



Nociplastic pain

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Nociplastic pain refers to pain arising from altered nociception without evidence of tissue or somatosensory damage. It encompasses various clinical conditions with shared neurophysiological mechanisms involving different organ systems. Nociplastic pain can occur independently or alongside chronic pain conditions with a nociceptive or neuropathic origin. This review introduces the concept of nociplastic pain, its clinical manifestations and the underlying pathophysiology. Taking a biopsychosocial approach can lead to a better understanding of nociplastic pain and improved treatment outcomes for affected individuals.

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INTRODUCTION

The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. The IASP has reported six key aspects of pain. 1) Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors. 2) Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons. 3) Individuals learn the concept of pain through their life experiences. 4) A person's report of an experience as pain should be respected. 5) Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being. 6) A verbal description is only one of several behaviors for expressing pain, and the inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.¹ The IASP definition of pain recognizes that pain can occur even when there is no identifiable tissue damage. The first key aspect of pain embraces a biopsychosocial approach, implying that pain is considered to result from a dynamic interaction among biological, psychological, and social factors.

The IASP categorizes pain into three descriptive groups: nociceptive, neuropathic, and nociplastic. The purpose of this categorization is to offer insights into the mechanisms that underlie the pain. Pain mechanisms have traditionally been divided into nociceptive and

neuropathic types. Nociceptive pain is defined as pain arising from actual or threatened damage to non-neural tissue, and is due to the activation of nociceptors. Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system. Neuropathic pain is a clinical description (rather than a diagnosis) that requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria. Nociceptive pain is defined in terms of its differences from neuropathic pain. Nociceptive pain is used to describe pain occurring with a normally functioning somatosensory nervous system, to contrast with the abnormal functioning seen in neuropathic pain.² Nociceptive pain is the prevailing type of chronic pain, including in conditions such as arthritis and various forms of spinal pain. Around 15–25% of chronic pain cases are categorized as neuropathic, with the prevalent conditions including diabetic neuropathy, postherpetic neuralgia, and radiculopathy.³ In general, nociceptive pain responds to peripherally directed treatments such as nonsteroidal anti-inflammatory drugs, injections, and surgical interventions, while opioids may also be effective for acute nociceptive pain. For neuropathic pain, apart from targeting any underlying inflammatory processes, treatments directed locally at nerves such as surgery, injections, or topical treatments, as well as medications targeting the central nervous system (CNS) may be beneficial.⁴

In 2016 the IASP introduced the term “nociplastic pain” as the third mechanistic descriptor for pain in addition to nociceptive and neuropathic pain.⁵ This review focuses on the concept of nociplastic pain and its clinical manifestations, underlying pathophysiology, and treatment methods.

CONCEPT OF NOCIPLASTIC PAIN

The IASP defined nociplastic pain as pain arising from altered nociception despite the absence of clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for a disease or lesion of the somatosensory system causing the pain.² The IASP and World Health Organization collaborated to create a new classification of chronic pain for the 11th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-11).⁶ This classification distinguishes chronic primary and chronic secondary pain syndromes,

with the former qualifying as a separate disease entity.^{6,7} The categories of nociplastic pain syndrome and diseases classified as chronic primary pain in ICD-11 are closely related. They encompass conditions such as chronic widespread pain and fibromyalgia, complex regional pain syndrome, chronic primary headaches, and orofacial pain, as well as chronic visceral pain syndromes and chronic primary musculoskeletal pain.^{8,9}

It is important to note that these terms represent different aspects, since “nociplastic” refers to the pain mechanism, while “chronic primary pain” relates to a diagnostic concept.^{7,10} The classification of nociplastic pain does not introduce a new diagnosis; rather, it indicates the likelihood of specific pain mechanisms regardless of the underlying diagnosis, such as osteoarthritis and fibromyalgia.¹⁰

While central sensitization is probably the primary mechanism in nociplastic pain conditions, the term “nociplastic pain” should not be used interchangeably with the neurophysiological term “central sensitization”. Furthermore, the potential involvement of peripheral sensitization in these pain conditions also should be considered.¹⁰

CLINICAL MANIFESTATIONS OF NOCIPLASTIC PAIN

Nociplastic pain is characterized by a dull, deep, aching sensation similar to nociceptive pain, but patients may also experience neuropathic characteristics such as burning or shooting pain. The pain location and intensity fluctuate, and it can be increased by physical activity, environmental factors, and emotional distress. Patients may exhibit symptoms of neuropathic pain, such as dysesthesia, hyperalgesia, and allodynia. Pain locations vary and they can be segmental or widespread.⁸

