BJA

British Journal of Anaesthesia, 130 (5): 611–621 (2023)

doi: 10.1016/j.bja.2022.12.013
Advance Access Publication Date: 24 January 2023
Pain

PAIN

Towards precision pain medicine for pain after cancer: the Cancer Pain Phenotyping Network multidisciplinary international guidelines for pain phenotyping using nociplastic pain criteria

Jo Nijs[1,2,4,*], Astrid Lahousse[1,2,3,14], César Fernández-de-las-Peñas[12], Pascal Madeleine[17], Christel Fontaine[5], Tomohiko Nishigami[19], Christine Desmedt[9], Marian Vanhoeij[7,8], Kenza Mostaqim[1], Antonio I. Cuesta-Vargas[11], Eleni Kapreli[16], Paraskevi Bilika[16], Andrea Polli[1,3,10], Laurence Leysen[1], Ömer Elma[1], Eva Roose[1,14,15], Emma Rheel[1,13], Sevilay Tümkaya Yılmaz[1], Liesbet De Baets[1], Eva Huysmans[1,2,3], Ali Turk[18] and İsmail Saraçoğlu[6]

[1]Pain in Motion Research Group (PAIN), Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Belgium, [2]Chronic Pain Rehabilitation, Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Belgium, [3]Research Foundation – Flanders (FWO), Brussels, Belgium, [4]Department of Health and Rehabilitation, Unit of Physiotherapy, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden, [5]Medical Oncology Department, University Hospital Brussels, Belgium, [6]Kütahya Health Sciences University, Kütahya, Turkey, [7]Breast Clinic, University Hospital Brussels, Belgium, [8]Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Belgium, [9]Katholieke Universiteit Leuven, Belgium, [10]Laboratory of Clinical Epigenetics, Department of Public Health and Primary Care, Centre for Environment & Health, KU Leuven, Leuven, Belgium, [11]Cátedra de Fisioterapia, Universidad de Malaga, Andalucia Tech, Instituto de Investigacion Biomédica de Malaga (IBIMA) Grupo de Clinimetria (F-14), Malaga, Spain, [12]Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), Alcorcón, Madrid, Spain, [13]Department of Experimental-Clinical and Health Psychology, Ghent University, Ghent, Belgium, [14]Rehabilitation Research (RERE) Research Group, Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education & Physiotherapy (KIMA), Vrije Universiteit Brussel, 1090 Brussels, Belgium, [15]Universiteit Hasselt, REVAL, Agoralaan-gebouw A, 3590 Diepenbeek, Belgium, [16]Clinical Exercise Physiology & Rehabilitation Research Laboratory, Physiotherapy Department, Faculty of Health Sciences, University of Thessaly, Lamia, Greece, [17]Sport Sciences - Performance & Technology, Department of Health Science & Technology, Aalborg University, Aalborg, Denmark, [18]Kutahya Health Sciences University, Faculty of Medicine, Department of Radiation Oncology, Kütahya, Turkey and [19]Prefectural University of Hiroshima, Japan

*Corresponding author. E-mail: jo.nijs@vub.be

This article is accompanied by an editorial: Diagnosing nociplastic pain in cancer survivors: a major step forward by de Verspyck & Nattal, *Br J Anaesth* 2023:130:515–518, doi: https://doi.org/10.1016/j.bja.2023.02.006

Summary

Pain after cancer remains underestimated and undertreated. Precision medicine is a recent concept that 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. Applying this to pain after cancer, the ability to classify post-cancer pain into the three major pain phenotypes (i.e. nociceptive, neuropathic, and nociplastic pain) and tailor pain treatment accordingly, is an emerging issue. This is especially relevant because available evidence suggests that nociplastic pain is present in an important subgroup of those patients

Received: 1 September 2022; **Accepted:** 10 December 2022

experiencing post-cancer pain. The 2021 International Association for the Study of Pain (IASP) clinical criteria and grading system for nociplastic pain account for the need to identify and correctly classify patients according to the pain phenotype early in their treatment. These criteria are an important step towards precision pain medicine with great potential for the field of clinical oncology. Within this framework, the Cancer Pain Phenotyping (CANPPHE) Network, an international and interdisciplinary group of oncology clinicians and researchers from seven countries, applied the 2021 IASP clinical criteria for nociplastic pain to the growing population of those experiencing post-cancer pain. A manual is provided to allow clinicians to differentiate between predominant nociceptive, neuropathic, or nociplastic pain after cancer. A seven-step diagnostic approach is presented and illustrated using cases to enhance understanding and encourage effective implementation of this approach in clinical practice.

Keywords: cancer pain; central sensitisation; guidelines; neuropathic pain; nociceptive pain; nociplastic pain; oncology; precision medicine

Editor's key points

- Classifying post-cancer pain as predominant nociceptive, neuropathic, or nociplastic pain might direct cancer survivors towards tailored pain mechanism-based pain management.
- The International Association for the Study of Pain clinical criteria for nociplastic pain have great potential for clinical oncology.
- The Cancer Pain Phenotyping (CANPPHE) Network applied clinical criteria for nociceptive, neuropathic, and nociplastic pain to develop multidisciplinary guidelines for phenotyping pain in the growing population of cancer survivors with chronic pain.
- A stepwise approach provides a manual for post-cancer pain phenotyping that is mechanism-based and should therefore have better outcomes that can now be prospectively evaluated.

Pain is one of the most disabling and prevalent symptoms[1] seen in up to 40% of people in the early post-cancer treatment period,[2] and its impact remains underestimated.[3] A pharmacological approach is the standard treatment for cancer-related pain,[3] but pain management is often suboptimal, leaving many people undertreated.[4] This is concerning as available data indicate that the presence of pain affects quality of life[5] and leads to reduced survival in people with cancer.[6]

Precision medicine allows classification of patients into subgroups that differ in their susceptibility, pathology, or prognosis for a particular disease, or in their response to a specific treatment, allowing treatment to be tailored to the individual patient.[7] Applying this to pain after cancer, the ability to classify the pain of cancer survivors as being dominantly nociceptive, neuropathic, or nociplastic pain (the three major pain phenotypes as defined by the International Association for the Study of Pain [IASP]) is an emerging and clinically relevant issue because it might direct cancer survivors towards tailored pain mechanism-based pain management.[8]

Nociplastic pain is defined by the IASP 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*'.[9] The term 'nociplastic pain' was introduced in 2017 as a third mechanistic pain descriptor in addition to nociceptive and neuropathic pain.[9,10] In 2021, the IASP released the first set of clinical criteria and a grading system for nociplastic pain.[11] These criteria account for the need to identify and correctly classify patients with chronic pain early according to their pain phenotype in order to provide appropriate pain treatment and improve precision pain medicine practices.[8] These new criteria[11] align with the 2014 clinical criteria for predominant central sensitisation pain[12] but are more robust, comprehensive, and developed and hold more potential.[13] Although primarily intended for patients with chronic pain located in the musculoskeletal system,[11] the IASP nociplastic criteria hold potential for clinicians and researchers working in the field of oncology, and more specifically for cancer survivors suffering from chronic pain.

Several recent studies support the idea that the nociplastic pain phenotype is predictive of pain after breast cancer surgery.[14–16] Both chronic pain of the musculoskeletal system and nociplastic pain appear to be common among cancer survivors.[17–19] The application of the 2014 clinical criteria for predominant central sensitisation pain to cancer survivors[20] has proven very useful.[17] Because the IASPnociplastic pain criteria[11] replace the older 2014 central sensitisation criteria,[12] previous guidelines for pain phenotyping in cancer survivors[20] are outdated and require updating.

