

21. Stranak Z, Semberova J, Barrington K, et al. International survey on diagnosis and management of hypotension in extremely preterm babies. *Eur J Pediatr* 2014; **173**: 793–8
22. Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome. Report of a joint working group of the British association of perinatal medicine and the research unit of the royal College of physicians. *Arch Dis Child* 1992; **67**: 1221–7
23. Choi SN, Ji SH, Jang YE, et al. Predicting hypotension during anesthesia: variation in pulse oximetry plethysmography predicts propofol-induced hypotension in children. *Paediatr Anaesth* 2021; **31**: 894–901
24. Hillgruber RJ, Lutskov P, West NC, Whyte S, Gorges M. Blood pressure nomograms for children undergoing general anesthesia, stratified by age and anesthetic type, using data from a retrospective cohort at a tertiary pediatric center. *J Clin Monit Comput* 2022; **36**: 1667–77
25. Pasma W, Peelen LM, van den Broek S, van Buuren S, van Klei WA, de Graaff JC. Patient and anesthesia characteristics of children with low pre-incision blood pressure: a retrospective observational study. *Acta Anaesthesiol Scand* 2020; **64**: 472–80
26. Davis AL, Carcillo JA, Aneja RK, et al. The American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: executive summary. *Pediatr Crit Care Med* 2017; **18**: 884–90
27. Ing C, DeStephano D, Hu T, et al. Intraoperative blood pressure and long-term neurodevelopmental function in children undergoing ambulatory surgery. *Anesth Analg* 2022; **135**: 787–97

British Journal of Anaesthesia, 130 (5): 515–518 (2023)

doi: [10.1016/j.bja.2023.02.006](https://doi.org/10.1016/j.bja.2023.02.006)

Advance Access Publication Date: 6 March 2023

© 2023 British Journal of Anaesthesia. Published by Elsevier Ltd. All rights reserved.

Diagnosing nociplastic pain in cancer survivors: a major step forward

Emmanuel Verspyck¹  and Nadine Attal^{1,2,*} 

¹CETD, Ambroise Pare Hospital, APHP, Boulogne-Billancourt, France and ²Inserm U987, UVSQ-Paris-Saclay University, Ambroise Pare Hospital, APHP, Boulogne-Billancourt, France

*Corresponding author. E-mail: nadine.attal@aphp.fr



This editorial accompanies: Towards precision pain medicine for pain after cancer: the Cancer Pain Phenotyping Network multidisciplinary international guidelines for pain phenotyping using nociplastic pain criteria by Nijs et al., *Br J Anaesth* 2023;130:611–621, doi: <https://doi.org/10.1016/j.bja.2022.12.013>

Summary

Nociplastic pain syndromes include particular fibromyalgia, irritable bowel syndrome, headache, complex regional pain syndrome, and idiopathic orofacial pain. Several mechanisms have been proposed to account for nociplastic pain including central sensitisation, alterations of pain modulatory controls, epigenetic changes, and peripheral mechanisms. Importantly, nociplastic pain might also be present in patients with cancer pain, particularly those with pain related to complications of cancer treatment. Increased awareness of nociplastic pain associated with cancer should have important implications for monitoring and managing such patients.

Keywords: cancer pain; central sensitisation; fibromyalgia; IDC-11 classification; nociplastic pain; pain modulation

The term ‘nociplastic pain’ was proposed in 2017 by the International Association for the Study of Pain (IASP) to refer to a third pain type in addition to the well-known neuropathic and nociceptive pain conditions.^{1–3} 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 nervous system causing the pain’.² Classical nociplastic pain syndromes include

fibromyalgia, irritable bowel syndrome, headache, complex regional pain syndrome, and idiopathic orofacial pain.⁴ Most of these are now also categorised as primary pains as part of the *International Classification of Diseases, 11th Revision (ICD-11)*.⁵ Interestingly, although the term nociplastic is new, descriptions of neurasthenia in the 19th century were strikingly similar to fibromyalgia,⁶ and the terms dysfunctional pain, psychogenic pain,⁷ somatisation, somatoform disorders,⁸ or medically unexplained symptoms⁸ have also been commonly used in the past to refer to these pain syndromes. However, these were mostly derogatory terms, which encompassed a spectrum of

symptoms including pain, whereas the new terminology is focused on pain and less stigmatisation.

