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Why Rheumatologists Should Know About Nociplastic Pain

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Introduction

The story of nociplastic pain in rheumatology practice begins with fibromyalgia (FM). More than three decades ago, rheumatologists played a leading role in establishing criteria for FM, with early criteria requiring examination of tender points.[1] With increasing knowledge that FM encompassed more than pain alone, along with evidence that the tender point examination showed poor reliability, the American College of Rheumatology developed updated criteria. These updates eliminated tender point assessment and instead incorporated the concept that FM was a syndrome that included "central" symptoms of fatigue, unrefreshed sleep, and cognitive dysfunction, as well as associated conditions such as headaches, abdominal pain, and depression.[2] At that time, the concept of pain sensitization as an explanation for "invisible pain" was being actively studied by basic scientists, but had not yet translated into the clinical domain. The wide range of subjective symptoms experienced by patients with FM were difficult to explain, with many believing that symptoms were exaggerated or primarily psychiatric in origin. With growing recognition, it is now understood that nervous system sensitization is a plausible explanation for "invisible" pain that cannot be sufficiently explained by tissue abnormality. This mechanism

is now identified as nociplastic pain, the third pain phenotype alongside nociceptive and neuropathic pain.[3] Nociplastic pain is common and often unrecognized in patients with rheumatic diseases (**Table 1**).

Why Should Rheumatologists Acquire Knowledge About Pain Mechanisms?

Over the past decade, FM has served as the flagship condition for nociplastic pain. As FM has increasingly shifted outside of rheumatology practice, with patients commonly managed in primary care, the relevance of FM/nociplastic pain within rheumatic disease has become an important element in rheumatology practice. Many patients with inflammatory rheumatic conditions deemed well controlled by recognized parameters continue to experience persisting pain. Early studies described this phenomenon as "remaining pain" in patients with clinically controlled rheumatoid arthritis (RA), but without a precise understanding of the operative mechanisms.[4] It is now recognized that overlapping pain phenotypes, particularly prominent nociplastic pain, likely account for these findings, with over three quarters of patients with "well-controlled" RA reporting inadequate pain control.[4]

Nociplastic pain occurs across a range of musculoskeletal conditions including those of soft tissues and myofascia (i.e., shoulder tendonitis), degenerative and inflammatory arthritis, and spinal disease.[5] While the population prevalence of FM is estimated at 2–8%, the prevalence of FM/nociplastic pain in rheumatic diseases is considerably higher. Pooled prevalence estimates range from 18–24% in RA, 14–16% in axial spondyloarthritis, and 18% in psoriatic arthritis, to name just a few.[6] When FM co associates with rheumatic disease, patients experience considerably greater pain severity, higher measured disease activity, reduced functional capacity, and poorer quality of life. Of critical importance is that unrecognized nociplastic pain can lead to erroneous management strategies that focus on controlling the underlying rheumatic condition, rather than addressing the underlying pain mechanism (**Table 2**).

Understanding Pain Mechanisms

Traditionally nociceptive pain has been viewed as arising from disturbances of tissue structure, mediated by localized inflammatory processes that activate peripheral primary afferent neurons. In this context, pain intensity is typically proportional to the nociceptive input. In contrast, nociplastic pain is a disorder of pain processing with resulting upregulation of nociception, termed pain sensitization.[3] In nociplastic pain states, pain is perpetuated by enhanced neuronal function and is no longer directly coupled to the noxious input. Instead, it becomes a self-sustaining, dysfunctional response to normally non-painful sensory inputs.[7] Pain sensitization is a complex process that occurs at multiple levels in the nervous system. Alterations in excitatory neurotransmitter signalling can induce changes in nervous system gene expression, leading to neuronal hyperexcitability, with changes at multiple levels across the spinal cord and brain regions. These central nervous system changes are associated with symptoms of fatigue, sleep disturbances, and cognitive changes.[8] A downstream effect is disinhibition of descending inhibitory pathways (the descending analgesic system), resulting in increased pain signalling within the spinal cord.[7]

Why Do Some Patients Develop Nociplastic Pain?

Musculoskeletal nociplastic pain typically begins with a persistent anatomical noxious input, such as chronic joint inflammation or anatomical abnormality—that induces nervous system hyperresponsiveness and is influenced by a multitude of biopsychosocial factors, leading to a combination of pain mechanisms sometimes termed 'overlapping pain'.[9] Predisposing factors for the development of nociplastic pain include a genetic predisposition, with studies pointing to a polygenic trait, as well as background psychological and physical stressors, previous pain experiences, precipitating physical events, and social disadvantage.[10,11] At its core, central sensitization represents a detrimental form of neuroplasticity.

