methylation, histone acetylation and non-coding RNA expression, mediate lasting changes in gene transcription following injury or stress. For instance, hypermethylation of the μ -opioid receptor promoter region reduces receptor availability [112], while microRNA-124 downregulation in the dorsal horn enhances glial activation and cytokine release [113].

Aroke et al. [114] conducted a genome-wide DNA methylation study in chronic low back pain patients stratified by pain stigma. They identified 3,665 CpG sites with differential methylation, including 527 loci with $\geq 10\%$ methylation differences between patients with high vs. low internalized pain stigma [114]. Notably, genes encoding the somatostatin receptor (SSTR5), FOXP2, and the IL-22 receptor (IL22RA1) - all previously implicated in pain or mood regulation - showed altered methylation in the high-stigma group [114]. These findings illustrate how psychosocial stressors become biologically embedded via epigenetic modifications, translating environmental and inflammatory cues into persistent neuronal and glial alterations and offering promising targets for novel analgesic therapies.

6.1 Genetic Predispositions

Genetic polymorphisms in genes encoding ion channels, neurotransmitter receptors, and inflammatory mediators are associated with chronic pain susceptibility [115]. Key examples include:

1. **SCN9A Gene:** Mutations in the SCN9A gene, encoding the NaV1.7 sodium channel, are linked to congenital insensitivity to pain, erythromelalgia, and small-fibre neuropathy [116]. NaV1.7 inhibitors are under investigation for neuropathic pain [117].

2. **COMT Gene:** Variants in the catechol-O-methyltransferase (COMT) gene, which regulates dopamine and norepinephrine metabolism, influence pain sensitivity and opioid response [115]. The Val158Met polymorphism is associated with fibromyalgia and temporomandibular disorder (TMD) [118].
3. **Cytokine Genes:** Polymorphisms in IL-6, IL-10, and TNF- α genes are associated with altered inflammation and pain in fibromyalgia, osteoarthritis, and neuropathic pain [119].
4. **OPRM1 Gene:** Variants in the mu-opioid receptor gene (OPRM1) influence opioid sensitivity and chronic pain susceptibility [120].

Genome-wide association studies (GWAS) have identified additional pain-related loci. For example, a large GWAS of ~380,000 individuals in the UK identified over 30 risk loci for multisite chronic pain, implicating genes involved in synaptic plasticity and immune regulation [121]. Another large multi-ancestry genome-wide association meta-analysis (553,000+ individuals) recently uncovered 67 new genetic loci associated with chronic back pain [122]. Notably, one of the top new variants lies in the brain-expressed FOXP2 gene, and several genes at these loci (e.g. DRD2, HTT) encode targets of existing CNS drugs [122]. These findings more than doubled the known genetic risk factors for back pain and point to previously unrecognized dopamine and serotonin pathways as contributors to chronic pain susceptibility. However, the clinical utility of findings like these is still limited by complex gene-environment interactions and relatively small effect sizes of individual variants.

6.2 Epigenetic Modifications

Epigenetic mechanisms, including DNA methylation, histone acetylation, and microRNA expression, modulate gene expression in chronic pain [123]. Doehring et al. [124] found increased OPRM1 promoter methylation and reduced μ -opioid-receptor mRNA with chronic

opioid use, suggesting a potential epigenetic contribution to tolerance. Histone deacetylase inhibitors, such as valproic acid, can restore pain-related gene expression and reduce pain in preclinical models [123, 125]. MicroRNAs, such as miR-124, miR-155, and miR-146a, regulate neuroinflammation and pain signalling by targeting cytokine and ion channel genes [126-127]. Environmental factors, including stress, diet, and early-life adversity, induce epigenetic changes that increase pain susceptibility [123]. For example, childhood trauma is associated with hypermethylation of pain-related genes, contributing to fibromyalgia and IBS [128-129].

6.3 Gene-Environment Interactions

Gene-environment interactions play a critical role in chronic pain susceptibility. For example, individuals with high-risk COMT polymorphisms who are exposed to significant stress exhibit increased pain sensitivity [118]. Similarly, early-life stress induces epigenetic changes in the glucocorticoid receptor gene, increasing HPA axis reactivity and pain vulnerability [130]. These findings underscore the importance of personalised medicine approaches that account for both genetic and environmental factors, especially since genome-wide studies show only small effects unless environment is accounted for [131].

