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New concepts of pain

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A B S T R A C T

Active research is being conducted on musculoskeletal pain, and recent concepts will help clinicians and researchers to develop better approaches:
-the new pain taxonomy recently has been modified with a third descriptor with the concept of nociplastic pain.
-the latest International Classification of Diseases (ICD-11) includes an IASP task force that developed a new classification system for pain. In this new classification, one can differentiate primary musculoskeletal pain including fibromyalgia and low back pain and secondary musculoskeletal pain related to specific etiologies.
-the concept of central sensitization in inflammatory rheumatic diseases is increasingly discussed. In these conditions, even with very active biological treatment, almost a third of patients are still complaining of persisting pain. These persisting pain states under adequate treatment, without any sign of inflammation, led researchers to look for evidence of central sensitization states.

Introduction

Continuous advances are being made in the field of musculoskeletal pain research. Previously, pain was described as either nociceptive or neuropathic; this dichotomous vision, however, excluded many

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patients. Indeed, patients with fibromyalgia or nonspecific low back pain have neither an obvious activation of nociceptors nor a proven lesion or disease of the somatosensory nervous system. A third descriptor was therefore needed to better classify patients. As detailed in this chapter, the new descriptor is called nociplastic pain.

Another classification problem emerged in the International Classification of Diseases. Indeed, in the 10th edition, musculoskeletal pain is included in the diagnosis codes of musculoskeletal diseases or connective tissue diseases. Yet again, with the 11th International Classification of Diseases on its way, an IASP-WHO joint task force developed a classification system. Indeed, chronic pain conditions such as fibromyalgia, complex regional pain syndrome, or nonspecific back pain required proper diagnosis codes that would recognize them as diseases in their own rights. On the other hand, pain due to a primary disease needed diagnosis codes to identify it as chronic secondary musculoskeletal pain.

Finally, a current emerging challenge is persistence of pain in patients with chronic inflammatory rheumatism. Increasing evidence shows that many patients still complain of persisting pain under adequate treatment, even without any sign of persisting inflammation. This clinical finding could lead to excessive switch in disease-modifying antirheumatic drug with frequently a pileup of treatment failure. The mechanism underlying such persisting pain is still being investigated, and researchers are looking for evidence of central sensitization through clinical, neurological, and neuroimaging features.

New concepts in pain taxonomy

Nociplastic pain concept

The present current definition of pain as endorsed by the IASP is “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. The note added to this definition adds that, “Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage.” [1]. Therefore, historically, there have been definitions of potential mechanistic pain terminology. The first mechanistic definition for neuropathic pain was set in 1994 by the IASP council as “Pain initiated or caused by a primary lesion or dysfunction in the nervous system.” This definition was changed for a new one in 2005 when the nociceptive terminology appeared. Nociceptive pain was defined as “Pain due to stimulation of primary nociceptive nerve endings,” and neuropathic pain was defined as “Pain due to lesion or dysfunction of the nervous system."

Both definitions were periodically reviewed, and currently, nociceptive pain is a “pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors,” and neuropathic pain is a “Pain caused by a lesion or disease of the somatosensory nervous system” [1]. The note accompanying the nociceptive pain definition states that this term is designed to differentiate it from neuropathic pain. The term is used to describe pain occurring with a normally functioning somatosensory nervous system to differentiate it from the abnormal function seen in neuropathic pain [1]. This note contradicts both definitions; moreover, the latest definition of neuropathic pain leaves aside the idea of dysfunction of the nervous system [2]. This dichotomy between pain mechanistic definitions created a gap for numerous patients without activation of neither nociceptors nor lesion or disease of the nervous system. In rheumatology setting, a large number of patients are concerned: nonspecific back pain, nonspecific peripheral joint pain, fibromyalgia, and complex regional pain syndrome (CRPS) type 1.

