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NOCICEPTIVE, NEUROPATHIC, OR NOCIPLASTIC LOW BACK PAIN? THE LOW BACK PAIN PHENOTYPING (BACPAP) CONSORTIUM'S INTERNATIONAL AND MULTIDISCIPLINARY CONSENSUS RECOMMENDATIONS

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Abstract

The potential to classify low back pain as being characterised by dominant nociceptive, neuropathic, or nociplastic mechanisms is a clinically relevant issue. Preliminary evidence suggests that these low back pain phenotypes might respond differently to treatments; however, more research must be done before making specific recommendations. Accordingly, the low back pain phenotyping (BACPAP) consortium was established as a group of 36 clinicians and researchers from 13 countries (five continents) and 29 institutions, to apply a modified Nominal Group Technique methodology to develop international and multidisciplinary consensus recommendations to provide guidance for identifying the dominant pain phenotype in patients with low back pain, and potentially adapt pain management strategies. The BACPAP consortium's recommendations are also intended to provide direction for future clinical research by building on the established clinical criteria for neuropathic and nociplastic pain. The BACPAP consortium's consensus recommendations are a necessary early step in the process to determine if personalised pain medicine based on pain phenotypes is feasible for low back pain management. Therefore, these recommendations are not ready to be implemented in clinical practice until additional evidence is generated that is specific to these low back pain phenotypes.

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Introduction

Low back pain has a mean global lifetime prevalence of about 40% in the adult population,[1] with more than half a billion prevalent cases worldwide in 2020.[2] 1 year after the onset of low back pain, approximately one third of patients continue to experience pain.[3] Chronic low back pain is a global health problem and the leading cause of disability[2] and people seeking health care.1, 4 Despite its high-priority societal concern, current pain management seems to have a modest effect at best.[5] 80–90% of patients with low back pain are considered to have non-specific low back pain, meaning that a specific pathoanatomical cause explaining pain or disability cannot be identified.[6]

Similar to other persistent pain conditions, chronic low back pain can be characterised by nociceptive, neuropathic, or nociplastic mechanisms, a combination of these mechanisms, or in some cases, is not classifiable (table 1). It is proposed that personalised pain medicine treatment might be more effective if allocated based on the underlying pain phenotype.[30] For example, two studies suggested that individuals with chronic low back pain with features consistent with a nociplastic pain phenotype might respond better to treatments that address sensitisation.31, 32 The first reported a post-hoc analysis of pooled data from four double-blind, randomised, placebo-controlled trials of the serotonin-norepiphrenine reuptake inhibitor duloxetine (60 mg per day for 12–14 weeks) in adult patients with chronic low back pain.[31] Although the differential effect of the drug was only tested in one of the four trials, it showed that patients with multiple pain sites, a feature of nociplastic pain,[15] responded better to duloxetine than those without such features.[31] The second, a double-blind, randomised, cross-over trial of 150 patients with chronic low back pain, showed no effect of imipramine (a tricyclic antidepressant) when the whole group was considered, but a greater effect than placebo for patients with features of nociplastic pain (ie, greater sensitivity to heat and cold pain).[32] For oxycodone and clobazam, no predictor of analgesic effect in patients with chronic low back pain was found.[32] On the other hand, in a trial that was done before the release of the nociplastic pain criteria,[15] treatment with pregabalin did not influence outcomes in patients with sciatica (ie, patients with a predominant neuropathic phenotype).[33] However, methodological issues prevented robust conclusions being drawn.[34] Similarly, clinical trials in other musculoskeletal pain conditions (ie, temporomandibular disorder and shoulder pain) have not shown a benefit for personalised approaches to pain relief.35, 36 Collectively these data suggest that although the idea of applying treatments matched to a specific phenotype is appealing for pain medicine, future research is needed to guide clinical practice.

The potential to classify chronic low back pain as being characterised either by dominant nociceptive, neuropathic, or nociplastic mechanisms (ie, the three major pain phenotypes)12, 37 is an emerging and clinically relevant issue for two related reasons. First, the aforementioned preliminary evidence suggests that the different chronic low back pain phenotypes might respond differently to treatments often used in patients with chronic low back pain, including surgery[38] and centrally-acting drugs.31, 32 Second, accurate classification might improve the ability to deliver mechanism based treatments in a personalised manner for patients with low back pain.24, 30, 39, 40 A systematic review identified 200 methods that have been used to discriminate between these pain phenotypes for musculoskeletal pain conditions.[39] A subsequent Delphi study among pain experts found consensus for 76 features of which 17 were considered unique to nociceptive, 37 to neuropathic, and 22 to nociplastic pain mechanisms.[41] All this useful information requires a clear framework for studying the potential of low back pain

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phenotyping. This framework could be used to guide future research efforts in establishing reliability for classification decision making, and in testing efficacy in clinical trials. Hence, there is a need to develop recommendations regarding phenotyping between nociceptive, nociplastic, and neuropathic chronic low back pain. These recommendations could be especially beneficial for providing standard approaches for the use of these phenotypes in future clinical research.

