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Narrative Review

Is Fibromyalgia a Nociplastic or a Mixed-pain Condition? International, Multidisciplinary Recommendations for Pain Phenotyping in Fibromyalgia Syndrome

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Background: Fibromyalgia syndrome (FMS) is a complex condition characterized by numerous symptoms, especially long-lasting widespread pain. Available evidence suggests that the main causes of FMS are nociplastic pain mechanisms, but nociceptive and neuropathic pain components can also be involved, which would in these cases characterize FMS as a mixed-pain condition. In 2021, a comprehensive set of clinical criteria and grading systems was developed in accordance with the International Association for the Study of Pain. The establishment of these criteria is an important step toward precision pain medicine, with great potential for the assessment and treatment of FMS.

Objectives: The aim of this study was to develop clinical recommendations for pain phenotyping, including the phenotyping of mixed pain, in patients with FMS.

Study Design: Narrative review.

Methods: Within this framework, an international and multidisciplinary group of pain specialists have developed clinical recommendations for integrating a mixed pain phenotype into the current framework of phenotyping FMS. A modified nominal group technique was used to develop the consensus recommendations. A manual is provided to allow clinicians to differentiate between predominant nociplastic pain and mixed pain when phenotyping FMS patients.

Results: A 7-step diagnostic approach, performed in 2 parts, is presented and illustrated using 3 case examples to enhance understanding and encourage effective implementation of this approach in research settings and clinical practice.

Limitations: Studies examining the clinometric properties of these recommendations and this grading system for mixed pain in FMS are warranted.

Conclusion: The current recommendations systematically summarize the methods that allow individuals with FMS to be classified into nociplastic or mixed pain phenotypes, based on potential nociceptive and neuropathic pain components.

Key words: Fibromyalgia syndrome, mixed pain, neuropathic pain, nociceptive pain, nociplastic pain, precision medicine

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Fibromyalgia syndrome (FMS) is a complex condition characterized by chronic widespread pain, numerous other symptoms (including fatigue, sleep disturbance, and cognitive dysfunction), and a strong association with psychiatric disorders (1). The prevalence of FMS has been estimated to affect approximately 2 to 3% of the population worldwide, and the syndrome is much more commonly present in individuals with rheumatic diseases than in the general population (2-4). Although the mechanisms underlying FMS are not fully understood, its symptomatology is thought to be related to central nervous system sensitization, characterized by dysfunction of neuro-circuits, and resulting in enhanced pain and sensitivity to stimuli (5-7). FMS can impair people's daily functionality, reduce their ability to engage in occupational and social activities, and exert a negative impact on patients' quality of life (8,9).

Many years ago, pain was categorized as either nociceptive or neuropathic. In 2017, the International Association for the Study of Pain (IASP) introduced the term "nociplastic pain" as a third mechanistic pain descriptor, providing a label for pain disorders characterized by altered nociception and central sensitization (CS) processes (10). In 2019, a fourth pain phenotype, labeled as mixed pain, was proposed to characterize a complex overlap of different pain types in any combination (nociceptive, neuropathic, and/or nociplastic) (11).

The American College of Rheumatology (ACR) criteria for diagnosing FMS, including the typical FMS widespread pain pattern, suggest that FMS is a nociplastic pain condition (12). Recently, however, a group of researchers have associated common symptoms of FMS, such as numbness, tingling, burning, and paresthesia, with small fiber neuropathy originating from the dorsal root ganglia (13-15). People with FMS can suffer from other comorbid conditions, including neurological disorders, such as polyneuropathy (16), disc herniation (17), myelopathy (18), or carpal tunnel syndrome (19). Moreover, nociceptive pain components might be seen in people with FMS in the presence of musculoskeletal injuries (20), degenerative changes, inflammatory osteoarthritis (21), and rheumatoid arthritis (22). These observations suggest that nociceptive and neuropathic pain can be important components in the presentation of some patients' FMS symptoms, in addition to nociplastic pain.