Given this situation with 2 descriptors and a large gray area in between, a third descriptor was proposed in 2016 [3]. The new descriptor chosen by the IASP council in 2017 following the proposition of Kosek et al. is nociplastic pain. This choice was supported by abundant literature confirming changes in cerebral activation in once-called “dysfunctional diseases” [4,5]. Baliki et al. also showed changes in cerebral connectivity across multiple chronic pain conditions; all patient groups (chronic back pain, CRPS, and osteoarthritis) showed decreased connectivity of medial prefrontal cortex to the posterior constituents of the default mode network and increased connectivity to the insular cortex in proportion to the intensity of pain [6]. Yet, in these patients, no “lesion or disease of the somatosensory

nervous system" can be found, and they therefore do not qualify for neuropathic pain definition but can now enter the new scope of nociplastic pain definition. The chosen definition for nociplastic pain is "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" [1,3]. The note accompanying with this definition states that patients can have a combination of nociceptive and nociplastic pain [3].

The chosen nociplastic adjective has been discussed by Brummet et al. who would have preferred the term "centralized pain," which they considered to be widely used [7]. It was replied to this proposition that first, on the contrary to nociceptive and neuropathic pain, "centralized pain" implies an anatomically based description, whereas the other two are physiological descriptors, and second "centralized pain" implies that all forms of nociplastic pain are only of central origin, which is yet to demonstrate [8].

In another letter, Granan finds this new descriptor rather vague and imprecise [9]. In his comment, he argues that such a descriptor does not help explain the pain experienced in unexplained conditions. As he reminds, in all chronic pain cases, central changes have been described, regardless of the causes, and these changes cannot fully explain why pain arises [9]. In their answer, Kosek et al. remind that patients whose pain can be described as nociceptive or neuropathic are, per definition, excluded of the new nociplastic pain definition [10]. Moreover, nociplastic pain refers to patients in whom altered nociception can be demonstrated; therefore, it cannot apply to patients reporting pain without hypersensitivity [10]. This clearly distinguishes patients with altered nociception from those in whom the biomedical mechanisms are still unknown and for whom the description of pain should be "pain of unknown origin" [10].

This new descriptor of pain serves also the purpose of promoting a systematic screening for altered nociceptive function in patients who have chronic pain [10]. Characterization of signs of altered nociception is yet to be developed by the IASP [11]. It may also help defining a better tailored treatment by identifying those who are likely to respond better to centrally rather than to peripherally targeted therapies [10].

Mixed pain concept

Another frequently used terminology is the term "mixed pain." This term is widely used yet does not exist in the IASP taxonomy. The common definition of mixed pain is a pain with "an overlap of nociceptive and neuropathic symptoms" [12]. Rainer Freynhagen formed an international group of pain specialists to address the question of a definition of the term "mixed pain."

The group based their discussion on a literature review from 1990 to 2018. The report of mixed pain in the literature is increasing throughout the last 20 years [12]. Multiple chronic pain is considered to be mixed pain states, and the authors reported the following types of pain: cancer pain, lower back pain, osteoarthritis pain, postsurgical pain, and pain in primary care [12].

Regarding the musculoskeletal pain, in low back pain: a literature review in 2012 reports that a quarter to a half of the patients with chronic low back pain had a greater than 90% likelihood of having a neuropathic pain component [13]. These numbers are also found in a 2016 review [14]. In the latter, the authors remind the results of Attal et al., who, using the DN4, observed that 8% of patients with strict lumbar area pain had a neuropathic pain component, and prevalence of neuropathic pain component increased to 80% of patients with pain radiating toward the foot in a dermatomal distribution, with neurological signs corresponding to typical radiculopathy [15]. In osteoarthritis, most studies have concluded that a neuropathic component is present in one-third of all patients with painful OA [16]. In chronic inflammatory rheumatism, the existence of a neuropathic pain component was also reported in a few studies. In a cohort of 300 patients with RA, 9.3% had likely/possible neuropathic pain using the painDETECT questionnaire [17]. In the DANBIO registry, more than 7000 patients (with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and other spondyloarthritis (SpA)) completed a painDETECT questionnaire, and more than 20% of the patients had likely a neuropathic pain component [18].

In their attempt to define mixed pain, Freynhagen et al. remind that little is known regarding the underlying mechanism(s) of mixed pain generation. However, it should be noted that patients with

mixed pain have, for example, in osteoarthritis higher pain intensity scores and a significantly decreased quality of life [16]. These results were corroborated by a large cross-sectional Spanish study [19]. In the latter, in primary care and orthopedics setting, pain had a mixed component in more than 59% of the more than 5000 patients [19]. The patients experiencing mixed pain "showed a greater clinical complexity," had more comorbidities, had more adverse psycho-social factors, and had a lower health-related quality of life [19]. Moreover, patients with mixed pain responded less to treatments and had a higher utilization health care resource [19].