Other symptoms associated with the CNS often accompany nociplastic pain, including fatigue, sleep disturbances, cognitive impairment, increased sensitivity to external stimuli, and mood disturbances. Physical fatigue may be described as a heaviness in the body or an inability to perform the activities of daily living. Mental fatigue may present as lethargy, concentration difficulties, or memory impairments. Additionally, mood disturbances including depression and anxiety are frequently observed in individuals with nociplas-

tic pain. These symptoms can lead to increased pain sensitivity and significantly impact the overall health status.^{4,8}

The IASP introduced clinical criteria for nociplastic pain of the musculoskeletal system. Patients need to conform with the following criteria to be clinically classified with nociplastic pain: 1) report having experienced pain for at least 3 months, 2) report a regional rather than a discrete pain distribution, 3) report pain that cannot entirely be explained by nociceptive or neuropathic mechanisms, and 4) show clinical signs of pain hypersensitivity (i.e., evoked pain hypersensitivity phenomena such as static or dynamic mechanical allodynia, heat or cold allodynia, and/or painful after-sensations after any of these assessments of evoked pain hypersensitivity) that are at least present in the region where pain is experienced. Furthermore, the patient is classified as having probable nociplastic pain if they have a history of pain hypersensitivity in the region where pain is experienced (sensitivity to touch, movement, pressure or heat/cold) and they present with at least one of the defined comorbidities (increased sensitivity to sound and/or light and/or odors,

sleep disturbance with frequent nocturnal awakenings, fatigue or cognitive problems such as difficulty in attention focus, or memory disturbances) (Table 1).^{10,11}

UNDERLYING PATHOPHYSIOLOGY OF NOCIPLASTIC PAIN

The pathophysiology underlying nociplastic pain is not fully understood, but central sensitization is believed to play a key role.^{3,8} Central sensitization refers to an increased responsiveness of nociceptive neurons in the CNS to normal or subthreshold inputs.² This concept explains the pain hypersensitivity observed in various chronic pain conditions, including peripheral neuropathic pain, fibromyalgia, headache, and irritable bowel syndrome.⁸ Besides central sensitization, other mechanisms such as diminished inhibitory pathways, peripheral sensitization, and immune system activation are also believed to be involved in nociplastic pain.^{3,8}

Table 1. IASP clinical criteria for nociplastic pain of the musculoskeletal system

	Value
Mandatory criteria	
Pain (all)	Chronic (>3 months) Regional rather than discrete in distribution No evidence of nociceptive pain (if present, it is not entirely responsible for the pain) No evidence of neuropathic pain (if present, it is not entirely responsible for the pain)
Clinically elicited evoked pain hypersensitivity phenomena in the region of pain (any one)	Static mechanical allodynia Dynamic mechanical allodynia Heat or cold allodynia Painful after-sensations following the assessment of allodynia
Optional criteria	
History of pain hypersensitivity in the region of pain (any one)	Sensitivity to touch Sensitivity to pressure Sensitivity to movement Sensitivity to heat or cold
Comorbidities (any one)	Increased sensitivity to sound and/or light and/or odors Sleep disturbance with frequent nocturnal awakenings Fatigue Cognitive problems such as difficulty to focus attention, memory disturbances

IASP, International Association for the Study of Pain.

DIAGNOSING CENTRAL SENSITIZATION

Central sensitization is commonly assessed using different forms of quantitative sensory testing (QST), conditioned pain modulation (CPM), functional magnetic resonance imaging (fMRI), and questionnaires.¹² While QST, CPM, and functional MRI studies are valuable research tools, they are not yet integrated into clinical practice.⁸

QST evaluates sensory functions by measuring the threshold at which calibrated sensory stimuli are detected or by rating the intensity of stimuli above the threshold. Increased facilitative activity associated with central sensitization can be observed through phenomena such as temporal summation, expansion of receptive fields, hyperalgesia, and allodynia. While QST measures of hyperalgesia in the painful body region may not specifically indicate central sensitization, since they can also reflect peripheral sensitization, increased sensitivity to sensory input in nonpainful and healthy body parts is generally accepted as a sign of central sensitization.¹³ Interpreting QST results requires consideration of factors such as sex, age, race, and the measurement site, since these can influence central sensitization.^{8,12,13}