Accordingly, the low back pain phenotyping (BACPAP) consortium was established to address the generation of consensus recommendations for phenotyping that include application of the 2021 International Association for the Study of Pain (IASP) clinical criteria for nociplastic pain[15] and the 2016 update of the guideline for the classification of neuropathic pain.[11] The consortium is aimed at developing and providing recommendations to identify the dominant pain phenotype in patients with chronic low back pain, and potentially adapting pain management strategies. For that purpose, a modified Nominal Group Technique, commonly used for developing clinical guidelines,42, 43 was applied as a consensus development method. The BACPAP consortium's consensus recommendations will add to the existing literature as a necessary early step in the process to determine if personalised pain medicine based on pain phenotypes is feasible for low back pain management.

Table 1. The low back pain phenotypes at a glance

	Low back pain characterised by nociceptive pain mechanisms	Low back pain characterised by neuropathic pain mechanisms	Low back pain characterised by nociplastic pain mechanisms
Definition	Pain attributable to the activation of the peripheral receptive terminals of primary afferent neurons in response to noxious chemical, mechanical or thermal stimuli,[7] or as pain arising from actual or threat of damage to non-neural tissue and is due to the activation of nociceptors[8]	Pain caused by a primary lesion or disease of the somatosensory nervous system[8]	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 features	Pain is proportional to nociceptive input[10]	A lesion or disease of the nervous system (either central or peripheral) is identifiable;[11] shooting pain within dermatomal distribution; symptoms such as pins and needles in the legs, numbness and muscle weakness; for many neuropathic low back pain conditions, a true diagnostic criterion may be lacking (ie, there is no gold standard test) thus confirmation is often based on clustering of key clinical signs and symptoms; and compared with nociceptive low back pain, neuropathic low back pain is often associated with higher levels of pain, greater disability, anxiety, depression and reduced health-related quality of life[12,13,14]	Pain cannot entirely be explained by either nociceptive or neuropathic pain mechanisms; commonly presents as disproportionate and unpredictable pain response with widespread hypersensitivity; increased responsiveness to a variety of sensory inputs (eg, tactile stimuli); and hypersensitivity to non-musculoskeletal stimuli (eg, chemical substances, odours, light, sound, heat, cold, stress, and electricity)[15,16]
Pain distribution	Discrete	Neuroanatomically plausible	Regional, multifocal, or widespread
Possible low back pain examples	The lumbopelvic region includes a large number of tissues capable of generating nociceptive input, including intervertabral discs,[17] muscles,[18] fascia,[19] bone,[20] facet joints including the capsule,[21] sacroiliac joints,[21] symphysis pubis, and ligaments;[22] nociceptive pain classification acknowledges each of these tissues as having the potential to generate nociceptive input; however, it is often impossible and unnecessary to confirm which specific tissue is generating the input in order to classify an individual with (predominant) nociceptive pain; in addition to structural damage, nociceptive pain can also be due to an inflammatory spinal disorder	Symptomatic lumbar radiculopathy (also called lumbosacral radicular syndrome);[23] radiculitis (ie, inflammation of one or more nerve roots);[24] and entrapment neuropathy of the L1–L2 dorsal ramus over the iliac crest[25]	In contrast to studies in patients with acute low back pain, where only a subgroup presents with generalised hyperalgesia,[26] features of nociplastic pain have been consistently detected in patients with chronic and recurrent low back pain, using subjective responses to sensory stimulation, objective electrophysiological paradigms, and evidence of enhanced central nociceptive processing following sensory stimulation in brain imaging;[27,28] a recent systematic review identified pressure pain sensitivity, compared with other quantitative sensory tests, to be most consistently altered in patients with subacute and chronic low back pain[29]

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Methods

CONSORTIUM CREATION

The BACPAP consortium is a convenience sample of individuals with expertise in pain, low back pain, or both. Care was taken to create a multidisciplinary, international group of experts. The invitation process was led by the lead author (JN) and resulted in a group of 36 experts from 13 countries (five continents) and 29 institutions. The represented disciplines of the group included: pain medicine (n=3), rehabilitation (n=4), rehabilitation medicine (n=2), anaesthesiology (n=1), rheumatology (n=1), physiotherapy (n=30), manual therapy (n=9), epidemiology (n=2), general practice (n=1), and human movement science (n=1).

MODIFIED NOMINAL GROUP TECHNIQUE

Within the health-care literature, the Nominal Group Technique and Delphi Technique are commonly used consensus methods for research that is directed at problem-solving, idea-generation, or determining priorities.[42] When applied together, the Nominal Group and Delphi techniques generate the same outcomes and are therefore both recommended for use in health services research.[44] Given the availability of a recent systematic literature review,[39] as well as two Delphi studies on clinical indicators of nociceptive versus neuropathic and nociplastic pain,[7,41] it was deemed unnecessary to apply similar methodologies. In addition, compared with the Delphi technique, the Nominal Group technique has the advantages of yielding a closer consensus and a greater understanding of reasons for disagreement.[43] For all these reasons, the Nominal Group Technique was used as the consensus development method.[42,43]

Under the auspice of the BACPAP consortium, three coordinators (JN, EKo, and SZG) were selected to lead the development of the consensus recommendations via Nominal Group Technique. The modified Nominal Group Technique involved: (1) an introduction and explanation, (2) generation of manuscript and clinical examples, (3) several rounds of sharing of manuscript and clinical examples (idea generation and clarification phases),[42] (4) group discussion, and (5) voting on final recommendations and case studies. Given the size and scope of this group, which is much larger than commonly used on Nominal Group Technique studies,[42] completing the Nominal Group Technique process entirely as synchronous work was deemed infeasible. Therefore, two separate nominal groups[42] were created by the three coordinators, with a researcher and a clinicians group, even though the expertise of the consortium members is not mutually exclusive to one of those labels. The majority of the work was completed via directed email exchanges (rather than face-to-face communication), along with one online meeting for group discussion. To complete the Nominal Group Technique, a vote of the final version of consensus recommendations and case studies was performed anonymously.[42] For the voting, a 90% quorum for accepting the results and a minimum agreement score of 70% was applied.[45] The resulting voting scores were summed and presented to the group for discussion.[42] More details describing the methodology can be found in the appendix (p 1).