How to Recognize Nociplastic Pain

Nociplastic pain may be generalized, as in FM, or regional, and cannot be accurately confirmed by objective bedside tests, biomarkers or imaging studies. The pain is not binary, but exists along a continuum. Some individuals exhibit minimal amplification of nociceptive input, others demonstrate the ability to naturally

Pain Type	Mechanism	Key Features	Clinical Relevance
Nociceptive	Peripheral tissue inflammation/damage	Proportional to structural abnormality, localized	Responds to anti-inflammatory and analgesic treatments
Neuropathic	Lesion/disease of somatosensory nervous system	Burning, electric, dermatomal distribution	Requires specific neuropathic agents
Nociplastic	Upregulation of nervous system pain processing, termed pain sensitization.	Disproportionate intensity, widespread, fluctuating, with fatigue/sleep/cognitive symptoms	Poor response to conventional analgesics; requires biopsychosocial approach

Table 1. Key Concepts of Pain Phenotypes; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Condition	Estimated Prevalence of FM/Nociplastic Pain	Clinical Impact
Rheumatoid Arthritis	18–24%	Higher pain, ↑ disease activity scores, ↓ function
Axial Spondyloarthritis	14–16%	Persistent pain despite controlled inflammation
Psoriatic Arthritis	18%	Worse quality of life and function
General Inflammatory Arthritis	20%	Risk of overtreatment of inflammation

Table 2. Prevalence of Nociplastic Pain in Rheumatic Diseases; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

inhibit nociceptive signalling, while still others experience marked nociceptive magnification. These differences are influenced by factors such as expectations, attentional processes, and psychological characteristics.

The Clinical History

Identifying nociplastic pain begins with a clinical history that explores the pain characteristics and associated symptoms. Nociplastic pain does not conform to traditional concepts of pain; it is often reported as severe, fluctuating in intensity, and can occur without clear provocation, or be influenced by environmental factors such as temperature, stressors, and psychological status. Pain is typically more widespread than expected, and is usually associated with subjective symptoms of fatigue, sleep disturbance, cognitive difficulties, depression, or hypervigilance.[12] Patients may also report other pain complaints such as migraine headaches, irritable bowel syndrome, or bladder symptoms. Patients may complain of heightened sensitivity to touch, with discomfort elicited by normally non-painful stimuli, such as clothing with a rough texture, or a gentle caress that gives an unpleasant sensation. Gentle pressure, such as a child sitting on the lap, may induce pain. Pain can be aggravated by environmental factors of heat, cold, or stress, and additional associated comorbidities including hypervigilance to light, sound, or smell, sleep disturbances, fatigue, myriad gastrointestinal and genitourinary symptoms, or cognitive difficulties. Collectively, these subjective yet valid experiences point to the phenomenon of central sensitization (**Table 3**).

Physical Examination

Physical examination will reveal features of the underlying musculoskeletal condition, which for an inflammatory condition could appear clinically quiescent (**Box 1**). In addition, signs of pain hypersensitivity can be identified by a few simple bedside manoeuvres. These may include tactile allodynia to light touch/brushing, mechanical hyperalgesia following application of pressure, hyperalgesia related to cold or warm stimuli, and persistence of after sensations,

Assessment Component	Tools, Findings
History	Pain more widespread, complaints often vague, fatigue, sleep disturbance, depression, hypervigilance, other pain complaints (e.g., migraine, irritable bowel symptoms)
Physical examen	Excessive sensitivity to non painful stimuli: allodynia, hyperalgesia, temporal summation
Questionnaires	FSQ, painDETECT, CSI
Advanced testing	QST (PPT, TS, CPM) currently in the research setting

Table 3. Clinical Assessment of Nociplastic Pain; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Abbreviations: CPM: conditioned pain modulation; **CSI:** Central Sensitization Inventory; **FSQ:** Fibromyalgia Survey Questionnaire; **PPT:** pressure pain threshold; **QST:** quantitative sensory testing; **TS:** temporal summation

described as an echo of the stimulus, for a few seconds following a sensory input.[13] Temporal summation, characterized by progressively increasing pain in response to repeated, identical (low-level) noxious stimuli (a sharp object) rather than accommodation or extinction, is a hallmark feature of central sensitization. Although further validation is required, these simple clinical steps can guide clinicians toward a diagnosis of nociplastic pain and overlapping pain mechanisms.

Clinical Features of Nociplastic pain
Pain characteristics: severe, diffuse, non-anatomical distribution, fluctuating, disproportionate to tissue damage.
Triggers: underlying rheumatic condition, stress, temperature, emotional factors.
Sensory symptoms: allodynia, hyperalgesia, after-sensations.
Associated symptoms: fatigue, sleep disturbance, cognitive dysfunction.
Comorbidities: depression, anxiety, hypervigilance.