Finally, Freynhagen et al. point out that there are no validated tools yet to screen for mixed pain and for the nociceptive component [12].

The proposed definition of mixed pain by the authors is "Mixed pain is a complex overlap of the different known pain types (nociceptive, neuropathic, and nociplastic) in any combination, acting simultaneously and/or concurrently to cause pain in the same body area. Either mechanism may be more clinically predominant at any point of time. Mixed pain can be acute or chronic." [12].

New concepts in musculoskeletal pain classification

Primary pain

Pain is one of the symptoms with the highest frequency when seeking medical care, and among patients suffering from pain, half of the final diagnosis are due to musculoskeletal cause [20]. In musculoskeletal diseases, pain is the symptom that weighs the most in disease burden [21] and low back pain is the first cause of years lived with disability [22]. In chronic pain conditions, it was shown by Breivik et al. in 2006 that musculoskeletal pain was the most prevalent of all painful conditions [23].

In the 10th edition of International Classification of Diseases (ICD-10), chronic pain diagnoses are not represented systematically [24]. The IASP developed jointly with the WHO a new classification of chronic pain for the 11th edition of the ICD. In the proposition, the taskforce distinguished chronic primary and chronic secondary pain syndromes given that primary chronic pain should qualify as a disease in its own right [24]. In musculoskeletal pain, this renders it possible to classify fibromyalgia, complex regional pain syndrome, and nonspecific low back pain as primary pain disorders [24].

Chronic secondary musculoskeletal pain

Moreover, the taskforce developed classification of chronic secondary musculoskeletal pain [25]. This definition is limited to nociceptive pain and excludes pain being perceived as musculoskeletal but not arising therefrom [24]. As secondary musculoskeletal pain is due mostly to three main causes, they were integrated in the classification as follows: chronic secondary pain.

- From persistent inflammation
- Associated with structural changes
- Due to diseases of the nervous system [25].

Chronic secondary musculoskeletal pain from persistent inflammation has been divided into 3 categories, as inflammation has several etiologies [25]. The first one is persistent inflammation due to infection. The infection can be active or latent, and pain can persist after adequate infectious treatment [25]. The second category is persistent inflammation due to crystal deposition. In crystal deposition conditions, chronic pain may occur after episodes of acute inflammation, and in these cases, pain intensity is not correlated to the degree of crystal deposition [25]. The third category is persistent inflammation due to autoimmune and autoinflammatory disorders. There again, chronic pain is secondary to the primary inflammatory disease, but pain intensity is not correlated to the activity of the underlying disease [25].

Chronic secondary musculoskeletal pain associated with structural changes has also been divided into 3 categories, i.e., pain due to osteoarthritis, pain due to spondylosis, or pain after musculoskeletal injury [25].

Finally, chronic secondary musculoskeletal pain due to diseases of the nervous system includes musculoskeletal pain associated with Parkinson diseases, multiple sclerosis, or peripheral neurologic disease. In the latter, pain occurs due to altered motor or sensory function (for example, Charcot joint disease) and pain due to nerve entrapment has to be classified as chronic neuropathic pain [25].

Central sensitization in inflammatory rheumatisms

In rheumatoid arthritis, studies focusing on patients' reported outcomes highlight the fact that even when the disease seems to be controlled, more than 75% of patients with RA still report moderate to severe pain [26]. Moreover, more than 60% of the patients report disappointment with their arthritis pain [26]. In a large cohort study of more than a thousand patients with RA, Altawil et al. showed remaining pain after 3 months of methotrexate treatment in 29% of patients with a good EULAR response [27]. Hence, despite a good therapeutic response, a substantial number of patients still complain of persistent joint pain.