To illustrate the BACPAP consortium's consensus recommendations, the appendix (pp 9–26) provides four case studies of patients with chronic low back pain developed by four clinicians (JRC, EKo, DB, and

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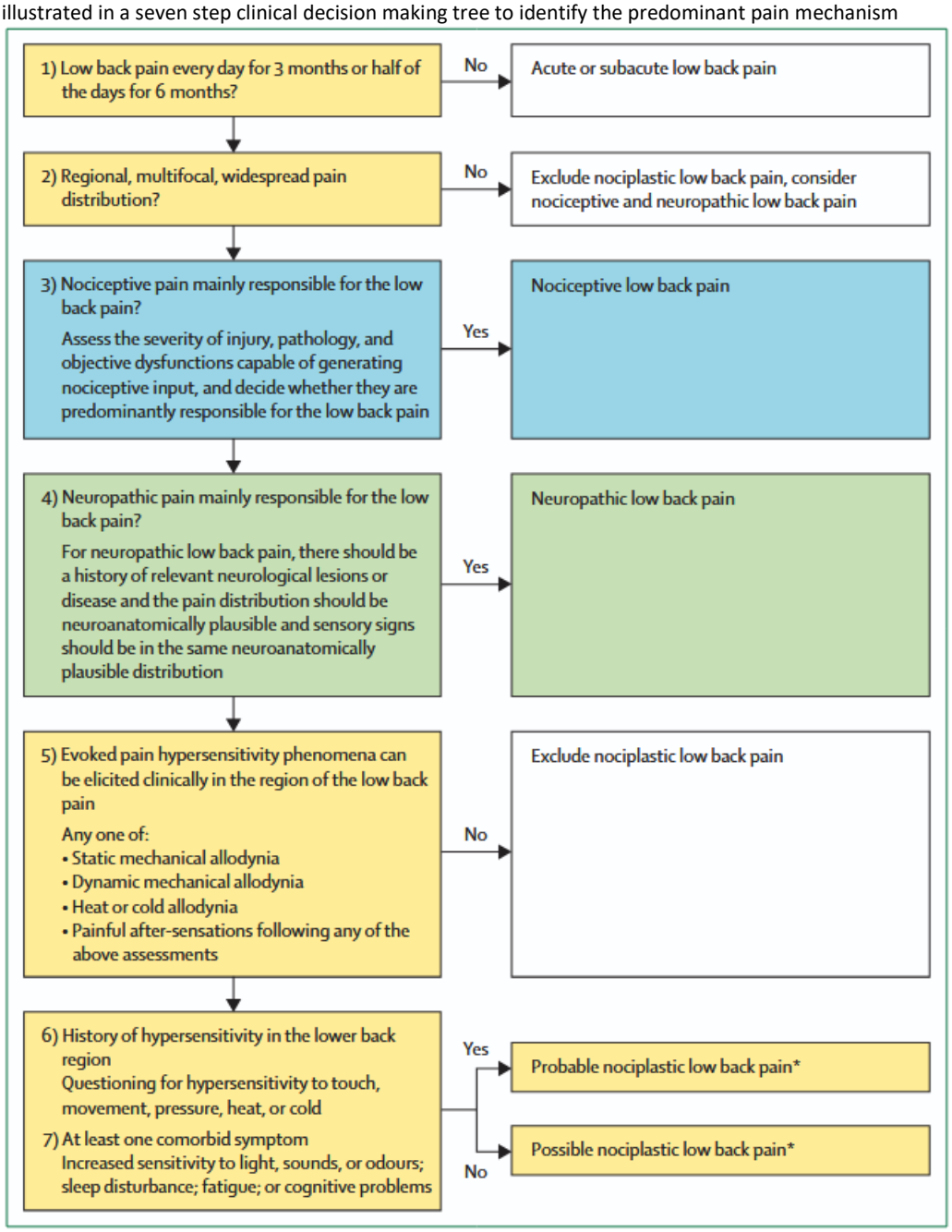
PB) from three different settings in three different countries (Australia, Greece, and New Zealand). These case descriptions illustrate the way the BACPAP consortium's consensus recommendations for pain phenotyping can be applied to patients with chronic low back pain.

Figure. The BACPAP consortium's consensus recommendations for pain phenotyping in patients with chronic low back pain illustrated in a seven step clinical decision making tree to identify the predominant pain mechanism



Modified from Kosek et al,[15] by permission of Wolters Kluwer Health, and Nijs et al,[47] by permission of the authors.
*Depending on the outcome of steps 3 and 4, it can be either nociplastic pain, mixed nociplastic and nociceptive pain, or mixed nociplastic and neuropathic pain.

