Chronic Pain 2

Nociplastic pain: towards an understanding of prevalent pain conditions

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This is the second in a **Series** of three papers about chronic pain

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Nociplastic pain is the semantic term suggested by the international community of pain researchers to describe a third category of pain that is mechanistically distinct from nociceptive pain, which is caused by ongoing inflammation and damage of tissues, and neuropathic pain, which is caused by nerve damage. The mechanisms that underlie this type of pain are not entirely understood, but it is thought that augmented CNS pain and sensory processing and altered pain modulation play prominent roles. The symptoms observed in nociplastic pain include multifocal pain that is more widespread or intense, or both, than would be expected given the amount of identifiable tissue or nerve damage, as well as other CNS-derived symptoms, such as fatigue, sleep, memory, and mood problems. This type of pain can occur in isolation, as often occurs in conditions such as fibromyalgia or tension-type headache, or as part of a mixed-pain state in combination with ongoing nociceptive or neuropathic pain, as might occur in chronic low back pain. It is important to recognise this type of pain, since it will respond to different therapies than nociceptive pain, with a decreased responsiveness to peripherally directed therapies such as anti-inflammatory drugs and opioids, surgery, or injections.

Introduction

Development of a new pain descriptor

Previously, chronic pain was thought to arise via two sources: nociceptive, which is associated with an ongoing input from real or threatened tissue injury, and neuropathic, caused by injury or disease affecting the peripheral nervous system or CNS. This belief left other chronic pain conditions with well defined phenotypes, but without clear evidence of nociceptive or neuropathic involvement, in a nebulous zone. In 2016, the term nociplastic pain was proposed as a mechanistic descriptor for chronic pain states not characterised by obvious activation of nociceptors or neuropathy, "but in whom clinical and psychophysical findings suggest altered nociceptive function".[1] Nociplastic pain can be mechanistically defined as pain arising from the altered function of pain-related sensory pathways in the periphery and CNS, causing increased sensitivity.[2] Nociplastic pain can occur in isolation or as a comorbidity in individuals with chronic pain conditions that are primarily nociceptive or neuropathic.

Nociplastic pain should be viewed as an overarching terminology that can be applied to a diverse range of clinical conditions that share common neurophysiological mechanisms, involving various organ systems. Distinct from a specific disease, this term provides validity for pain complaints previously identified by stigmatising terms such as dysfunctional pain or medically unexplained somatic syndromes. Given that there are overlapping conditions characterised by nociplastic pain, findings from more studied conditions (eg, fibromyalgia) may be extrapolated to more obscure conditions, because mechanism-based pain treatment is considered theoretically superior to symptom or disease-based treatments.[3] By recognising the characteristics of nociplastic pain and identifying concomitant symptoms, physicians can establish a diagnosis even in the absence of defining biomarkers. Accumulated scientific understanding of the neurobiology of pain prompted the Terminology Task Force of the International Association for the Study of Pain (IASP)[1] to propose this new term, which is mechanistically and clinically distinct from the other two pain categories. Nociplastic pain refers to a physiologically based category that is particularly applicable to chronic primary pain conditions outlined in the new International Classification of Diseases 11th edition, published by WHO.[4] The IASP has subdivided chronic primary pain conditions, defined as chronic pain in one or more anatomic regions associated with notable emotional distress or disability that cannot be better explained by another chronic pain condition, into the following five categories: chronic widespread pain (eg, fibromyalgia), complex regional pain syndrome, chronic primary

Search strategy and selection criteria

From January, 2019, to January, 2020, we searched the databases MEDLINE, Ovid, Google Scholar, and Google using the key words "chronic pain", "diffuse pain", "chronic pain disorder", "nociplastic pain", "functional pain", "somatoform disorder", "somatization", "somatic symptom disorder", and "widespread pain", along with key words adapted for individual conditions (eg, "fibromyalgia", "fibrositis", "temporomandibular disorder", "temporomandibular joint pain"). For treatment sections and tables, our selection criteria gave precedence to systematic reviews, guidelines, meta-analyses, and large, randomised trials, but did not exclude any data source. We imposed no date or language restrictions.

headache and orofacial pain, chronic primary visceral pain, and chronic primary musculoskeletal pain.[5] The term chronic primary pain presupposes the causal dysfunction of nociceptive processing, which distinguishes it from somatic symptom disorders, which are defined by psychological symptoms irrespective of any underlying somatic disease that might explain the physical symptoms.

Challenges in treatment and understanding

Caring for patients with nociplastic pain is challenging; the pain complaint is often difficult to describe, there are associated subjective symptoms, and pathognomonic clinical findings or biomarkers are absent. Nociplastic pain conditions are frustrating for both health-care professionals and patients, with physicians uncertain regarding diagnosis and patients resentful that their symptoms are doubted. Nociplastic pain represents a dynamic interplay of various mechanisms causing or amplifying pain, arising de novo or triggered by pain generator(s) that can be driven by the peripheral nervous system or the CNS, psychologically driven, or a combination. It is a phenotypic expression of multifactorial processes originating from different inputs, which could be either a bottom-up response to a peripheral nociceptive or a neuropathic trigger (ie, often referred to as central sensitisation), or a top-down CNS-driven response.[6] Categorising pain as being confined to one mechanistic group is an oversimplification, and many or even most pain states represent a mixed-pain picture with substantial mechanistic overlap.[7] With the improved understanding of pain mechanisms, the current list of nociplastic pain conditions will probably evolve.