Initially, most of these patients exhibiting persistent pain were classified as having concomitant fibromyalgia. For example, using the Fibromyalgia Rapid Screening Tool (FiRST) [28], fibromyalgia was detected in 22.6% of 172 patients with RA and in 27.8% of 122 patients with systemic sclerosis in a multicentric cohort study [29]. In a study with more than 500 patients with axial spondyloarthritis initiating a biological disease-modifying antirheumatic drug, 37.8% had a positive FiRST at baseline [30]. In a large cohort of more than 6000 patients in the United States, fibromyalgia was associated in 21% of patients with rheumatoid arthritis, 37% of patients having a systemic lupus erythematosis, and 17% patients with osteoarthritis [31].

These observations led clinicians to question the existence of central sensitization in rheumatoid arthritis. Indeed, this central sensitization has already been linked to many other musculoskeletal painful conditions such as osteoarthritis and chronic low back pain [32]. In chronic inflammatory rheumatism, the supposed mechanism of central sensitization is the persistence of a painful stimulus from a joint that would exaggerate the sensitivity of the central nervous system to pain, inducing manifestations that resemble primary fibromyalgia [33]. Moreover, in the event of central sensitization, the pain may be accompanied with symptoms generally seen in primary fibromyalgia, such as fatigue and sleep disturbances [33].

As defined by IASP, central sensitization is “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub threshold afferent input,” and the underneath note to sensitization reminds that: “Sensitization can include a drop in threshold and an increase in supra threshold response. Spontaneous discharges and increases in receptive field size may also occur. This is a neurophysiological term that can only be applied when both input and output of the neural system under study are known, e.g., by controlling the stimulus and measuring the neural event. Clinically, sensitization may only be inferred indirectly from phenomena such as hyperalgesia or allodynia.” [1].

Clinical evidence

It remains controversial that the painDETECT questionnaire, designed to identify neuropathic pain in patients suffering from low back pain [34], has been used to identify central sensitization. The psychometric properties of the questionnaire in rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis have been validated recently [35].

A few studies have used the painDETECT questionnaire in RA patient population. In 2014, in a cohort of 100 patients with RA, with a mean DAS-28 of 2.09, 54% of the patients reported severe pain defined by pain intensity of 54/100 or more. In the same cohort, 33% of the patients had possible or likely neuropathic pain identified by painDETECT [36]. In the DANBIO register, the painDETECT was answered by more than 3000 patients with RA, and 44% of the participants had possible or likely neuropathic pain in this cohort [18]. In a prospective study with the hypothesis that a high painDETECT score would correlate with poorer treatment outcome, Rifbjerg-Madsen et al. had almost 35% of patients with a painDETECT score more than 13 at baseline [37]. In another cohort study, among 159 patients with RA, most of them being in remission or having low disease activity, again more than 38% had a painDETECT

score more than 13 [38]. Moreover, there was a positive correlation between high pain intensity and painDETECT score [36,38].

In spondyloarthritis and psoriatic arthritis, more than 1000 patients, from the DANBIO register, with either of the two diagnoses answered the painDETECT questionnaire, and 55% of the patients with psoriatic arthritis and 45% of the patients with spondyloarthritis had possible or likely neuropathic pain [18]. For patients with psoriatic arthritis, 28% had painDETECT scores >18, which was significantly higher than those for patients with RA and SpA ($p < 0.001$). On the other hand, statistically significantly fewer (45% vs. 56% of RA and 55% of SpA) patients with PsA had a painDETECT score <13 ($p < 0.001$) indicating primarily non-neuropathic pain [18].

As there is controversy about the ability of the painDETECT questionnaire to identify central sensitization, other research used quantitative sensory testing (QST) to identify abnormal pain mechanism.

Assessment of central sensitization with quantitative sensory testing

One of these QST used in patients with RA is the measure of pain pressure thresholds (PPT). In a small study of 10 patients with RA and 10 age- and gender-matched controls, Hodge et al. reported that patients with RA had significantly reduced plantar pain pressure thresholds [39]. This reduced threshold in RA was also found in other studies such as the one by Joharatnam et al., in which a cohort of 50 patients with active RA demonstrated low pain pressure threshold values at articular sites and even at extra-articular sites (anterior tibia and sternum) [40]. Moreover, lower pain pressure threshold values were associated with higher DAS28, and looking individually at DAS28 components, the association was attributable to the patients' reported global health visual analog scale and tender-joint count [40]. These results were corroborated by Lee et al. in a study of various QST in 139 patients with RA [41]. This decrease in PPT in patients with active RA was also seen in two other controlled studies: the first one with 38 women with active RA women compared to 38 healthy controls [42] and the second one with 46 patients with RA and 20 healthy controls [43]. In both studies, the differences between groups were significant. In ankylosing spondylitis (AS) and PsA, pain pressure threshold was found to be significantly lower in 23 patients with PsA than in controls, but no difference has been detected in ankylosing spondylitis as compared to controls [44]. This absence of pain pressure threshold assessment confirmed the previous results of Incel and colleagues who showed in a study with 20 patients with SpA that patients with SpA did not have lower PPT than controls [45].