In a paper in this issue of the *British Journal of Anaesthesia*, Nijs and colleagues¹ apply the clinical diagnostic criteria for nociplastic pain recently proposed by Kosek and colleagues² to patients with cancer pain. These criteria represent a first step towards standardisation and only apply to chronic pain (i.e. pain persisting or remitting for at least 3 months). They include any one of the following: (1) chronic regional pain; (2) pain not entirely explained by a nociceptive or neuropathic process; (3) the presence of any evoked pain (e.g. allodynia, hyperalgesia); and (4) a history of pain hypersensitivity and comorbidities. Importantly, these criteria suggest the presence of specific pain mechanisms regardless of the underlying diagnosis. They also emphasise that generalised hypersensitivity, beyond hyperalgesia, must be reported by patients. Hypersensitivity to auditory or visual stimuli has indeed been documented in patients with fibromyalgia.^{9,10} However, these criteria are not strictly validated and only apply to musculoskeletal pain (and not to visceral pain, for example). Another potential limitation is that they imply the presence of evoked pain at examination in all cases. Yet, it is unclear whether all patients with nociplastic pain present with allodynia or hyperalgesia. For example, a study using quantitative sensory testing in fibromyalgia showed that one-third had no signs of hyperalgesia.¹¹

It may be argued that defining specific diagnostic criteria for nociplastic pain is over-simplistic. Indeed, nociplastic pain is a continuum rather than a strictly distinctive entity. This is in keeping with the proposed concept of 'fibromyalgiansess',¹² and the findings of frequent overlap between pain entities.¹³ Beyond diagnostic criteria, what the article by Nijs and colleagues¹ emphasises is that any chronic pain including pain associated with cancer can include a nociplastic dimension. In some patients surviving from cancer, oncologists have described the presence of psychoneurological symptoms, called cancer symptom clusters,¹⁴ which include depressive symptoms, anxiety, fatigue, sleep disturbance, and sometimes pain. However, there is limited consistency and lack of agreement about clinically relevant criteria for these symptoms and the characteristics of pain were not described.¹⁴ Furthermore, in cancer survivors the risk of nociplastic pain is enhanced by cancer treatments including aromatase inhibitors, the first-line treatment for oestrogen depletion in women with breast cancer.¹⁵

Several mechanisms, which are not mutually exclusive, have been proposed to account for nociplastic pain or the nociplastic dimension of pain. They mainly include central sensitisation, alterations in central pain modulatory controls, epigenetic changes, and peripheral mechanisms. Central sensitisation is a neurophysiological term that refers to 'increased responsiveness of nociceptive neurones in the central nervous system to their normal or subthreshold afferent input'.³ Clinical surrogates of central sensitisation include evoked pain (particularly hyperalgesia, allodynia and temporal summation, which refers to enhanced pain in response to repeated stimuli), and questionnaires such as the Central Sensitization Inventory¹⁶ have been validated to assess symptoms suggestive of central sensitisation in patients.

Central sensitisation has been investigated largely in animals but has also been suggested in patients.¹⁷ For example, intravenous ketamine, which has a potent effect on central sensitisation, reduces pain and temporal summation in patients with fibromyalgia.¹⁸ Multiple studies based on quantitative sensory testing in these patients have found evidence

for widespread allodynia, hyperalgesia, and temporal summation at painful and non-painful sites.^{19,20} Recent studies using the thermal grill illusion, a psychophysical method by which alternate warm and cool bars induce a paradoxical pain sensation (generally described as burning), have also demonstrated reduced threshold and enhanced pain intensity and unpleasantness in response to the thermal grill in patients with irritable bowel syndrome and fibromyalgia, which supports central sensitisation.²¹ Electrophysiological studies using the nociceptive flexion reflex (RfII), which is considered a reliable marker of central sensitisation in humans, have shown a reduction of this reflex in patients with fibromyalgia.²² Increased neuronal activation in pain-processing regions of the brain has been shown in neuroimaging studies, mainly using functional MRI.²³