Nociplastic pain as part of a continuum

Although the proposed definition identifies nociplastic pain as a unique category devoid of actual or threatened tissue or somatosensory damage, there is evidence for the overlap of nociceptive, neuropathic, and nociplastic pain, indicating that nociplastic pain is not a distinct entity, but part of a chronic pain continuum.[1] For example, the term mixed pain has been used to describe conditions such as chronic low back pain that might have nociceptive, neuropathic, and nociplastic components.[8] This effect occurs in individuals with both nociceptive (eg, rheumatic disorders) and neuropathic pain (eg, small fibre neuropathy) whereby nociplastic mechanisms, often identified as comorbid fibromyalgia, are viewed as a concurrent condition.[9] For some conditions, more than a third putatively involve nociceptive, neuropathic, and nociplastic mechanisms in combination.[7] Studies that make use of instruments predating the concept of nociplastic pain have found neuropathic-like components in 12% of patients with low back pain and more than a third of patients with knee or hip arthritis, which probably represent nociplastic mechanisms.[10,11] Similar to other chronic pain conditions, nociplastic pain is associated with other symptoms, leading experts to propose expansive terminology to include the term syndrome, namely nociplastic pain syndrome. The addition of the term syndrome acknowledges the presence of a constellation of symptoms with no clearcut pathophysiological mechanism(s), which differs from a disease with well defined pathophysiological mechanisms and objective diagnostic test results.

Neurophysiological underpinning

The mechanistic common denominator of nociplastic pain is the amplified processing of or decreased inhibition of pain stimuli at multiple levels in the nervous system, or both. There are probably numerous initiating routes that lead to a final common pathway of the amplification of nociceptive perception, transduction, and transmission (figure).

The concept that pain hypersensitivity after a traumatic noxious stimulus in the periphery could be mediated by both peripheral and CNS changes was first proposed by Woolf,[12] who used the term central sensitisation to refer to the spinal mechanisms that augmented the ongoing peripheral nociceptive input. Subsequent studies identified a plethora of spinal and supraspinal mechanisms capable of causing, amplifying, or perpetuating pain, with an operative emphasis on nociceptive input.[13–15] In the mid-1990s, the concept of central sensitisation was introduced to explain the regional and diffuse pain hypersensitivity associated with various chronic pain conditions, including peripheral neuropathic pain,[16] fibromyalgia,[17] headache,[18] temporomandibular disorder,[19] irritable bowel syndrome (IBS),[20] and interstitial cystitis.[21] In these conditions, pain alterations identified by quantitative sensory testing (QST) extended to more than localised body regions.

The pattern of expanding pain that was characterised by hyperalgesia (increased pain in response to painful stimuli) and allodynia (pain in response to normally non-painful stimuli) suggested supraspinal rather than purely spinal dysfunction.[22] In addition to widespread pain and tenderness, patients had other symptoms that were suggestive of CNS involvement, including fatigue, sleep, mood and memory difficulties, and sensitivity to non-nociceptive sensory stimuli such as light (photosensitivity) and sound (hyperacusis). Dynamic QST tests have shown that other abnormalities in pain processing in the CNS and peripheral nervous system, including an increase in facilitative activity and decreased descending inhibition, contribute to pain amplification.[23] Examples of facilitative activity include temporal summation or increasing pain perception after repeated noxious stimulus secondary to a so-called wind-up (ie, an enhanced spinal neuron response after C-fibre or, less commonly, A-δ stimulation), and the expansion of receptive fields and hyperalgesia or allodynia, or both, secondary to central sensitisation.

Diminished descending modulation might manifest as allodynia or hyperalgesia, and can be measured by conditioned pain modulation (figure).

Imaging findings

Newer imaging techniques, such as functional, chemical, and structural brain imaging, have elucidated the underlying CNS mechanisms driving central sensitisation.[24] Differential neural activation in brain regions involved in pain and sensory processing are shown by functional MRI scans in healthy individuals subjected to acutely painful stimuli, corroborating QST.[25,26] The increased activation of brain regions involved in processing pain and other sensory information have been shown in fibromyalgia, IBS, and low back pain.[27–29]

With the use of functional MRI, increased connectivity has been identified between brain regions involved in augmenting pain and emotion (eg, regions of the default mode network and insular cortex), and decreased activity in brainstem regions involved in descending analgesic mechanisms.[30,31] Changes in the size and shape of brain regions in individuals with chronic pain states, originally thought to represent atrophy, are now believed to be indicative of neuroplasticity.[32,33] Proton spectroscopy can probe specific neurotransmitters involved in these processes, with subsets of individuals displaying increased glutamatergic activity or decreased GABAergic activity in key pain processing regions such as the insula.[34,35] Positron emission tomography can examine the function of neurotransmitter systems, such as the endogenous opiate pathways, supporting the concept of neuroinflammation and glial cell involvement.[36–39]