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Findings

RECOMMENDATIONS FOR PAIN PHENOTYPING IN PATIENTS WITH LOW BACK PAIN

The BACPAP consortium considers dominant features for each of the three pain phenotypes, assuming that these might not be entirely mutually exclusive (hence the option of mixed type of low back pain). The BACPAP consortium's consensus recommendations build on the established clinical criteria for neuropathic,[11] nociplastic pain,[15] and inflammatory low back pain,[46] and follows the stepwise approach of pain phenotyping proposed in the IASP nociplastic pain criteria.[15] To aid application of the BACPAP consortium's consensus recommendations for pain phenotyping in patients with low back pain during the clinical reasoning process, a seven-step decision-making tree has been generated to adhere to the proposed stepwise process (figure). In routine clinical care, physical examination is typically followed by medical history. Hence, the seven steps in the figure do not align with routine clinical care, but clinicians are advised to collect all information as they normally would and check the seven steps after. Evidence supporting the different steps of the BACPAP consortium's consensus recommendations for pain phenotyping in the low back pain population is in the appendix (pp 2–4). The voting results show that the a priori set 90% quorum and the minimum agreement score of 70% for accepting the results was achieved for the BACPAP recommendations in general (97% agreement), each of the seven steps (agreement ranged between 91% and 97%), the treatment recommendations for predominant nociceptive (91% agreement), neuropathic (88% agreement), and nociplastic low back pain (97% agreement), and the four case studies (appendix pp 6–9; agreement scores ranged between 86% and 91%; table 2).

Table 2. Voting results of the BACPAP consortium's consensus recommendations for low back pain phenotyping

	Participation rate (n=36)	Agreed	Disagreed	No opinion
Consensus recommendations in general	35 (97%)	34 (97%)	0	1 (3%)
Step 1—low back pain duration	33 (92%)	30 (91%)	3 (9%)	0
Step 2—low back pain distribution	35 (97%)	34 (97%)	1 (3%)	0
Step 3—nociceptive pain mainly responsible for low back pain	35 (97%)	34 (97%)	0	1 (3%)
Step 4—neuropathic pain mainly responsible for low back pain	35 (97%)	33 (94%)	0	2 (6%)
Step 5—pain hypersensitivity	34 (94%)	33 (97%)	1 (3%)	0
Step 6—history of hypersensitivity	35 (97%)	34 (97%)	0	1 (3%)
Step 7—comorbid symptoms	35 (97%)	32 (91%)	1 (3%)	2 (6%)
Case study 1 (appendix pp 9–14)	35 (97%)	32 (91%)	1 (3%)	2 (6%)
Case study 2 (appendix pp 15–20)	35 (97%)	32 (91%)	1 (3%)	2 (6%)
Case study 3 (appendix pp 21–23)	35 (97%)	30 (86%)	3 (9%)	2 (6%)
Case study 4 (appendix pp 24–26)	35 (97%)	32 (91%)	1 (3%)	2 (6%)
Treatment recommendations for predominant nociceptive low back pain	35 (97%)	32 (91%)	2 (6%)	1 (3%)
Treatment recommendations for predominant neuropathic low back pain	35 (97%)	31 (89%)	2 (6%)	2 (6%)
Treatment recommendations for predominant nociplastic low back pain	35 (97%)	34 (97%)	0	1 (3%)

BACPAP=The low back pain phenotyping.

STEP 1—LOW BACK PAIN DURATION

The first step implies that, to clinically classify nociplastic pain, patients have to report pain of at least 3 months duration (ie, 3 consecutive months since onset). It implies that, according to the IASP clinical criteria,[15] nociplastic pain can only be considered in patients having chronic low back pain. Chronic low

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back pain can be defined as pain every day for 3 months or pain for at least half the days in the last 6 months,[48] allowing some flexibility when dealing with patients with recurrent low back pain. For the purpose of this classification, patients with acute or subacute low back pain (ie, less than 3-months duration) cannot be categorised as having nociplastic pain. Patients having recurrent low back pain can comply with this criterion if they are experiencing a low back pain episode of at least 3 months duration or if they report pain for at least half the days in the last 6 months.

STEP 2—LOW BACK PAIN DISTRIBUTION

As a second mandatory criterion for nociplastic low back pain, patients must report a regional, multifocal or widespread, rather than discrete pain distribution. To screen this criterion, a thorough assessment and interpretation of the patient's self-reported pain distribution, in light of the identified possible sources of nociception and neuropathy, is required. More specifically, in nociplastic low back pain the spreading of the pain is greater than one would expect (disproportionate) if only nociceptive mechanisms were present (for differentiating with nociceptive pain), and the distribution of pain extends beyond the innervation territory of the lesioned or diseased nervous structure (for differentiating with neuropathic pain).[15] Indeed, pain caused by nociceptor activation is likely to be predictable and consistent in location,[41] even though it can possibly lead to referred pain (in a neuroanatomically plausible way). Pain drawings can be used to standardise and optimise the assessment of the individual's pain distribution in a reliable and valid way.[49] In view of the concept of overlapping chronic pain conditions,[50] it is recommended to enquire about a history of other or previous diagnoses of chronic pain syndromes in other locations (eg, chronic tension headache or endometriosis) and interpret the pain distribution accordingly.

STEP 3—IS NOCICEPTIVE PAIN MAINLY RESPONSIBLE FOR THE LOW BACK PAIN?

