

Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system

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1. Introduction

The term “nociplastic pain” was introduced by the International Association for the Study of Pain (IASP) in 2017 as a third mechanistic pain descriptor in addition to nociceptive and neuropathic pain [15, IASP website <https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698>]. Nociplastic pain is defined as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.” The term is intended for both clinical and research usage to identify individuals in whom there is pain and hypersensitivity in regions with apparently normal tissues and without any signs of neuropathy.¹⁵ Although central sensitization is most likely a dominating mechanism in nociplastic pain conditions, the term

nociplastic pain should not be regarded as synonymous with the neurophysiological term “central sensitization”.¹⁵ In addition, a contribution of peripheral sensitization cannot be excluded. The concept of nociplastic pain harmonizes with the current view that certain forms of chronic pain are better understood as conditions or diseases of their own, rather than symptoms of other underlying pathology or diseases.²⁶ The latter is reflected in the ICD-11 classification of chronic pain into primary—pain as a disease—and secondary—pain as a symptom—²⁶ where most, if not all, of the primary pain subgroups consist of conditions with nociplastic pain. However, it must be recognized that the terms reflect different dimensions as “nociplastic” is a mechanistic term, whereas “primary pain” is a diagnostic concept.

Chronic pain conditions such as fibromyalgia, complex regional pain syndrome type 1, and irritable bowel syndrome are examples of pain conditions, where nociplastic pain is typically present.¹⁵ These conditions have documented changes of nociceptive processing in the nervous system,^{12,17–19} thus precluding the classification of their pain as “pain of unknown origin” (idiopathic pain). The classifier “pain of unknown origin” should be reserved for patients with pain that cannot be designated as nociceptive, neuropathic, or, now, nociplastic and is a label awarded by exclusion.

It is becoming increasingly understood that many individuals have pain states, wherein there is more than one pain mechanism present. For example, patients with lumbar disk herniations often suffer from a nociceptive pain in the back and neuropathic pain (radiculopathy) in the leg. Nociplastic pain can also co-occur with neuropathic and particularly with nociceptive pain mechanisms. The latter is highlighted by the note in the nociplastic pain definition stating that “patients can have a combination of nociceptive and nociplastic pain.” In fact, it seems as though having ongoing nociceptive pain is a risk factor for developing nociplastic pain because hypersensitivity is associated with longer duration of nociceptive pain,^{16,21} and high rates of nociplastic pain states, such as fibromyalgia, are seen in individuals with osteoarthritis, rheumatoid arthritis, and other nociceptive pain disorders.^{5,28} Given that hypersensitivity is often seen also in nociceptive pain,^{14,16,24} the clinician is faced with an unresolved problem, namely, when should a patient with nociceptive pain be classified as also having nociplastic pain?

Research in nociplastic pain states has used sophisticated techniques to specifically identify the dysfunctions involved. Quantitative sensory testing may be useful for assessing temporal summation¹ and conditioned pain modulation,³⁰ whereas offset analgesia³² and functional neuroimaging can identify changes in cerebral pain processing.¹² However, these techniques are not always available for use in clinical practice or even in all research

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settings. Thus, the need for clinical criteria for nociplastic pain was recognized by the IASP, and an IASP Terminology Task Force (TTF) was formed to develop clinically useful criteria for nociplastic pain. It was recognized that different sets of clinical criteria would most likely be required for nociplastic pain manifested in the musculoskeletal system and viscera. Therefore, the criteria presented in this article are designed for nociplastic pain manifested within the musculoskeletal system. The intention is that criteria for nociplastic pain perceived in the viscera will be defined by another IASP task force consisting of experts in visceral pain and presented in a future article.

