Comprehensive Review

Low Back Pain: Guidelines for the Clinical Classification of Predominant Neuropathic, Nociceptive, or Central Sensitization Pain

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Background: Low back pain (LBP) is a heterogeneous disorder including patients with dominant nociceptive (e.g., myofascial low back pain), neuropathic (e.g., lumbar radiculopathy), and central sensitization pain. In order to select an effective and preferably also efficient treatment in daily clinical practice, LBP patients should be classified clinically as either predominantly nociceptive, neuropathic, or central sensitization pain.

Objective: To explain how clinicians can differentiate between nociceptive, neuropathic, and central sensitization pain in patients with LBP.

Study Design: Narrative review and expert opinion.

Setting: Universities, university hospitals and private practices.

Methods: Recently, a clinical method for the classification of central sensitization pain versus neuropathic and nociceptive pain was developed. It is based on a body of evidence of original research papers and expert opinion of 18 pain experts from 7 different countries. Here we apply this classification algorithm to the LBP population.

Results: The first step implies examining the presence of neuropathic low back pain. Next, the differential diagnosis between predominant nociceptive and central sensitization pain is done using a clinical algorithm.

Limitations: The classification criteria are substantiated by several original research findings including a Delphi survey, a study of a large group of LBP patients, and validation studies of the Central Sensitization Inventory. Nevertheless, these criteria require validation in clinical settings.

Conclusion: The pain classification system for LBP should be an addition to available classification systems and diagnostic procedures for LBP, as it is focussed on pain mechanisms solely.

Key words: Chronic pain, neuroscience, diagnosis, clinical reasoning, examination, assessment

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Despite extensive global research efforts, chronic pain remains a challenging issue for clinicians and a huge socio-economic problem. Within the chronic pain population, low back pain (LBP) is one of the most prevalent musculoskeletal disorders, affecting 70% – 85% of the adult population at some point in life (1). Twelve months after the onset of LBP, 45% – 75% of patients still experience pain (2), accounting for major expenses in health care and disability systems (1).

Nociceptive pain is defined as pain arising from actual or threatening damage to non-neural tissue and is due to the activation of nociceptors (3), or as pain attributable to the activation of the peripheral receptive terminals of primary afferent neurons in response to noxious chemical, mechanical, or thermal stimuli (4). For clinical purposes, the term nociceptive pain can be used when pain is proportional to nociceptive input, and it was designed to contrast with neuropathic pain. The latter is defined as pain caused by a primary lesion or disease of the somatosensory nervous system (3). Within the LBP population, lumbar radiculopathy is a common type of lumbar neuropathic pain, while myofascial tissue (i.e., thoracolumbar fascia) (5) and some lumbar ligaments (6) contain nociceptors capable of generating nociceptive pain. Both nociceptive and neuropathic pain can be classified as "specific LBP" when there is a clear patho-anatomical diagnosis. However, a precise patho-anatomical diagnosis cannot be given in approximately 85% of LBP patients (7), resulting in the label "non-specific low back pain." Imaging findings like lumbar osteoarthritis or (small) disc lesions often do not account for the symptoms experienced by LBP patients (8-10) hence, they cannot be categorized *per se* as having primarily nociceptive pain.

Modern pain neuroscience has advanced our understanding about pain, including the role of central sensitization (CS) in amplifying pain experiences. CS is defined as "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity" (11), "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (3), or "an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors" (12). Although one might say that these definitions differ substantially, they all point to the same underlying neurophysiological mechanism of increased neuronal response to stimuli in the central nervous system (i.e., central hyperexcitability). The definitions originate from laboratory research, but the awareness that the concept of CS should be translated to the clinic is growing (13,14).

CS encompasses various related dysfunctions within the central nervous system, all contributing to altered (often increased) responsiveness to a variety of stimuli like mechanical pressure, chemical substances, light, sound, cold, heat, stress, and electricity (13). Such dysfunctions of the central nervous system include altered sensory processing in the brain (15), malfunctioning of descending anti-nociceptive mechanisms (16,17), increased activity of nociceptive facilitatory pathways, and enhanced temporal summation of second pain or wind-up (18,19). In addition, the pain (neuro)matrix is overactive in the case of CS pain, with increased brain activity in areas known to be involved in acute pain sensations (insula, anterior cingulate cortex, and prefrontal cortex) as well as in regions not involved in acute pain sensations (various brain stem nuclei, dorsolateral frontal cortex, and parietal associated cortex) (20).