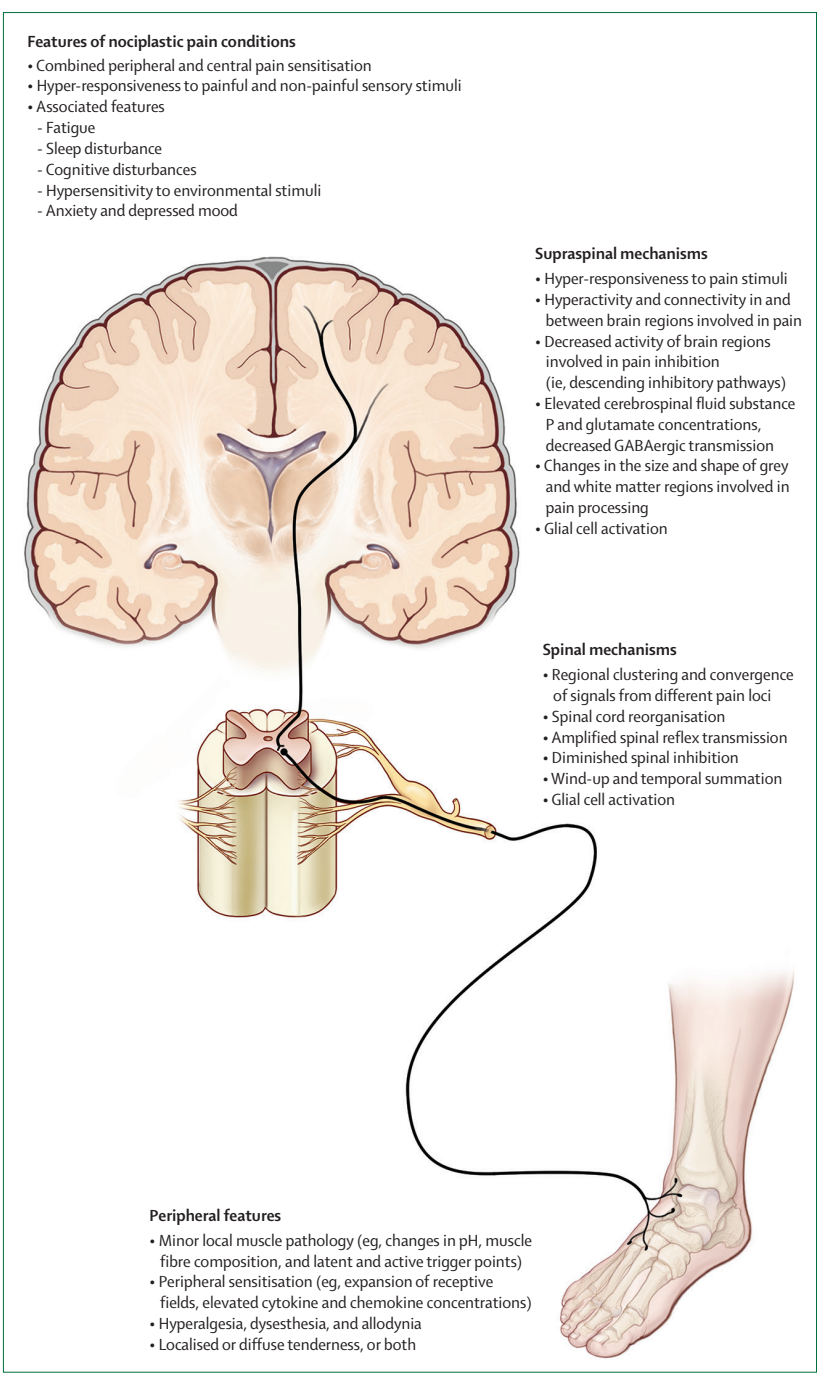

Figure: **Mechanisms and features of nociplastic pain**
Figure created by Joe Kanasz.

Prevalence

There is great variability in the prevalence rates for nociplastic conditions (table). With chronic pain estimated to affect one in five people, for many people with chronic pain the operative mechanisms probably represent a mixed-pain pathophysiology, clinically expressed as chronic overlapping pain conditions with a prominent nociplastic pain component.[56,57] These pain conditions cross all geographical, demographic, and social strata, with the prevalence generally higher for female individuals. In one review it was estimated that between 5% and 15% of the general population suffers from nociplastic pain.[58] Genetic, environmental, psychosocial, and epigenetic factors probably play a role in the expression of various syndromes.[57,59]

Causes

The biopsychosocial model is particularly relevant for nociplastic pain disorders.[60,61] Although often sought out, a causal factor is usually not evident. Common predisposing factors include a family history of pain, a history of pain experiences, and psychosocial factors such as psychological, emotional, sexual, or physical abuse, or a combination of these.[62] Aggregation within families might be because of genetics and epigenetics, learned behaviour, or environmental exposures, with genetic studies identifying several candidate genes that might someday be useful as biomarkers.[63] Triggering factors might include general psychosocial stressors

(eg, workplace and family conflicts) and organ-specific biological factors such as gastrointestinal infections (identified as a trigger in 10–20% of patients with irritable bowel syndrome), and underlying inflammatory rheumatic diseases (up to 25% with comorbid fibromyalgia).[9,64,65] However, the causal relationship between a patient-reported inciting event and a chronic pain condition is often unclear, because many patients