2. Procedures and processes

The objective was to use a consensus procedure within an expert group consisting of the IASP TTF, to define a set of clinically and research applicable criteria for nociplastic pain presented in the musculoskeletal system. From a preliminary draft of classification criteria proposed by the chair to initiate further discussions, each member of the IASP TTF, ie, the authors, was asked to present his or her own set of criteria. Eight anonymized propositions were reviewed and voted on by the task force with 3 votes per member. Four propositions with the lowest amounts of votes (1, 2, 2, and 3, respectively) were excluded. Two very similar propositions received 4 votes each and were pooled into alternative A after a slight modification. In addition, the 2 alternatives that received the highest number of votes from the TTF members (alternative B: 6 votes and alternative C: 8 votes) were kept for further consideration.

In collaboration with the IASP office an “external” stakeholder group was identified, consisting of “experts” suggested by the TTF members and IASP “leaders” (IASP Councilors, Chapter Presidents, the SIG Leadership, and a few other IASP representatives) identified by the office. Feedback was received from 21 “experts” and 34 “leaders”. The group voted on the criteria, answered 3 questions (Table 1), and could freely provide comments or suggestions. The questions were based on issues that raised particular debate within the TTF. Among the stakeholders, 35% voted for alternative A, 25% for alternative B, and 40% for alternative C. The main differences between alternatives A and C was that alternative A included examination with quantitative sensory testing (QST), but not nonpain symptoms, whereas alternative C included nonpain symptoms, but not QST. In a separate vote, 57% of the stakeholders voted for including nonpain symptoms and 6 provided personal comments advising against QST because the method is not widely available. Furthermore, several stakeholders stated that the criteria should be kept simple. The proposed grading was based on the classification of neuropathic pain as possible, probable, or definite⁷ (Table 1). Most felt that grading possible or probable nociplastic pain was the most appropriate choice (43%), rather than no grading (19%) or grading possible, probable, or definite (38%). For 2/3 of the criteria, most agreed that the proposed clinical criteria developed for musculoskeletal pain would not be suitable to use also for visceral

pain. After the voting, the TTF continued working on the set of clinical criteria preferred by the “external” group as well as the TTF (C), discarding the 2 other alternatives. To accommodate suggestions for improvement from the “external” group as well as the TTF, the criteria were clarified to reduce the need of long notes, referred pain on palpation was omitted as a sign of nociplastic pain, the word comorbidities was used instead of nonpain symptoms, and the order of the criteria was changed to a better fit clinical practice (ie, history first and examination last).

3. Clinical criteria for nociplastic pain affecting the musculoskeletal system

Following the procedures outlined above, the IASP TTF proposes the set of criteria with a grading system encompassing possible and probable nociplastic pain, as outlined in Table 2. A flow chart depicting the algorithm for assessing nociplastic pain is presented in Figure 1.

4. Discussion

The main purpose of the clinical criteria is to define aspects that must be considered before assigning the descriptor nociplastic pain. In summary, to classify nociplastic pain, the subject has to meet the requirements of the first and fourth section of the criteria, ie, 4 conditions have to be fulfilled: I) pain duration > 3 months (1), II) a regional rather than discrete distribution (1), III) the pain cannot entirely be explained by nociceptive or neuropathic mechanisms (1), and IV) clinical signs of pain hypersensitivity are present in the region of pain (4). The presence of a history of pain hypersensitivity in the region of pain (2) and defined comorbidities (3) strengthen the probability of nociplastic pain, and both have to be present to designate probable nociplastic pain. All the elements of the proposed criteria are discussed below.

4.1. Obligatory criteria

The working group carefully considered all the elements of the proposed criteria and found that the clinical relevance of defining acute pain as nociplastic is doubtful, given that altered nociception increases with longer pain duration.^{12,16,21} Therefore, the proposed criteria are meant to be used to identify individuals with chronic nociplastic pain, using the classic demarcation of 3 months of pain. The emphasis in the criteria on regional rather than discrete pain is meant to stress the fact that when central sensitization is present as the underlying neurophysiological mechanism, the receptive fields of the sensitized neurons expand. The resulting perception ranges from an expanded single region of pain to multifocal pain or widespread pain, and the distribution of hypersensitivity also increases. It is extremely common for nociplastic pain to be superimposed on nociceptive pain, and patients can also have coincidental nociplastic and neuropathic pains. In the first case, the spatial involvement of the pain (ie, how widespread the pain is) will be greater than one would

Table 1

Questions sent out to the stakeholders.