Taken together, the 2021 IASP clinical criteria for nociplastic pain[11] are an important step towards precision pain medicine[13] with great potential for the field of clinical oncology. Here the Cancer Pain Phenotyping (CANPPHE) Network, an international and interdisciplinary group of 22 oncology clinicians and researchers from seven countries and 18 institutions, applies the 2021 IASP clinical criteria for nociplastic pain[11] to the growing population of cancer survivors with chronic pain. This approach adheres to the definition of survivorship introduced by the European Organisation of Research and Treatment of Cancer Survivorship Task Force that a cancer survivor is any person who has been diagnosed with cancer, has completed primary treatment (with the exception of maintenance therapy) and has no evidence of active disease.[21,22] In line with the global move towards precision medicine, it allows clinicians to identify the dominant pain phenotype in cancer survivors and adapt pain management accordingly. This includes explaining how clinicians can differentiate between predominant nociceptive, neuropathic, or nociplastic pain in patients after cancer treatment. This differentiation process is important because neuropathic and

mixed cancer pain (a mixture of nociceptive, neuropathic, and/or nociplastic pain) are considered to be more challenging to treat than pure nociceptive pain.[23,24] Furthermore, the classification of the correct pain phenotype is relevant to selecting the most suitable treatment approach for pain after cancer.[23] In contrast to symptomatic treatments, diagnosis-based treatments, or both, mechanism-based treatments are likely to have better outcomes.[8,25]

Approach

The CANPPHE Network was created by approaching experts in pain, oncology, or both. Given the multidisciplinary nature of cancer care and the post-cancer pain issue in particular, care was taken to create a multidisciplinary group of experts. In addition, given the global nature of the interest in post-cancer pain phenotyping, efforts were taken to create a large international panel with representatives from multiple countries. This resulted in a team of 22 experts, including pain experts, physiotherapists, oncologists, medical oncologists, breast cancer surgeons, movement scientists, and post-cancer pain researchers from seven countries and 18 institutions.

Under the auspices of the CANPPHE Network, two co-ordinators (JN and IS) were designated to draft the initial version of the post-cancer pain phenotyping guidelines, which was further developed with all 22 experts by integrating their clinical expertise and scientific evidence from the literature to apply the 2021 IASP clinical criteria for nociplastic pain[11] to the growing population of cancer survivors with chronic pain. Hence, the CANPPHE guidelines build on the established clinical criteria for neuropathic[26] and nociplastic pain,[11] and primarily follow the stepwise approach of pain phenotyping proposed in the IASP nociplastic pain criteria[11] applied to post-cancer pain.

Pain phenotypes in cancer survivors and its treatment implications

Table 1 compares the three post-cancer pain phenotypes (nociceptive, neuropathic, and nociplastic post-cancer pain), including definitions, key features, pain distribution, and common examples within the cancer survivor population.[27,28] For clinical purposes, the term predominant nociceptive pain can be used when pain is proportional to nociceptive

Table 1 Post-cancer pain phenotypes at a glance: nociceptive, neuropathic, and nociplastic post-cancer pain.

	Nociceptive pain	Neuropathic pain	Nociplastic pain
Definition	Pain attributable to the activation of the peripheral receptive terminals of primary afferent neurones in response to noxious chemical, mechanical, or thermal stimuli,[27] or as pain arising from actual or threat of damage to non-neural tissue and is attributable to the activation of nociceptors.[28]	Pain caused by a primary lesion or disease of the somatosensory nervous system.[28]	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.[9]
Key feature	Pain is proportional to nociceptive input.[12]	A lesion or disease of the nervous system (either central or peripheral) is identifiable, and the pain is limited to a 'neuroanatomically plausible' distribution.[26]	Pain cannot entirely be explained by either nociceptive or neuropathic pain mechanisms.
Pain distribution	Discrete	Neuroanatomically plausible	Regional, multifocal, or widespread
Possible examples in cancer survivors	Pain related to: - Connective tissue fibrosis[29,30] - Scar tissue formation - Lymphatic cording after axillary surgery for breast cancer[31,32] - Bony injuries (fractures) - Oedema[33] - Rashes, ulcers - Myofascial pain and arm movement dysfunction (e.g. scapular dyskinesis after breast cancer surgery)[20,34,35]	- Intercostobrachial neuropathy owing to a direct insult during axillary lymph node dissection.[39] - Postsurgical adhesions and inflammation in the nerve area.[40] - Platinum–taxane chemotherapy-induced peripheral neuropathic pain.[36,42] - Lumbosacral plexus neuropathy owing to irradiation of pelvic organs.[40] - Radiation therapy-induced connective tissue fibrosis within neural tissue.[36,42]	- Patients exposed to anti-hormone therapy.[17] - 'Unexplained' post-cancer pain. - Any type of post-cancer pain that does not entirely fit into the nociceptive or neuropathic pain phenotype.

input.[12,29–35] Although connective tissue fibrosis is frequent among cancer survivors previously treated with surgery, radiation therapy, or both,[30] it can result in both nociceptive and neuropathic pain.[28,36–38] Neuropathic pain is often a consequence of various life-preserving treatments for cancer, such as surgery, radiation therapy, and chemotherapy.[39–42]

CNS sensitisation (or central sensitisation) is the major underlying mechanism of nociplastic pain,[10,11] and is also common in neuropathic pain.[43] Central sensitisation is defined as an amplification of neural signalling within the CNS that elicits pain hypersensitivity,[44] which can potentially explain unexplained somatic symptoms in cancer survivors.[17,45] Central sensitisation encompasses various related mechanisms within the central and peripheral nervous systems, including altered sensory processing in the brain[46] with a disrupted resting state functional connectivity in the default mode and salience networks,[47] and increased brain activity in areas known to be involved in acute pain sensation (anterior cingulate cortex, insula, and prefrontal cortex) and in other regions (dorsolateral frontal cortex, various brain stem nuclei, and the parietal associated cortex).[48] Such altered brain activity patterns are responsible for orchestrated nociceptive facilitatory pathways[46,49] and poor functioning of endogenous analgesia,[50,51] two other features of central sensitisation. Together, these CNS mechanisms not only contribute to increased responsiveness to a variety of sensory inputs, such as tactile stimuli, but can also lead to hypersensitivity to non-musculoskeletal stimuli, such as chemical substances, odours, light, sound, heat, cold, touch, stress, and electricity.[52]

Emerging evidence suggests that central sensitisation plays a role in explaining pain in a subgroup of cancer survivors.[19,53,54] Available evidence suggests that nociplastic pain is present in an important subgroup of cancer survivors,[17,55] with studies reporting symptoms of central sensitisation,[18] spreading of pain,[17] and widespread mechanical hyperalgesia.[19,35] Studies have revealed widespread pressure pain hypersensitivity in patients treated for breast or colon cancer,[19,53,54] with pressure pain thresholds reduced both at the affected site and contralateral side,[56] and at more distal sites.[35] However, other studies have found only local hypersensitivity,[54,57] suggesting more peripheral than central sensitisation. Also, evidence regarding nociceptive facilitatory pathways and endogenous analgesia in cancer survivors is not conclusive.[56,58,59]

Together, these findings support the view that not all cancer survivor pain is related to central sensitisation, and indicate the need for clinical criteria allowing clinicians and researchers to correctly classify cancer survivors according to their dominant pain phenotype. A study of 91 breast cancer survivors identified 'pure' nociplastic pain in more than 15% of the patients, but also revealed features of central sensitisation in most of the patients who were classified as having mixed pain (41%; mixed pain phenotype can be a combination of neuropathic and nociplastic pain, nociceptive and neuropathic pain, nociceptive and nociplastic pain, or a combination of all three pain phenotypes).[17] Interestingly, the odds for nociplastic pain were 26 times higher in patients exposed to anti-hormone therapy compared with the patients not exposed to hormone therapy.[17]

Recent studies furthermore suggest that the nociplastic pain phenotype can be used to improve precision pain medicine practices.[8] Classification into the nociplastic pain phenotype might have significance beyond the cancer survivor continuum. Women undergoing breast cancer surgery with preoperative phenotypic characteristics of nociplastic pain, including high temporal summation (large increases in pain perception during repeated stimulation of constant intensity[8]) and negative affect, are at greater risk of significant postoperative pain and continued opioid use independent of known surgical risk factors.[14] In women without pre-existing chronic pain receiving breast cancer surgery, poorer functioning of endogenous analgesia predicted greater postoperative pain, whereas higher pain sensitivity (assessed using a questionnaire) and pain catastrophising scale scores predicted greater postoperative pain.[15] In a prospective cohort study, the preoperative pain sensitivity questionnaire score (higher scores representing higher sensitivity to pain) was an independent risk factor for moderate pain in the first 24 h after breast cancer surgery.[16] It is thus clear that pain phenotyping, and in particular identifying nociplastic pain phenotype characteristics, is of utmost importance from both a clinician and a cancer survivor perspective, in order to provide optimal patient-targeted pain treatment.