Another quantitative sensory testing used to identify pain mechanism abnormalities is temporal summation. Temporal summation is a physiological process through which the patient will perceive increasing pain when repeatedly exposed to a painful stimulus of the same intensity. In the same study, Vladimirova et al. also tested temporal summation in their RA cohort; the temporal summation index was significantly higher in patients with RA than in healthy controls [42]. An increase in the temporal summation index expresses central pain sensitization according to the authors [42]. As seen with pain pressure threshold, temporal summation was significantly associated with patient's global assessment [41]. These results are supported by another study, where 11 patients with RA were compared to healthy controls. A significantly higher temporal summation score was observed in patients with RA than in the controls [46]. On the contrary, Meeus et al. did not find significant difference in temporal summation in patients with RA compared to healthy controls [47].

Conditioned pain modulation (CPM) is another type of quantitative sensory testing. It is used to assess pain descending pathways. The conditioned pain modulation paradigm is activating pain descending inhibitory pathways with a noxious stimulus, called the conditioning stimulus, which modulates another, called the test stimulus [48]. In studies on CPM, results are conflicting. In the study of Meeus et al. with 16 patients with RA and 18 controls, CPM did not show significant difference between groups [47], confirmed by another recent study in which CPM in the two groups (RA and controls) did not show any significant differences [46]. On the other hand, Lee et al. in a larger study with 58 women with RA and 54 age-matched controls, median CPM levels were lower among patients with RA than among controls without chronic pain conditions [49]. Unlike for pain pressure threshold and temporal summation, CPM was not associated with patient's global assessment but was associated with tender joint count [41].

Brain imaging

Brain imaging is also another area of research to understand pain mechanisms in rheumatoid arthritis. Studies have looked at brain structure and function using mostly MRI. Structural changes were assessed in two studies. In a study with 31 patients with RA and 25 healthy controls, Wartolowska and colleagues measured the volume of various brain regions [50]. They observed an increase in gray matter volume, especially in the nucleus accumbens and caudate nucleus. In addition, no difference was seen in cortical gray matter [50]. In a small cohort of 15 patients with RA, Andersson et al. looked at the hippocampus volume [51]. Patients having a small hippocampus volume reported more severe health assessment questionnaire (HAQ) score and higher pain on a visual analog scale [51].

In a study with 17 patients with AS and 17 age- and sex-matched controls, structural MRI showed an increase in gray matter volume in the putamen and thalamus and cortical thinning in 5 brain regions (left primary somatosensory cortex, left insula, left anterior mid-cingulate cortex, right supplemental motor cortex, and right anterior cingulate cortex) [52].