The third mandatory criterion for nociplastic low back pain implies that patients with low back pain should report pain that cannot predominantly be explained by nociceptive pain mechanisms.[15] This includes either identifying or refuting nociceptive pain as the predominant low back pain phenotype. It is appropriate here to assess the severity of injury, inflammation, pathology, and objective dysfunctions capable of generating nociceptive input.[51] The latter is important for identifying movement dysfunctions in the lower back and pelvic joints,[52] increased tension or myofascial trigger points, or both, in the lumbopelvic muscles.[53] When interpreting clinical examination findings, the identification of a predictable and proportionate relationship with postures, movement, and mechanical tests suggests predominant nociceptive low back pain.[41] Conversely, patients with nociplastic low back pain are more likely to present with an inconsistent pain response to lumbar movements or joint loading.[16,41] More specifically, patients with predominant (noninflammatory) nociceptive low back pain can respond with consistent pain provocation in response to certain lumbar postures, movements, and mechanical tests, including not having pain provocation in response to several other postures, movements, and tests (which in some way confirm the positive tests). On the contrary, patients with predominant nociplastic low back pain might have pain in a variety of tests, postures, and movements, in a way that cannot be related to a particular source of nociception (including neural provocation), and the confirmatory negative tests are often scarce. In addition, when interpreting the severity of injury, pathology, and objective dysfunctions, clinicians should be aware

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that not all potential nociceptive sources are of clinical importance for patients with low back pain.[24] This fact is illustrated by imaging findings of lumbar osteoarthritis, which are very poorly related to functional status in patients with low back pain,[54] or even the presence of low back pain.[55] Spinal degeneration features like intervertebral disk narrowing, facet joint osteoarthritis, and spondylolysis are commonly seen on lumbar CT assessment,[56] and also in asymptomatic individuals.[57] Likewise, annular tears or Schmorl's nodes identified through MRI are often unrelated to low back pain.[57] Only spinal stenosis,[56] Modic type 1 changes,[58] spondylolisthesis,[59] intense, extensive zygapophyseal edematous changes,[60] and in some cases also ossification due to diffuse idiopathic skeletal hyperostosis[61] can be considered as imaging findings that, to some extent, relate to self-reported low back pain. Metastasis and rare bone disorders should be considered. Similar to many of the imaging findings in patients with low back pain, the issue of myofascial tissues as a candidate source of (ongoing) nociception in patients with low back pain should be critically appraised (for more details refer to appendix p 5).[53]

In addition, inflammatory spinal disorders (eg, axial spondyloarthritis with or without psoriasis, inflammatory bowel disease, uveitis, enthesitis, and septic spondylodiscitis) are an important possible source of nociceptive low back pain to consider, as such inflammatory spinal disorders might be masked by other diagnoses such as fibromyalgia.[62] Therefore, history taking should include a family and personal history to exclude features that could point to an inflammatory spinal disorder. Inflammatory spinal disorders are often accompanied by pain at night, morning stiffness, and typically improve with exercise, but not with rest.[46,63,64] If indicated, additional testing including HLA-B27, C-reactive protein, and MRI will be required.[65]

Nociceptive low back pain can only be diagnosed by combining typical symptoms and findings with objective findings (imaging and neurophysiology), and sometimes an interdisciplinary assessment (and consensus) will be required. When nociceptive mechanisms are considered to be predominantly responsible for the low back pain, the pain should be classified as nociceptive low back pain. In individuals in whom nociceptive pain is not considered the predominant mechanism for the low back pain, clinicians should continue to step 4. Given the potential overlap between nociceptive and nociplastic low back pain, it is important to stress that the presence of a source of nociceptive pain does not exclude the possibility of nociplastic low back pain, but the region of pain must be more widespread than can be explained by the identifiable source of nociception.[15] Hence, steps 2 (pain distribution assessment) and 3 must be related.

STEP 4—IS NEUROPATHIC PAIN MAINLY RESPONSIBLE FOR THE LOW BACK PAIN?

A fourth mandatory criterion for nociplastic low back pain implies that the low back pain cannot predominantly be explained by neuropathic pain mechanisms.[15] This includes either identifying or refuting neuropathic pain as the predominant low back pain phenotype. To do so, clinicians can rely on available guidelines for the classification of neuropathic pain.[11] The neuropathic low back pain phenotype remains under-recognised.[66] The neuropathic pain criteria specify that a lesion or disease of the nervous system (either central or peripheral) is identifiable and that pain is limited to a neuroanatomically plausible distribution.[11] How clinicians can examine the presence of neuropathic low back pain through review of the patient's medical record, detailed history taking, and physical examination is illustrated in the appendix (p 6).

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It is important to highlight that neuropathic pain can be characterised or accompanied by sensitisation; peripheral and central (segmentally-related) pain pathways can become hyperexcitable in patients with neuropathic pain.[67,68] Such mixed pain phenotypes can be a combination of neuropathic and nociplastic low back pain, but can also combine nociceptive pain with neuropathic low back pain (eg, axial spondyloarthritis combined with a neuropathic component of low back pain),[69] or a combination of all three pain phenotypes.

STEP 5—PAIN HYPERSENSITIVITY

Step 5 implies screening for clinical signs of pain hypersensitivity that are at least present in the painful region.[15] This step entails the clinical examination of (mainly) allodynia, defined as evoked pain in response to stimuli that normally do not elicit pain, in the painful region. This can be assessed by evoked pain hypersensitivity phenomena such as static or dynamic mechanical allodynia, heat or cold allodynia, painful after-sensations, or all of the above, after any of the mentioned evoked pain hypersensitivity assessments (explained in appendix p 8). However, it should be mentioned that clinical signs of pain hypersensitivity are not specific to nociplastic low back pain, as they can also be found in neuropathic low back pain[70] as well as nociceptive pain conditions.[71] If the requirements of the first five steps are met, the individual can be classified as having possible nociplastic low back pain,[15] and clinicians should proceed towards step 6 to examine whether the likelihood of nociplastic low back pain can be increased towards probable nociplastic low back pain.