An increasing number of studies have examined the role of CS in patients with LBP, and the findings are equivocal (21). Some studies have demonstrated exaggerated pain responses after sensory stimulation of locations outside the painful region, while others did not report differences between LBP patients and healthy patients (21). However, studies analyzing brain structure and function in relation to (experimentally induced) pain have provided evidence for altered central nociceptive processing in subgroups of patients with chronic LBP (21). Evidence of several studies in chronic LBP suggests that CS is present in a subgroup of the LBP population (22-24). This potentially impacts upon clinical practice, as LBP patients with a predominant CS pain type require treatment targeted at the central nervous system rather than the lower back (14,21,25). Hence, in order to select an effective and preferably also efficient treatment in daily clinical practice, LBP patients should be classified clinically as experiencing predominantly either nociceptive, neuropathic, or CS pain (22,26).

Recently, a clinical method for classifying any pain as either predominant CS pain, neuropathic, or nociceptive pain was developed, based on a body of evidence from original research papers and expert opinion of 18 pain experts from 7 different countries (27). Here we apply this classification algorithm to the LBP population, and explain how clinicians can differ-

entiate clinically between predominant nociceptive, neuropathic, and CS pain in their LBP patients.

Examining the Presence of Neuropathic Low Back Pain as the First Step

Chronic lumbar radicular pain is the most common neuropathic pain syndrome which affects 20% to 35% of patients with LBP (28). People with neuropathic LBP often experience higher levels of pain, disability, anxiety, depression, and reduced quality of life as compared to nociceptive LBP (22,29). Following identification of red flags, excluding the possibility of neuropathic LBP is often the first step in clinical practice (30,31). Guidelines have been published for the classification of neuropathic pain (32,33). The 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. The neuropathic pain criteria preclude the use of the term "neuropathic pain" for people with diffuse or widespread pain and nervous system sensitization (i.e., CS pain), as the latter is free of a history of a lesion or disease of the nervous system and is typically characterized by a pain distribution that that is not neuroanatomically plausible (27).

Box 1 illustrates how clinicians can examine the presence of neuropathic LBP and includes detailed history taking and physical testing. These are important parts of the screening of the examination of any LBP patient, and might even reveal rare causes of neuropathic pain in long lasting LBP (e.g., entrapment neuropathy of the L1-L2 dorsal ramus over the iliac crest [34]). Other causes of neuropathic LBP are more common like radiculitis (i.e., inflammation of one or more nerve rout[s]), resulting in pain radiating along the corresponding dermatome. Hence, clinicians should be able to identify such patients with radiculitis using the questions provided in Box 1.

It is important to highlight the issue of sensory dysfunction for the differential diagnosis between neuropathic and CS LBP. Sensory testing can be of importance for the diagnosis of neuropathic pain, although it should always be combined with diagnostic procedures confirming or refuting the nervous system lesion or disease (32,33). While in neuropathic LBP the location of the sensory dysfunction should be neuroanatomically logical, it is spread in non-segmentally related areas of the body in CS LBP. Clinical examination in CS LBP typically reveals increased sensitivity at sites segmentally unrelated to the primary source of nociception (13,27). A study of 377 patients with sciatica revealed that self-reported sensory loss (assessed through history taking) doubled the odds of having nerve root compression, and tripled the odds of having disc herniation (35). However, the diagnostic accuracy of history taking in general for predicting the presence of lumbosacral nerve root compression or disc herniation on magnetic resonance imaging (MRI) in patients with sciatica was rather poor (35), underscoring the need for combining history taking with a more comprehensive screening, including clinical tests.

Following the screening criteria outlined in Box 1 will either result in establishing or excluding neuropathic pain as an underlying cause of the patient's LBP. Although the presence of neuropathic pain does not exclude the options of CS LBP 2 options remain if neuropathic pain is excluded: predominant nociceptive or CS LBP. Neuropathic pain may be characterized or accompanied by sensitization; peripheral and central (segmentally related) pain pathways can become hyperexcitable in patients with neuropathic pain (39,40). Such overlap illustrates that LBP patients can have both neuropathic and CS pain.