7. Specific Chronic Pain Syndromes

Chronic pain encompasses diverse syndromes distinguished by their underlying mechanisms, clinical features and therapeutic needs. Recognising these syndromes allows clinicians to tailor assessment and management strategies, improving diagnostic accuracy and patient outcomes. Neuropathic pain, arising from lesions or diseases of the somatosensory system, manifests as burning, shooting or electric-shock sensations and affects conditions such as diabetic neuropathy and post-herpetic neuralgia. Nociceptive syndromes, driven by ongoing

tissue injury or inflammation, include osteoarthritis and rheumatoid arthritis, characterised by aching or throbbing discomfort. Nociceptive pain presents without clear tissue damage or nerve lesion, typified by disorders such as fibromyalgia and irritable bowel syndrome, and involves altered central processing. Below, we examine key chronic pain syndromes—neuropathic, nociceptive, and nociplastic—highlighting how their pathophysiological profiles inform targeted interventions.

7.1 Neuropathic Pain

Neuropathic pain, resulting from nerve injury or dysfunction, is characterised by burning, shooting pain, and sensory abnormalities [14]. Peripheral nerve injury triggers ectopic activity in damaged axons, driven by upregulation of sodium channels (NaV1.7, NaV1.8) and neuropeptides (substance P, CGRP) [14]. Central sensitisation, glial activation, and loss of inhibitory control in the spinal cord sustain pain [11]. Conditions like diabetic neuropathy, postherpetic neuralgia, and chemotherapy-induced peripheral neuropathy exemplify neuropathic pain, with treatments targeting ion channels (e.g., gabapentin, pregabalin), neurotransmitters (e.g., duloxetine), and sodium channels (e.g., lacosamide) [132]. Emerging therapies, such as high-concentration (8%) capsaicin patches and botulinum toxin A injections, target peripheral mechanisms to provide relief [14, 133].

7.2 Fibromyalgia

Fibromyalgia is a primary chronic pain condition characterised by widespread pain, fatigue, cognitive dysfunction, and sleep disturbances [95]. It exemplifies a nociplastic pain syndrome, arising from central sensitisation and dysregulated nociceptive processing without clear peripheral pathology [6]. Central sensitisation, altered descending pain modulation, and neuroendocrine dysregulation are key mechanisms in fibromyalgia [95]. Functional MRI

studies reveal hyperactivation of pain-processing regions (somatosensory cortex, insula) and reduced connectivity in inhibitory networks (PAG, RVM) [47, 134]. Genetic polymorphisms in COMT and serotonin transporter genes contribute to fibromyalgia susceptibility [135]. Interestingly, emerging evidence suggests an immunological component: autoantibodies from fibromyalgia patients can induce fibromyalgia-like pain and allodynia in mice, indicating a potential autoimmune contribution to this syndrome [136]. Treatment involves a multimodal approach, including pharmacotherapy (e.g., pregabalin, duloxetine, milnacipran), exercise and physical therapy, and psychological interventions such as CBT and MBSR [95, 137].

7.3 Osteoarthritis

Osteoarthritis (OA) is a secondary chronic pain condition driven by joint degeneration, inflammation, and biomechanical stress [138]. Peripheral sensitisation in subchondral bone, synovium, and periarticular tissues, coupled with central sensitisation, contributes to OA pain [138]. Cytokines (IL-1 β , TNF- α) and matrix metalloproteinases (MMPs) drive cartilage degradation and nociceptor activation [57]. NGF inhibitors (e.g., tanezumab) and intra-articular corticosteroids target peripheral pain mechanisms, while duloxetine addresses central sensitisation [139-140]. However, while anti-NGF therapy provides significant pain relief, clinical trials have noted adverse joint effects (e.g., accelerated cartilage loss) in a subset of patients, raising safety concerns [141]. Joint replacement is effective for end-stage OA, though central sensitisation may persist post-surgery in some patients, contributing to residual pain [142].

7.4 Chronic Low Back Pain

Chronic low back pain (CLBP) is a heterogeneous condition with nociceptive, neuropathic, and psychosocial components [143]. Degenerative disc disease, facet joint arthritis, and

myofascial pain contribute to peripheral nociceptive input, while central sensitisation and catastrophising amplify symptoms [143]. Neuroimaging reveals altered connectivity in the DMN and salience network, reflecting maladaptive neuroplasticity associated with chronic back pain [41, 144]. Multidisciplinary interventions, including physical therapy, exercise, CBT, and mindfulness-based therapies, are effective in managing CLBP [145]. Interventional approaches such as epidural steroid injections and radiofrequency ablation can target specific pain generators, though their long-term efficacy is debated [146].