Appropriate pain treatment for post-cancer pain should be tailored to the pain phenotype. For nociceptive post-cancer pain, treatment should target the source of nociception if possible. For example, if oedema,[33] rash, or ulceration is identified as the dominant source of nociception, the treatment should target those issues primarily. Likewise, if myofascial pain and arm movement dysfunction (e.g. scapular dyskinesis after breast cancer surgery)[20,34,35] are the dominant sources of nociception, myofascial pain treatment and exercise therapy are indicated to correct the movement dysfunction. Besides conservative treatment of the underlying source of nociception, short-term use of non-opioid analgesics such as paracetamol or NSAIDs (in cases of local inflammation) can be considered for nociceptive post-cancer pain.[60,61] Management of neuropathic and nociplastic post-cancer pain is significantly different from the management of nociceptive post-cancer pain with respect to pharmacological and non-pharmacological strategies.[62] Antidepressants (e.g. seroton-in–norepinephrine reuptake inhibitors such as duloxetine, tricyclic antidepressants such as amitriptyline[63]) and α2–δ subunit ligands (e.g. gabapentin and pregabalin) can be considered for neuropathic post-cancer pain.[61,64,65] These centrally acting drugs can also be considered for nociplastic post-cancer pain,[66] but most medications provide only modest benefits in patients with nociplastic pain, and adverse effects are more likely in these patients.[67] Therefore, management of nociplastic post-cancer pain should prioritise non-pharmacological management,[67] such as cognitive behavioural therapy, pain neuroscience education, sleep management, stress management, exercise therapy,[67–70] or multidisciplinary treatment.[65] Use of opioid analgesics for nociplastic pain is strongly discouraged.[8,66,67] Finally, explaining pain to cancer survivors should be tailored to the relevant pain phenotype (e.g. explaining central sensitisation should be limited to those presenting with nociplastic or neuropathic post-cancer pain).[71]

The IASP clinical criteria and grading system for nociplastic pain applied to pain after cancer

This section provides a stepwise guide to the nociplastic pain criteria[11] in a way that aims to best represent the pain phenotyping process for clinicians dealing with pain after cancer, focused on the differential diagnosis between nociceptive, neuropathic, nociplastic, or mixed-type post-cancer pain (Fig 1). Appendices 1, 2, and 3 in the supplementary material

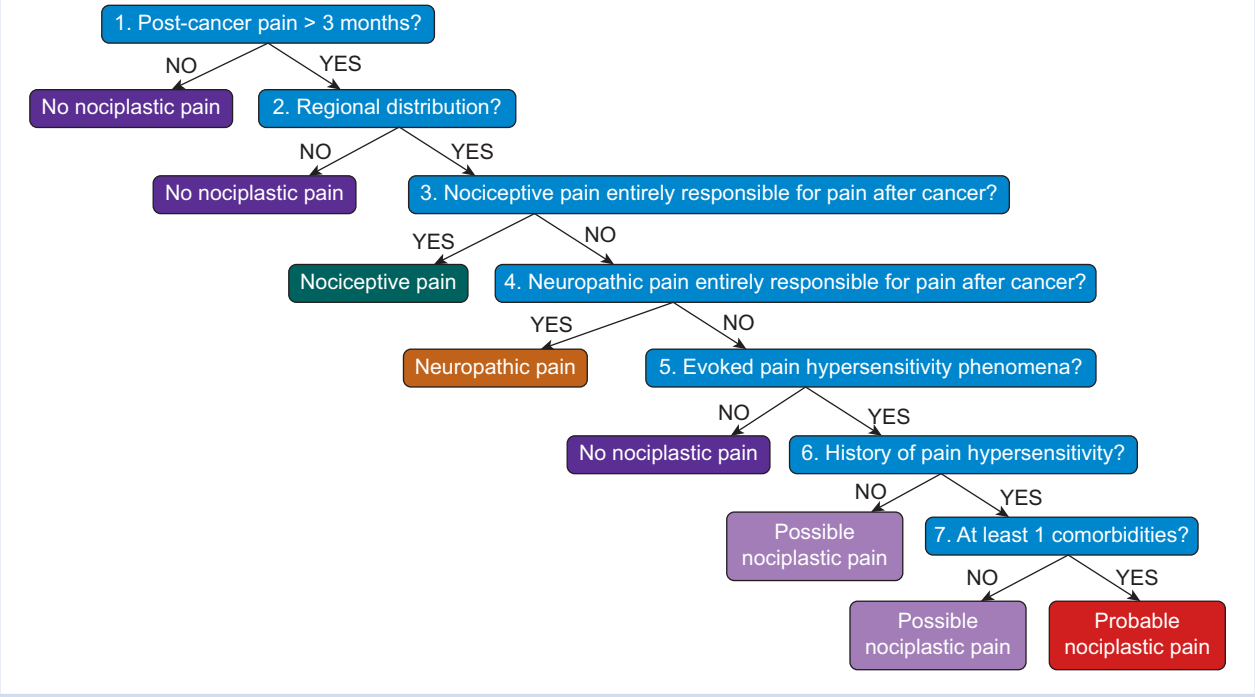

Fig. 1. The seven-step clinical decision-making tree of the IASP clinical criteria for nociplastic pain applied to post-cancer pain (modified for post-cancer pain from Nijs and colleagues[13]).

provide three case studies of cancer survivors having chronic pain. These case descriptions illustrate the way the IASP nociplastic pain criteria for pain phenotyping can be clinically applied to cancer survivors suffering from chronic pain, and how appropriate pain treatment for post-cancer pain should be tailored to the pain phenotype.

Step 1

The first step in applying the IASP clinical criteria for nociplastic pain requires that patients report pain of at least 3 months' duration. This can be easily applied to cancer survivors suffering from pain. According to the IASP clinical criteria,[11] nociplastic pain can only be considered in patients having chronic pain.