In 2021, a comprehensive set of clinical criteria and grading systems for phenotyping nociplastic pain was developed in accordance with the IASP (23). However, the characterization of FMS as a purely nociplastic pain condition may be too limiting for some patients, so international and multidisciplinary recommendations for updating this algorithm for FMS populations are needed. Distinguishing accurately between pain phenotypes in people with FMS is important for providing the best patient-tailored care. Both nociplastic and mixed pain types tend to respond best to a multimodal and interdisciplinary treatment approach (24). The systematic identification pain phenotypes—differentiating which ones are primarily nociplastic from which ones are mixed—in people with FMS may improve the success of treatments for this complex disorder. From this perspective, our international and multidisciplinary group of pain specialists developed updated clinical recommendations for phenotyping people with FMS by integrating a mixed pain phenotype into a guided assessment framework.

Diagnostic Criteria for Fibromyalgia Syndrome

Though recommendations for identifying FMS were presented as early as 1977 (25), the first "official" criteria for diagnosing the condition were proposed by the ACR in 1990 (26). In 2010, the ACR proposed updating those recommendations to eliminate the use of tender point evaluations and base the diagnosis on 2 patient-reported outcome measures: the Widespread Pain Index (WPI) and the Symptom Severity Scale (SSS) (though a physician's assessment and interpretation of the SSS were still required) (27). Two subsequent revisions to these criteria were proposed in 2011 and again in 2016, which simplified the SSS and essentially eliminated the requirements of a physician's assessment, so that the diagnosis could be made completely with patient-reported data (12). The 2016 revision introduced 2 changes to the 2011 criteria: a) the removal of the statement that the patient could not have another condition that explained the symptoms and b) the addition of a criterion that pain be present in at least 4 out of 5 body regions (independent of the actual WPI score). This latter change was introduced to prevent the misclassification of patients with severe forms of regional pain as having FMS. (These patients would have high WPI scores based on the intensity of the pain as well as high SSS from distress, but only certain regions of the body would be affected) (28). The revised criteria from 2016 point out that the misclassification of patients with severe regional pain may be more relevant in tertiary pain clinic settings than in "general care" set-

tings (12). Despite these proposed revisions, it should be noted that only the 1990 and the 2010 criteria have been officially recognized by the ACR, as reflected on the ACR Web site (29).

Because we believe the proposed 2016 diagnostic criteria for FMS are an improvement over the approved 2010 ACR criteria, we have chosen to refer to the 2016 criteria in the remainder of this article (12). Of special concern about the 2010 ACR criteria in the present study is that an FMS diagnosis is excluded if the patient has "another disorder that would otherwise explain the pain." This exclusion makes a mixed pain phenotype for FMS (as proposed in the present study) problematic. The 2016 criteria specify that an FMS diagnosis is valid irrespective of other diagnoses. The 2016 criteria also simplify the classification methodology, minimize misclassification of regional pain disorders, and are believed to capture more psychosocial triggers related to FMS (29,30).

Pain Types in FMS

Nociceptive Pain and FMS

According to the IASP, pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (31). Nociceptive pain is defined by the IASP as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors" (32). FMS is characterized by the absence of well-defined organic injury or disorders of the non-neural tissues (33), poor response to analgesics and nonsteroidal anti-inflammatory drugs (34), and the presence of abnormal nociceptive processing (35-37). However, a nociceptive pain component may still be present in some people with FMS. Some studies point at possible abnormalities in the skin and muscles (38-40), and these abnormalities have been reported as sources of nociceptive input in FMS (37). As noted previously, people with FMS may also have nociceptive pain due to several comorbidities (e.g., osteoarthritis [21], rheumatoid arthritis [22], etc.) and/or additional musculoskeletal injuries (17,19). Nociception cannot be entirely responsible for the pain of FMS and should thus be considered a possible contributing component to nociplastic pain instead of the sole pain phenotype.

Changing Views about Nociception and Pain

Notably, pain and nociception can be related, but they do not always have a causal relationship, and pain sensations are not determined solely by activity in sensory neurons (31). Therefore, the terms "pain" and "nociception" should not be used interchangeably. For example, a patient under general anesthesia responds to surgical stimulation with increased heart rate and blood pressure, which is nociception but not pain. Similarly, a patient with central neuropathic pain after a stroke may experience pain without any nociception. People with pain disorders, including FMS, may have difficulty accepting this distinction. Even health care providers may struggle to grasp the concept. Older belief systems about nociception and pain have resulted in a classification of FMS as a psychosomatic disorder, which has led to negative connotations for both patients and providers (41) and may have given rise to reductive approaches to treatment by physicians. New approaches for defining pain and nociception can potentially help break the stigma around people with FMS and other CS-related pain disorders. It is currently impossible to reveal the biological mechanisms underlying an individual's pain experience (42). Despite the undeniable development of nervous system imaging techniques in the last decades, there are multiple methodological problems in translating nervous system activity to mind states and perceptions, including pain (43).