	Diagnostic criteria and source	Associated characteristics in history and examination	Epidemiological prevalence and sex ratio (female:male)	Evidence-based international and interdisciplinary guidelines	Comments
Chronic widespread pain	2016 criteria[40] and IASP;[5] musculoskeletal pain in four or five body regions, and in at least three or more body quadrants (upper-lower or left-right side of the body and axial skeleton, including the neck, back, chest, and abdomen)	Somatic diseases, mental health disorders and low socioeconomic status	8–11%; 2:1	No	No ICD-10 code available; diagnostic criteria differ in the number of required pain sites and pain regions; heterogeneous medical conditions depending on comorbidities
Fibromyalgia	ACR[40] and AAPT;[41] chronic widespread pain and associated sleep disturbance, fatigue, and other cognitive and somatic symptoms	Fatigue, sleep disturbance, cognitive symptoms, environmental hypersensitivity, mood disorder, and post-traumatic stress; often associated with concomitant rheumatic disease; diffuse musculoskeletal tenderness	2–4%; 2:1 (in the general population)	EULAR;[42] stepwise approach according to severity: (1) non-pharmacological self-management strategies; (2) multimodal treatments including mental health care in case of mental disorder; (3) selected drug therapies with low dose tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors, and anticonvulsants, and avoidance of opioids	Diagnostic criteria differ regarding the number of pain sites, pain regions, and required non-pain symptoms; underdiagnosed in men; phenotypic expression depends on comorbidities; unclear importance of small fibre neuropathy or pathology in a small number of patients
Chronic low back pain of unknown causes (non-specific low back pain)[43]	IASP;[5] pain that is present for at least 3 months, with associated emotional distress and interference in daily activities; previously named non-specific low back pain	85% of chronic back pain is non-specific, with no clear pathoanatomic explanation; absence of red flags that suggest cancer, spinal inflammation or infection, cauda equina syndrome, major nerve root compression, vertebral fracture or abdominal aortic aneurysm[44]	Up to 10%; sex ratio influenced by country, socioeconomic status, and work activity	Clinical guidelines committee of the American College of Physicians;[44] non-pharmacological treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, etc; if there is an inadequate response to non-pharmacological treatments, proceed to drug treatment with non-steroidal anti-inflammatory drugs as a first line treatment, or tramadol or duloxetine as a second line treatment	More prevalent in the working population; leading cause of disability globally in some populations
Chronic temporomandibular pain (TMJ) disorders	AAPT;[45] chronic orofacial pain for at least 2 h per day on at least 50% of days for at least 3 months; there are two distinct phenotypes: (1) myogenous, which includes pain in masticatory muscles; and (2) arthrogenous, which includes pain in the TMJ or associated tissues; patients might have mixed phenotypes	Stiffness, cramping, pressure, soreness, or aching, or a combination, in TMJ region; fatigue and incoordination associated with jaw movement; pain on palpation of temporalis or masseter muscle, or lateral pole of TMJ	10–15%, (only 5% seek treatment); 2:1	National Institutes of Health Technology Assessment Conference Statement 1996; management of temporomandibular disorders;[46] (1) efficacy for most treatments are unknown; (2) non-invasive therapies are preferred including relaxation, behavioural therapies, etc; (3) physical therapies need validation; (4) surgery for selected patients with documented pathology of the TMJ suspected of causing pain	Frequently associated with fibromyalgia and headaches; typically associated with activities (incident pain)
Irritable bowel syndrome	Rome IV criteria;[47] symptom onset at least 6 months before diagnosis; pain on at least 1 day per week in the last 3 months associated with two or more of the following: (1) related to defecation; (2) change in stool frequency; (3) change in stool appearance; variations include irritable bowel syndrome with predominant constipation; with predominant diarrhoea; or with mixed bowel habits	Onset may be after gastrointestinal infection or antibiotic treatment, or both	5–10%; 2:1	NICE guidance:[48] (1) dietary and lifestyle advice, (2) pharmacological therapy based on severity, (3) psychological interventions if not responsive to pharmacological treatments after 12 months, and (4) discourage use of acupuncture and reflexology	Higher prevalence when assessed by population questionnaires, lower prevalence (2%) from administrative data; linked to motility disturbances, visceral hypersensitivity, altered mucosa and gut microbiota, local and systemic immune system dysfunction, and impaired CNS processing

(Table continues on next page)

	Diagnostic criteria and source	Associated characteristics in history and examination	Epidemiological prevalence and sex ratio (female:male)	Evidence-based international and interdisciplinary guidelines	Comments
(Continued from previous page)					
Chronic primary bladder pain syndrome	ICS,[49] ESSIC;[50] pain in bladder region with at least one other symptom: (1) increased pain with bladder filling; or (2) urinary frequency	Dyspareunia, urinary urgency, pain or discomfort in the pelvis, perineum, labia, vagina, or urethra; tenderness in groin, suprapubic, rectal, or vaginal regions	3–6%; 2–10:1	EAU;[51,52] stepwise approach: (1) education, physiotherapy, behavioural modification (eg, timed voiding, fluid modification, bladder training), psychological therapies as indicated; (2) pharmacotherapy (eg, low dose tricyclic antidepressants, antispasmodics, drugs that affect gastrointestinal motility and secretions); (3) intravesical injections with local anaesthetic, dimethyl sulfoxide, botulinum toxin, and other medications; (4) neuromodulation	Disagreement between guidelines on the exact definition of bladder pain syndrome and the nomenclature to describe it; disparity in recommended diagnostic investigations with hydrodistension and bladder biopsy either recommended, considered optional, or not recommended; underdiagnosed in men
Chronic primary pelvic pain syndrome in men	NIH classification of prostatitis;[53] category 3B identified when there is an absence of evidence for infection (insignificant white blood cell count in prostatic secretions, third bladder void, or semen); localised to the pelvic region outside of the distribution pattern of a specific visceral structure; often used synonymously with chronic prostatitis without a documented infection	Pain in abdomen, inguinal or groin region, or rectum; pain brought on or worsened by urination; pain associated with ejaculation, ejaculatory dysfunction, loss of libido; strong association with anxiety and depression; muscle tenderness in abdominal or pelvic regions	2–16% in USA in men, 2–9% in Asia in men; 0:1	EAU;[51,54] (1) education and physical therapy; (2) myofascial trigger point release; (3) drug therapy (eg, non-steroidal anti-inflammatory drugs, botulinum toxin injections); (4) phytotherapy; and (5) psychological therapies	..
Chronic primary pelvic pain syndrome in women	No standardised international definition of chronic pelvic pain in women; pain localised in the pelvic region with a referral pattern from pelvic internal organs often outside of typical distribution maps	Cyclical, intermittent, situational, or consistent pelvic pain with radiation to the low back, groin, and upper leg; can be associated with menstruation, sexual intercourse, urination, and defecation; tenderness in pelvic region (genital organs, pelvic floor)	15% of women (60–80% have no identifiable somatic pathology, eg, endometriosis, adhesions); 1:0	EAU,[51] ISPOG;[55] include: (1) education; (2) physiotherapy; (3) physical therapies (eg, trigger point injections); (4) psychological therapies; (5) drug therapy does not have adequate evidence; antidepressants or other adjuvants might be considered in individual cases	There are few randomised controlled trials available that guide treatment for patients without organic pathology

AAPT=Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks and American Pain Society Pain Taxonomy. ACR=American College of Rheumatology. EAU=European Association of Urology. ESSIC=European Society for the Study of Interstitial Cystitis. EULAR=European League Against Rheumatism. IASP=International Association for the Study of Pain. ICS=International Continence Society. ICD-10=International Classification of Diseases 10th edition. ISPOG=International Society of Psychosomatic Obstetrics and Gynaecology. NICE=National Institutes for Health and Clinical Excellence. NIH=National Institute of Health. TMJ=temporomandibular joint.