STEP 6—HISTORY OF HYPERSENSITIVITY

Step 6 implies examining whether patients with low back pain present with a history of self-reported hypersensitivity in the lower back region, which can be examined by assessing their sensitivity to touch, movement, pressure, heat or cold. This process along with history taking can spontaneously reveal such hypersensitivity to (mechanical) pressure, for instance in patients with low back pain who perceive clothing against the skin, belts, or handbags as unpleasant or painful.[15,16] Other examples include pain flares during or following a cold or warm bath or shower (hypersensitivity to heat or cold) or following habitual physical activities of low to moderate intensity such as walking, gardening, or grocery shopping (hypersensitivity to movement).[15,16] Nevertheless, movement-evoked pain is also common in nociceptive and neuropathic low back pain. In predominant nociceptive or neuropathic low back pain, pain is expected to be predictably and proportionately related to movement, whereas in predominant nociplastic low back pain, pain is expected to be unpredictable and disproportionate to body movement.

STEP 7—COMORBID SYMPTOMS

The final step implies screening for comorbid symptoms in patients with low back pain. This criterion is met if any of the following comorbid symptoms are present: increased sensitivity to sound, light or odours, or both, sleep disturbance with frequent nocturnal awakenings, fatigue, or cognitive problems (eg, concentration difficulties).[15] Similar to step 6, screening for these comorbid symptoms is done during the interview and history taking or by using the central sensitisation inventory.[72] The central sensitisation inventory has been shown to generate reliable and valid data regarding symptoms of central sensitisation in patients with chronic low back pain,[72] but should not be considered as the gold

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standard measure for assessing features of central sensitization.[73] Other candidate measures for assessing comorbid symptoms include the Pain Sensitivity Questionnaire.[74]

According to the IASP clinical criteria for nociplastic pain,[15] low back pain is classified as probable nociplastic pain when a patient with low back pain presents with features that are consistent with the requirements of the first 5 steps, presents with a history of pain hypersensitivity in the low back region (step 6), and at least one of the defined comorbid symptoms is present (step 7).[75]

RECOMMENDATIONS BY LOW BACK PAIN PHENOTYPES

LOW BACK PAIN CHARACTERISED BY NOCICEPTIVE MECHANISMS

For predominant nociceptive low back pain, treatment could plausibly be expected to be effective if it targets what is driving the nociceptive input.[76] This implies that the first line treatment should target that nociceptive driver and this could include conservative interventions such as activity modifications (eg, pacing periods of standing and walking), limited oral medications or topical treatment, physical therapy, lifestyle modifications, and selected, evidence-based intervention techniques (table 3). Within this view it is important to take into account that radiofrequency denervation has no added value over exercise therapy for patients with chronic low back pain originating in the facet joints, sacroiliac joints, or a combination of facet joints, sacroiliac joints, or intervertebral disks.[77] In patients with non-inflammatory, nociceptive low back pain who do not improve with conservative management, surgery (eg, decompressive laminectomy) might be appropriate and can be considered.[78] In general, pharmacological treatment of predominant nociceptive low back pain should emphasise the short-term use of non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase-2 inhibitors, depending on the type of nociceptive input (ie, inflammatory or not).[79] In patients with inflammatory spinal disorders NSAIDs are the first line treatment.[80] Opioids can be considered for predominant nociceptive low back pain only if established non-pharmacological treatments and established nonopioid analgesics are not effective, not tolerated, contraindicated, or not available.[81]

Table 3. The BACPAP consortium's consensus recommendations for the treatment of low back pain phenotypes

	Low back pain characterised by nociceptive pain mechanisms	Low back pain characterised by neuropathic pain mechanisms	Low back pain characterised by nociplastic pain mechanisms
Treatment target	Nociceptive driver	Personalised based on the type of neuropathy	Perpetuating factors such as sleep impairments, stress intolerance, physical inactivity, and maladaptive beliefs
Conservative treatment	To constitute first line treatment—eg, activity modifications, limited oral medications, physical therapy, lifestyle modifications, and selected intervention technique	Exercise therapy and neural mobilisations can be considered	Prioritise non-pharmacological management, such as psychological therapies, pain neuroscience education, exercise therapy, or multidisciplinary treatment
Surgery	Can be considered in patients who do not improve with conservative management	Can be considered when multimodal conservative treatment did not improve pain or function and if imaging findings match the clinical presentation	Unlikely to be indicated
Pharmacology	Emphasise short-term use of non-opioid analgesics such as NSAIDs, and cyclo-oxygenase-2 inhibitors, depending on the type of nociceptive input (ie, inflammatory or not)	Antidepressants (eg, serotonin-noradrenaline reuptake inhibitors such as duloxetine and tricyclic antidepressants such as amitriptyline) yield small and not clinically important analgesic effects	Most medications provide only modest benefits, and adverse effects are more likely to occur; use of opioid analgesics is strongly discouraged

BACPAP=The low back pain phenotyping. NSAIDs=non-steroidal anti-inflammatory drugs.