(1) Should nonpain symptoms (eg, disturbed sleep, fatigue, cognitive symptoms, and/or increased sensitivity to light, sound, or odors) be included in the criteria for nociplastic pain?

(2) Should there be a grading of “possible,” “probable,” and “definite” nociplastic pain (similar to the neuropathic pain classification)?

(3) The intention of the IASP Terminology Task Force is to develop clinical criteria for nociplastic visceral pain at a later stage, intended for conditions such as irritable bowel syndrome, bladder pain syndrome, and the like. Would any of the presented alternatives be suitable also for visceral nociplastic pain conditions?

Table 2**Clinical criteria and grading for nociplastic pain affecting the musculoskeletal system.**

1. The pain is
 - 1a. Chronic (>3 mo);
 - 1b. Regional (rather than discrete) in distribution*;
 - 1c. There is no evidence that nociceptive pain (a) is present or (b) if present, is entirely responsible for the pain; and
 - 1d. There is no evidence that neuropathic pain (a) is present or (b) if present, is entirely responsible for the pain.†
2. There is a history of pain hypersensitivity in the region of pain.

Any one of the following:

 - Sensitivity to touch
 - Sensitivity to pressure
 - Sensitivity to movement
 - Sensitivity to heat or cold
3. Presence of comorbidities:

Any one of the following:

 - 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, etc.
4. Evoked pain hypersensitivity phenomena can be elicited clinically in the region of pain.

Any one of the following:

 - Static mechanical allodynia
 - Dynamic mechanical allodynia
 - Heat or cold allodynia
 - Painful after-sensations reported following the assessment of any of the above alternatives.

Possible nociplastic pain: 1 and 4.

Probable nociplastic pain: all the above (1, 2, 3, and 4)‡

* Musculoskeletal pain is deep, rather than cutaneous and regional, multifocal, or widespread in distribution (rather than discrete). In case of multifocal pain states that can be caused by different chronic pain conditions (eg, shoulder myalgia and knee osteoarthritis), each chronic pain condition or pain region must be assessed separately.

† The presence of a source of nociceptive pain, such as osteoarthritis, or of neuropathic pain, such as a peripheral nerve lesion, does not exclude the concurrence of nociplastic pain, but the region of pain must be more widespread than that which can be explained by the identifiable pathology.

‡ The purpose of the grading system is to indicate the level of certainty that a patient has nociplastic pain and, as mentioned above, was inspired by the current grading system for neuropathic pain.⁷ However, because of the lack of clinically useful, reliable diagnostic tests to confirm the presence of altered nociception, currently nociplastic pain is graded as possible or probable but not definite. If future diagnostic tests are developed and validated, the introduction of the term "definite nociplastic pain" should be considered.

expect if only the nociceptive mechanisms were present, as, eg, the widespread pain and hypersensitivity of fibromyalgia in a patient suffering from osteoarthritis of the hip. In the second case, the distribution of pain and hypersensitivity would extend well beyond the innervation territory of the lesioned or diseased nervous structure.

4.2. How should the history of pain hypersensitivity be assessed in the clinic?

To fulfill the second criterion, a history of pain hypersensitivity to touch, pressure, movement, or heat cold must be present. It is therefore recommended to question patients regarding their current hypersensitivity to these modalities.²⁰ Patients may perceive the touch of clothing against the skin and/or the pressure from belts, handbags, and bras as unpleasant or painful. They may report hugging to be painful and/or note that it is painful to sit in a chair for any prolonged periods. Hypersensitivity to movement can be assessed by asking how habitual physical activities of moderate intensity, such as walking, affect their pain, with exercise-induced reductions of pain intensity considered to be the normal response and exercise-induced exacerbations of pain representing a sign of altered pain modulation,²² providing they are not better explained by a specific peripheral pathology. A history of increased pain during a cold or warm bath or shower is a typical sign of thermal hypersensitivity.