Neuropathic Pain and FMS

The IASP Neuropathic Pain Special Interest Group (NeuPSIG) has recommended that pain be classified as neuropathic if the following conditions are met: (1) the presence of a lesion/disease in the somatosensory nervous system is identified, (2) pain symptoms have a neuroanatomically plausible distribution, and (3) the existence of the pain is supported by both a physical examination and laboratory and/or imaging findings (44).

Neuropathic pain can be attributed to various comorbid diseases (16-19). Common clinical symptoms of neuropathic pain include tingling, numbness, paresthesia, hyperalgesia, and allodynia (45). Neuropathic pain disorders are often associated with central sensitization, resulting in some symptom overlap with FMS (e.g., hyperalgesia and allodynia) (45,46), but such conditions are generally not associated with the full clinical symptomatology of FMS (including insomnia, stress intolerance, cognitive dysfunctions, fatigue, etc.). Therefore, neuropathic pain should be considered a pain component rather than a predominant pain phenotype in people with FMS.

Previous studies on the assessment of neuropathic

pain in people with FMS (47,48) have often used self-report instruments such as the Self-Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) (49) and the painDETECT (50-52) questionnaires. However, because these scales are only screening tools and have shown relatively low specificity in identifying somatosensory abnormalities, their use is not considered appropriate for the diagnosis of neuropathic pain (53). In addition, similarities in symptoms and sensory profiles between neuropathic and nociplastic pain groups can make questionnaire results difficult to interpret (51). Therefore, results of self-reported questionnaires should be cautiously interpreted in those cases and used only with additional examination. When damage to a nerve is suspected, positive identification through imaging or a nerve conduction study can provide definitive evidence of neuropathic pain. Alternatively, some authors have suggested that quantitative sensory testing (QST) (54) should be included in the routine assessment of neuropathy in individuals with FMS, in addition to self-reported questionnaires. Because QST methodologies are often impractical in standard clinical practice, new methodologies for low-cost and time-efficient "bedside QST" are being studied, with promising results (55).

Nociplastic Pain and FMS

Nociplastic pain is defined by the IASP as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain." According to the IASP criteria published in 2021, pain is classified as nociplastic if it cannot be fully explained by nociceptive or neuropathic mechanisms, persists for more than 3 months, and is associated with pain hypersensitivity (23). The pain characteristics and symptoms of FMS align almost completely with the definition of and criteria for nociplastic pain.

It should be noted that the IASP criteria do not require nociceptive triggers to initiate sensitization of the nociceptive system (56,57). In fact, 2 separate types of nociceptive pain patterns have been proposed (58). The "bottom-up" pattern of nociceptive pain is caused by ongoing peripheral nociceptive input. This type is the traditional model of CS, in which pain hypersensitivity can be produced with the repeated administration of a painful stimulus and will likely resolve when the painful stimulus is removed (59). The proposed "top-down" pattern of nociplastic pain does not require nociceptive input and is associated with a variety of other variables, including genetic predisposition, exposure to extreme or prolonged environmental stressors (including physical and psychological trauma), psychiatric comorbidity, and sensitivity to a range of painful and non-painful stimuli (60). It is likely that most individuals with FMS fit a top-down pattern of nociplastic pain. Consequently, in these cases, a thorough biopsychosocial assessment to identify "top-down" related factors is needed for treatment purposes.

The first notable feature of nociplastic pain in FMS is pain hypersensitivity, with a variable, inconsistent, and widespread pain distribution that is neuroanatomically difficult to explain (61). Traditional markers of hypersensitivity such as hyperalgesia (defined as an exaggerated pain response to painful stimuli), allodynia (defined as pain in response to stimuli that are not normally painful), and common palpation sensitivities, known as tender points, are frequently observed in FMS (62). The second important feature of FMS is the occurrence of nonpainful central nervous system symptoms such as fatigue, non-restful sleep, cognitive slowing (sometimes called "fibrofog"), and mood disorders (63). Third, individuals with FMS are often hypersensitive to chemical and environmental stimuli, such as odors or perfume, bright lights, loud noises, and cold (5,64,65). Lastly, a recent retrospective study found that people with FMS were 12 times more likely to have severe intolerances to multiple drugs than a control sample (66).