LOW BACK PAIN CHARACTERISED BY NEUROPATHIC MECHANISMS

The management of predominant neuropathic and nociplastic low back pain is substantially different from the management of predominant nociceptive low back pain with respect to pharmacological[79]

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and nonpharmacological[82] strategies, including surgery. In neuropathic pain, treatment should be personalised based on the type of neuropathy. For instance, superior and middle cluneal nerve entrapment neuropathy can potentially benefit from a nerve block and neurolysis,[83] whereas surgery for lumbar radiculopathy has high success rates (75–80%)[84–86] and consequently can be considered when multimodal conservative treatment did not improve pain or function and if imaging findings match the clinical presentation.[87] Theoretically, antidepressants (eg, serotonin-noradrenaline reuptake inhibitors such as duloxetine and tricyclic antidepressants such as amitriptyline) can be considered for predominant neuropathic low back pain.[79] The analgesic effects of antidepressants for the treatment of low back pain are small and not clinically important,[88] but studies examining their efficacy in patients with predominant neuropathic low back pain (rather than low back pain in general) might give clear and more reliable evidence to help clinicians and policy makers.[89] For instance, tricyclic antidepressants and serotonin-noradrenaline reuptake inhibitors might be effective for sciatica, but the certainty of evidence is low to very low.[90] Similar to antidepressants, anticonvulsants (α2δ ligands) such as gabapentin and pregabalin target the neuropathic component of low back pain,[79,91] but systematic reviews of trials indicate indicate that these drugs are not an efficacious treatment for low back pain with or without radiculopathy, and are associated with an increased risk of adverse events.[33,92,93] Importantly, opioids are only a third line choice (ie, weak recommendation for use) for neuropathic pain.[94] The efficacy of the different classes of drugs appears to be unrelated to the underlying neuropathic pain aetiology, while the side effects can be, therefore, general recommendations for the pharmacological management of neuropathic pain have been formulated.[95] Regarding conservative management of predominant neuropathic low back pain, exercise therapy[96] and neural mobilisations[97] can be considered.

LOW BACK PAIN CHARACTERISED BY NOCIPLASTIC MECHANISMS

Centrally-acting drugs can also be considered for predominant nociplastic low back pain,[82] but most medications provide only modest benefits in patients with nociplastic pain, and adverse effects are more likely to occur in these patients.[98] For this reason, the management of predominant nociplastic low back pain should prioritise non-pharmacological management,[98] such as psychological therapies,[99] pain neuroscience education,[100] exercise therapy,[101] or multidisciplinary treatment,[102] and should consider targeting perpetuating factors such as sleep impairments[103] and stress intolerance.[30,98] In cases of possible or probable nociplastic pain (and the associated sensitisation), careful consideration and potential modification in the application of conservative management approaches might be necessary or the timeframes for improvement can differ from patients without nociplastic pain.[104] Surgery is unlikely to be indicated for treating predominant nociplastic low back pain,[30] and the use of opioid analgesics is strongly discouraged.[81,98,105] Finally, explaining pain to patients with low back pain should be personalised to the relevant and predominant pain phenotypes (eg, explaining central sensitisation should be preferably limited to those presenting with nociplastic or neuropathic low back pain),[30] and should include the discouragement of excessive unnecessary investigations and over medicalisation.

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Discussion

The principle findings of the BACPAP consortium is the development of international and multidisciplinary consensus recommendations for identifying the dominant pain phenotype in patients with low back pain, and potentially adapting pain management strategies accordingly. These findings are expert opinion consensus on pain phenotypes for low back pain but before moving towards clinical implementation future research is required to fully establish utility for agreement on classification, examining its prognostic value, and guiding selection of personalised pain treatments. Clinical reasoning is not a linear process, nor a one-time event,[106,107] though the stepwise process such as that presented in the BACPAP consortium's consensus recommendations allows broad, shared interdisciplinary understanding. Classification of pain mechanisms facilitated by the BACPAP consortium's consensus recommendations should be interpreted in the broader biopsychosocial understanding of the patient's presentation.[108] Indeed, a drawback for applying such an approach might be neglecting the individual variability within each low back pain phenotype.[47] Therefore, personalised pain medicine for low back pain is more than accounting for the low back pain phenotype. It also implies addressing relevant comorbidities (eg, insomnia, obesity, and depression)[109] and lifestyle factors (eg, diet and stress) that sustain the pain mechanism of the relevant pain phenotype. One should also consider the social and cultural context when using the consensus recommendations. Likewise, for the predominant nociceptive low back pain phenotype, identification of nociceptive mechanisms can be enough for pain phenotyping, but identifying and addressing what is driving the nociceptive input is mandatory for a targeted approach.[76]