4.3. What is the rationale for including comorbidities?

Whether to include comorbidities was a significant area of discussion. Three coauthors preferred criteria without non-nociception-related features as clinical criteria for identifying a

descriptor of pain itself. Others argued that data show that these nonpain symptoms are nearly always present and, in many settings, have been shown to be discriminative in identifying individuals with nociplastic pain mechanisms. In addition to a history of hypersensitivity to somatosensory stimuli as noted above, individuals with nociplastic pain will typically report increased sensitivity to sound, light, and odors.^{8–10} In addition, although not specific for nociplastic pain, disturbed sleep,²⁵ fatigue, and cognitive problems⁶ are common. Furthermore, in nociplastic pain conditions such as fibromyalgia, the widespreadness of pain (eg, measured as the Widespread Pain Index in the 2011/2016 fibromyalgia criteria)²⁹ as well as the presence and severity of these comorbid symptoms (as measured in the accompanying symptom severity score)²⁹ each contribute nearly equal variance in predicting outcomes of nociplastic pain such as opioid nonresponsiveness or nonresponsiveness to surgery intended to relieve pain^{3,4,11} and also the relative responsiveness to other nonopioid pharmacological treatments addressing comorbidities.

4.4. How should the pain hypersensitivity phenomena be assessed in the clinic?

Dynamic mechanical allodynia can be assessed by gently stroking the skin with a brush or a cotton pad and asking whether the resulting sensation is painful or not. Static mechanical allodynia is usually assessed by digital palpation with a weight of approximately 4 kg (nailbed blanching) and reporting pain on this palpation would be considered pressure allodynia.²⁷ Cold allodynia can easily be tested by holding a metal object kept at room temperature (approx. 20°C) against the skin, and the same