Step 2

In addition to having chronic pain, patients must also report a regional, multifocal, or widespread, rather than discrete pain distribution to be clinically classified as having nociplastic pain. A thorough assessment and interpretation of self-reported pain distribution using body charts, in light of the identified possible sources of nociception and neuropathy, is required. More specifically, in nociplastic post-cancer pain the spread of the pain is greater than one would expect if only nociceptive mechanisms are present (for differentiation from nociceptive pain), and the distribution of pain extends beyond the innervation of the lesioned/diseased nervous structure (for differentiating with neuropathic pain).[11] Such regional pain distribution has been found in patients with pain after breast and colon cancer treatment,[19,35,53,54,72] and is considered a sign of central sensitisation.[72–77] Pain drawings[78,79] can be used to standardise and optimise assessment of pain distribution in a reliable and valid way, as shown in a study in patients undergoing cancer treatment,[80] and also as an outcome measure for cancer-related abdominal pain.[81] In patients receiving cancer treatment, the spread of pain assessed using pain drawing relates to symptom burden severity and interference.[80]

Step 3

The third mandatory criterion is that cancer survivors should report pain that cannot entirely be explained by nociceptive pain mechanisms.[11] This includes either identifying or refuting nociceptive pain (including inflammatory pain) as the dominant post-cancer pain phenotype. It is appropriate here to assess the severity of the injury, pathology, and objective dysfunction capable of generating nociceptive input.[20] This includes imaging techniques for identifying nociceptive sources in cancer survivors (e.g. musculoskeletal ultrasonography, radiography, MRI, and CT),[20] but also an in-depth patient interview and clinical/behavioural assessment (including palpation, inspection, and physical testing including quantitative sensory testing). Next, during clinical reasoning, oncology clinicians need to consider whether the amount and severity of injury, pathology and objective dysfunction capable of generating nociceptive input is sufficient to explain the cancer survivor's subjective pain experience.[20]

When nociceptive mechanisms are considered to be entirely responsible for the post-cancer pain, the pain should be classified as nociceptive post-cancer pain. In cases where nociceptive pain is not entirely responsible for the pain experience, clinicians should continue to step 4. It is important to stress that the presence of a source of nociceptive pain, such as connective tissue fibrosis,[29,30] lymphatic cording after axillary surgery for breast cancer[31,32] or bone pain (e.g. because

of fractures) does not exclude the possibility of nociplastic pain, but the region of pain must be more widespread than can be explained by the identifiable source of nociception.[11] Hence, step 2 (pain distribution assessment) and step 3 go hand in hand. The possibility of pain caused by metastasis, such as bone metastasis or visceral metastasis, should always be considered. Therefore, in step 3, it may be necessary to rule out causes of cancer metastasis or recurrence using imaging and blood tests.

Step 4

Similar to nociceptive pain, a fourth mandatory criterion for nociplastic post-cancer pain is that cancer survivors report pain that cannot entirely be explained by neuropathic pain mechanisms.[11] This includes either identifying or refuting neuropathic pain as the dominant post-cancer pain phenotype. Clinicians can rely on the current guideline for classification of neuropathic pain,[26] the IASP neuropathic pain special interest group guidelines,[82] and the older European Federation of Neurological Societies guidelines[83] on neuropathic pain assessment,[84,85,88] and can consider using the Douleur Neuropathique DN4 questionnaire as it includes patient examination (touch, prick, brushing).[87,88] The neuropathic pain criteria specify that a lesion or disease of the central or peripheral nervous system is identifiable and that pain is limited to a 'neuroanatomically plausible' distribution.[26,84,85] Hence, diagnostic procedures confirming or refuting the nervous system lesion or disease are mandatory for diagnosing neuropathic pain.[84,85] For instance, electroneuromyography is useful for identification of the level of plexus damage, whereas MRI and CT scans are used to differentiate from cancer recurrence and for identification of compressive nerve fibrosis.[36,42] Imaging might also involve a review of tumour location and a review of surgical notes might reveal whether nerves were identified, preserved, or damaged during surgery.[86] Box 1 briefly illustrates how clinicians can examine the presence of neuropathic post-cancer pain through review of the patient's medical record, detailed history taking, and physical testing.

When neuropathic pain is considered to be entirely responsible, the pain should be classified as neuropathic post-cancer pain. In cases where neuropathic pain is not exclusively responsible for the post-cancer pain, clinicians should continue to step 5. However, it is important to recognise the overlap between neuropathic and nociplastic post-cancer pain. Indeed, neuropathic pain can be characterised or accompanied by sensitisation. In patients with neuropathic pain, peripheral and central nociceptive pathways can become hyperexcitable (i.e. central sensitisation),[43] explaining the spreading of pain beyond the innervation territory of the lesioned/diseased nervous structure. Thus, cancer survivors can have both neuropathic and nociplastic pain, as shown in a pain phenotyping study where 22 of 91 (24%) breast cancer survivors demonstrated a mixed neuropathic and nociplastic pain phenotype.[17] Therefore, presence of neuropathic pain does not exclude the co-existence of nociplastic pain and mixed pain types as acknowledged by the IASP nociplastic pain criteria.[11] Indeed, if neuropathic pain is present but is not considered entirely responsible for the pain, clinicians should continue to step 5.

Step 5

Step 5 includes screening for clinical signs of pain hypersensitivity that are at least present in the region of pain.[11] This step entails clinical examination of (mainly) allodynia, defined as pain in response to stimuli that normally do not elicit pain in the region of the pain, but also outside the painful region. Indeed, in patients with nociplastic post-cancer pain, allodynia is often more widespread.[11] This can be assessed by evoked pain hypersensitivity phenomena such as static or dynamic mechanical allodynia, heat or cold allodynia, and/or painful after-sensations after any of the mentioned evoked pain hypersensitivity assessments. For assessing static mechanical allodynia, digital palpation with a weight of approximately 4 kg (i.e. nailbed blanching) can be used. Reporting pain in response to such digital palpation is considered mechanical allodynia.[11] If such static mechanical allodynia is present, this criterion is met and one can proceed to the next step (step 6). However, if static mechanical allodynia is not present, additional tests (i.e. tests for assessing dynamic mechanical allodynia, heat and cold allodynia) are required to examine whether allodynia is present or not. Dynamic mechanical allodynia can be assessed by gently stroking the skin

Box 1
Screening criteria for neuropathic pain[26] in patients with post-cancer pain.

Is there a history of a relevant neurological lesion or disease? In patients with post-cancer pain, such a lesion or disease of the nervous system can be a past tumour that, through compressing a peripheral nerve or the spinal cord, resulted in permanent neural damage, but also surgical neuropathies such as intercostal neuralgia or phantom breast pain after breast surgery, radiation-induced neural tissue fibrosis, chemotherapy-induced peripheral neuropathy, among others. Evidence for a 'relevant neurological lesion or disease' is mandatory and can be provided from relevant diagnostic investigations (e.g. electrodiagnostic techniques, myelography, CT, MRI).

Is the post-cancer pain distribution neuroanatomically plausible? In order to classify the post-cancer pain as neuropathic pain, the pain distribution reported by the patient should be anatomically consistent with the suspected location of the neurological lesion or disease.[26]

Is the post-cancer pain associated with sensory signs in the same neuroanatomically plausible distribution? Sensory signs are related to the presence of neuropathy. Tests for sensory signs include testing of the function of the sensory fibres with simple tools (e.g. a soft brush for touch, a tuning fork for vibration, a sharp pin, and cold/warm objects for temperature), which typically assess the relationship between the stimulus and the perceived sensation.[85] In response to such sensory testing, several outcomes can be suggestive of neuropathic post-cancer pain: hyperaesthesia, hypoaesthesia, hyperalgesia, hypoalgesia, allodynia, paraesthesia, dysesthesia, and aftersensations. However, sensory testing cannot serve as diagnostic test, but instead should always be combined with diagnostic procedures confirming or refuting the nervous system lesion or disease.[84,85] Indeed, sensory signs are also present in nociceptive and nociplastic pain, but not within a neuroanatomical plausible distribution.

in the painful area, but also in a remote area, with a brush or a cotton pad.[11] If this triggers pain, it is considered allodynia. By holding a metal object (e.g. a coin[89]) at room temperature (~20°C) against the skin in the painful area and a remote area, cold allodynia can be examined. Likewise, the same object can be heated with warm water (~40°C), or by holding the coin in the pocket for at least half an hour[89] to assess heat allodynia in the painful area and in remote areas.[11] Immediate pain responses to any of these allodynia tests is considered a positive allodynia examination, and hence fulfils this criterion. However, one should also question the patient for possible after-sensations (i.e. ask whether the sensation of the sensory stimulation lingers after the stimulus has been removed). If the five requirements of the first five steps are met, the patient can be classified as having 'possible nociplastic pain',[11] and clinicians should proceed to step 6 to examine whether the likelihood of nociplastic pain can be increased to 'probable nociplastic pain'.

