Topical Review

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Do we need a third mechanistic descriptor for chronic pain states?

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1. Introduction

The redefinition of neuropathic pain,[23] which specifically excludes the concept of "dysfunction," has left a large group of patients without a valid pathophysiological descriptor for their experience of pain. This group comprises people who have neither obvious activation of nociceptors nor neuropathy (defined as disease or damage of the somatosensory system) but in whom clinical and psychophysical findings suggest altered nociceptive function. Typical such patient groups include those labelled as having fibromyalgia, complex regional pain syndrome (CRPS) type 1, other instances of "musculoskeletal" pain (such as "nonspecific" chronic low-back pain), and "functional" visceral pain disorders (such as irritable bowel syndrome, bladder pain syndrome). The aim of this topical review was to propose, for debate, a third mechanistic descriptor intended for chronic pain characterized by altered nociceptive function.

1.1. Historical review

Before developing any argument for a third descriptor to accommodate these patients, it is worthwhile reviewing the history of pain terminology. Traditionally, pain mechanisms have been divided into "nociceptive" and "neuropathic" categories. See **Table 1** for the historical overview of these definitions.

1.2. Implications of the changed definition of "neuropathic pain"

In the 2005 iteration, "nociceptive" pain was the norm, the "default" or common sense experience of injury = damage ≤pain, familiar to humans. But it evolved that *any* pain that was not "nociceptive" might be termed "neuropathic" because the latter descriptor included "dysfunction," which was taken to include any inferred change in nociceptive function. Although it has always been possible to invoke another category, such as "unknown" or "idiopathic," that strategy runs a poor third to the other 2, as there is no implication of a putative mechanism.

The 2011 redefinition of neuropathic pain makes biological and etymological sense. The note that accompanies this definition is stringent: *Neuropathic pain is a clinical description* (*and not a diagnosis*), which requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria. This robust definition is not being challenged.

However, the note that accompanies the 2011 redefinition of *nociceptive* pain—pain that arises from actual or threatened damage to nonneural tissue and is due to activation of nociceptors—states: *This term* ***is designed to contrast with neuropathic pain***. *The term is used to describe pain occurring with a normally functioning somatosensory nervous system to contrast with the abnormal function seen in neuropathic pain* (emphasis added). This perpetuates the "nociceptive–neuropathic" dichotomy as above, except that now the "default" position is neuropathic pain, so that any pain condition that is not characterized by damage to neuronal tissue may attract the term "nociceptive." This is not only counterintuitive, as surely "a normally functioning somatosensory nervous system" should be taken as the basis for any contrast, but also it fails to accommodate a large group of patients in whom "activation of nociceptors" cannot be confidently established.

2. Proposals

This situation requires clarification. The proposals put forward here, as presented in **Table 2**, include:

(1) Assertion of nociceptive pain
(2) Confirmation of definition of neuropathic pain, but not as default
(3) Need for a third descriptor.

2.1. Assertion of nociceptive pain

"Nociceptive pain" is the most common human experience of pain. Therefore, we propose that the current IASP 2011 definition of nociceptive pain be used, but that the note be shortened to: "The term is used to describe pain occurring with a normally functioning somatosensory nervous system." Nociceptive pain should not be defined as the alternative to neuropathic pain. This

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Table 1

Historical overview of mechanistic pain terminology.

	Nociceptive	Neuropathic
1994*	Not defined	Pain initiated or caused by a primary lesion or dysfunction in the nervous system
2005*	Pain due to stimulation of primary nociceptive nerve endings	Pain due to lesion or dysfunction of the nervous system
2007-2010	Pain due to activation of primary nociceptors Pain arising from activation of nociceptors Pain resulting from noxious stimulation of normal tissue with a normal somatosensory nervous system	
2011*	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors	Pain caused by a lesion or disease of the somatosensory nervous system

* Adopted by IASP council in those years.

common-sense biological position presumes that the tissue was "normal" before the noxious stimulus and that the somatosensory apparatus is also "normal."