The ability to identify nociplastic pain characteristics of a patient's symptom presentation during an initial clinical assessment can provide an opportunity for the early diagnosis of FMS. Moreover, because the symptoms of FMS can fluctuate over time, it may be more rational to place greater focus on the patient's nociplastic pain features than on symptom-based diagnoses (67).

Mixed Pain and FMS

Although the term "mixed pain" is not included in the IASP taxonomy, it is increasingly recognized that patients can have overlapping symptoms of nociceptive, neuropathic, and nociplastic pain, in any combination, and in the same body regions (11). Uncertainty regarding the mechanisms that contribute to mixed pain may factor into the absence of a formal IASP definition of this type of pain, especially considering that clinical criteria for identifying patients with mixed pain have been proposed only recently (68). While FMS is

regarded as a predominantly nociplastic pain phenotype, some patients may also meet the IASP criteria for comorbid nociceptive and/or neuropathic pain, and a diagnosis of FMS does not exclude the presence of other painful medical conditions (12). Therefore, it may be logical to classify some cases of FMS as involving mixed pain, in which nociplastic pain overlaps with nociceptive and/or neuropathic pain components.

The IASP Clinical Criteria and Grading System for Determining Nociplastic or Mixed Pain Types (Nociceptive and/or Neuropathic) in Individuals with FMS

Consensus Methodology

The consortium is a convenience sample of researchers with expertise in chronic pain, fibromyalgia, or both. The invitation process was led by the lead authors (IS and JN) and resulted in a group of 16 researchers from 8 countries. The modified nominal group technique (MNGT) was used to develop the consensus recommendations for pain phenotyping in FMS patients. The nominal group technique (NGT) has been used widely in published consensus approaches in health care research aimed at problem-solving, idea-generating, or priority-setting (69). Two coordinators (IS and JN) were chosen to manage the development of the consensus recommendations. The MNGT involved 1) an introduction and explanation, 2) the generation of a manuscript and clinical examples, 3) several rounds of sharing that manuscript and those clinical examples (idea generation and clarification phases) (69), 4) group discussion, and 5) voting on the final recommendations and the case reports. This process was completed primarily through multiple rounds of e-mail communication and online meetings. After the anonymous voting for the consensus recommendations and cases, the NGT was completed. For interpreting the voting results in line with previous NGT studies, a 90% quorum for accepting the results and a minimum agreement score of 70% were applied (70,71).

Findings

The application of the consortium's consensus recommendations for pain phenotyping during the clinical reasoning process requires aiding. To that end, a 2-part, 7-step decision-making tree has been generated to adhere to the proposed stepwise process for determining the pain phenotypes in individuals with FMS diagnosed using the proposed 2016 criteria—namely, whether those phenotypes are primary nociplastic or mixed. Three FMS case studies are presented in the supplemental materials (Appendix 1-3). These case studies demonstrate how the IASP nociplastic pain criteria for pain phenotyping can be applied clinically to individuals with FMS.

The voting results show that the a priori set 90% quorum and the minimum agreement score of 70% for accepting the results were achieved for the consortium's recommendations in general (97% agreement), recommendations in Part 1 (full agreement), recommendations in Part 2 (full agreement), each of the 7 steps (full agreement) and the 3 case studies (Appendix 1-3; agreement scores between 93% and 100%; Table 1).

Part 1: Interrogate/Confirm Nociplastic Pain

This part comprises 5 steps to confirm nociplastic pain in people with FMS who meet 2016 FMS diagnostic criteria (12). Because it is assumed that all people with FMS are positive for nociplastic pain, those who do not meet the following criteria should be referred to a relevant specialist to review or rule out the FMS diagnosis.

Step 1

The first step in applying the IASP clinical criteria for nociplastic pain requires patients to report pain for at least 3 months. FMS is a chronic condition, and although its duration varies, the symptoms usually last for years (72). The 2016 FMS diagnostic criteria also specify that symptoms must last for at least 3 months (12). Therefore, every person with FMS is expected to meet this criterion.