The role of alterations in descending brain pain modulatory pathways has also been emphasised, particularly in patients with fibromyalgia. Electrophysiological studies show a decrease in conditioned pain modulation, a measure of descending pain modulation,²⁰ and alterations in intracortical modulation,²⁴ whereas functional MRI studies show decreased activity in several brain regions involved in descending modulation.²³ A gene–environment interaction might also predispose to nociplastic pain. Several studies have pointed to the role of epigenetic changes (heritable changes in gene function that can influence gene expression and phenotype) in stress gene regulation in the pathophysiology of fibromyalgia.^{25,26} The latter could result from early life stressors or trauma such as childhood abuse. In particular, changes in DNA methylation (an epigenetic marker involved in regulation of gene expression) affecting for example *GMR2* (which encodes glutamate metabotropic receptor 2 that controls glutamate release, a major mediator of central sensitisation) seem to be associated with increased risk of fibromyalgia.²⁷ These epigenetic changes might lead to dysregulation of the hypothalamic–pituitary–adrenal axis, autonomic nervous system and immune system.²⁵ Finally, recent studies have focused on peripheral mechanisms. Up to 45% of patients with fibromyalgia have evidence of small nerve fibre pathology or neuropathy based on skin punch biopsy, which might be a marker of severity.²⁸ It remains to be determined whether these alterations are specific, are responsible for the pain, or whether there are common central contributing factors to small fibre impairment and fibromyalgia.²⁹

Increased awareness of nociplastic pain should have major implications for the monitoring and management of patients with chronic pain. Nociplastic-like phenotype predicts increased opioid consumption after surgery (hysterectomy, arthroplasty, thoracic surgery)^{30,31} and poorer outcome after hip or shoulder arthroplasty.^{32,33} Patients with nociplastic pain obtain limited benefit from conventional analgesics including opioids,⁴ that can even contribute to opioid-induced hyperalgesia, which seems to be more prevalent in these patients.³⁴ In patients with cancer reporting chronic pain, detection of a nociplastic pain dimension is of paramount importance to avoid therapeutic escalation with opioids and unnecessary procedures (e.g. serial spine MRIs for back pain) which might ultimately exacerbate patient distress. Nociplastic pain should encourage the development of multimodal therapeutic approaches, which are recommended for this pain type.³⁵ These include physical exercise, psychoeducation, psychotherapies, and psychotropic drugs such as antidepressants (e.g. tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitors such as duloxetine) and gabapentinoids (pregabalin,

gabapentin), in a step-by-step individualised approach.³⁵ Brain neuromodulatory techniques such as repetitive transcranial magnetic stimulation can be tried for refractory patients.³⁶

In summary, Nijs and colleagues emphasise that the concept of nociplastic pain applies not only to chronic non-cancer pain, but also to patients with cancer. They show that this dimension can be detected relatively easily based on a simple standardised clinical assessment, which contributes to a more rational therapeutic management strategy in these patients.

Declaration of interests

NA is an editor of the *British Journal of Anaesthesia*. NA has received honoraria from Merz, Grunenthal, Pfizer, and Biogen over the past 36 months, none of which are relevant to this editorial.