2.2. Confirmation of definition of neuropathic pain, but not as default

The new definition of neuropathic pain does not require amendment. However, because it is not as common as nociceptive pain and it does not reflect the usual experience of pain, it should not be the default descriptor.

2.3. Need for a third descriptor

Even with these points of clarification, the situation of only 2 descriptors will remain unsatisfactory for those patients in whom "activation of nociceptors" cannot be confidently demonstrated or assumed and who also do not meet the definition of "definite" or "probable" neuropathic pain. Appending "possible" neuropathic pain leaves them in taxonomic limbo.

In the current state of knowledge, there are reasons to infer that altered nociceptive function does occur in patients experiencing pain in a regional (or more widespread) distribution, unassociated with frank signs of neuropathy but characterized by hypersensitivity in apparently normal tissues. The similarity of such findings to those in frank neural injury or disease suggests that common mechanism(s) may be relevant. A reasonable inference from the presence of these findings is that there has occurred a change in nociceptive processing, probably in the central nervous system. The latter is supported by the findings of demonstrated changes in cerebral activation,[16,19,38,39,45] connectivity,[4,14,20,25,33,37,41,50] and even in specific cerebral structures[1,5,18,22,24,31,36,44] in certain clinical pain states, when also adjusted for depression or anxiety.[5,18,21,22,36] However, in these pain conditions, there is no consistent evidence of a lesion or disease of the

Table 2

Proposed taxonomy for the classification of pain compared with the existing IASP taxonomy from 2011 (http://www.iasp-pain.org/Taxonomy), changes highlighted.

Descriptor	Definition	Notes
Nociceptive pain	Pain that arises from actual or threatened damage to nonneural tissue and is due to the activation of nociceptors	***The term is used to describe pain occurring with a normally functioning somatosensory nervous system***
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system	Neuropathic pain is a clinical description (and not a diagnosis) that requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria. The term *lesion* is commonly used when diagnostic investigations (eg, imaging, neurophysiology, biopsies, laboratory tests) reveal an abnormality or when there was obvious trauma. The term *disease* is commonly used when the underlying cause of the lesion is known (eg, stroke, vasculitis, diabetes mellitus, genetic abnormality). *Somatosensory* refers to information about the body per se including visceral organs, rather than information about the external world (eg, vision, hearing, or olfaction). The presence of symptoms or signs (eg, touch-evoked pain) alone does not justify the use of the term *neuropathic*. Some disease entities, such as trigeminal neuralgia, are currently defined by their clinical presentation rather than by objective diagnostic testing. Other diagnoses such as postherpetic neuralgia are normally based on the history. It is common when investigating neuropathic pain that diagnostic testing may yield inconclusive or even inconsistent data. In such instances, clinical judgment is required to reduce the totality of findings in a patient into one putative diagnosis or concise group of diagnoses
Nociplastic/algopathic/nocipathic pain	***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***	***Patients can have a combination of nociceptive and nociplastic/algopathic/nocipathic pain***
Pain of unknown origin (previously idiopathic pain)	***Pain of unknown cause and origin***	***Pain that cannot be classified as neuropathic, nociceptive or nociplastic/algopathic/nocipathic***

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somatosensory system as a primary cause of the pain, thus disqualifying the pain from attracting the neuropathic descriptor.

2.4. Proposal for a third descriptor

It is proposed that a new term be introduced to describe pain states characterized by clinical and psychophysical findings that suggest altered nociception, despite there being no clear evidence of actual or threatened tissue damage causing the activation of nociceptors or evidence for disease or lesion of the somatosensory system causing the chronic pain.

The candidate adjectives for this third descriptor include:

(1) "**Nociplastic,**" from "*nocic*eptive *plastic*ity," to reflect change in *function* of nociceptive pathways.