Box 1. Clinical features of nociplastic pain; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Additional Testing

Although not commonly used in clinical practice, quantitative sensory testing (QST) in research settings can identify sensitivity of the somatosensory system to nociceptive input, providing information on abnormal pain processing. Findings from QST have greatly strengthened the concept of nociplastic pain associated with musculoskeletal conditions, particularly through measures such as the pressure pain threshold, temporal summation, and conditioned pain modulation. Several questionnaires can support the identification of nociplastic pain, with the Fibromyalgia Survey Questionnaire most commonly used in the context of rheumatic diseases.[2] Other questionnaires applicable to clinical practice include the painDETECT questionnaire and the Central Sensitization Inventory, both easily self-administered.

Consequences of Nociplastic Pain in the Musculoskeletal Context

Across all inflammatory arthritis, the prevalence of nociplastic pain is approximately 20% and is associated with higher pain scores, overall reduced function, more global suffering, and elevated scores on standard questionnaires to assess disease activity. This latter finding is of critical importance as the inflammatory disease could be misjudged as inadequately controlled, leading to inappropriate adjustments of disease modifying agents (**Box 2**). Nociplastic pain is also a risk factor for poor outcomes following interventions, including surgery. Notably, up to 20% of those with nociplastic pain experience chronic, persistent pain after knee replacement, with consequences of decreased function, lower satisfaction, and poorer mental health outcomes.[14] While non-pharmacological supports, such as

cognitive behavioural therapy and exercise, should be integrated early into the clinical care pathway in any chronic pain condition, it is of utmost importance for patients presenting with nociplastic pain.

Although degenerative changes of the spine may involve multiple anatomical structures, there is a poor correlation between pain severity, imaging, and anatomically-directed interventions such as injections. Nearly one third of patients with low back pain exhibit nociplastic features, which are associated with poorer physical and psychological functioning, greater disability, and reduced responsiveness to procedures. Even in conditions affecting the hand, such as trigger finger, carpal tunnel syndrome, and osteoarthritis, the coexistence of fibromyalgia is associated with higher healthcare utilization and increased surgery rates.

Consequences of Unrecognized Nociplastic pain
Misinterpretation of disease activity.
Overtreatment, polypharmacy.
Increased risk of persistent pain after surgery.
Increased utilisation of the healthcare system.

Box 2. Consequences of unrecognized nociplastic pain; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Treatment Recommendations for Musculoskeletal Nociplastic Pain

Treatments for nociplastic pain generally reflect those recommended for FM, beginning with a stepwise, multimodal approach that incorporates non-pharmacological strategies as a cornerstone, with additional drug therapy when indicated. Comorbid mental health conditions such as anxiety, depression, and post traumatic stress disorder should be addressed. Pharmacologic treatments are not a panacea, are often associated with adverse events, and generally provide only modest benefit, with few patients experiencing remarkable improvement.[15,16] Traditional management strategies that address nociceptive pain, including analgesic or anti-inflammatory medications, or anatomically-focused interventions, are less successful and should be discouraged (**Table 4**).

Non-pharmacological Treatments

Education should emphasize the biopsychosocial model that promotes active patient participation and discourages reliance on passive practitioner-administered treatments. Often overlooked are recommendations for good lifestyle practices such as sufficient physical activity, attention to diet, strategies to control stress, pacing of activities, and setting realistic outcome goals. Integrating psychological measures that include cognitive behavioural therapy (often available on-line), acceptance/mindfulness-based therapies, and attention to stress can improve treatment effects.[17] Mind-body interventions, such as yoga, support care by harmonizing physical and psychological factors.

Regular and sufficient physical exercise (at least 150 minutes per week of moderate activity) is recommended. However, individuals with nociplastic pain are more likely to respond to a graded exercise approach in a pain-contingent manner combined with pacing of activities.[18] Patients should be encouraged to choose forms of physical activity that are easily accessible and enjoyable, with no specific exercise recommended.

Although patients frequently request advice about the ideal diet, there is no single dietary intervention with sufficient evidence to be recommended. Overall the less healthy Western diet, high in fat and sugar and low in fibre content, should be adjusted to incorporate whole foods that are prepared in the home. Studies examining various whole-food dietary interventions report modest reductions in pain, but no single diet has shown excellent or consistent benefit. The gut microbiome dysbiosis plays a role in the modulation of chronic pain by acting at the interface between the neuroimmune-endocrine system and the microbiome-gut-brain axis. Strategies aimed at restoration of the gut microbiota, including probiotic supplementation and more recently fecal microbiota transplantation, have been explored with preliminary but promising-results.

Neuromodulation techniques that deliver electrical or magnetic stimulation to the central or peripheral nervous system are being studied, with the aim of facilitating neuroplasticity and modulating pain. Although these studies are generally small and carry a high risk of bias, short-term reductions in pain have been reported.