The voting results (table 2) show that the modified Nominal Group Technique as applied here, resulted in nearly complete agreement among the BACPAP consortium members. This shows the strong consensus supporting the BACPAP recommendations in general, for each of its seven steps, the treatment recommendations, and the four case studies. Importantly, the BACPAP consortium's consensus recommendations for pain phenotyping in the low back pain population is supported by the finding from a systematic review that a combination of features and methods, rather than a single method, is generally recommended to discriminate between pain phenotypes.[39] In addition, the BACPAP consortium's consensus recommendations are supported by the findings from two Delphi studies on features and assessment findings that are unique to at least one of the pain phenotypes,[7,41] and an original research study of 464 patients with low back pain on predictors that would today be associated with nociplastic, versus peripheral neuropathic and nociceptive low back pain.[110] The scientific foundation for, and limitations of the seven steps of the BACPAP consortium's consensus recommendations for pain phenotyping in the low back pain population are outlined in the appendix (pp 2–4). Neither individual features or methods, nor the BACPAP consortium's consensus recommendations proposed here are yet validated as a gold standard framework for pain phenotyping in the low back pain population.[15,39] This represents an important area for further research. To serve this purpose, clinical vignettes might be useful. Clinical vignettes are short scenarios that describe a situation (ie, real cases of low back pain) in which participants typically answer a series of open-ended or closed-ended questions related to the scenarios included in the vignettes.[111] These clinical situations are available to multiple evaluators simultaneously and identically, providing the opportunity to examine the intra-rater and inter-rater reliability and content validity of the BACPAP consortium's

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consensus recommendations for pain phenotyping in patients with low back pain. In addition, the reliability, diagnostic accuracy (in terms of sensitivity and specificity), and prognostic value of the BACPAP consortium's consensus recommendations for pain phenotyping in patients with low back pain require more research, which can be explored in diagnostic accuracy studies and longitudinal cohort studies, respectively. Moreover, the feasibility of using this classification system in clinical practice and research should be explored with qualitative research with health-care professionals. In addition, the BACPAP consortium's consensus recommendations for pain phenotyping in patients with low back pain allow researchers to examine the true prevalence of each of the three low back pain phenotypes using standard definitions.

Limitations of the BACPAP consortium's consensus recommendations include the arbitrary nature of the 3 months pain duration (step 1), which relates to the focus on chronic low back pain. Neuropathic and nociplastic pain mechanisms might become dominant in subacute stages. A second limitation is the possibility for patients to not fit in any of the three groups (ie, neither predominant nociceptive, neuropathic, nociplastic, or mixed type of low back pain) and move between groups over time. The former might be due to limitations of current technologies in identifying the source of nociception or neuropathy, or due to the lack of a fourth group (possibly characterised by predominant psychosocial and behavioural factors, as previously suggested).[24] In addition, medical associations were not invited to comment on the recommendations. Although this is often done when developing guidelines, the BACPAP consortium chose not to do so as the number of potentially relevant medical associations is too large. Now that the recommendations are completed, the BACPAP consortium will engage with relevant medical and professional associations to aid with dissemination to their respective members.

Search strategy and selection criteria

From December 2022, to June 2023, we searched PubMed and Web of Science databases using the key words "phenotyping", "nociplastic", "neuropathic", or "nociceptive" in combination with "low back pain" and cross-referenced with key words tailored for specific sections (eg, "diagnosis", "treatment", and "management"). There were no restrictions on language, article type, or date of publication, but we excluded preclinical studies, unpublished material, and conference abstracts. We prioritised studies published after the release of the IASP clinical criteria for nociplastic pain in 2021 or later.

Finally, the prognostic or modifying effect, or both, of the BACPAP consortium's consensus recommendations for pain phenotyping in patients with low back pain remains unexplored; this can be examined in cohort studies that follow patients for long-term outcomes and randomised clinical trials examining treatment approaches that aim at specifically targeting underlying mechanisms of nociceptive, neuropathic, or nociplastic pain. Therefore, low back pain researchers are encouraged to add this classification system to the baseline assessment of patients with low back pain in their cohort studies or trials. Future work should also develop consensus recommendations for phenotyping pelvic

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pain, including consideration of pain that could be cyclical (related to menstruation),[112] non-cyclical, or pregnancy-related.[113,114]

Conclusions

Here the BACPAP consortium provides an international and multidisciplinary recommendation to differentiate between predominant nociceptive, neuropathic, or nociplastic low back pain. The BACPAP consortium's consensus recommendations account for the need to identify and correctly classify patients according to the low back pain phenotype, which is an important preliminary step towards personalised pain medicine[47] and low back pain management. Before implementation, studies examining the classification accuracy, predictive ability, and efficacy of personalised treatments when following the BACPAP consortium's consensus recommendations are needed. Therefore, these recommendations are not ready to be implemented in clinical practice until additional evidence is generated that is specific to these low back pain phenotypes.

Contributors

JN, EKo, and SZG coordinated the development of the consensus recommendations and were responsible for the study design, data analysis, and data interpretation. JN, EKo, SZG, DB, PB, JRC, and EKa were involved in writing the original draft. JN was responsible for data collection and conceptualisation. All authors were actively involved in group discussions, voting, literature search, validation, and writing of the report and its' subsequent review and editing. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

BM received consultation fees from Haleon, GSK, and Grünenthal, and honoraria from Haleon, GSK, Grünenthal, Krka, Mundipharma, and Viatris, is the past president of the European Pain Federation and program director of the Belgian Interuniversity Course in Pain Management. AC received payment for work as group tutor for the course in Clinimetrics (EpidM, Amsterdam, Netherlands). JN and the Vrije Universiteit Brussel received lecturing or teaching fees from various professional associations and educational organisations. EKo received royalties for textbook chapters from Liber and Studentlitteratur, payment for a lecture from Eli Lilly, and is a member of the scientific board of the Swedish Rheumatism Association. PH received travel support from the German Osteopathic Society, the Icelandic Physiotherapy Association, and the Finish Musculoskeletal Medicine Society. All other authors declared no competing interests.

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