In addition, lumbar radiculopathy is a typical example of neuropathic LBP, but if treated surgically can also develop towards post-surgical nociceptive or (more likely) CS pain. In specific cases of non-responders to conservative treatment and a negative evolution, surgery is a recommended, evidence-based treatment for lumbar disc herniation with radiculopathy (41,42). However, a substantial portion (23% – 28%) of patients develops chronic back +/- leg pain following surgical treatment of lumbar radiculopathy (41). In such cases, neuropathic pain remains possible: removing the mechanical pressure on the nerve(s) does not per se guarantee restoration of its complete function. The underlying mechanisms of neuropathic pain might have established itself, resulting in long-term neuropathic pain, or mechanical pressure has caused irreversible damage to the root. In such cases it is expected that the post-surgical pain distribution and related signs/symptoms still comply with the diagnostic criteria proposed for neuropathic pain (Fig. 1). If not, the post-surgical pain is unlikely to be of neuropathic nature, leaving clinicians with the options of nociceptive and CS pain.

Differentiating Predominant Nociceptive and Central Sensitization Low Back Pain Using a Classification Algorithm

To differentiate predominant nociceptive and CS LBP, clinicians are advised to use the algorithm present-

Is there a history of a lesion or disease of the nervous system, either central or peripheral nervous system?
In relation to LBP, a lesion or disease of the nervous system can vary from a tumor compressing a peripheral nerve or spinal cord, a traumatic lesion of a nerve to post-stroke LBP. For radicular pain, several patho-anatomical dysfunctions have the potential to compromise directly the dorsal root ganglion or indirectly the spinal nerve: foraminal stenosis (e.g., due to osteophytes), prolapsed intervertebral disc, or radiculitis (e.g., caused by a viral infection like herpes zoster) (3). In any case, there should be evidence from diagnostic investigations (e.g., electrodiagnostic techniques, myelography, computed tomography [CT], MRI) to reveal an abnormality of the nervous system, or post-traumatic damage to the nervous system (in the spinal cord, peripheral nerves, or brain) resulting in a neuroanatomically plausible neuropathic LBP pattern.

If comorbidities are present, are they related to neuropathic pain (e.g., cancer, stroke, diabetes, herpes zoster, or neurodegenerative disease)?
This question partly overlaps with the first question, but is presented here in order to highlight the importance of questioning comorbidities.

Is the pain distribution neuroanatomically logical?
For radicular pain, neuroanatomically logical refers to the distribution of a spinal nerve. However, caution is required as not all patients with radicular pain have a dermatomal pain pattern (36) and patient report is an unreliable method of identifying the anatomical source of pain or paraesthesia caused by nerve root compression (37). The validity of strictly dermatomal distributions of pain as a predictor of nerve root pain/peripheral nerve pain could be undermined by variations in dermatomal maps and the geography of dermatomes between individuals. Despite the variability it seems that, at the very least, pain referred into the leg extending below the knee, if not in a strictly dermatomal distribution, is a useful predictor of nerve root compression and by extension peripheral nerve pain (36).

Is the pain described as burning, shooting, or pricking?
Each of these descriptions is considered a sign of neuropathic (low back) pain (4,38).

Is the location of the sensory dysfunction neuroanatomically logical?
This includes testing of the function of the sensory fibers with simple tools (e.g., a tuning fork for vibration, a soft brush for touch, a sharp pin, and cold/warm objects for temperature), which typically assess the relationship between the stimulus and the perceived sensation (33). Several options arise here, all suggestive of neuropathic pain: hyperaesthesia, hypoaesthesia, hyperalgesia, hypoalgesia, allodynia, paraesthesia, dysesthesia, aftersensations, etc.

Fig. 1. *Screening the criteria for neuropathic pain (32,33) in LBP patients.*

ed in Fig. 2. The algorithm guides the clinician through the screening of 3 major classification criteria, each of which is explained below.