CPM is a measure of the efficacy of descending pain pathways, which exert both facilitatory and inhibitory effects. CPM is of clinical value since it can act as a surrogate measure of the brain's capacity to activate endogenous analgesic mechanisms, possibly via the descending tracts.¹⁴ The mechanism of CPM can be summarized as "pain inhibits pain", where a nociceptive stimulus applied to one part of the body inhibits pain in another part when this phenomenon is activated. This process can be activated by applying a first nociceptive stimulus (the test stimulus) followed by a second nociceptive stimulus (the conditioning stimulus), and finally reapplying the test stimulus to assess if the conditioning stimulus has triggered an analgesic effect.¹⁵

Functional MRI studies have revealed increased connectivity between brain regions associated with amplifying pain and emotion, such as those in the default-mode network and insular cortex. The default-mode network is active during passive rest and mind-wandering, which typically involves thoughts about others, self-reflection, reminiscing about the past, and envisioning the future. This network primarily comprises the dorsal medial prefrontal cortex, posterior cingulate cortex, precuneus, and angular gyrus. Conversely, decreased activity is observed in brainstem regions

responsible for descending analgesic mechanisms. Neuroplasticity involves changes in the size and shape of brain regions in individuals with chronic pain, which previously were attributed to atrophy.⁸

The Central Sensitization Inventory is a self-report tool used to identify patients with symptoms that might be linked to central sensitization. This tool can be used to both screen for central sensitization and as an outcome measure for assessing the effects of treatments.^{12,16}

BIOPSYCHOSOCIAL MODEL OF CHRONIC PAIN

According to the biopsychosocial model, pain and disability involve multidimensional and dynamic interactions among biological, psychological, and social factors that mutually affect each other. Various biological factors such as genetics, age, sex, sleep, hormones, and the endogenous opiate systems play roles in the development of chronic pain. Psychological factors such as depression, anxiety, stress, poor coping skills, and catastrophization affect chronic pain, as do sociocultural factors such as educational attainment, cultural background, and social support.³

ICD-11 describes chronic primary pain as chronic pain characterized by significant emotional distress (anxiety, anger/frustration, or depressed mood) or functional disability (interference in the activities of daily living and reduced participation in social roles). This pain syndrome is multifactorial, being affected by biological, psychological, and social factors.^{6,7}

The biopsychosocial model is highly applicable to nociceptive pain, which lacks a clear identifiable cause. Predisposing factors for nociceptive pain include a family history of pain, previous experiences with pain, and various psychosocial factors such as abuse. The clustering of pain within families may be influenced by genetics, epigenetics, or learned behaviors.⁸

TREATMENT OF NOCICEPTIVE PAIN

Clinicians should acknowledge that pain is a genuine and personal experience. It is also essential to recognize that var-

ious factors can influence the intensity and impact of pain, including biological, psychological, and social aspects.

Nonpharmacological treatment methods are prioritized due to the inadequate efficacy and potential side effects of pharmacological treatments. These methods include education, physical therapy, cognitive behavioral therapy, mindfulness, and lifestyle modifications. Social support plays a significant role in reducing pain severity and enhancing coping in the presence of chronic pain conditions.^{4,8,13}

Traditional pain medications such as muscle relaxants, nonsteroidal anti-inflammatory drugs, paracetamol, and opioids are less effective for nociplastic pain than for nociceptive pain. However, certain antidepressant medications (e.g., tricyclic antidepressants and selective serotonin-norepinephrine-reuptake inhibitors) and antiepileptic medications (e.g., gabapentin and pregabalin) have been shown to be effective in managing nociplastic pain, like they have been in neuropathic pain.^{4,8,13}

Meta-analyses have provided evidence that both pharmacological and nonpharmacological strategies help to reduce central sensitization and improve patient outcomes. The effect sizes of available treatments remain small, but they are valuable as part of a multimodal and comprehensive approach to chronic pain. Pain management should focus on reducing symptoms and improving overall function and the quality of life, rather than attempting to completely eliminate pain.¹³

CONCLUSION

Nociplastic pain is a term used to describe chronic pain conditions that do not fit into the classifications of nociceptive and neuropathic pain. The categories of nociplastic pain syndrome exhibit significant overlap and primarily manifest as subjective clinical features. Acknowledging the concept of nociplastic pain can help prevent stigmatization and facilitate early interventions, thereby preventing severe functional disability in affected patients. Ongoing research is expected to improve the understanding of the pathophysiology and biomarkers contributing to nociplastic pain. Such advancements will aid in developing more-effective treatment strategies for these pain conditions. It is hoped that this review will assist clinicians in managing nociplastic

pain by providing a comprehensive understanding of this condition.

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

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