Table: **Most common nociplastic pain syndromes**

identify precipitating events that do not have a pathoanatomical basis.[66,67]

Natural course

The diagnosis of nociplastic pain is typically delayed, with physicians still adhering to the adage of a so-called diagnosis of exclusion for many conditions. This delay often results in excessive health-care use and further exacerbates mistrust towards medical professionals. The natural course of most nociplastic conditions is one of persistent and sometimes lifelong symptoms, although some patients, often with localised symptoms, have complete remission. In one survey involving 900 patients in Europe and Latin America, it took an average of 35 months and interactions with 4·5 physicians before a diagnosis of fibromyalgia was made, with the mean duration of symptoms being 89 months (longer in Latin America).[68] Persistent symptoms have been reported for adolescents and adults with fibromyalgia.[69,70] The prognosis for other nociplastic conditions might be better than that for widespread pain. For irritable bowel syndrome, a systematic review found that 2–5% of patients were diagnosed with an alternative disorder during a 6-year follow-up, 2–18% had worsening symptoms, 30–50% had relatively stable symptoms, and the rest of the patients (approximately a third) saw improvement in their symptoms.[71] In a Danish cohort study with 5-year follow-up, persistent symptoms of IBS were associated with more health-care visits, greater sickness and disability benefits, and excess unadjusted health-care costs of €680 per year.[72] A cohort study evaluating untreated temporomandibular disorders reported that three-quarters of the patients had a decrease or resolution of their symptoms at a 2·5-year follow-up, with the other 25% having no improvement or requiring

treatment.[73] Another study done in patients with temporomandibular disorders found that a better baseline health predicted less pain at a mean follow-up period of 8 years.[74] 72% of patients in this cohort continued to have a diagnosis of a temporomandibular disorder at the 8-year follow-up, with the average pain intensity felt by these patients being 31% less. Although some patients have symptom eradication, this does not happen in most; however, over time, most patients are able to identify some effective treatment strategies.[70]

Nociplastic pain syndrome categories

Examples of common conditions, diagnostic criteria, clinical characteristics, and guidelines are shown in the table. Previously used descriptive terms, such as chronic low back pain and chronic pelvic pain, covered a wide spectrum of pain disorders that ranged from exclusively nociceptive to exclusively nociplastic mechanisms.[75] Across syndromes, severity can vary from a minor inconvenience to incapacitating symptoms, with comorbid CNS symptoms present to variable degrees.

Chronic widespread pain and fibromyalgia

Chronic widespread pain might be a stand-alone diagnosis, but is more commonly the cornerstone for fibromyalgia, with diagnostic criteria requiring the presence of associated symptoms, including sleep disturbances or fatigue, or both.[41] Originally thought to occur mainly in women, newer criteria have removed the numerical and threshold (pain when 4 kg of pressure is applied threshold to designate a tender point) requirements for identifying tender points that led to the underdiagnosis of this condition in male individuals; thus, the condition is now believed to have a 2:1 female predominance.[76] Up to 30% of patients identify a preceding physical or psychological trigger,[77] although in a majority of patients, no pathoanatomical connection can be established. Another consideration is the increased trend to overdiagnose fibromyalgia in some regions (eg, North America), which should be balanced against underdiagnosis.[78]

Complex regional pain syndrome

Complex regional pain syndrome can be subclassified as type 1 (without nerve injury) or type 2 (with an identifiable nerve injury) and is the only nociplastic and neuropathic condition with clearly identifiable clinical findings, which involve both signs and symptoms of sensory, vasomotor, sudomotor, or motor changes, or a combination.[79] Among all nociplastic conditions, complex regional pain type 1 represents an outlier in symptom severity and clinical findings, which might be substantial. Signs and symptoms should be disproportionate to the inciting event, not caused by another medical condition, and involve symptoms and pathology outside of the distribution of a single nerve or nerve root.

Chronic primary headaches and orofacial pain

Chronic primary headaches and orofacial pain include six defined syndromes with established diagnostic criteria for chronic migraine, chronic tension-type headache, trigeminal autonomic cephalalgias, chronic temporomandibular disorder pain, chronic burning mouth, and chronic primary orofacial pain.[5] Burning mouth syndrome does not have clear criteria, and is not clearly categorised as either neuropathic or nociplastic pain.

Chronic visceral pain syndromes

The IASP has classified chronic visceral pain syndromes into six subgroups: chest, epigastric, abdominal, bladder, and pelvic pain syndromes, and irritable bowel syndrome, with the anatomical location reflecting pain patterns that often deviate from referral maps from internal organs (eg, IBS might result in a more diffuse pain pattern than inflammatory bowel disease affecting the same segment).[80] Each syndrome can be identified by symptoms referable to the organ system involved, has proposed criteria regarding the duration and frequency of symptoms, and these syndromes frequently overlap with each other. Similar to other nociplastic conditions, psychological issues and constitutional symptoms are widespread among patients. Some groups have proposed further subdivisions; for example, the Rome IV criteria for functional gastrointestinal disorders identified five oesophageal, four gastroduodenal, two gallbladder and sphincter of Oddi, and three anorectal disorders.[81] These disorders are classified by gastrointestinal symptoms related to combinations of motility disturbances, visceral hypersensitivity, altered mucosal and immune function, gut microbiota, or CNS processing.