Criterion 1: Low Back Pain Experience Disproportionate to the Nature and Extent of Injury or Pathology (27)

Per definition, CS is characterized by "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity" (11) and "augmented responsiveness of central nervous system neurons to their normal or subthreshold afferent input" (3,12). These overlapping definitions imply that CS pain is disproportionate to the nature and extent of injury or pathology, making it a go-no-go criterion for CS pain.

Applied to the LBP population, for complying with this first criterion the severity of the LBP must be disproportionate to the nature and extent of injury or pathology (i.e., tissue damage or structural impairments which might cause nociceptive LBP). This contradicts nociceptive LBP, where the severity of the LBP is more or less proportionate to the nature and extent of the injury or pathology. Indeed, a Delphi study including 103 clinical experts revealed that "clear, proportionate mechanical/anatomical nature to aggravating and easing factors" and "clear, consistent and proportionate mechanical/anatomical pattern of pain reproduction on movement/mechanical testing of target tissues" were the criteria most strongly suggestive of nociceptive pain, while "disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors," and "disproportionate, inconsistent, non-mechanical/non-anatomical pattern of pain provocation in response to movement/mechanical testing" were most suggestive of "central pain" (4). In addition, a multi-center study of 464 LBP patients identified "disproportionate, non-mechanical, unpredictable pattern of pain provocation in response to multiple/non-specific aggravating/easing factors" as the strongest predictor of CS in patients

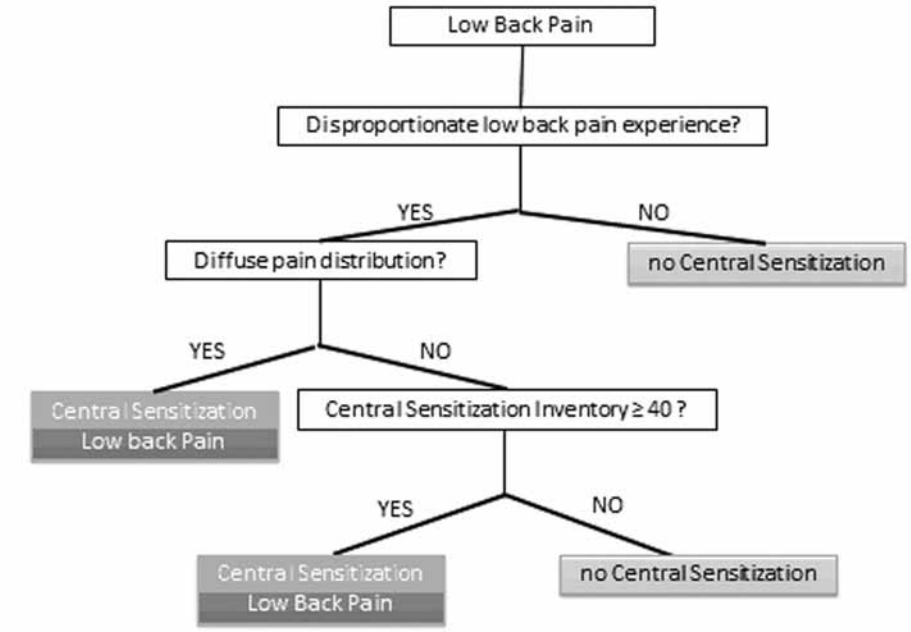

Fig. 2. *Algorithm for the differential diagnosis of predominant nociceptive versus central sensitization low back pain (modified from [27]).*

with LBP (23). However, in absence of a gold standard for CS pain, the clinicians participating in the study used their own expert judgement for classifying LBP patients into the 3 groups (peripheral neuropathic, nociceptive, or CS LBP) (23).

For screening this first criterion, it is necessary to assess the patient's amount of injury, pathology, and objective dysfunctions capable of generating nociceptive input in the lumbopelvic region. This includes imaging techniques for identifying such nociceptive sources (e.g., X-rays, CT scan, and NMRI), but also the clinical examination. The latter is important for identifying movement dysfunctions in the lower back and pelvic joints (43,44), increased tension and/or myofascial trigger points in the lumbopelvic muscles (45), etc. The lumbopelvic region includes a large number of tissues capable of generating nociceptive input, including intervertabral discs (41,46-49), muscles (50,51), fascia (5,52), bone (53), facet joints (46,47,54-56), sacroiliac joints (46,47,57,58), symphysis pubis joint, ligaments (6), and joint capsules (55) (e.g., facet joint capsules contain nociceptors [54]), etc.