Step 2

For their pain to be clinically classified as nociplastic, patients should report a regional, multifocal, or widespread pain distribution rather than a discrete anatomically logical pain distribution. The WPI, as specified in the 2016 FMS diagnostic criteria (12), can be used to confirm this criterion.

Step 3

The third step involves screening for signs of pain hypersensitivity, including hyperalgesia (defined as an exaggerated pain response to painful stimuli) and allodynia (defined as pain in response to stimuli that are not normally painful) (45). A physical exam, with manual palpation or QST methodologies, can be used to assess for pain hypersensitivity.

Table 1. *Voting results of the consortium's consensus recommendations on pain phenotyping for patients with FMS.*

	Participation rate (n = 16)	Agreed	Disagreed	No opinion
Consensus recommendations in general	15 (94%)	15 (100%)	0	0
Consensus recommendations in Part 1: Interrogate/Confirm Nociplastic Pain	15 (94%)	15 (100%)	0	0
Step 1—pain duration	15 (94%)	15 (100%)	0	0
Step 2—pain distribution	15 (94%)	15 (100%)	0	0
Step3—pain hypersensitivity	15 (94%)	15 (100%)	0	0
Step 4—history of hypersensitivity	15 (94%)	15 (100%)	0	0
Step 5—comorbid symptoms	15 (94%)	15 (100%)	0	0
Consensus recommendations in Part 2: Determine whether mixed pain is present	15 (94%)	15 (100%)	0	0
Step 6— Determine whether nociceptive pain component is present	15 (94%)	15 (100%)	0	0
Step 7— Determine whether neuropathic pain component is present	15 (94%)	15 (100%)	0	0
Case study 1 (appendix 1)	15 (94%)	14 (93%)	1 (7%)	0
Case study 2 (appendix 2)	15 (94%)	15 (100%)	0	0
Case study 3 (appendix 3)	15 (94%)	14 (93%)	(7%)	0

If the conditions of the first 3 steps are met, the patient is classified as having "possible nociplastic pain," and clinicians should proceed to step 4 to investigate whether the likelihood can be raised to "probable nociplastic pain."

Step 4

The fourth step examines whether the individual with FMS has a history of hypersensitivity to pain during activities of daily living. This criterion can be evaluated by questioning the patient in detail about sensitivity to touch, movement, pressure, and heat/cold. Allodynic responses (Table 2) during activities of daily living are characteristic of FMS and are commonly reported during a patient interview (7).

Step 5

The final step involves screening for comorbid symptoms in individuals with FMS. This criterion is met if any of the following comorbid symptoms are present: increased sensitivity to sound, light, and/or odors; sleep disturbance with frequent nocturnal awakenings and nonrestorative sleep; fatigue; or cognitive problems. If this criterion is also met, the pain associated with FMS should be classified as "probable nociplastic pain" (23). The SSS questionnaire may be useful for assessing this criterion (12).

Part 2: Determine Whether Mixed Pain Is Present

The 2 steps required to examine whether mixed pain is present entail assessing whether individuals with FMS have a nociceptive or neuropathic pain component in addition to nociplastic pain.

Step 6

This purpose of this step is to identify pain symptoms that can be explained at least partially by nociceptive mechanisms. Unlike the widespread pain pattern associated with FMS, nociceptive pain will be more localized and explained by an identifiable source of nociception (21). Questioning the patient in detail about comorbid diseases that may cause nociceptive activation is the most rational way to follow this step. In accordance with clinical indicators of nociceptive pain (73), an in-depth patient interview regarding medical history and an evidence-based physical examination can help confirm a potential source of nociception. Since routine diagnostic procedures of musculoskeletal disorders often rely on radiographic examinations (74), imaging techniques (e.g., musculoskeletal ultrasonography, radiography, MRI, etc.) may be considered to identify a source of nociception that could be contributing to the patient's symptoms. However, imaging results (especially spinal imaging) should be interpreted with caution and ought not to be used as proof of nociception without additional supporting evidence. For instance, evidence of spinal degeneration (including bulges, protrusion, and loss of disc height) is present in high proportions of asymptomatic individuals, likely part of the normal aging process, and unassociated with pain (75). In addition, a recent meta-analysis determined that routine referrals for spinal and knee imaging by general practitioners found no clear pathological diagnoses in patients whose complaints persisted for more than 6 weeks; the researchers concluded that imaging "yield[ed] little to no benefit" in treatment outcomes (76). Thus, when evaluating for a possible nociceptive pain component in patients with FMS, spinal imaging should be interpreted by an experienced medical ex-

Table 2. *Typical hypersensitivity histories (unpleasant or painful activities) in FMS patients.*

✓ Clothing, belts, bras, jewelry, handbags
✓ Hugging or shaking hands
✓ Prolonged sitting
✓ Cold/warm showers
✓ Habitual physical activities

pert (e.g., a neurosurgeon, physiatrist, pain physician, physiotherapist, etc.) in conjunction with an in-depth patient interview and clinical physical examination.