Chronic primary musculoskeletal pain

Chronic primary musculoskeletal pain includes primary cervical, thoracic, low back, and limb pain, with spinal pain previously called non-specific back (or neck) pain. In these conditions, pain might occur spontaneously or following a trigger, but the extent of pain and suffering is greater than that expected for the underlying pathology. Structural changes in the spine are age-related and prevalent in a majority of patients by the fourth decade of life in all spinal regions, but are insufficient to account for symptoms.[82] Studies have generally found a poor correlation between MRI findings and pain intensity or quality of life measures.[83] These statistics, along with the high false-positive rate of diagnostic spine injections, underscore the inherent challenges involved in linking spine pathology to symptoms.[84] As an example, low back pain that is non-specific typically has phenotypic features of nociceptive, neuropathic, and nociplastic pain.[43] In the absence of a specific pathoanatomical cause, therapies are focused on reducing pain and preserving function, with treatments following a stepwise approach beginning with conservative care and avoiding unnecessary tests and procedures.[43]

Overlapping nociplastic pain syndromes

The clinical and pathophysiological (ie, those related to central sensitisation) features of chronic pain syndromes overlap considerably, leading the US National Institutes of Health to coin the clinical term chronic overlapping pain conditions.[57] This overlap is exemplified by bladder pain syndrome, with some patients having symptoms confined to the bladder (ie, only nociceptive pain), whereas others have widespread pain outside the pelvic region, as well as prominent fatigue, sleep, memory, and mood symptoms.[85] When symptoms are confined to the bladder, results of QST testing or functional neuroimaging are identical to healthy controls, but when the pain is more widespread, the findings are similar to fibromyalgia and patients have a poorer prognosis.[86] The diagnosis of nociplastic pain does not require the exclusion of pathophysiological factors such as low-grade inflammation that might be concurrent or function as a perpetuating trigger. Nociplastic features can occur in subsets of individuals with chronic pain conditions where there is documented ongoing nociceptive input, and might worsen the prognosis. For instance, comorbid fibromyalgia occurs in approximately 20% of patients with inflammatory arthritis, and up to 25% of patients with osteoarthritis,[87,88] and previously was sometimes labelled as secondary fibromyalgia.

Clinical characteristics of nociplastic pain syndromes

Nociplastic pain, as typified by the pain of fibromyalgia, is typically described as dull, deep, and aching (adjectives classically associated with nociceptive pain), but with many patients describing a neuropathic quality (eg, burning or shooting). The pain characteristically fluctuates both in location and intensity, and may be aggravated by physical activity, environmental stimuli (eg, weather changes), or emotional distress. Some patients might have dysaesthesia (unpleasant abnormal sensation, whether spontaneous or evoked), hyperalgesia (exaggerated pain from a stimulus that normally causes pain), or even tactile or temperature allodynia (pain from a stimulus that does not normally cause pain). Activity-induced pain or mechanical hyperalgesia, or both, result from mechanoreceptor sensory inputs gaining access to central pain-related neural systems (eg, abdomen and pelvic wall in IBS and pelvic pain, or muscles in fibromyalgia).[2]

The pain location might be segmental (eg, localised musculoskeletal area, abdomen, head, and face) or widespread and outside a specific dermatome, myotome, or sclerotome. Widespread pain typifies fibromyalgia, with localised presentations observed in most overlapping pain conditions. Nociplastic conditions represent a continuum of pain manifestations with varying degrees of severity and presentations.[76]

Non-pain symptoms

Nociplastic pain seldom occurs in isolation, and is usually accompanied by other CNS-associated symptoms, such as fatigue and sleep disturbances, cognitive impairment, hypersensitivity to external stimuli, and mood disturbances, classically described in fibromyalgia.[41] Reduced sleep quality adversely affects long-term prognosis.[89,90] Sleep deprivation in patients and healthy controls is associated with increased pain sensitivity, cognitive deficits, and mental and physical fatigue, creating a vicious cycle detrimental to the patient's health.[91] Physical fatigue might be described as a heaviness in the body or inability to do daily activities, whereas mental fatigue manifests as lethargy or concentration or memory problems. Mood problems, especially depression and anxiety, are common.

Panel 1: Overarching principles for diagnosis of nociplastic pain

- A detailed clinical history that includes:
  - A pain complaint
  - Associated fatigue and sleep disturbance
  - Associated mood and memory problems
  - Other somatic symptoms such as sensitivity to sensory stimuli
  - Other organ system symptoms that are distant from the primary pain complaint
  - Functional status
- Comprehensive physical examination to identify other conditions that could function as a peripheral pain trigger (eg, osteoarthritis or peripheral neuropathy)
- Selective testing that is condition-specific (eg, laboratory tests, imaging, or specific investigations as recommended by relevant guidelines)
- Selective use of symptom-specific questionnaires (eg, sleep, mood, fatigue, or global function)
- Assessment of severity of pain (eg, mild, moderate, or severe)
- Avoid unnecessary investigations or specialist referrals

Clinical evaluation

The foundation for diagnosing a nociplastic condition is a comprehensive evaluation, paying attention to the characteristics of the pain, the presence of other somatic and psychological symptoms, and physical examination to identify underlying differential diagnostic and comorbid conditions (panel 1). Historical features that point towards a nociplastic condition include a family or childhood history of pain, and prominent symptoms such as fatigue, cognitive problems, multiple environmental sensitivities, and psychological symptoms (panel 2).

Questionnaires

Pain assessment should include location (eg, with the use of a body map), intensity, and interference with function. Assess comorbid symptoms by clinical enquiry or with the use of short instruments such as the four-item National Institutes of Health Patient-Reported Outcomes

Measurement Information System measures.[40,92] The 2011 Fibromyalgia Survey Criteria is a composite symptom severity scale measuring pain location and other symptoms (fatigue, cognition, sleep quality, abdominal pain, and headache).[40] As a surrogate measure for central sensitisation, this scale can be used to assess how much nociplastic pain contributes to the symptom burden in other chronic pain conditions. The Patient Health Questionnaire-4, an ultra-short survey can be used to screen for depression and anxiety.[93] The Central Sensitisation Inventory was designed to assess central sensitisation and can quantify symptom severity.[94] Symptom-focused questionnaires that assess sleep or fatigue include the Pittsburgh Sleep Quality Index and the Multidimensional Fatigue Inventory.[95] A novel and objective indicator of restfulness during sleep can be obtained with the use of wrist actigraphy, which provides a 24-h measure of motor activity.[96]