Step 6

Step 6 involves examining whether the cancer survivor presents with a history of hypersensitivity in the region of pain. This can be assessed by questioning the patient for sensitivity to touch, movement, pressure, or heat/cold. The patient interview and history often spontaneously reveal such hypersensitivity to (mechanical) pressure, for instance in patients who perceive clothing against the skin, belts, jewellery, handbags, or bras as unpleasant or painful.[11,52] Other examples include pain flares during hugging (i.e. hypersensitivity to touch, pressure, or both), after prolonged sitting on a comfortable chair (hypersensitivity to pressure), during or after a cold/warm bath or shower (hypersensitivity to heat/cold), or after habitual physical activities of low to moderate intensity such as walking, gardening, or grocery shopping (hypersensitivity to movement).[11,52]

Step 7

The final step involves screening for comorbidities in cancer survivors. This criterion is met if any of the following comorbidities are present: increased sensitivity to sound, light, and/or odours, sleep disturbance with frequent nocturnal awakening, fatigue, or cognitive problems.[11] Similar to step 6, screening for these comorbidities is done during the patient interview and history. Even though it is not mandatory, clinicians might consider using the central sensitisation inventory (CSI) for screening comorbidities. In fact, all comorbidities included in the 2021 IASP clinical criteria for nociplastic pain[11] are covered by items included in the CSI (i.e. item numbers 12, 13, 17, and 20 questioning sleep, concentration, energy level, and hypersensitivity to odours).[13] The CSI has been shown to generate reliable and valid data regarding symptoms of central sensitisation,[90–93] including in cancer survivors suffering from pain,[94,95] but should not be considered as the gold standard measure for assessing features of central sensitisation.[96] Guidelines on interpreting the CSI item or total scores for pain phenotyping in cancer survivors are currently unavailable, but for the purpose of screening step 7, we advise looking at individual item scores rather than total scores. One issue with applying the 2021 IASP nociplastic pain criteria to post-cancer pain is that many of the comorbidities, including fatigue,[97,98] sleep disturbances,[99] and cognitive problems (e.g. impairments in memory, processing speed, attention, and executive functions),[100] are very common among cancer survivors, including cancer survivors free of pain. Thorough clinical reasoning is required to decide whether these comorbidities can contribute to pain phenotyping in cancer survivors.

Post-cancer pain is classified as 'probable nociplastic pain' when cancer survivors fulfil the criteria of steps 1–5, the patient presents with a history of pain hypersensitivity in the region of pain (step 6), and at least one of the defined comorbidities is present (step 7).[11] Fig 1 provides a clinical decision-making tree for applying the IASP clinical criteria for nociplastic post-cancer pain during the clinical reasoning process,. Although not mandatory, it is advisable to complete all seven steps before making a final decision, or in cases where nociplastic pain can be excluded earlier in the process (e.g. after step 2 for case 2; Supplementary material Appendix 2).

Towards precision pain medicine for cancer survivors

Knowledge regarding central sensitisation has revealed a paradigm shift in understanding and management of chronic pain that allows clinicians, including both oncologists and general practitioners, to think beyond muscles and joints,[20] and to account for the role of pain modulation mechanisms in the CNS.[8] Central sensitisation is a key underlying mechanism of nociplastic pain.[10,11] The IASP clinical criteria and grading system for nociplastic pain[11] provide the first set of clinical criteria linked to nociplastic pain as a third mechanistic pain descriptor in addition to nociceptive and neuropathic pain.[13] Clinical criteria for nociplastic pain allow targeting treatment according to the pain phenotype. A potential pitfall for clinicians and patients applying such an approach is that the focus of treatment might rely too much on improving the underlying pain mechanism, that is decreasing central sensitisation in patients with nociplastic post-cancer pain.[13] Rather, the focus should be to regain the ability to perform and enjoy activities of daily living and hence to improve quality of life. Another potential pitfall for clinicians applying a cancer pain phenotyping approach is that one might neglect the individual variability within one pain phenotype.[13] Therefore, precision pain medicine for cancer survivors with pain involves more than accounting for the pain phenotype. It also implies addressing relevant comorbidities and lifestyle factors that sustain the pain mechanism of the relevant pain phenotype. Insomnia[101] and obesity[102] are relevant comorbidities for nociplastic pain, whereas stress,[103] physical inactivity,[104] and an unhealthy diet[105] are lifestyle factors[106] that can sustain central sensitisation.

Research agenda

It is important to stress that more research is necessary to examine the reliability and validity of the 2021 IASP clinical criteria for nociplastic pain[11] in cancer survivors. To serve this purpose, clinical vignettes[107,108] can be useful. Clinical vignettes are short scenarios that describe a situation (i.e. real cases) in which participants typically answer a series of open-ended or closed-ended questions related to the scenarios included in the vignettes.[109] With this technique, these clinical situations are available to multiple evaluators simultaneously, providing the opportunity to examine the intra-rater and inter-rater reliability and content validity of the IASP clinical criteria for nociplastic pain after cancer.

The prognostic value and responsiveness of the IASP clinical criteria for nociplastic pain after cancer also require more

research. For example, the prognostic value of nociplastic pain after cancer, established using the IASP nociplastic pain criteria,[11] on key outcomes such as pain, quality of life, and health care expenditure, can be explored in longitudinal cohort studies. Likewise, the responsiveness to change of the IASP nociplastic pain criteria[11] in cancer survivors can be examined in RCTs examining treatment approaches that aim to specifically target underlying mechanisms of nociplastic pain, such as central sensitisation (e.g. trials on centrally acting drugs or conservative interventions that focus on comorbidities such as insomnia[101] and obesity,[102] which are potentially driving central sensitisation[103,110]). Depending on the outcome of such studies, integration into medical education curricula can be advocated.

Finally, involving people with lived experience of chronic post-cancer pain in the co-production of guidelines for phenotyping pain after cancer would have clear added value. The lack of patient involvement in the development of the CANP-PHE guidelines is a limitation.

Conclusions

Pain after cancer remains underestimated and undertreated. Applying the global move towards precision pain medicine in pain after cancer, by classifying cancer survivors into three major pain phenotypes (nociceptive, neuropathic, and nociplastic pain) is an emerging approach as evidence suggests that nociplastic pain is present in a subgroup of the cancer survivor population.[17–19] The 2021 IASP clinical criteria and grading system for nociplastic pain[11] allow early identification and classification of patients according to pain phenotype, and are an important step towards precision pain medicine[13] with great potential for the field of clinical oncology.

Here we applied the 2021 IASP clinical criteria for nociplastic pain[11] to the growing population of cancer survivors with chronic pain. Using a stepwise approach including seven consecutive steps, clinicians are offered a manual for differentiating between predominant nociceptive, neuropathic, or nociplastic pain after cancer. Pain phenotyping is important for three principal reasons: (1) neuropathic and mixed cancer pain are considered to be more difficult to treat than pure nociceptive pain[23,24]; (2) classification of the pain phenotype is relevant regarding the choice of cancer pain treatment[23]; and (3) compared with symptomatic treatments, diagnosis-based treatments, or both, mechanism-based treatments should have better outcomes.[8,25] Studies examining the clinometric properties of the 2021 IASP clinical criteria and grading system for nociplastic pain[11] in cancer survivors are warranted, and individual variability within one pain phenotype should not be neglected.