Next, the amount of injury, pathology, and objective dysfunctions capable of generating nociceptive input in the lumbopelvic region is weigthed with the patient's subjective LBP experience (i.e., the self-reported LBP). In case imaging findings and the clinical examination hardly identify potential sources of lumbar nociception, the presence of disabling pain will suffice for fulfilling this criterion. However, in many (if not all) patients with LBP the clinical examination and/or imaging reveals some type of potential nociceptive source, which makes thorough clinical reasoning necessary for weighting the nociceptive input with the experienced pain. This includes taking into account all personal and environmental factors.

Such clinical reasoning includes 1) focusing on the patient's current health status (i.e., at the time he/she comes to see the clinician); and 2) interpreting the amount of injury, pathology, and objective dysfunctions in light of the evidence favoring or refuting its clinical importance in patients with LBP. Injured tissue might have lead to nociception in the (sub)acute phase, but once healed it is unlikely to serve as a continuous or current source of nociceptive input.

When interpreting the amount of injury, pathology, and objective dysfunctions, clinicians should be aware that not all potential nociceptive sources are of clinical importance for LBP patients. This is illustrated by imaging findings of lumbar osteoarthritis, which

are very poorly related to functional status in patients with LBP (59) or even the presence of LBP (60). In fact, up to 47% of older people without LBP show evidence of lumbar facet joint osteoarthritis on CT assessment (60). Spinal degeneration features like intervertebral disc narrowing, facet joint osteoarthritis, and spondylolysis are commonly seen on CT assessment of the lumbar spine, but the only degenerative feature associated with self-reported LBP is spinal stenosis (61). Severe facet joint osteoarthritis (especially if several facet joints are affected) is associated with back pain in community-based older adults (60).

MRI findings of annular tears or Schmorl's nodes are unrelated to LBP (62). That same study showed that the presence of intervertebral disc herniation or intervertebral disc degeneration doubled the chance of having LBP (62). Still, the available evidence suggest that only Modic type 1 changes and intense, extensive zygapophyseal edematous changes are relatively correlated with LBP (63). Modic type 1 changes refer to vertebral endplate changes with an edematous appearance, hypointense on T1-weighted images and hyperintense on T2-weighted images, with enhancement after gadolinium injection (63).

Similarly, although the available evidence suggests that paraspinal muscles are significantly smaller in chronic LBP patients and on the symptomatic side of patients with chronic unilateral LBP (64), the density of paraspinal muscles like the multifidus and erector spinae is unrelated to LBP (65). This brings us to the issue of myofascial tissues as a candidate source of (ongoing) nociception in patients with LBP. In addition to muscle nociceptors, animal research has recently established the muscle fascia as a candidate source of nociception (5,52), but human studies are currently limited to experimental pain induction in asymptomatic people (5). The pain associated with myofascial trigger points is thought to arise from a hypersensitive nodule in a taut band of the skeletal muscle (66), and they are capable of activating muscle nociceptors (67). Upon sustained noxious stimulation, myofascial trigger points may even result in primary hyperalgesia (68). Indeed, in the vicinity of myofascial trigger points the tissue differs from normal muscle tissue by its lower pH levels (i.e., more acid), increased levels of substance P, calcitonin gene-related peptide, tumour necrosis factor-α, and interleukine-1α, each of which has its role in increasing pain sensitivity (69). Sensitised muscle nociceptors are more easily activated and may respond excessively to normally innocuous and weak stimuli such as light pressure or muscle movement (67,69).

In the case of myofascial trigger points, the pathophysiology appears to be in line with evidence from clinical studies: the number of active myofascial trigger points in patients with non-specific LBP is associated with self-reported pain intensity (51), but more studies are required to confirm these findings. In addition, serious concerns are raised regarding the reliability of trigger point palpation in low back muscles (70,71). Still, at this point myofascial trigger points are candidate peripheral sources of nociception in patients with LBP.