Intervention	Key elements
Non-pharmacologic	
Education	Biopsychosocial model, active participation
Exercise	≥150 min/week, graded approach
Psychological therapies	CBT, mindfulness, acceptance
Lifestyle	Sleep, diet, stress management
Neuromodulation	Modulate neuroplasticity
Pharmacologic	
Antidepressants	Moderate benefit (for some)
Anticonvulsants	Small benefits, side effects
Analgesics, NSAIDs	Ineffective
Opioids	Discouraged

Table 4. Treatment Recommendations; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

Abbreviations: CBT: cognitive behavioural therapy; **NSAIDs:** nonsteroidal anti-inflammatory drugs

Pharmacologic Treatments

Drug treatments, although often expected by patients, offer only a modest benefit for some. The strongest available evidence, largely derived from studies in FM, is for the use of antidepressants and anticonvulsants, although the strength of this evidence remains contentious. Medications should be prescribed cautiously, as patients with nociplastic pain often exhibit heightened sensitivity to adverse effects. When used at low to moderate doses, these medications may offer meaningful effects for some and can have synergistic effects. However, routine escalation to maximal doses can have deleterious effects both in the short- and long-term for quality of life and functional outcomes.

Centrally-acting medications, such as tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and α2δ ligands are considered agents of choice, although central nervous system side effects may limit their use.[18] Whereas gabapentinoids are not recommended by guidelines for arthritis or spine pain, clinicians frequently prescribe low doses, especially at night, to primarily promote sleep and with some benefit for nocturnal pain.

Antidepressants increase concentrations of serotonin and norepinephrine in the presynaptic cleft and thereby modulate descending inhibitory pathways. Both the older TCAs and more recent SNRIs have been best studied, demonstrating short- to medium-term improvements in pain and quality of life. However, among these agents, duloxetine is the only medication identified as moderately effective across all outcomes at standard doses. Anticonvulsants primarily depress dorsal horn sensitivity via calcium channel regulation, leading to decreased release of pain-inducing neurotransmitters such as glutamate, substance P, and others, also exert effects on descending inhibitory mechanisms. Within the gabapentinoid class, studied largely in FM, pregabalin has shown a small benefit in reducing pain and improving sleep, but with high dropout rates and a number needed to harm of approximately 13.

Conventional pain-management agents, including acetaminophen, nonsteroidal anti-inflammatory drugs and opioids, have shown no benefit in nociplastic pain and are not recommended. Given the well-recognized risks inherent with the use of opioids, their use should be strongly discouraged. Although some studies do show a small reduction in pain and improved physical functioning with opioids, problematic use has been reported for over one third of patients. Given the personal and societal risks associated with opioid use, even small modest gains in pain reduction are currently viewed as unacceptable trade-offs. Cannabinoid-based products are

promoted as pain modulators, especially for nociplastic pain; however, high-quality clinical trials to support their effectiveness are lacking.

A range of novel pharmacologic and interventional treatments are currently under investigation for nociplastic pain, but none have sufficient evidence to recommend universal use. These include agents with N-Methyl-D-Aspartate antagonist properties, such as ketamine, dextromethorphan, memantine, and magnesium, as well as nutritional supplements such as N-acetyl cysteine and alpha lipoic acid. Paradoxically, low-dose naltrexone (an opioid antagonist) has shown some efficacy in select nociplastic conditions such as irritable bowel syndrome and FM. In addition, suzetrigine, a NaV1.8 blocker, currently indicated only for acute pain, may have promising potential for managing chronic pain.

Conclusion

Nociplastic pain is a pain phenotype that commonly overlaps with nociceptive pain across all rheumatic conditions and leads to substantial reductions in quality of life. Key clinical messages are summarized in **Box 3**. Recognition requires a heightened clinical alertness, prompted by the unique clinical characteristics of the pain, the presence of associated "central" symptoms such as fatigue, sleep disturbance, cognitive difficulties, and hypervigilance, along with physical findings suggestive of pain sensitization, in the absence of an objective biomarker to confirm diagnosis. Treatments should adopt a biopsychosocial approach, with emphasis on non-pharmacological strategies, and using pharmacologic therapies cautiously, as no single medication provides substantial benefit for the majority of patients.

Key Clinical Messages
Nociplastic pain is common and must be routinely considered in the context of rheumatic diseases.
Nociplastic pain commonly overlaps with underlying nociceptive pain (which is a trigger to pain sensitization).
Clinical reasoning is important because there are no biomarkers.
Non-pharacological treatments should be prioritized.

Box 3. Key clinical messages; *courtesy of Mary-Ann Fitzcharles, MD and Hance Clarke, MD.*

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