Although questionnaires might assist clinicians in diagnosis and gauging symptom severity, no diagnosis should depend solely on a questionnaire threshold. Because symptoms of nociplastic conditions fluctuate, a strict cutoff value in a questionnaire at a cross-section in time will result in false-positive and false-negative results. Questionnaires should not overburden patients or providers and should never replace clinical judgment. Investigations to exclude other conditions should be selective, because unnecessary testing can exacerbate patient distress and lead to overmedicalisation (eg, serial spine MRIs for non-specific back pain). Even without a pathognomonic biomarker, physicians should feel comfortable making a diagnosis and assessing the severity of complaint. Further tests including QST, functional MRI, or positron emission tomography studies are outside the realm of usual clinical practice and are still considered to be research tools.[17,97]

Treatment strategies

General principles

An established diagnosis should be empathetically communicated to patients, and their symptoms acknowledged as real. Management strategies are directed towards attenuating, rather than eradicating, symptoms, with overarching principles (panel 3) that can be individually tailored (precision medicine). In addition to pain alleviation, treatment objectives should include improving function and other quality of life indicators. Setting realistic expectations is crucial, because low expectations might lead to poorer outcomes and higher stress levels, whereas overly optimistic expectations can lead to disappointment and disengagement.[98]

Although severe symptoms might necessitate a specialty referral, most patients can be managed in primary care, as is recommended for fibromyalgia.[42] Unnecessary investigations should be discouraged, to avoid promoting a sick role. Treatments are ideally multimodal, and should follow a stepwise approach according to severity, similar to that advocated by the US Veteran's Health Administration, beginning with education and self-care and progressing towards more sophisticated treatments as needed.[99]

Panel 2: **Clues in patient's history suggestive of nociplastic pain syndrome**

- Childhood and adolescent symptoms of pain (eg, headache, abdomen, or low back)
- General symptoms (eg, fatigue and cognitive problems)
- Hypersensitivity to environmental stimuli (eg, light or sound)
- Psychological symptoms (eg, anxiety or depression)
- Symptoms causing a high amount of emotional strain
- A family history of chronic pain and mental health problems
- High use of health-care services (eg, many doctor visits or investigations)
- Poor or no response to conventional analgesics (including opioids)

Extrapolated from the EULAR revised recommendations for the management of fibromyalgia.[42] EULAR=European League Against Rheumatism.

Non-pharmacological therapies

The management of nociplastic pain should prioritise non-pharmacological measures, because most medications provide only a modest benefit and are often associated with adverse effects, which are more likely to occur in nociplastic conditions.[100] Education should highlight the tenets of the biopsychosocial model and promote good lifetime habits, such as engaging in physical activity, weight management, sleep hygiene, and stress reduction. Self-management and a strong internal locus of control should be encouraged. Psychological strategies might include cognitive behavioural therapies, mindfulness and acceptance-based interventions, psychodynamic therapies, biofeedback, and hypnotherapy, all of which should be integrated into a multidisciplinary care programme. A Cochrane review reported that cognitive behavioural therapy (CBT) has small beneficial effects in reducing pain, disability, and distress, whereas the benefits from behavioural therapy were uncertain because of the poor quality of studies included.[101] Although strategies such as acceptance commitment therapy, emotional expression, and psychodynamic psychotherapy are commonly recommended, the evidence for their effectiveness (and for adverse effects) is insubstantial,[101] as is the case for many treatments for chronic pain. For example, a meta-analysis involving nine studies and 750 patients examining mindfulness and acceptance-based interventions for fibromyalgia reported a small benefit for pain (standardised mean difference, 0·46; 95% CI –0·75 to –0·17), and conflicting results for quality of life (standardised mean difference, –0·74; 95% CI –2·02 to 0·54).[102]

A systematic review of non-invasive, non-pharmacological therapies for various chronic pain conditions

***Panel 3*: Overarching principles of treatment of nociplastic pain**

- Non-pharmacological treatments as a preferred first step
  - Trustful doctor–patient relationship acknowledging the validity of symptoms
  - Patient education
    - Communicate neurophysiological mechanisms with the use of simple terminology such as a hyper, sensitised, or fired-up nervous system
    - Explanation of treatment strategies
    - Realistic expectations
  - Promotion of self-management and internal locus of control
  - Continued life participation (eg, work, physical, and social activities)
  - Maintain good lifetime habits
    - Health-related physical activity
    - Diet and weight management
    - Proper sleep hygiene
    - Stress reduction
- Psychological therapies
  - Cognitive-behavioural therapies
  - Acceptance-based therapies
  - Other modalities (eg, hypnotherapy or psychodynamic therapies)
- Psychiatric–psychotherapeutic treatment of mental comorbidities (depression, anxiety, or post-traumatic stress disorder)
- Interdisciplinary care, if available
- Practitioner-administered treatment as indicated
  - Physical therapies and chiropractic treatment, acupuncture, massage, or naturopathic treatments
- Pharmacological treatments
  - Centrally acting drugs (pain modulators)
    - Tricyclic antidepressant drugs
    - Serotonin–norepinephrine reuptake inhibitors
    - Gabapentinoids and other membrane stabilisers
  - Simple analgesics and non-steroidal anti-inflammatory drugs have small effects
  - Ideally avoid opioids, which are less effective and carry serious risks
- Neuromodulation (including brain stimulation and transcutaneous approaches) and other centrally acting drugs (eg, N-methyl-D-aspartate antagonists or cannabis-based medicines) may have potential for selected patients but require further research

Extrapolated from the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks and American Pain Society Pain Taxonomy Diagnostic Criteria for Fibromyalgia.[41]