Taken together, the weighting of the identified current sources of nociception with the self-reported pain and disability can result in a number of outcomes:

The patient with LBP presents insufficient evidence of injury, pathology, or objective dysfunctions capable of causing the self-reported pain. This would imply that the LBP patient fulfills this first out of 3 criteria for CS LBP. At this point, the patient may have predominant CS pain, but the clinician needs to proceed with screening of the remaining criteria (Fig. 2) before making a conclusion.

There is evidence of injury, pathology, or objective dysfunctions capable of causing back pain, but not enough nociceptive input for explaining the pain experienced by this LBP patient. Again, this would imply that the patient fulfills this first out of 3 criteria for CS LBP. The patient may have predominant CS LBP, and the clinician must proceed with screening of the remaining criteria (Fig. 2).

If the LBP experienced by the patient is not considered disproportionate as there is evidence of injury, pathology, or objective dysfunctions which justify the self-reported pain and disability, CS can be ruled out at this point.

Criterion 2: Neuroanatomically Illogical Pain Pattern (27)

This criterion is related to the issue of a neuroanatomically plausible pain pattern: a neuroanatomically illogical pain pattern is present when the LBP patient presents with a pain distribution that is not neuroanatomically plausible for the presumed sources of (lumbar) nociception. For screening this criterion, a thorough assessment and interpretation of the patient's self-reported pain distribution, in light of the identified possible sources of nociception, is required. Examples of pain distribution patterns that fulfill this criterion are bilateral pain/mirror pain (i.e., a symmetrical pain pattern), pain varying in (anatomical) location, large pain

areas with a non-segmental (i.e., neuroanatomically illogical) distribution, widespread pain, and/or allodynia/hyperalgesia outside the segmental area of (presumed) primary nociception (27). Referred pain patterns can be either neuroanatomically logical (e.g., when the referred pain pattern stays within one or 2 neighboring segmental areas related to the source of nociception) or illogical.

As is the case with the first criterion, this second is supported by a Delphi study on clinical indicators of nociceptive versus neuropathic and central pain, showing that "widespread, non-anatomical distribution of pain" obtained up to 96% consensus level agreement among expert clinicians as a clinical indicator of central pain (4). Also in a study of 464 LBP patients, "non-segmental/diffuse areas of tenderness on palpation" was identified as one of the 4 key predictors of CS LBP versus peripheral neuropathic and nociceptive LBP (23), even though this finding should be interpreted in light of the limitation discussed above.

Assessing the pain distribution in LBP patients relies on thorough questioning and asking the patient to complete a body chart (e.g., the Margolis pain drawing [72] is a reliable method in chronic pain patients [73]). Even after additional training, myofascial trigger points examination has limited reliability to assess referred pain patterns in LBP patients (70). Internal lumbar disc disruption, lumbar facet joint pain, and sacroiliac joint pain each have a local (non-diffuse) pain distribution (46). Midline LBP increases the probability of lumbar internal disc disruption and reduces the probability of symptomatic facet joint pain or sacroiliac joint pain, while isolated paramidline LBP increases the probability of symptomatic facet or sacroiliac joint pain, but mildly reduces the likelihood of lumbar internal disc disruption (46). Still, lumbar intervertebral discs are capable of generating leg pain that extends below the knee; the pain pattern then originates proximally and progresses distally (48). Sacroiliac joint dysfunction generates an area of buttock hyperaesthesia extending approximately 10 cm caudally and 3 cm laterally from the posterior superior iliac spine (58), which can be applied successfully to diagnosing sacroiliac joint dysfunction in patients (58). Finally, it is advocated to use classical movement tests (e.g., lumbar flexion and extension) for examining whether the pain distribution changes in response to lumbar movements/joint loading. Patients with CS LBP will typically present with an inconsistent pain response to lumbar movements/joint loading (13).

According to the recently proposed classification method (27), if neuropathic LBP is excluded and criteria 1 and 2 are both met, the classification of predominant CS LBP can be established. In the case where neuropathic LBP is excluded, and only the first (disproportionate LBP) but not the second criterion is met, further screening of criterion 3 is required (Fig. 2).