Authors' contributions

Concept and design: JN.
Acquisition, analysis, and interpretation of literature findings: JN, IS.
Drafting of the manuscript: JN, IS.
Clinical findings of the cases presented in the appendices: IS.
Substantial contributions to analysis and interpretation of the literature: AL, CFP, PM, CF, TN, CD, MV, KM, AICV, EK, PB, AP, LL, ÖE, ERo, ERh, STY, LDB, AT.
Critical revision of the manuscript for important intellectual content: AL, CFP, PM, CF, TN, CD, MV, KM, AICV, EK, PB, AP, LL, ÖE, ERo, ERh, STY, LDB, AT.
All authors approved the final version of the submitted work and agreed to be accountable for all aspects of the work.

Declarations of interest

JN and the Vrije Universiteit Brussel received lecturing/teaching fees from various professional associations and educational organisations. JN authored a Dutch book on central sensitisation. The remaining authors declare that they have no conflicts of interest.

Funding

The Research Foundation Flanders (FWO), Belgium (11B1920N to AL, 1108621N to EH, G040919N to LL; and AP, a postdoctoral fellow). Stand Up To Cancer (Kom op tegen Kanker) (ANI25 to ER, KM, and LL), a Belgian cancer charity. FWO (G040919N to LL). JN holds a Chair in oncological rehabilitation funded by the Berekuyl Academy, the Netherlands. Grant support for ER was provided by a Chair funded by the Berekuyl Academy/European College for Decongestive Lymphatic Therapy, the Netherlands, and awarded to the Vrije Universiteit Brussel, Belgium. PB is funded by the Research, Innovation and Excellence Structure (DEKA) of the University of Thessaly.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.12.013.

References

1. Leysen L, Beckwée D, Nijs J, et al. Risk factors of pain in breast cancer survivors: a systematic review and meta-analysis. *Support Care Cancer* 2017; **25**: 3607–43
2. Glare PA, Davies PS, Finlay E, et al. Pain in cancer survivors. *J Clin Oncol* 2014; **32**: 1739–47
3. De Groef A, Penen F, Dams L, Van der Gucht E, Nijs J, Meeus M. Best-evidence rehabilitation for chronic pain: Part 2. Pain during and after cancer treatment. *J Clin Med* 2019; **8**: 979
4. Oldenmenger WH, Geerling JI, Mostovaya I, et al. A systematic review of the effectiveness of patient-based educational interventions to improve cancer-related pain. *Cancer Treat Rev* 2018; **63**: 96–103
5. Wang X, Wang N, Zhong L, et al. Prognostic value of depression and anxiety on breast cancer recurrence and mortality: a systematic review and meta-analysis of 282,203 patients. *Molecular Psychiatry* 2020; **25**: 3186–97
6. Quinten C, Coens C, Mauer M, et al. Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials. *Lancet Oncol* 2009; **10**: 865–71
7. National Research Council Committee on A Framework for Developing a New Taxonomy of Disease. *Toward precision medicine: building a knowledge network for biomedical research and a new taxonomy of disease*. Washington, DC: National Academies Press; 2011
8. Nijs J, George SZ, Clauw DJ, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *Lancet Rheumatol* 2021; **3**: e383–92
9. International Association for the Study of Pain (IASP). *IASP terminology* 2017. Available from: https://www.iasp-

pain.org/terminology?navItemNumber=576#Centralsensitization. accessed 28 March 2019
10. Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? *Pain* 2016; **157**: 1382–6
11. 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
12. Nijs J, Torres-Cueco R, van Wilgen CP, et al. Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain. *Pain Physician* 2014; **17**: 447–57
13. Nijs J, Lahousse A, Kapreli E, et al. Nociplastic pain criteria or recognition of central sensitization? Pain phenotyping in the past, present and future. *J Clin Med* 2021; **10**: 3203
14. Schreiber KL, Zinboonyahgoon N, Xu X, et al. Preoperative psychosocial and psychophysical phenotypes as predictors of acute pain outcomes after breast surgery. *J Pain* 2019; **20**: 540–56
15. Ruscheweyh R, Viehoff A, Tio J, Pogatzki-Zahn EM. Psychophysical and psychological predictors of acute pain after breast surgery differ in patients with and without pre-existing chronic pain. *Pain* 2017; **158**: 1030–8
16. Rehberg B, Mathivon S, Combescure C, Mercier Y, Savoldelli GL. Prediction of acute postoperative pain following breast cancer surgery using the pain sensitivity questionnaire: a cohort study. *Clin J Pain* 2017; **33**: 57–66
17. Leysen L, Adriaenssens N, Nijs J, et al. Chronic pain in breast cancer survivors: nociceptive, neuropathic, or central sensitization pain? *Pain Pract* 2019; **19**: 183–95
18. De Groef A, Meeus M, De Vrieze T, et al. Pain characteristics as important contributing factors to upper limb dysfunctions in breast cancer survivors at long term. *Musculoskelet Sci Pract* 2017; **29**: 52–9
19. Fernandez-Lao C, Cantarero-Villanueva I, Fernandez-de-las-Penas C, Del-Moral-Avila R, Menjon-Beltran S, Arroyo-Morales M. Widespread mechanical pain hypersensitivity as a sign of central sensitization after breast cancer surgery: comparison between mastectomy and lumpectomy. *Pain Med* 2011; **12**: 72–8
20. Nijs J, Leysen L, Adriaenssens N, et al. Pain following cancer treatment: guidelines for the clinical classification of predominant neuropathic, nociceptive and central sensitization pain. *Acta Oncol* 2016; **55**: 659–63
21. Moser EC, Meunier F. Cancer survivorship: a positive side-effect of more successful cancer treatment. *EJC Suppl* 2014; **12**: 1–4
22. Dirven L, van de Poll-Franse LV, Aaronson NK, Reijneveld JC. Controversies in defining cancer survivorship. *Lancet Oncol* 2015; **16**: 610–2
23. Knudsen AK, Aass N, Fainsinger R, et al. Classification of pain in cancer patients—a systematic literature review. *Palliat Med* 2009; **23**: 295–308
24. Fainsinger RL, Nekolaichuk CL, Lawlor PG, Neumann CM, Hanson J, Vigano A. A multicenter study of the revised Edmonton Staging System for classifying cancer pain in advanced cancer patients. *J Pain Symptom Manag* 2005; **29**: 224–37
25. Levin M. Changing the face of pain management. Mechanism-based treatment most likely to succeed. *Postgrad Med* 2004; **116**: 45–8
26. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain* 2016; **157**: 1599–606
27. Smart KM, Blake C, Staines A, Doody C. Clinical indicators of 'nociceptive', 'peripheral neuropathic' and 'central' mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. *Man Ther* 2010; **15**: 80–7
28. Merskey N, Bogduk N. Part III: pain terms, a current list with definitions and notes on usage. In: *Classification of chronic pain*. Seattle, WA: IASP Press; 1994. p. 209–14
29. Kinahan KE, Sharp LK, Seidel K, et al. Scarring, disfigurement, and quality of life in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor study. *J Clin Oncol* 2012; **30**: 2466–74
30. Westbury CB, Yarnold JR. Radiation fibrosis—current clinical and therapeutic perspectives. *Clin Oncol (R Coll Radiol)* 2012; **24**: 657–72
31. Tilley A, Thomas-Maclean R, Kwan W. Lymphatic cording or axillary web syndrome after breast cancer surgery. *Can J Surg* 2009; **52**: E105. –e6
32. Moskovitz AH, Anderson BO, Yeung RS, Byrd DR, Lawton TJ, Moe RE. Axillary web syndrome after axillary dissection. *Am J Surgery* 2001; **181**: 434–9
33. Kim SJ, Park YD. Effects of complex decongestive physiotherapy on the oedema and the quality of life of lower unilateral lymphoedema following treatment for gynecological cancer. *Eur J Cancer Care* 2008; **17**: 463–8
34. Crosbie J, Kilbreath SL, Dylke E, et al. Effects of mastectomy on shoulder and spinal kinematics during bilateral upper-limb movement. *Phys Ther* 2010; **90**: 679–92
35. Rasmussen GHF, Madeleine P, Arroyo-Morales M, Voigt M, Kristiansen M. Pain sensitivity and shoulder function among breast cancer survivors compared to matched controls: a case-control study. *J Cancer Surviv* 2021 Jan 26. https://doi.org/10.1007/s11764-021-00995-y. Epub ahead of print. PMID: 33495914.
36. Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. *Radiother Oncol* 2012; **105**: 273–82
37. Schreiber KL, Kehlet H, Belfer I, Edwards RR. Predicting, preventing and managing persistent pain after breast cancer surgery: the importance of psychosocial factors. *Pain Manage* 2014; **4**: 445–59
38. Bennett MI, Rayment C, Hjermstad M, Aass N, Caraceni A, Kaasa S. Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. *Pain* 2012; **153**: 359–65
39. Peuckmann V, Ekholm O, Rasmussen NK, et al. Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. *Eur J Pain* 2009; **13**: 478–85
40. Kim JH, Dougherty PM, Abdi S. Basic science and clinical management of painful and non-painful chemotherapy-related neuropathy. *Gynecol Oncol* 2015; **136**: 453–9
41. Chen AM, Wang PC, Daly ME, et al. Dose-volume modeling of brachial plexus-associated neuropathy after radiation therapy for head-and-neck cancer: findings from a prospective screening protocol. *Int J Radiat Oncol Biol Phys* 2014; **88**: 771–7
42. Burton AW, Fanciullo GJ, Beasley RD, Fisch MJ. Chronic pain in the cancer survivor: a new frontier. *Pain Med* 2007; **8**: 189–98
43. Ferrini F, De Koninck Y. Microglia control neuronal network excitability via BDNF signalling. *Neural Plast* 2013; **2013**, 429815

44. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011; **152**: S2–15
45. Cuesta-Vargas AI, Roldan-Jimenez C, Neblett R, Gatchel RJ. Cross-cultural adaptation and validity of the Spanish central sensitization inventory. *SpringerPlus* 2016; **5**: 1837
46. Staud R, Craggs JG, Perlstein WM, Robinson ME, Price DD. Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. *Eur J Pain* 2008; **12**: 1078–89
47. van Ettinger-Veenstra H, Lundberg P, Alfoldi P, et al. Chronic widespread pain patients show disrupted cortical connectivity in default mode and salience networks, modulated by pain sensitivity. *J Pain Res* 2019; **12**: 1743–55
48. Seifert F, Maihofner C. Central mechanisms of experimental and chronic neuropathic pain: findings from functional imaging studies. *Cell Mol Life Sci* 2009; **66**: 375–90
49. Bosma RL, Mojarad EA, Leung L, Pukall C, Staud R, Stroman PW. FMRI of spinal and supra-spinal correlates of temporal pain summation in fibromyalgia patients. *Hum Brain Mapp* 2016; **37**: 1349–60
50. Yarnitsky D. Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): its relevance for acute and chronic pain states. *Curr Opin Anaesthesiol* 2010; **23**: 611–5
51. Endogenous analgesia system. In: Gebhart GF, Schmidt RF, editors. *Encyclopedia of pain*. Berlin: Springer; 2013. p. 1144
52. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. *Man Ther* 2010; **15**: 135–41
53. Caro-Moran E, Diaz-Rodriguez L, Cantarero-Villanueva I, Galiano-Castillo N, Arroyo-Morales M, Fernandez-Lao C. Nerve pressure pain hypersensitivity and upper limb mechanosensitivity in breast cancer survivors: a case-control study. *Pain Med* 2014; **15**: 1715–23
54. Sanchez-Jimenez A, Cantarero-Villanueva I, Molina-Barea R, Fernandez-Lao C, Galiano-Castillo N, Arroyo-Morales M. Widespread pressure pain hypersensitivity and ultrasound imaging evaluation of abdominal area after colon cancer treatment. *Pain Med* 2014; **15**: 233–40
55. Kumar SP. Cancer pain: a critical review of mechanism-based classification and physical therapy management in palliative care. *Indian J Palliat Care* 2011; **17**: 116–26
56. Vilholm OJ, Cold S, Rasmussen L, Sindrup SH. Sensory function and pain in a population of patients treated for breast cancer. *Acta Anaesthesiol Scand* 2009; **53**: 800–6
57. Fernandez-Lao C, Cantarero-Villanueva I, Fernandez-de-Las-Penas C, Del-Moral-Avila R, Arendt-Nielsen L, Arroyo-Morales M. Myofascial trigger points in neck and shoulder muscles and widespread pressure pain hypersensitivity in patients with postmastectomy pain: evidence of peripheral and central sensitization. *Clin J Pain* 2010; **26**: 798–806
58. Edwards RR, Mensing G, Cahalan C, et al. Alteration in pain modulation in women with persistent pain after lumpectomy: influence of catastrophizing. *J Pain Symptom Manage* 2013; **46**: 30–42
59. Schreiber KL, Martel MO, Shnol H, et al. Persistent pain in postmastectomy patients: comparison of psychophysical, medical, surgical, and psychosocial characteristics between patients with and without pain. *Pain* 2013; **154**: 660–8
60. Krakowski I, Theobald S, Balp L, et al. Summary version of the Standards, Options and Recommendations for the use of analgesia for the treatment of nociceptive pain in adults with cancer (update 2002). *Br J Cancer* 2003; **89**: S67–72
61. Jara C, Del Barco S, Grávalos C, et al. SEOM clinical guideline for treatment of cancer pain (2017). *Clin Transl Oncol* 2018; **20**: 97–107
62. Taverner T. Neuropathic pain in people with cancer (part 2): pharmacological and non-pharmacological management. *Int J Palliat Nurs* 2015; **21**: 380–4
63. Eija K, Tiina T, J NP. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. *Pain* 1996; **64**: 293–302
64. Fallon MT. Neuropathic pain in cancer. *Br J Anaesth* 2013; **111**: 105–11
65. Chang PJ, Asher A, Smith SR. A targeted approach to post-mastectomy pain and persistent pain following breast cancer treatment. *Cancers* 2021; **13**: 5191
66. Nijs J, Leysen L, Vanlauwe J, et al. Treatment of central sensitization in patients with chronic pain: time for change? *Exp Opin Pharmacother* 2019; **20**: 1961–70
67. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. *Lancet* 2021; **397**: 2098–110
68. Nijs J, Leysen L, Pas R, et al. Treatment of pain following cancer: applying neuro-immunology in rehabilitation practice. *Disabil Rehabil* 2018; **40**: 714–21
69. Gutiérrez-Sánchez D, Pajares-Hachero BI, Trinidad-Fernández M, et al. The benefits of a therapeutic exercise and educational intervention program on central sensitization symptoms and pain-related fear avoidance in breast cancer survivors. *Pain Manag Nurs* 2022; **23**: 467–72
70. Rasmussen GHF, Kristiansen M, Arroyo-Morales M, Voigt M, Madeleine P. The analgesic effect of resistance training after breast cancer (ANTRAC): a randomized controlled trial. *Med Sci Sports Exerc* 2022. https://doi.org/10.1249/MSS.0000000000003034
71. Nijs J, Wijma AJ, Leysen L, et al. Explaining pain following cancer: a practical guide for clinicians. *Braz J Phys Ther* 2019; **23**: 367–77
72. Caro-Morán E, Fernández-Lao C, Díaz-Rodríguez L, Cantarero-Villanueva I, Madeleine P, Arroyo-Morales M. Pressure pain sensitivity maps of the neck-shoulder region in breast cancer survivors. *Pain Med* 2016; **17**: 1942–52
73. Meeus M, Nijs J, Huybrechts S, Truijen S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: a case control study. *Clin Rheumatol* 2010; **29**: 393–8
74. Aranda-Villalobos P, Fernandez-de-Las-Penas C, Navarro-Espigares JL, et al. Normalization of widespread pressure pain hypersensitivity after total hip replacement in patients with hip osteoarthritis is associated with clinical and functional improvements. *Arthritis Rheum* 2013; **65**: 1262–70
75. Chiarotto A, Fernandez-de-Las-Penas C, Castaldo M, Villafane JH. Bilateral pressure pain hypersensitivity over the hand as potential sign of sensitization mechanisms in individuals with thumb carpometacarpal osteoarthritis. *Pain Med* 2013; **14**: 1585–92
76. Coombes BK, Bisset L, Vicenzino B. Thermal hyperalgesia distinguishes those with severe pain and disability in