References

- Nijs J, Lahousse A, Fernández-de-Las-Peñas C, et al. Towards precision pain medicine for pain after cancer: the Cancer Pain Phenotyping Network multidisciplinary international guidelines for pain phenotyping using nociplastic pain criteria. *Br J Anaesth* 2023; **130**: 611–21
- Kosek E, Clauw D, Nijs J, et al. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain* 2021; **162**: 2629–34
- Terminology. International Association for the Study of Pain (IASP), 2011 <https://www.iasp-pain.org/resources/terminology/>.
- Fitzcharles M-A, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. *Lancet* 2021; **397**: 2098–110
- Nicholas M, Vlaeyen JWS, Rief W, et al. IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain* 2019; **160**: 28–37
- Beard F. Neurasthenia or nervous exhaustion. *Boston Med Surg J* 1869; **80**: 217–21
- Engel GL. Psychogenic pain. *Med Clin North Am* 1958; **42**: 1481–96
- Heinrich TW. Medically unexplained symptoms and the concept of somatization. *WMJ* 2004; **103**: 83–7
- Geisser ME, Glass JM, Rajcevska L, et al. A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. *J Pain* 2008; **9**(5): 417–22
- Dorris ER, Maccarthy J, Simpson K, McCarthy GM. Sensory perception quotient reveals visual, scent and touch sensory hypersensitivity in people with fibromyalgia syndrome. *Front Pain Res* 2022; **3**, 926331
- Rehm S, Sachau J, Hellriegel J, et al. Pain matters for central sensitization: sensory and psychological parameters in patients with fibromyalgia syndrome. *Pain Rep* 2021; **6**, e901
- Wolfe F. *Fibromyalgianess*. *Arthritis Rheum* 2009; **61**: 715–6
- Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping chronic pain conditions: implications for diagnosis and classification. *J Pain* 2016; **17**: T93–107
- Dong ST, Butow PN, Costa DSJ, Lovell MR, Agar M. Symptom clusters in patients with advanced cancer: a systematic review of observational studies. *J Pain Symptom Manage* 2014; **48**: 411–50
- Laroche F, Coste J, Medkour T, et al. Classification of and risk factors for estrogen deprivation pain syndromes related to aromatase inhibitor treatments in women with breast cancer: a prospective multicenter cohort study. *J Pain* 2014; **15**: 293–303
- Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract* 2012; **12**: 276–85
- Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009; **10**: 895–926
- Graven-Nielsen T, Kendall SA, Henriksson KG, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *Pain* 2000; **85**: 483–91
- Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. *Nat Rev Rheumatol* 2010; **6**: 599–606
- O'Brien AT, Deitos A, Triñanes Pego Y, Fregni F, Carrillo-de-la-Peña MT. Defective endogenous pain modulation in fibromyalgia: a meta-analysis of temporal summation and conditioned pain modulation paradigms. *J Pain* 2018; **19**: 819–36
- Adam F, Jouët P, Sabaté JM, et al. Thermal grill illusion of pain in patients with chronic pain: a clinical marker of central sensitization? *Pain* 2023; **164**: 638–44
- Desmeules JA, Cedraschi C, Rapiti E, et al. Neurophysiologic evidence for central sensitization in patients with fibromyalgia. *Arthritis Rheum* 2003; **48**: 1420–9
- Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. *Semin Arthritis Rheum* 2014; **44**: 68–75
- Mhalla A, de Andrade DC, Baudic S, Perrot S, Bouhassira D. Alteration of cortical excitability in patients with fibromyalgia. *Pain* 2010; **149**: 495–500
- Polli A, Godderis L, Ghosh M, Ickmans K, Nijs J. Epigenetic and miRNA expression changes in people with pain: a systematic review. *J Pain* 2020; **21**: 763–80
- Ciampi de Andrade D, Maschietto M, Galhardoni R, et al. Epigenetics insights into chronic pain: DNA hypomethylation in fibromyalgia—a controlled pilot-study. *Pain* 2017; **158**: 1473–80
- Gerra MC, Carnevali D, Ossola P, et al. DNA methylation changes in fibromyalgia suggest the role of the immune-inflammatory response and central sensitization. *J Clin Med* 2021; **10**: 4992
- Evdokimov D, Frank J, Klitsch A, et al. Reduction of skin innervation is associated with a severe fibromyalgia phenotype. *Ann Neurol* 2019; **86**: 504–16
- Leone C, Galosi E, Esposito N, et al. Small-fibre damage is associated with distinct sensory phenotypes in patients with fibromyalgia and small-fibre neuropathy. *Eur J Pain* 2023; **27**: 163–73
- Janda AM, As-Sanie S, Rajala B, et al. Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. *Anesthesiology* 2015; **122**: 1103–11
- Larach DB, Sahara MJ, As-Sanie S, et al. Patient factors associated with opioid consumption in the month following major surgery. *Ann Surg* 2021; **273**: 507–15
- Ohashi Y, Fukushima K, Uchida K, et al. Differences in outcomes after total hip arthroplasty for osteoarthritis

- between patients with and without central sensitivity syndromes other than fibromyalgia. *Sci Rep* 2022; **12**, 15327
33. Moverman MA, Puzzitiello RN, Pagani NR, et al. Functional somatic syndromes are associated with suboptimal outcomes and high cost after shoulder arthroplasty. *J Shoulder Elbow Surg* 2022; **31**: 48–55
 34. Wasserman RA, Brummett CM, Goesling J, Tsodikov A, Hassett AL. Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. *Reg Anesth Pain Med* 2014; **39**: 13–7
 35. Häuser W, Perrot S, Clauw DJ, Fitzcharles M-A. Unraveling fibromyalgia—steps toward individualized management. *J Pain* 2018; **19**: 125–34
 36. Passard A, Attal N, Benadhira R, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain* 2007; **130**: 2661–70