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EDITORIAL

Phenotyping nociceptive, neuropathic, and nociplastic pain: who, how, & why?

In this third contribution to the comprehensive pain management editorial series[1] we build on the previous editorial that provided a terminology update regarding central sensitization and nociplastic pain.[2] Consistent with the global move towards precision medicine, it is explained why pain phenotyping is of potential relevance, and for which patients pain phenotyping might be useful. Finally, we briefly explain how clinicians can differentiate between predominant nociceptive, neuropathic, and nociplastic pain, and adapt pain management accordingly.

Why should clinicians consider implementing pain phenotyping?

Clinicians wondering why they should consider integrating pain phenotyping into their clinical reasoning can pose themselves the following questions: *"Do you consider all myofascial pain to be predominant nociceptive pain?"*, *"Do you consider all carpal tunnel syndrome or lumbar radiculopathy pure neuropathic pain?"*, and *"Do you explain pain in the same way to patients with nociceptive, neuropathic, and nociceptive pain?"*. If at least one of the questions triggers your interest, we invite you to continue reading.

Thanks to high-throughput innovations into health care (research), such as (genome-wide) DNA-sequencing, imaging, wireless (real-time) monitoring devices, and big data, it is now widely accepted that the heterogeneity of many disease processes — including many chronic pain conditions[3-5] - requires treatment strategies that must be tailored or 'personalized' to the individual's unique (*epi*)genetic, biochemical, physiological, and/or behavioural profile.[6,7] Within this view, the terms precision and personalized medicine have often been used (interchangeably), with the term personalized medicine having the potential to be misinterpreted as if treatments are developed uniquely for each patient. Precision medicine refers to the ability to classify patients into subgroups that differ in their susceptibility to, biology, or prognosis of a particular disease, or in their response to a specific treatment, and thus to tailor treatment to the individual patient characteristics.[8] Hence, rather than personalized medicine, pain phenotyping potentially fits within the global move to precision medicine.[5]

Pain phenotyping holds potential for clinicians because predominant neuropathic, nociplastic, as well as mixed pain types (i.e., a mixture of nociceptive, neuropathic, and/or nociplastic pain) are considered to be more challenging to treat than predominant nociceptive pain.[9-12] Further, the classification of the predominant pain phenotype might be relevant to guide the selection of the most suitable treatment approach, although currently the evidence favouring such a stratified approach is scarce (especially for the physical therapy profession). This comes as no surprise, as there has been considerable debate regarding how to differentiate between predominant nociceptive, neuropathic, and nociplastic pain,[13] and clinical criteria for nociplastic pain only became available in 2021.[14] Clinical criteria are undergoing further development[15] and testing for reliability and validity, as well as being adapted to specific chronic pain conditions (e.g., pain after cancer[4]). Pain phenotyping might be a valuable alternative to the 'nonspecific pain' label. Indeed, 'nonspecific' can be stigmatizing for patients, and can generate nocebo-effects, whereas terms such as 'nociplastic pain', which possibly accounts for many categorised as 'nonspecific', connects the patient's pain condition to a body of scientific evidence.[16] Finally, pain phenotyping fosters the use of the biopsychosocial model[17] and integration into a multidisciplinary healthcare system. However, it should be stressed that pain phenotyping is only one ingredient of the patient's comprehensive biopsychosocial assessment. It provides guidance to the types of treatments that might be expected to be effective or ineffective (e.g., surgery might be an appropriate choice for a patient with specific types of nociceptive pain, but would have no impact if pain is nociplastic), but additional assessment is required to formulate the intervention plan. The Pain - Somatic factors - Cognitive factors - Emotional factors - Behavioral factors - Social

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factors - Motivation (PSCEBSM) model can be applied for such comprehensive assessment, as it allows assessing the provoking and perpetuating biopsychosocial factors together with establishing the predominant pain phenotype, to facilitate individually tailored pain management.[18] According to this view, pain management could be tailored using evidence-based strategies to address the patient's relevant cognitive, behavioural, and lifestyle factors along with guidance provided by consideration of the pain phenotype regarding treatments that are likely to address the relevant mechanisms.

For which patients is pain phenotyping potentially relevant?

Theoretically, all patients who experience pain can be phenotyped. However, according to the IASP clinical criteria for nociplastic pain,[14] per definition, only patients with chronic pain, defined as pain of at least 3 months duration, can be phenotyped into predominant nociplastic or mixed pain type. This sounds arbitrary, but does make sense when it comes to early differentiating between predominant nociceptive and nociplastic pain (i.e., it would be challenging to decide whether pain is maintained in the absence of nociceptive input in a very acute stage). Pain phenotyping is of particular interest in pain conditions where neuropathic (e.g., cancer survivors) or nociplastic (e.g., fibromyalgia, rheumatoid arthritis, whiplash associated disorders, low back pain, osteoarthritis) features are prevalent. In essence, all kinds of chronic pain conditions, including temporomandibular disorders, shoulder pain, knee pain, hip pain, tendinopathies, headaches, post-surgical pain, and pregnancy-related pelvic girdle pain, can be considered from a perspective of pain phenotyping. This also accounts for apparently predominant neuropathic pain conditions such as carpal tunnel syndrome, lumbar or cervical radiculopathy, and spinal stenosis. Each of these conditions imply 'an identifiable lesion or disease of the peripheral or central nervous system', but to fulfill the neuropathic pain criteria the pain should be limited to a neuroanatomically plausible distribution.[19] If the pain spreads beyond that area, mixed neuropathic and nociplastic pain can be present. In addition, not all patients with spinal stenosis will have a neuropathy, and therefore can present as a predominant nociceptive pain.

