

## Title:

### **Not being able to measure what is important, does not make things we can measure important**

*Comment to Kosek E, Clauw D, Nijs J, Baron R, Gilron I, Harris RE, Mico JA, Rice ASC, Sterling M. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. Pain. 2021 Nov 1;162(11):2629-2634. doi: 10.1097/j.pain.0000000000002324. PMID: 33974577.*

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## Manuscript:

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Comment to Kosek E, Clauw D, Nijs J, Baron R, Gilron I, Harris RE, Mico JA, Rice ASC, Sterling M. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain*. 2021 Nov 1;162(11):2629-2634. doi: 10.1097/j.pain.0000000000002324. PMID: 33974577.

We commend the authors on their efforts to create clinical criteria and a grading system for *chronic nociplastic pain* localised to the musculoskeletal system. We do however have some reservations about the pragmatic usefulness of the proposed grading system.

## *Are the proposed criteria specific to a mechanism(s)?*

We appreciate the desire to operationalise nociplastic pain for research purposes. But ultimately, “nociplasticity” is more descriptive than observable, and while it may include changes, such as central sensitisation, these are not exclusive to nociplastic pain [3]. The definition of nociplastic pain is in itself somewhat contradictory, since it is defined by altered nociception (current IASP definition: the neural process of encoding noxious stimuli) in a condition lacking noxious stimuli. Also, we find it problematic that the proposed algorithm relies on a new pain class, which has not been endorsed by the IASP (i.e., *pain of unknown origin*). The core of the matter is that very little is known about mechanisms specific to nociplastic pain and hence it is not a “mechanistic” term. Recent discoveries in conditions that are currently considered ‘nociplastic’ such as fibromyalgia highlight the complexity (and heterogeneity) of these conditions and their underlying mechanisms [2]. Moreover, can we be certain that the presence of the proposed types of comorbidities required to reach the classification of probable nociplastic pain point to a specific mechanism as the cause of pain? Maybe it would be helpful to discuss widespread pain with unknown cause and comorbidity in relation to the umbrella terminology of bodily distress syndrome or functional somatic disorders [1].

## *Are the proposed criteria sensitive and precise?*

As the mechanisms underlying (and specific to) nociplastic pain are unknown, can we confidently say that patients classified by exclusion as ‘*pain of unknown origin*’ are truly mechanistically different than patients who fall under the proposed category of nociplastic pain? The second clinical criterion (*a history of pain hypersensitivity in the region of pain*) seems misleading; according to the IASP definition, nociplastic pain is “pain that arises from altered nociception”. Consequently, hypersensitivities are limited to noxious stimuli, i.e., hyperalgesias but not allodynia. The fourth clinical criterion focuses on *evoked pain*. But how can we be confident that patients with ongoing pain only should be excluded? Importantly, abnormal evoked pain is present only in subgroups of nociceptive and neuropathic pain and it is extremely difficult to assess, in an individual patient, if a noxious stimulus induces hypersensitivity since sensitivity varies in the population and over time in individuals [4,6].

Thus, we argue that the algorithm creates an arbitrary separation between patients who meet the criteria proposed by Kosek et al. and those who do not [5]. Patients who do not fulfil the clinical criteria, but suffer from equally disabling pain, are excluded by proposition, not by mechanism. Therefore, we argue that hypersensitivity alone should not define or be used to grade any pain class. Rather, we suggest implementing the term “pain of unknown origin” instead of nociplastic pain, not in addition to it.

1 *How can the algorithm guide treatment and who are we leaving behind?*

2 Unlike for nociceptive and neuropathic pain, there is currently no evidence to support a specific  
3 mechanism(s) related to nociplastic pain that could be targeted by an intervention. Similarly, there  
4 is no firm knowledge on interventions that *should not* be used in those not fulfilling the criteria for  
5 nociplastic pain. Whereas the suggested grading system may facilitate research to shed more light  
6 on this area, its application in clinical settings seems premature. We are particularly concerned  
7 about how the clinical use of the algorithm might impact patients who are not classified as having  
8 nociceptive or neuropathic pain and who also do not meet the classification of having *possible* or  
9 *probable* nociplastic pain, and fear that they may feel invalidated.

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