(including low back and neck pain, fibromyalgia, and tension headache) reported that most studies were small with little evidence for long-term follow-up after 1 year, and generally found that improvements in pain and function were small.[103] For chronic low back pain (including non-specific back pain), the strength of the evidence for exercise improving intermediate-term functional outcome was graded as low (pooled standardised mean difference, –0·17; 95% CI –0·39 to 0·02); that for psychological therapies improving intermediate pain outcome was graded as moderate (pooled difference –0·71; 95% CI –0·97 to –0·46); that for mindfulness or mind–body practices were mostly graded as low for improving pain and function in the short term, intermediate term, and long term; and that for physical modalities such as ultrasonography, interferential therapy, laser therapy, or massage were mostly graded as insufficient or low for improving pain and function in the short-term, intermediate-term, or long-term.[103] In a systematic review of treatments for bladder pain syndrome, six of 13 included studies were rated as low quality, because the authors were not able to define a best approach to care.[104] Treatments included the instillation of hyaluronic acid, botulinum toxin A, lidocaine, hyperbaric oxygen, massage, and physiotherapy, but there were no treatments with more than a single clinical trial, precluding a meta-analysis.[104]

Dietary manipulation is commonly used by patients with chronic pain. In a systematic review of seven clinical trials for dietary interventions for fibromyalgia, there was a suggestion of improvement with hypocaloric, raw vegetarian, and low fermentable oligo-di-monosaccharides and polyols (FODMAP) diet, but the evidence was evaluated as being poor quality.[105] Elimination diets might improve the symptoms of IBS, with foods in the FODMAP category provoking symptoms.[106] In a systemic review of 12 eligible studies assessing nutritional factors for musculoskeletal pain (including fibromyalgia and generalised musculoskeletal pain), seven studies reported pain-relieving effects from dietary changes, with the pain threshold positively associated with protein intake, and pain severity associated with fat and sugar intake.[107] The review concluded that plant-based diets might have some effect in relieving musculoskeletal pain.

For temporomandibular disorder, a systematic review of eight non-blinded studies (seven of which were of a high methodological quality) found that manual therapy, depending on the specific techniques used, reduced pain and improved maximal mouth opening and pressure pain threshold.[108]

Some patients might benefit from practitioner-administered integrative treatments such as acupuncture, massage, or naturopathic therapies, although there is little evidence of effectiveness. An overview of reviews on complementary and alternate therapies in the treatment of fibromyalgia reported that although there is a growing body of evidence for these treatments, conclusions about efficacy are limited by methodological study flaws.[109] If interdisciplinary care is unavailable, individual components such as group education sessions, telehealth-administered CBTs, and physical activity programmes that are accessible by the community can be recommended. Recognising the co-existence of nociplastic pain with other illnesses allows treatments to be focused towards nociplastic pain management and prevents care being erroneously directed to a well controlled underlying condition (eg, unnecessary changes to disease-modifying therapy for inflammatory arthritis).

Pharmacotherapy

The detailed discussion of pharmacotherapy is beyond the scope of this review. Traditional analgesic treatments such as muscle relaxants, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and

opioids are less effective for nociplastic pain than for nociceptive pain, with the use of opioid analgesics strongly discouraged.[110] Apart from the known risks associated with opioid therapy, patients with nociplastic pain might be less responsive to opioids because of higher concentrations of endogenous opiates, the worsening of hyperalgesia, and interference with sleep architecture.[111,112] In fact, low dose naltrexone, an opioid antagonist that might work in part by increasing the density of opioid receptors and the subsequent response to endogenous opiates, has shown some benefit for fibromyalgia, chronic back pain, and complex regional pain.[113]

Some medications have received regulatory approval for nociplastic conditions, especially fibromyalgia, with differences across countries (eg, pregabalin, duloxetine, milnacipran for fibromyalgia, and duloxetine for musculoskeletal pain including low back pain).[114] Regulatory approval, however, does not necessarily indicate a clinically meaningful effect, as is shown by the widespread discrepancies between clinical practice guidelines and US Food and Drug Administration indications. The recent National Institute for Health and Care Excellence guidelines for the management of chronic primary pain have given strong support for non-pharmacological measures, but contrary to all other guidelines, they recommend antidepressants as the only medication category for consideration of use, and caution about the continued use of other medication categories that might have been prescribed.[115] A review of non-opioid pharmacological agents for the management of various chronic pain conditions (including fibromyalgia, low back pain, and chronic headaches) reported mostly small improvements (eg, 5–20 points on a 0–100 scale) for gabapentinoids, serotonin–norepinephrine reuptake inhibitors, (SNRIs) and NSAIDs for pain and function in the short term, with intermediate and long-term outcomes infrequently assessed.[116] Although non-opioid analgesics that act on the CNS, such as tricyclic antidepressants, SNRIs, and gabapentinoids, can provide some benefit, adverse reactions are frequent and might worsen fatigue and cognitive impairment.[116] Cannabis-based medicines hold promise but require formal study before the widespread use in patients at high risk for adverse effects. Emerging treatments such as neuromodulation have theoretical potential, but have few data on effectiveness.

Conclusions

Nociplastic has entered the medical vernacular in the past 2 years to describe pain conditions that are neither neuropathic nor nociceptive, but commonly experienced by people worldwide. The framework of nociplastic conditions will evolve in future decades as more conditions are recognised as having a component that is nociplastic, and discrete pathophysiological pathways and biomarkers are identified. These diverse pain syndromes have considerable overlap, and present with clinical features that are almost entirely subjective, except for tenderness. An improved understanding of the underlying mechanisms is crucial to developing effective treatment strategies. Questions for further research include why some conditions are localised to a single organ system, whereas others present more diffusely, identifying triggers that might lead to preventive strategies, and establishing the best treatments in the context of precision medicine.

Contributors

M-AF prepared the outline of the article, contributed to the preparation of the manuscript, figures, and tables, and approved the final version. SPC and DJC contributed to the preparation of the manuscript, figures, and tables, and approved the final version. GL and CU contributed to the preparation of the manuscript and tables and approved the final version. WH contributed to the outline of the article, preparation of the manuscript, figures, and tables, and approved the final version.

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