A few studies also focused on functional changes. First, Schweinhardt et al. in a study with 20 patients with active RA, fMRI showed that provocation of joint pain activated typical pain processing regions (insula, anterior cingulate cortex, thalamus, and primary and secondary somatosensory cortices) [53]. Moreover, they found a strong activation in medial prefrontal cortex, lateral prefrontal cortex, posterior cingulate cortex, temporal cortex, superior posterior parietal cortex, precuneus, primary motor cortex, and cerebellum. The magnitude of activation in the medial prefrontal cortex cluster was positively correlated with the tender-to-swollen ratio [53]. They also found evidence of a positive correlation between activation of the medial prefrontal cortex during provoked joint pain and depressive symptoms [53]. These results led the authors to hypothesize that the medial prefrontal cortex might be in the region of importance in the emotional processing of pain for patients with RA [53]. Another study with 24 patients with active RA (mean DAS-28 5.20 $\pm$ (1.14)) and 19 age- and sex-matched controls, Flodin and colleagues showed using fMRI that, compared to controls, patients with RA had an increased brain connectivity predominately for the supplementary motor areas, mid-cingulate cortex, and the primary sensorimotor cortex [54]. Moreover, the authors note an increase in brain connectivity between the insula and prefrontal cortex as well as between anterior cingulate cortex and occipital areas in patients with RA [54]. Recently, Basu et al. searched for neuroimaging features of fibromyalgia in patients with RA [55]. In a cohort of 54 patients with active RA with a clinically significant level of fatigue for at least 3 months, the level of fibromyalgianess (FMness) was assessed using the ACR FM survey criteria [31]. Regarding the fMRI results, there was a significant positive correlation between the default mode network (DMN; medial prefrontal cortex, posterior cingulate cortex, precuneus, inferior parietal lobule, hippocampal formation, and lateral temporal cortex [56]) connectivity to the left mid/posterior insula and FMness in patients with RA [55]. Dissecting the FMness score and its correlation to connectivity, both the widespread index and symptom severity sale were significantly associated with the DMN-insula connectivity [55]. For the authors, this indicates important contributions for both parts of the FMness score. On the other hand, no association existed between DMN-insula connectivity and pain reported at the time of the MRI [55]. The other correlations analysis between DMN-insula connectivity and RA disease features showed only a positive correlation with the DAS-28 score [55]. For the authors, these results provide neuroimaging evidence that RA is a mixed pain state displaying characteristics of central sensitization, as patients with RA who had high levels of FMness demonstrated significantly higher functional connectivity between the DMN and insula – a recognized neurobiological feature of "primary" FM [55].

In ankylosing spondylitis, Li et al. studied functional deficits using resting state fMRI [57]. The authors compared the amplitude of low-frequency fluctuations that can assess the amplitude of resting state spontaneous brain activity. Compared to controls, patients with AS had a significantly lower amplitude of low-frequency fluctuations in the left medial frontal gyrus, the right precentral gyrus, and the right posterior cingulate; on the other hand, patients exhibited higher amplitude of low-frequency fluctuations in the left cerebellum anterior lobe, the left middle temporal gyrus, the left superior occipital gyrus, the left postcentral gyrus, and the right precuneus [57]. Hemington and colleagues studied functional connectivity within the DMN and between the DMN and other brain regions in 51 patients with AS compared to controls [58]. In patients with AS reporting high levels of pain (mean pain

intensity 4.6 ± 1.6), there was significantly stronger (positive) cross-network connectivity between the DMN and the sensorimotor network than 22 age-matched healthy control participants [58].

Summary

The latest pain taxonomy includes the new concept of nociplastic pain defined as altered nociception, with no evidence of tissue or somatosensory damage. The IASP has yet to characterize signs of this altered nociception.

In the future ICD-11 classification, fibromyalgia, complex regional syndrome type 1, and nonspecific back pain will be considered as primary chronic pain syndrome.

Almost a third of patients with RA receiving adequate treatment complain of persisting pain despite a good control of inflammation. Persisting pain might be driven by central sensitization, and to date, there is increasing evidence for such hypothesis. With this new concept, future studies should focus on relieving this part of the pain component in patients.

Practice points

- A third descriptor of pain, nociplastic pain, now exists; nociplastic pain is defined as "Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain"
- The IASP proposed a new classification for chronic pain in the 11th International Classification of Diseases. Chronic primary and chronic secondary pain syndromes have been distinguished. Fibromyalgia is now classified in chronic primary pain syndrome.
- Persisting pain in patients with rheumatoid arthritis might be partially driven by central sensitization.

Research agenda

- With the new concept of nociplastic pain, clinicians should screen systematically for altered nociceptive function in patients suffering from chronic pain.
- Characterization of signs of altered nociception is yet to be developed by the IASP.
- With this new description, therapeutic research can be standardized and can identify patients who are likely to respond better to centrally rather than to peripherally targeted therapies.
- The new classification in ICD-11 of chronic pain syndromes will improve classification and diagnostic coding and help recognition of chronic pain as a health condition in itself.
- Persisting pain in RA due to central sensitization needs to be addressed in future therapeutic research studies.

Conflicts of interest

The authors declare no conflict of interest with regard to this publication.

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