unilateral lateral epicondylalgia. *Clin J Pain* 2012; **28**: 595–601
77. Koelbaek Johansen M, Graven-Nielsen T, Schou Olesen A, Arendt-Nielsen L. Generalised muscular hyperalgesia in chronic whiplash syndrome. *Pain* 1999; **83**: 229–34
78. Margolis RB, Chibnall JT, Tait RC. Test-retest reliability of the pain drawing instrument. *Pain* 1988; **33**: 49–51
79. Margolis RB, Tait RC, Krause SJ. A rating system for use with patient pain drawings. *Pain* 1986; **24**: 57–65
80. Trahan LH, Cox-Martin E, Johnson CE, et al. Psychometric study of the pain drawing. *J Appl Biobehav Res* 2017; **22**, e12095
81. Novy DM, Engle MP, Lai EA, et al. Effectiveness of splanchnic nerve neurolysis for targeting location of cancer pain: using the pain drawing as an outcome variable. *Pain Physician* 2016; **19**: 397–403
82. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011; **152**: 14–27
83. Cruccu G, Sommer C, Anand P, et al. EFNS guidelines on neuropathic pain assessment: revised 2009. *Eur J Neurol* 2010; **17**: 1010–8
84. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008; **70**: 1630–5
85. Haanpää M, Treede RD. Diagnosis and classification of neuropathic pain. *IASP Clin Updates* 2010; **18**: 1–6
86. Mulvey MR, Rolke R, Klepstad P, et al. Confirming neuropathic pain in cancer patients: applying the NeuPSIG grading system in clinical practice and clinical research. *Pain* 2014; **155**: 859–63
87. Beyaz SG, Ergonenc JS, Ergonenc T, Sonmez OU, Erkorkmaz U, Altintoprak F. Postmastectomy pain: a cross-sectional study of prevalence, pain characteristics, and effects on quality of life. *Chin Med J* 2016; **129**: 66–71
88. Bruce J, Thornton AJ, Powell R, et al. Psychological, surgical, and sociodemographic predictors of pain outcomes after breast cancer surgery: a population-based cohort study. *Pain* 2014; **155**: 232–43
89. Zhu GC, Böttger K, Slater H, et al. Concurrent validity of a low-cost and time-efficient clinical sensory test battery to evaluate somatosensory dysfunction. *Eur J Pain* 2019; **23**: 1826–38
90. Cuesta-Vargas AI, Neblett R, Chiarotto A, et al. Dimensionality and reliability of the central sensitization inventory in a pooled multicountry sample. *J Pain* 2018; **19**: 317–29
91. Gervais-Hupé J, Pollice J, Sadi J, Carlesso LC. Validity of the central sensitization inventory with measures of sensitization in people with knee osteoarthritis. *Clin Rheumatol* 2018; **37**: 3125–32
92. Kregel J, Vuijk PJ, Descheemaeker F, et al. The Dutch Central Sensitization Inventory (CSI): factor analysis, discriminative power, and test-retest reliability. *Clin J Pain* 2016; **32**: 624–30
93. Neblett R, Hartzell MM, Mayer TG, Cohen H, Gatchel RJ. Establishing clinically relevant severity levels for the central sensitization inventory. *Pain Pract* 2017; **17**: 166–75
94. Hurth A, Nijzink-Ter Steege J, Scheepbouwer P, et al. Assessment of central sensitization in breast cancer survivors: convergent validity and use of the central sensitization inventory (CSI) and its short-form as a clustering tool. *Clin Pract* 2021; **11**: 607–18
95. Roldán-Jiménez C, Pajares B, Iglesias Campos M, et al. Structural validity and reliability of the Spanish Central Sensitization Inventory in breast cancer survivors. *Pain Pract* 2021; **21**: 740–6
96. Nijs J, Huysmans E. Clinimetrics: the Central Sensitisation Inventory: a useful screening tool for clinicians, but not the gold standard. *J Physiother* 2022; **68**: 207
97. Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology* 2005; **30**: 92–100
98. Servaes P, Verhagen S, Bleijenberg G. Determinants of chronic fatigue in disease-free breast cancer patients: a cross-sectional study. *Ann Oncol* 2002; **13**: 589–98
99. Leysen L, Lahousse A, Nijs J, et al. Prevalence and risk factors of sleep disturbances in breast cancer survivors: systematic review and meta-analyses. *Support Care Cancer* 2019; **27**: 4401–33
100. Lange M, Joly F, Vardy J, et al. Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol* 2019; **30**: 1925–40
101. Johnson JA, Rash JA, Campbell TS, et al. A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. *Sleep Med Rev* 2016; **27**: 20–8
102. Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The impact of obesity on breast cancer diagnosis and treatment. *Curr Oncol Rep* 2019; **21**: 41
103. Nijs J, Loggia ML, Polli A, et al. Sleep disturbances and severe stress as glial activators: key targets for treating central sensitization in chronic pain patients? *Expert Opin Ther Targets* 2017; **21**: 817–26
104. Nugraha B, Karst M, Engeli S, Gutenbrunner C. Brain-derived neurotrophic factor and exercise in fibromyalgia syndrome patients: a mini review. *Rheumatol Int* 2012; **32**: 2593–9
105. Nijs J, Tumkaya Yilmaz S, Elma Ö, et al. Nutritional intervention in chronic pain: an innovative way of targeting central nervous system sensitization? *Expert Opin Ther Targets* 2020; **24**: 793–803
106. Lahousse A, Roose E, Leysen L, et al. Lifestyle and pain following cancer: state-of-the-art and future directions. *J Clin Med* 2022; **11**: 195
107. St Marie B, Jimmerson A, Perkhounkova Y, Herr K. Developing and establishing content validity of vignettes for health care education and research. *West J Nurs Res* 2021; **43**: 677–85
108. Steiner PM, Atzmüller C, Su D. Designing valid and reliable vignette experiments for survey research: a case study on the fair gender income gap. *J Methods Meas Soc Sci* 2017; **7**: 43
109. Ulrich Connie M, Ratcliffe Sarah J. Hypothetical vignettes in empirical bioethics research. In: Liva J, Laura AS, editors. *Empirical methods for bioethics: a primer*. Bingley, UK: Emerald Group Publishing Limited; 2007. p. 161–81
110. Nijs J, Elma O, Yilmaz ST, et al. Nutritional neurobiology and central nervous system sensitisation: missing link in a comprehensive treatment for chronic pain? *Br J Anaesth* 2019; **123**: 539–43

Handling editor: Hugh C Hemmings Jr