7.5 Chronic Visceral Pain

Chronic visceral pain, seen in conditions like IBS, interstitial cystitis, and endometriosis, is characterised by diffuse, poorly localised pain and visceral hyperalgesia [147]. Central sensitisation, altered gut-brain axis signalling, and neuroinflammation drive pain persistence in these syndromes [30]. The vagus nerve and the hypothalamic-pituitary-gut axis modulate visceral pain, with stress often exacerbating symptoms [148-149]. Treatments include antidepressants (e.g., low-dose amitriptyline), gut-targeted therapies (e.g., linaclotide for IBS), and neuromodulation techniques (e.g., sacral nerve stimulation for pelvic pain) [148].

7.6 Chronic Migraine

Chronic migraine, defined as headaches occurring ≥ 15 days per month, involves both peripheral and central mechanisms [150]. Trigeminal nerve activation and CGRP release drive meningeal nociceptor sensitisation, while cortical spreading depression and central sensitisation in pain pathways sustain chronic headache [150]. Neuroimaging reveals altered connectivity in the trigemino-thalamic pathway and insula in chronic migraine sufferers [151]. Treatments include CGRP pathway inhibitors (e.g., monoclonal antibodies such as

erenumab), triptans, onabotulinumtoxinA, and neuromodulation approaches (e.g., transcutaneous supraorbital nerve stimulation) [150].

8. Clinical Implications

Understanding the pathophysiology of chronic pain informs diagnostic and therapeutic strategies. Multidisciplinary approaches targeting both peripheral and central mechanisms are essential for effective management [7]. Comprehensive clinical assessments in the future could therefore integrate objective measures, such as quantitative sensory testing and functional neuroimaging, with patient-reported outcomes addressing mood, sleep and social functioning [152-153]. Biomarker-guided stratification, including genetic profiling for ion channel variants and inflammatory markers, can refine treatment selection and anticipate response patterns. Gopal et al. [154] used machine learning to analyse intraoperative EEG data from chronic pain patients undergoing spinal cord stimulation (SCS), achieving 88% accuracy in predicting treatment responders. Their model incorporated EEG features such as alpha-theta patterns during stimulation alongside patient data, indicating that combining objective biomarkers with AI could improve patient selection for interventions like SCS [154]. Collaborative care models that unite physicians, psychologists, physiotherapists and pain specialists facilitate coordinated intervention plans, ensuring that pharmacological, interventional and psychosocial therapies are delivered in concert [7]. By aligning diagnostic precision with mechanism-based therapies and addressing psychosocial determinants, clinicians can personalise care pathways, enhance analgesic efficacy and mitigate the risk of treatment-related adverse effects.

8.1 Pharmacological Interventions

Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen (paracetamol), anticonvulsants (e.g., gabapentin, pregabalin), and antidepressants (e.g., duloxetine, amitriptyline) target various pain pathways and are commonly used for chronic nociceptive and neuropathic pain relief [132, 155]. Opioid analgesics can provide short-term relief but are limited by issues of tolerance, dependence, and the risk of misuse, prompting exploration of non-opioid alternatives [132]. Long-term observational data indicate that 8-12% of opioid-naïve adults prescribed opioids for chronic non-cancer pain develop opioid-use disorder within five years [156], and an annualised fatal overdose risk of approximately 0.25% corresponds to a cumulative five-year risk of about 1.25% [157], whereas meta-analysis of randomised trials in chronic non-cancer pain reports a number needed to treat of around 9 for at least 50% pain relief at three months [158], yielding an approximate benefit-to-harm ratio of 10:1 when serious adverse events are considered. In certain neuropathic pain conditions, topical agents (e.g., lidocaine or capsaicin patches) and emerging treatments like medical cannabinoids are also considered as adjuncts [132, 159].

8.2 Non-Pharmacological Therapies

Psychological interventions such as CBT, MBSR, and ACT, as well as physical therapies including exercise and physiotherapy, address the psychosocial and functional aspects of pain [160]. A Cochrane overview reported that physical activity reduces pain severity and improves physical function across pain conditions, with graded exercise programs enhancing mobility and reducing deconditioning in conditions like OA, fibromyalgia, and CLBP [161]. Mechanistically, active rehabilitation can plausibly downshift peripheral and neuroimmune drivers (e.g., systemic inflammatory tone and ongoing nociceptive input from deconditioned tissues), while also engaging central pain-modulatory circuitry and adaptive neuroplasticity. Repeated bouts of muscle contraction trigger the release of myokines and related

immunometabolic mediators that transiently shift cytokine activity towards resolution (for example, increases in IL-4, IL-1Ra, IL-5, and IL-10 accompanied by reduced pro-inflammatory signalling such as TNF- α), and with ongoing training, this pattern is associated with lower levels of chronic low-grade inflammatory markers [162-165]. Integrative approaches like yoga and Tai Chi can also benefit pain and mood [166-168]. Several rehabilitation approaches also explicitly target maladaptive sensorimotor representations and related neuroplastic mechanisms implicated in chronic pain; for example, mirror therapy, graded motor imagery, and tactile training may help recalibrate disrupted cortical body maps [169].