(2) "**Algopathic**," from "algos" (Greek for pain) plus "pathic" (from Greek "patheia" for suffering), paraphrased as "a pathological perception/sensation of pain not generated by injury."

(3) "**Nocipathic**," from "*nocic*eptive *path*ology," to denote a pathological (ie, not "normal") state of nociception.

The term is intended for clinical usage and is neither a diagnosis nor a synonym for "central sensitization of nociception," which is a neurophysiological concept. It may well be that the phenomenon of hypersensitivity occurring in ostensibly normal, uninjured tissue without evidence of neuropathy leads to a clinical inference that sensitization may be the underlying mechanism, so that the term is used as a descriptor for that situation. Such reasoning is no different from the phenomenon of observable tissue damage leading to the inference of activation of nociceptors and applying the term "nociceptive pain," or from the phenomenon of signs of neuropathy leading to the inference of disease or damage of neural structures and applying the term "neuropathic pain."

3. Discussion

3.1. Do we need a third mechanistic descriptor?

The present IASP terminology does not reflect the current understanding that chronic pain is not necessarily a symptom but can result from altered nociceptive function and thus constitute a condition in itself. Consequently, the pain of some large patient groups suffering from altered nociceptive function is currently classified as "pain of unknown origin." An argument in favour of continuing to use the current nondescriptors "unknown" or "idiopathic" relies on confusion that might arise out of challenges in defining a new descriptor. However, the inability of the current IASP pain terminology to harmonize with current concepts has resulted in the use of other nondefined descriptors such as "dysfunctional"[40] or "pathological"[35] pain, which not only give no insight into possible mechanisms but also carry implications that may stigmatize patients.[9,10]

The use of a third mechanistic descriptor in clinical practice has the potential to confer validity on the patient's experience of pain and to facilitate communication between patients, clinicians, and other stakeholders. Clinicians would be encouraged to screen for signs of altered nociceptive function, thus improving diagnosis and treatment, as patients suffering from altered nociceptive function typically respond better to centrally than peripherally targeted therapies. The term would also facilitate research efforts, by identifying altered nociceptive function as an important area for mechanistic studies, establishment of treatment guidelines and development of new treatment strategies.

3.2. When should the descriptor be used and when not?

The descriptor is primarily intended for patients suffering from chronic pain conditions characterized by evidence of altered nociceptive processing, such as those currently labelled as fibromyalgia,[22] CRPS,[47] nonspecific chronic low-back pain,[16] irritable bowel syndrome,[39] and other "functional" visceral pain disorders.[8,48] In addition, patients suffering initially from nociceptive pain, such as osteoarthritis, may develop alterations in nociceptive processing manifested as altered descending pain inhibition[3,28] accompanied by spread of hypersensitivity.[2,17,29] These patients would then be considered to have a combination of nociceptive and "nociplastic/algopathic/nocipathic" contributors to their pain. The new descriptor is intended to distinguish patients suffering from conditions where altered nociception has been documented from those where the pain mechanisms are still truly unknown. Therefore, the new descriptor does not apply to patients reporting pain without hypersensitivity. As such, it is neither a synonym for idiopathic pain or pain of unknown origin nor a label awarded by exclusion.

3.3. Problems regarding validity and use of the new descriptor

Opponents of a new descriptor may argue that mechanisms implicit in the terms "nociceptive" and "neuropathic" are proven, in contrast to the inference of functional changes in the nervous system, which as yet cannot be confirmed. A nociceptive focus may be visualized by radiology or reflected in some laboratory findings. It is argued that neuropathy can be identified by quantitative sensory testing, nerve conduction studies, intra-epidermal nerve fiber density assessments, or by imaging of the central nervous system.