Criterion 3: Hypersensitivity of Senses Unrelated to the Musculoskeletal System (27)

CS LBP may reflect much more than generalized hypersensitivity to pain: It may be characterized by an increased responsiveness to a variety of stimuli, including but not limited to mechanical pressure (74,75). For instance, patients with LBP may have altered cold (76) or heat sensitivity (77). A study showed that chronic LBP patients have not only localized (i.e., the primary area of pain) but also generalized (i.e., in an area anatomically remote from the primary area of pain, namely the forearm) cold hyperalgesia (78). This manifestation appears to be absent in patients with acute LBP (78). Another study reported that spinal pain patients with high mechanical pressure and thermal sensitivity showed worse clinical outcome for pain intensity (77). This finding supports the clinical importance of sensory hyperexcitability in some LBP patients.

In line with this, it is important to understand that research has informed us that long-term opioid use can decrease thermal but not pain sensitivity in LBP patients (79), and that gender, fear avoidance beliefs, and pain catastrophizing are associated with thermal pain sensitivity in chronic LBP patients (80). Also a recent systematic literature review and meta-analysis has shown that sensory hypersensitivity does not seem to play a major role in the pain and disability reported by patients with spinal pain (81). Taken together, it is currently unclear what the exact value of cold and heat hyperalgesia (assessment) in LBP patients is, but its presence might point to CS.

Given the overall hyper-responsiveness of central nervous system neurons, CS may explain the altered sensitivity to many environmental (bright light, cold/heat, sound/noise, weather, stress, food [82]) or even chemical stimuli (odors, pesticides, medication), characteristic of those with CS LBP. Weather conditions do not account for new-onset LBP (83), but research findings also indicate that weather changes might have an important role in fluctuation of pain among individuals experiencing musculoskeletal pain, including those with LBP (84).

For assessing sensory hypersensitivity in patients

with LBP, clinicians can use quantitative sensory testing (QST). The required equipment is available in many specialized pain centers. However, a recent systematic literature review and meta-analysis concluded that QST-derived pain threshold is a poor marker of CS in patients with spinal pain (81). Many QST protocols are available and require further study, and its wider use may be hampered by its costs, complexity, and time-consuming nature.

Other less expensive and less time-consuming options are available for routine clinical practice. First, clinicians can question LBP patients with suspected CS for new-onset hypersensitivity to bright light, sound, smell, and hot or cold sensations (13,85). However, the authors are unaware of studies examining the clinimetric properties of such questioning. A second more valid option appears to the part A of the Central Sensitization Inventory (CSI) (86), which assesses symptoms common to CS, with total scores ranging from 0 to 100 and a recommended and validated cutoff score of 40 (87,88). An increasing number of studies support the clinimetric properties of the CSI for assessing self-reported signs and symptoms of CS in chronic pain patients (86-88). The cutoff of 40 on the CSI allows correct identification of over 82% of CS pain patients, but the chances of false-positives are relatively high (88), which supports our approach of combining this measure with a more comprehensive examination for identification of predominant CS LBP.

Discussion

The classification criteria presented here apply the recently established clinical classification criteria for CS pain (27) to the LBP population. Those classification criteria for CS pain are based on a body of evidence from original research papers, interpreted by 18 pain experts from 7 different countries (27). The application of the classification criteria to LBP patients as presented here is substantiated by the findings of a Delphi survey (4), a study of a large group of LBP patients (n = 464) (23), validation studies of the CSI (including its ability to discriminate between CS and non-CS pain patients) (86-88) as well as several original research findings in the field of LBP research that support parts of its framework (please refer to the references included in the text above). Nevertheless, the classification algorithm for differentiating neuropathic from predominant nociceptive and CS LBP requires validation in clinical settings, including examination of its clinical applicability. In addition, the classification algorithm currently lacks "objective" criteria, and there is little proof for an (semi-)objective biomarker for CS LBP (e.g., QST measurements are not advocated for establishing CS in spinal pain patients [81]).

Classification systems for chronic LBP have been criticized as they don't consider the multiple and interacting dimensions (i.e., psychological or movement dimensions) involved in the lived experience of people with LBP (89). Given the variety of classification systems currently available for LBP (90-94), one might argue that the last thing we need is another one. However, the present classification system for differentiating neuropathic, nociceptive, and CS LBP builds on the available "pain-mechanism based classification" system for LBP (23,24,38) and the classification criteria for CS pain (27). It should be an addition to available classification systems for LBP, as it is focussed on pain mechanisms solely. For instance, in patients classified as nociceptive LBP, further subgrouping based on imaging findings, movement dysfunctions, and psychosocial or contextual factors will be required to direct treatment and improve outcomes (95). Clinicians should not become fanatic supporters of one classification system for LBP (including the one presented in this paper), but incorporate in their clinical reasoning the multiple dimensions of LBP (including pain mechanisms), in order to better assess and treat people with LBP (89).