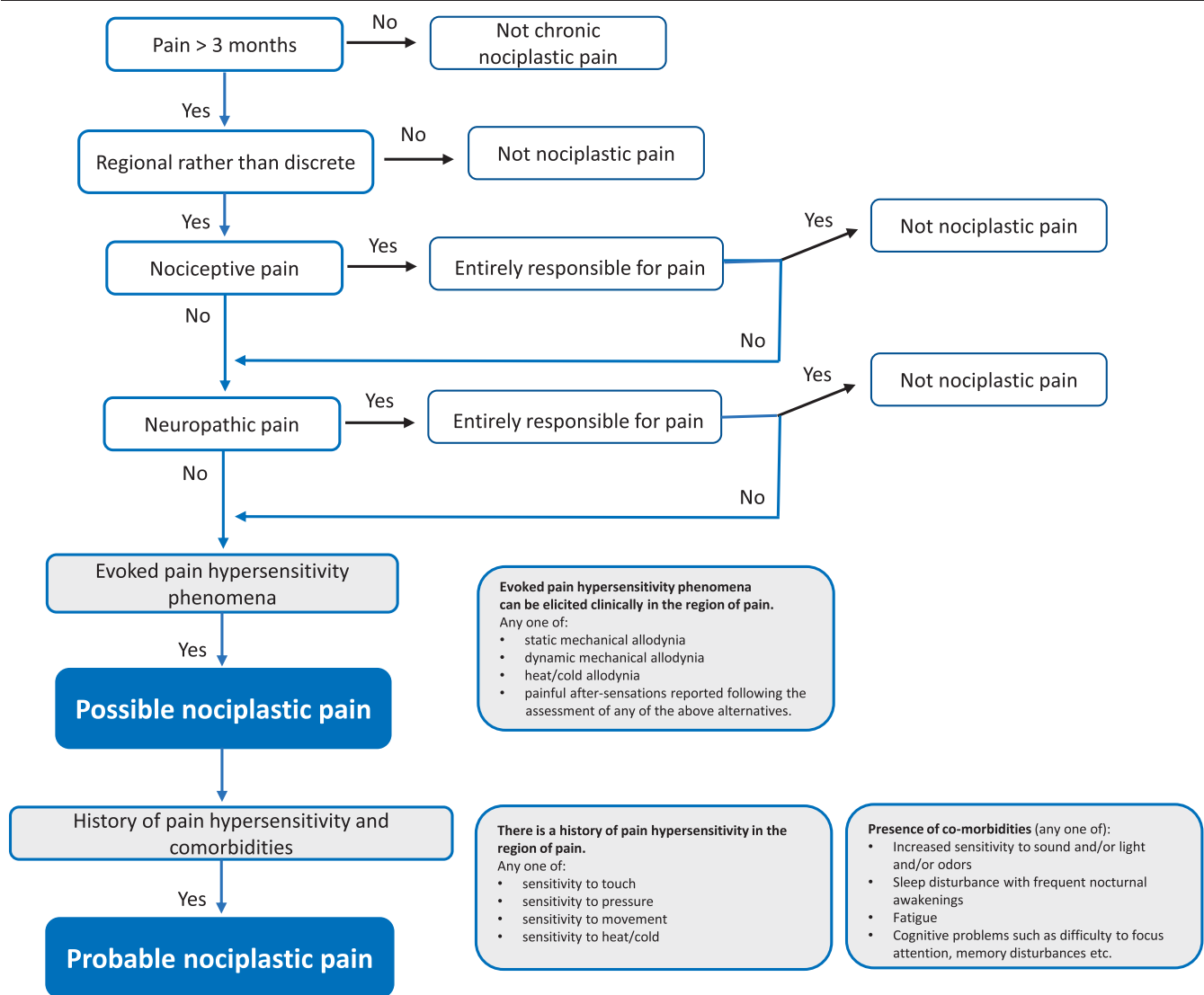


Figure 1. Flow chart of identifying and grading nociplastic pain affecting the musculoskeletal system. Musculoskeletal pain is deep, rather than cutaneous and regional, multifocal, or widespread in distribution (rather than discrete). In case of multifocal pain states that can be caused by different chronic pain conditions (eg, shoulder myalgia and knee osteoarthritis), each chronic pain condition or pain region must be assessed separately.

object can be heated with water to assess heat allodynia (approx. 40°C). After each examination, the subject is asked whether the sensation lingers after the stimulus has ended to check for the presence of after-sensations. Furthermore, it is helpful to first assess whether there is hypersensitivity only in the region of reported pain or whether, as typically seen in nociplastic pain, the hypersensitivity is more widespread.

In case quantitative sensory testing can be performed, pain hypersensitivity is typically assessed using special brushes, calibrated needles or filaments, pressure pain algometry, and various thermal testing devices,² and normative data have been published.²³ In addition, assessments indicative of central aberrations of sensory processing such as increased temporal summation³¹ or dysfunctional conditioned pain modulation^{13,31} or exercise-induced hypoalgesia²² can be performed, but the reliability of these tests in the clinical setting remains to be established.

4.5. The strengths and weaknesses of the clinical criteria

The proposed criteria are supported by expert opinion, which is a potential source bias. A research agenda including studies

exploring the clinical validity (ie, test–retest reliability, interobserver reliability, concurrent validity, content validity, etc.) of the proposed criteria is needed. Furthermore, future field testing of the criteria would be valuable. A major limitation of the criteria is the dependence on clinical judgement to decide when nociceptive and/or neuropathic mechanisms can be regarded as being entirely responsible for the pain and when not, a difficulty that is inherent every time pain mechanisms are to be attributed to painful conditions in the clinic. However, these judgments can be made. For example, in a patient suffering from polyneuropathy, bilateral pain below the knees would be considered neuropathic, but the patient's low back pain would not, and could be nociplastic. Another example would be a patient with rheumatoid arthritis initially presenting with pain localized to inflamed, tender, and swollen joints, regarded as nociceptive pain. Yet, when this patient, despite excellent inflammatory control, continues to complain of joint pain with tender, but not swollen joints, as well as muscular pain and tenderness in the extremities and back, the nociplastic pain criteria would most likely be fulfilled.