However, despite the fact that pathology can be documented for nociceptive and neuropathic pain, the relationship between that pathology and pain mechanisms remains elusive. The latter is illustrated by the low concordance between the degree of tissue damage/inflammation and pain[11] or by the low proportion of people with peripheral nerve injury who develop chronic neuropathic pain.[32] Although it is true that no specific structural pathology underlying "nociplastic/algopathic/nocipathic" pain has been found, altered nociceptive processing has been documented by quantitative sensory testing,[7,15,27,42,47,48] sensory evoked potentials,[12,13,34] and functional magnetic resonance imaging.[16,19,38,48] Importantly, these functional changes have in many instances been related to pain severity.[1,31,41,43] Therefore, while acknowledging these limitations in the current and the proposed pain terminology, there remains a rationale for using the new descriptor to distinguish patients with altered nociception from patients with pain of unknown origin.

One unresolved situation is when a patient with nociceptive pain could be classified as also having "nociplastic/algopathic/nocipathic" pain. Clinicians are faced with a continuum of signs of hypersensitivity in patients with chronic pain. Individual differences in sensitivity to stimuli are marked even in healthy subjects[26,30] and no clinically useful method to quantify nociceptor activation exists. Although tests of descending pain inhibition could be used clinically,[6] the validity and reliability of these tests in a clinical setting remain to be established.[49]

Therefore, nociceptive and "nociplastic/algopathic/nocipathic" pain should not be regarded as exclusive categorical labels but rather, pragmatically, as concurrent possible mechanistic contributors to the patient's pain. This would be similar to the concurrence of nociceptive and neuropathic contributors in other situations.

3.4. Is future progress in pain research likely to affect the use of the descriptors?

These mechanistic terms are descriptors of putative contributors to the experience of pain, not diagnoses; they are placeholders for current concepts and not "set in concrete." As our knowledge of pain mechanisms advances, so should pain terminology change.

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3.5. Concluding remarks

This topical review suggests introducing a third mechanistic pain descriptor to be used in patients with clinically determined altered nociception. If the suggestion is well received, the next step will be to define a set of clinically useful positive classification criteria. The term is mechanistic and thus complementary to, but not synonymous with, the proposed ICD-11 diagnostic term "primary pain."[46] By writing this article, the authors hope to open up a fruitful debate regarding modernization of mechanistic pain terminology.

Conflict of interest statement

E. Kosek has received consultancy and speaker fees in the past 36 months from Eli Lilly and Company and Orion and has ongoing research collaborations with Eli Lilly and Company and AbbVie. M. Cohen has received consultancy fees from Mundipharma and Pfizer for preparation and presentation of educational material. R. Baron has received grants/research support from Pfizer, Genzyme, Grünenthal, and Mundipharma. He is a member of the EU Project No 633491: DOLOR-isk. A member of the IMI "Europain" collaboration and industry members of this are: AstraZeneca, Pfizer, Esteve, UCB-Pharma, Sanofi Aventis, Grünenthal, Eli Lilly, and Boehringer Ingelheim. German Federal Ministry of Education and Research (BMBF): Member of the ERA_NET NEURON/IM-PAIN Project. German Research Network on Neuropathic Pain, NoPain system biology. German Research Foundation (DFG). He has received speaking fees from Pfizer, Genzyme, Grünenthal, Mundipharma, Sanofi Pasteur, Medtronic, Eisai, Lilly, Boehringer Ingelheim, Astellas, Desitin, Teva Pharmaceuticals, Bayer Schering, MSD, and bioCSL. He has been a consultant for Pfizer, Genzyme, Grünenthal, Mundipharma, Allergan, Sanofi Pasteur, Medtronic, Eisai, Lilly, Boehringer Ingelheim, Astellas, Novartis, Bristol-Myers Squibb, Biogenidec, AstraZeneca, Merck, AbbVie, Daiichi Sankyo, Glenmark Pharmaceuticals, and bioCSL. G. F. Gebhart, J. -A. Mico, and A. S.C. Rice have nothing to declare. W. Rief has received consultancy fees from Heel and speaker's fees from Bayer. K. Sluka has been Consultant for DJO, Inc, and Bayer, Inc, received research funding from Medtronic, Inc and royalties from IASP Press.

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