How can clinicians differentiate between predominant nociceptive, neuropathic, and nociplastic pain?

For differentiating between predominant nociceptive, neuropathic, and nociplastic pain (Table 1), the International Association for the Study of Pain (IASP) developed clinical criteria and a grading system for nociplastic pain,[14] which integrate the use of the classification guideline for neuropathic pain.[19] The neuropathic pain criteria specify that a lesion or disease of the nervous system (either central or peripheral) is identifiable and that pain and sensory symptoms (e.g., numbness) are limited to a 'neuroanatomically plausible' distribution.[19] Theoretically, the combined use of these criteria allows clinicians to identify and classify patients with chronic pain according to their predominant pain phenotype. More details can be found in the original guidelines.[14,19] Notably, there are not yet IASP clinical criteria for nociceptive pain and this is an ongoing project.[15] For those working with the growing population of cancer survivors experiencing pain, a manual illustrated with cases is available to allow clinicians to differentiate between predominant nociceptive, neuropathic, or nociplastic pain after cancer.[4] However, clinicians willing to implement the use of these clinical criteria should realize their reliability, validity, and prognostic ability remain to be established. Other work

Table 1 Essential features of the 3 main pain phenotypes.

	Nociceptive pain	Neuropathic pain	Nociplastic pain
What is it?	Pain arising from actual or threat of damage to non-neural tissue.	Pain arising from a lesion or disease of the somatosensory nervous system.	Pain that arises from altered nociception.
Pain localization	Mostly localized pain. Referred pain is possible, but can be linked to the presumed source of nociception.	Pain limited to the neuroanatomically plausible distribution.	Pain presenting in a non-neuroanatomically plausible distribution.
Non-pain symptoms?	Non-pain sensory symptoms are less common.	Non-pain sensory symptoms such as pins and needles, numbness, and muscle weakness are highly prevalent and should adhere to the neuroanatomically plausible distribution.	Fatigue, cognitive problems, and sleep problems are highly prevalent.
Medical diagnostic tests	Can reveal tissue damage, injury, or pathology that corresponds to the clinical pain presentation.	Reveal a lesion or disease of the nervous system.	Can reveal tissue damage or pathology, but such findings typically explain only part of the clinical picture.

Table 2 Pain management tailored according to the predominant pain phenotype.

Topic	Of relevance to what pain phenotypes?	Proposed tailoring according to the predominant pain phenotype
Mono- or multi-/ interdisciplinary care	All pain phenotypes	Most likely to be critical for complex cases of predominant neuropathic, nociceptive, or mixed pain type
Pain education	All pain phenotypes	Nociceptive pain: explain the presumed source of nociception Neuropathic pain: explain the lesion or disease of the nervous system + central sensitization Nociplastic pain: explain central sensitization
Exercise therapy	All pain phenotypes	Nociceptive pain: pain-contingent approach Neuropathic & nociplastic pain: cognitive behavioural (including time-contingent) approach
Neurodynamic mobilisations	Neuropathic pain	Should only be considered in neuropathic pain (either predominant or mixed pain types that include neuropathic pain)
Lifestyle interventions	All pain phenotypes	May be indicated for all phenotypes, but especially in predominant neuropathic, nociplastic, and mixed pain type.

has summarised[20] and then gained expert consensus[15] regarding a single tool, drawing on the established criteria, that can discriminate between the three pain mechanistic descriptors. Work is ongoing to operationalise and evaluate the criteria.

How can clinicians tailor treatment to the predominant pain phenotype?

First, the outcome of pain phenotyping can provide guidance to targets for management — treatments that address the nociceptive source are relevant in nociceptive pain, treatments to address neuropathology for neuropathic pain, and strategies to reduce sensitization and amplification of pain, including psychologically informed strategies for nociplastic pain. Second, pain phenotyping can contribute to deciding whether or not multi- or inter-disciplinary care is needed - complex cases of predominant neuropathic, nociplastic, or mixed pain type may require multi- or inter-disciplinary treatment (Table 2). Third, the outcome of pain phenotyping potentially influences the way clinicians explain pain. For instance, the presumed source of nociception (i.e., joint inflammation in rheumatic diseases) will be explained to patients with predominant nociceptive pain, whereas the mechanism of central sensitization can be discussed in patients with predominant nociplastic pain. In the latter group of patients, it is essential to explain that tissue damage and nociception are not the (main) drivers of the pain. In patients with predominant neuropathic pain, central sensitization together with the 'lesion or disease of the nervous system' can be explained. Fourth, pain phenotyping holds potential for the way exercise therapy is delivered. In patients with predominant nociceptive pain (e.g., rheumatic inflammatory pain) a pain-contingent approach seems warranted along with attention to *how* the individual moves and maintains posture, whereas a cognitive behavioural (including time-contingent) approach to exercise therapy and physical activity interventions (e.g., behavioural graded activity) is warranted for those with nociplastic pain with an aim to get people moving without detailed attention to how they move. Fifth, neurodynamic mobilisations are only likely to be relevant for patients with neuropathic pain (either predominant neuropathic or mixed pain type that includes neuropathic pain) and only for specific types of neuropathic pain. Sixth, while a focus on lifestyle interventions may be indicated for all types of chronic pain, its value might be even more important in predominant neuropathic, nociplastic, and mixed pain type.

Conflict of interest

We hereby declare that there are no conflicts of interest.

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