One might consider including the presence of maladaptive psychological features as a predictor of CS LBP, as was suggested by the study by Smart et al (23). Indeed, "cognitive emotional sensitization" refers to the modulation of brain-orchestrated descending pain inhibition/facilitation by factors like pain hypervigilance, anxiety, depressive feelings, catastrophizing, illness beliefs, and somatization (96). There is substantial evidence for the role of such psychological features in LBP (80,97-99), but also in nociceptive and neuropathic LBP (100-104), suggesting that they have poor discriminative ability between the 3 pain types within the LBP population. This makes sense when one considers the fact that all pain is in the brain (105), regardless of its mechanistic nature (i.e., being either nociceptive, neuropathic, or of central nature). All pain implies activation of the brain circuitry known as the pain (neuro)matrix, including brain activity in regions responsible for cognitive-emotional and affective processing of sensory input (i.e., amygdala, prefrontal cortex, anterior cingulate cortex, insula etc.). Still, it is advocated to include a thorough psychological screening in all patients with LBP, regardless of its mechanistic nature. This is important

for identifying important treatment goals, and should include assessing maladaptive psychological features and illness behavior. The Waddell score, consisting of 8 non-organic or behavioral signs for measuring illness behavior in patients with LBP, is a reliable tool with satisfactory construct validity (106,107). Studies examining how the Waddell score varies across LBP patients with neuropathic, CS and nociceptive pain seem warranted.

Further to this reasoning is the option of including a fourth pain type for classification of patients with LBP, namely predominant psychogenic pain. Having such a fourth pain type might be useful to other pain populations besides LBP. For identifying predominant psychogenic LBP in clinical practice, clinicians need to exclude the options of predominant nociceptive, neuropathic, or CS pain. If none of these 3 pain types appear to dominate the patient's clinical picture and the patient presents with a high Waddell score or other objective evidence of maladaptive psychological features and illness behaviour (e.g., pain catastrophizing combined with pain hypervigilance, depressive thoughts, and maladaptive pain coping style like avoidance behavior), then classification of predominant psychogenic LBP might be warranted.

Although LBP patients fulfilling the criteria for classifying their LBP as CS pain can have (relevant) nociception, it implies that central mechanisms rather than peripheral (lumbar) factors are dominating the clinical picture. Patients classified as having CS LBP may require specific treatment targeting the mechanisms underlying the hyperexcitability of the central nervous system rather than treatments targeted at the lumbar spine. A variety of treatment strategies target specifically pathophysiological mechanisms known to be involved in CS pain; i.e., they hold – at least theoretically – the capacity to desensitize the central nervous system. Such treatments include pharmacological options (25), electrotherapy targeting the brain (i.e., transcranial magnetic stimulation) (25), exercise therapy (108), stress management/neurofeedback training (25), cognitive behavioral therapy (14), virtual reality (25), transcutaneous electrical nerve stimulation (25), cranial electrotherapy stimulation (25), and pain neuroscience education (14). Some of the treatments listed here, including exercise therapy and electrotherapy, have peripheral as well as central effects.

Most treatment options target the brain (top-down approach) rather than peripheral nociceptive input (bottom-up). This appears to be a rational choice, especially if one considers CS to be the dominant feature in the LBP patient. However, the clinical picture of LBP patients is often mixed with some evidence of (limited) peripheral nociceptive input combined with evidence of CS. For these patients the question arises whether successful treatment of peripheral input will diminish (or even resolve) CS as well. From the available literature it is concluded that limited evidence in selected chronic pain populations supports treatment strategies that eliminate peripheral nociceptive input for the effective management of CS pain (14). Hence, treatment of predominant CS pain (including CS LBP), should be oriented to the brain (i.e., top-down strategies). However, this conclusion is not based on studies with LBP patients, underscoring the need for further research in this area.

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