The classification of nociplastic pain is not a new diagnosis; rather this mechanistic term indicates the likely presence of

specific pain mechanisms, regardless of the underlying diagnosis (eg, osteoarthritis, fibromyalgia, etc). The concept should be integrated into the clinical reasoning process because it points towards specific pain mechanisms, which can affect the treatment approach because patients with nociplastic pain are likely to respond better to centrally than peripherally targeted therapies. The term has the potential to facilitate communication and validate the patient's pain experience. Clinicians should explain the meaning of nociplastic pain to their patients providing simple explanations that help patients make sense of their pain and understand what can be done (and what they can do) about it, including the implications for treatment and prognosis as a result of the pain being classified with this mechanistic descriptor.

Conflict of interest statement

E. Kosek has received consultancy fees from Lundbeck and Eli Lilly. D. Clauw has received consultancy fees from Pfizer, Aptinyx, Samumed, Tonix, Lilly, IMC, and Lundbeck. R. Baron has received consultancy fees from Pfizer Pharma GmbH, Genzyme GmbH, Grünenthal GmbH, Mundipharma Research GmbH and Co, KG, Allergan, Sanofi Pasteur, Medtronic, Eisai, Lilly GmbH, Boehringer Ingelheim Pharma GmbH & Co, KG, Astellas Pharma GmbH, Novartis Pharma GmbH, Bristol-Myers Squibb, Biogen-idec, AstraZeneca GmbH, Merck, Abbvie, Daiichi Sankyo, Glenmark Pharmaceuticals S.A., Seqirus Australia Pty. Ltd, Teva Pharmaceuticals Europe Niederlande, Teva GmbH, Genentech, Mundipharma International Ltd, UK, Astellas Pharma Ltd, UK, Galapagos NV, Kyowa Kirin GmbH, Vertex Pharmaceuticals Inc, Biotest AG, Celgene GmbH, Desitin Arzneimittel GmbH, Regeneron Pharmaceuticals Inc, USA, Theranexus DSV CEA Frankreich, Abbott Products Operations AG Schweiz, Bayer AG, Grünenthal Pharma AG Schweiz, Mundipharma Research Ltd, UK, Akcea Therapeutics Germany GmbH, Asahi Kasei Pharma Corporation, AbbVie Deutschland GmbH & Co KG, Air Liquide Sante International Frankreich, Alnylam Germany GmbH, Lateral Pharma Pty Ltd, Hexal AG, Ethos Srl Italien and Janssen. I. Gilron reports personal fees from Adynxx, Biogen, Eupraxia, Novarmed, and Teva and nonfinancial support from Canopy Health, Toronto Poly Clinic, and CannTrust, outside the submitted work. A. Rice is an IASP Council Member and Chair 18th World Congress on Pain Scientific Programme Committee, undertakes consultancy and advisory board work for Imperial College Consultants—in the past 24 months, this has included remunerated work for the following: Abide, Pharmanovo, Lateral, Novartis, Pharmaleads, Mundipharma, Orion, Asahi Kasei, Toray & Theranexis, was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued on the acquisition of Spinifex by Novartis in July 2015 and from which payments continued until 2019, is named as an inventor on patents: Rice A.S.C., Vandevoorde S. and Lambert D.M Methods using N-(2-propenyl)hexadecanamide and related amides to relieve pain. WO 2005/079771 and Okuse K. et al. Methods of treating pain by inhibition of vgf activity EP13702262.0/WO2013 110,945. The remaining authors have no conflicts of interest to declare.

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