8.3 Neuromodulation

Transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), dorsal root ganglion (DRG) stimulation, and repetitive TMS modulate pain signalling pathways [170-172]. Non-invasive vagus nerve stimulation is being explored for headache and fibromyalgia, with preliminary evidence of efficacy [173]. SCS is effective for conditions such as failed back surgery syndrome and CRPS, while DRG stimulation targets focal neuropathic pain with improved precision [171]. In the double-blind EVOKE trial, closed-loop spinal-cord stimulation that maintains a constant evoked compound action potential produced significantly greater and more durable relief of back and leg pain than open-loop systems over 12 months [174]. While traditional SCS devices deliver fixed outputs, new closed-loop systems automatically adjust stimulation in real-time based on evoked compound action potentials. Recent RCTs showed that closed-loop SCS provides superior pain relief and functional outcomes compared to conventional SCS, with patients reporting more sustained pain reduction, improved quality of life, and less opioid use overall [175]. These

findings represent a leap forward in neuromodulation, offering adaptive, personalized pain control.

8.4 Interventional Therapies

Procedures like epidural steroid injections, facet joint blocks, and radiofrequency ablation are used to address specific nociceptive pain generators in chronic spinal pain [145]. Intra-articular injections (corticosteroids, hyaluronic acid) are commonly used for osteoarthritis pain [139]. While these interventions can provide temporary relief, their long-term benefits vary among patients [145].

8.5 Emerging Therapies

Novel biologics targeting inflammatory mediators (e.g., anti-TNF- α or anti-IL-6 antibodies) and gene therapies (e.g., antisense oligonucleotides, RNA interference) are under investigation for chronic pain conditions with immune components [176-178]. NGF-neutralising antibodies (like tanezumab) showed significant analgesic effects in osteoarthritis trials, although safety issues (joint degeneration) have complicated their development [139, 141]. Gene therapy approaches, such as viral vector delivery of enkephalin or silencing of NaV1.7 channels, have demonstrated pain relief in preclinical models and early clinical studies [178]. One example is a 2023 chemogenetic strategy using a modified receptor (PSAM4-GlyR) activated by varenicline to silence hyperactive nociceptors. Delivered to pain-sensing neurons, this approach reduced hypersensitivity in mouse models of arthritis and nerve injury and also inhibited hyperactive neurons derived from a chronic pain patient, underscoring its translational potential [179]. Likewise, microRNA-based therapies and genome editing (CRISPR-Cas9) are being explored in laboratory settings to modulate pain

pathways [127, 178]. While these emerging treatments hold promise for personalised pain management, further research is needed to establish their safety and efficacy.

9. Future Directions

Advancing our understanding of chronic pain requires multidisciplinary efforts that integrate molecular, systems-level and psychosocial research to develop more precise diagnostic tools and targeted therapies. Future studies should employ longitudinal cohort designs and innovative imaging techniques to trace the temporal evolution of pain-related neuroplastic changes, while leveraging single-cell sequencing and multi-omics approaches to unravel cell-type-specific mechanisms. Incorporating ecological momentary assessment and digital phenotyping will refine characterisation of pain trajectories in real-world settings, facilitating personalised intervention strategies. Moreover, clinical trials must adopt adaptive designs and stratify participants based on mechanistic biomarkers, including genetic, epigenetic and immunological profiles, to enhance treatment efficacy and reduce heterogeneity in outcomes. Finally, fostering collaborations between basic scientists, clinicians and patient communities will ensure that research priorities address the most pressing needs and translate swiftly into improved care pathways. Future research should prioritise:

1. **Biomarker Development:** Identifying reliable biomarkers for central sensitisation (e.g., CSF cytokine profiles, EEG or sensory testing signatures) and neuroinflammation (e.g., PET imaging of glial activation) to improve diagnosis and monitor treatment response [71, 180]. For instance, elevated pro-inflammatory cytokines in CSF or specific patterns of brain activity could potentially serve as objective markers of chronic pain states.
2. **Precision Medicine:** Leveraging genetic, epigenetic, and microbiome data to tailor therapies to individual patients [74, 115]. This includes identifying subgroups of

patients who may respond to certain medications (e.g., based on genotype or gut microbiome composition) and developing personalised pain management plans. Fillingim et al. [181] analysed subjects from UK Biobank using machine learning on genomics, blood assays, brain MRI, and questionnaires to predict chronic pain conditions, and found that conditions with prominent central sensitisation (e.g. fibromyalgia, chronic fatigue syndrome) were best predicted by brain functional connectivity patterns, whereas others (e.g. ankylosing spondylitis) were better predicted by genetic or inflammatory markers [181]. About half of chronic pain-related diagnoses could be classified with good accuracy (AUC >0.70) using integrated biological data [181]. Similarly, Tagliaferri et al. [182] applied fuzzy c-means clustering plus four classifiers to UK Biobank data and uncovered five reproducible psychosocial-neurobiological subtypes of chronic back pain, achieving $\geq 95\%$ internal classification accuracy. These studies highlight how AI-driven analysis of multi-omics and neuroimaging data can identify pain subtypes, moving towards the review's vision of mechanism-based, personalised pain medicine.

3. **Neuro-Immune Therapies:** Developing drugs and interventions targeting neuro-immune interactions, such as inhibitors of glial activation (e.g., ibudilast, propentofylline) or cytokine blockers (e.g., IL-1 or IL-6 antagonists), and exploring microbiome modulation (e.g., probiotics, dietary interventions) as pain treatments [68, 74]. The discovery of pain-promoting autoantibodies in conditions like fibromyalgia and CRPS also opens the door to immune therapies [136].
4. **Psychosocial Interventions:** Integrating social determinants into pain management programs to address disparities and improve access to care [85]. This includes community-based pain management resources, telehealth interventions for

underserved populations, and culturally tailored education to ensure all patient groups benefit from advances in pain treatment.

5. **Translational Research:** Bridging the gap between preclinical and clinical studies to validate novel targets such as specific microRNAs, epigenetic modifiers, and non-invasive brain or nerve stimulation techniques [123, 173, 183]. Collaborative research networks and longitudinal studies in patients will be key to translating laboratory findings into effective therapies.
6. **Artificial Intelligence (AI):** Utilising AI and machine learning to predict pain chronification, optimise treatment algorithms, and uncover novel pain phenotypes or subtypes [184-185]. Advanced algorithms can analyse large datasets, from genomics to electronic health records, to identify patterns that clinicians cannot easily discern, potentially leading to earlier interventions for those at risk of chronic pain and more efficient use of therapies.

10. Conclusion

Chronic pain is a multifaceted condition driven by peripheral and central sensitisation, maladaptive neuroplasticity, immune dysregulation, psychological factors, and genetic predispositions. Its pathophysiology involves complex interactions between biological, psychological, and social domains, necessitating a biopsychosocial approach to management. Advances in neuroimaging, genomics, immunology, and microbiome research have deepened our understanding of chronic pain, paving the way for novel diagnostics and therapies. However, challenges such as treatment resistance, opioid misuse, and health disparities persist. By fostering interdisciplinary collaboration, leveraging emerging technologies, and addressing social determinants, we can improve outcomes for the millions affected by chronic pain worldwide.

Conflict of Interest

The author(s) declare they have no conflicts of interest.

ACCEPTED

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Figure 1. Dynamic cascade of chronic pain chronification across the pain phenotype spectrum. The chronification cascade is nonlinear and the stages are heuristic rather than strictly sequential; mechanisms can overlap, recur, and reinforce one another. Peripheral sensitisation (Stage I) lowers nociceptor thresholds via inflammatory mediators and ion-channel dysregulation, promoting central sensitisation (Stage II) through synaptic potentiation, glial activation, and reduced inhibitory control, and is reinforced by dysfunctional descending modulation that can shift from inhibition to facilitation. With persistence, brain reorganisation (Stage III) embeds pain within large-scale neural networks linking sensory processing with affect, memory, and cognition, alongside measurable functional and structural change. Neuro-immune signalling and biologically embedded psychosocial factors act as system-wide modulators across stages. The lower panel highlights stage-matched therapeutic leverage points, aligning peripheral, central, descending/rewiring, and system-level interventions with dominant mechanisms at each phase.