When the criteria in Steps 6 are met and the pain symptoms are (partially) attributable to a nociceptive pain component, the clinician should proceed to Step 7 to examine the likelihood of a neuropathic pain component. Pain is expected to be classified as "probable mixed pain" (nociplastic and nociceptive pain) if the neuropathic pain component is excluded in Step 7.

Step 7

This step, intended to determine whether a neuropathic pain component is present, assesses whether individuals with FMS meet the NeuPSIG criteria (Fig. 1) for neuropathic pain.

First, the body is assessed for signs of a lesion or disease of the somatosensory nervous system, such as entrapment neuropathies, including carpal tunnel syndrome (57,58) and cervical or lumbar radiculopathy (77). Imaging and nerve conduction studies may help identify evidence of neuropathic pain. Although small fiber neuropathy has been identified in some individuals with FMS (13,15), its diagnosis remains challenging and debatable (78).

Second, neuropathic symptoms such as numbness, tingling, and burning, and a neuroanatomically plausible pain distribution must be present. The WPI and generalized pain chart used for pain localization in Step 2 may be insufficient for the assessment in this step. Pain drawings and questionnaires can be useful in the evaluation of neuroanatomical pain distributions and symptoms (79-81). The painDETECT questionnaire is potentially a good option when screening for neuropathic pain because this tool includes a standardized pain drawing and is available in a variety of different languages (82-84).

Finally, the individual's pain and other neurological symptoms should be supported by findings from a physical examination (81). Abnormal (hyposensitive or hypersensitive) responses to QST can support the presence of a neuropathic pain component.

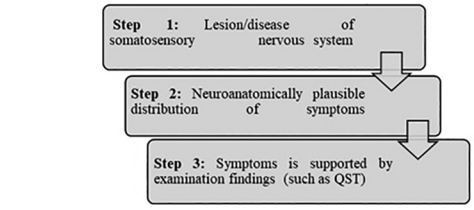

Fig. 1. *NeuPSIG criteria for neuropathic pain.*

If the criteria in Step 7 are met, then it can be determined that the pain symptoms are partially attributable to a neuropathic pain component, and pain can be classified as "probable mixed pain" (nociplastic and neuropathic pain) or (nociplastic, nociceptive, and neuropathic pain). In the absence of a nociceptive and neuropathic pain component, the classification is "probable nociplastic pain".

Fig. 2 outlines a clinical decision tree for validating the IASP clinical criteria for nociplastic pain and the proposed mixed pain phenotype in individuals with FMS.

Considering Pain Phenotypes in FMS

Although the ACR regularly publishes clinical guidelines on the diagnostic process of FMS, experts still report uncertainties about how to identify and treat this condition (85,86). In addition, a recent paper reported that many experts did not adhere to the ACR's diagnostic criteria and treatment advice (87). Assessing for nociplastic pain criteria in the first part of these recommendations can help confirm an FMS diagnosis, consistent with the 2016 criteria for diagnosing the condition (12). When an individual does not meet the criteria for nociplastic pain described in the first part (Steps 1-5), the clinicians should consider applying the recommended 2016 FMS diagnostic procedures (12) to confirm an FMS diagnosis.

In addition to the uncertainty and ambiguities involved in diagnosing FMS, attempting to apply treatment procedures not tailored to a patient's pain phenotype and personal characteristics can lead to failure and dissatisfaction in the management of the syndrome (88). Rather than taking a symptomatic or diagnosis-based management approach, it may be more rational to choose treatment strategies by classifying patients according to pain descriptors (89). For instance, if a nociceptive or neuropathic pain component is identified in a person with FMS and a medical cause for nociceptive or neuropathic pain can be identified and treated, additional treatment and management of the FMS symptoms is likely to be much more successful.

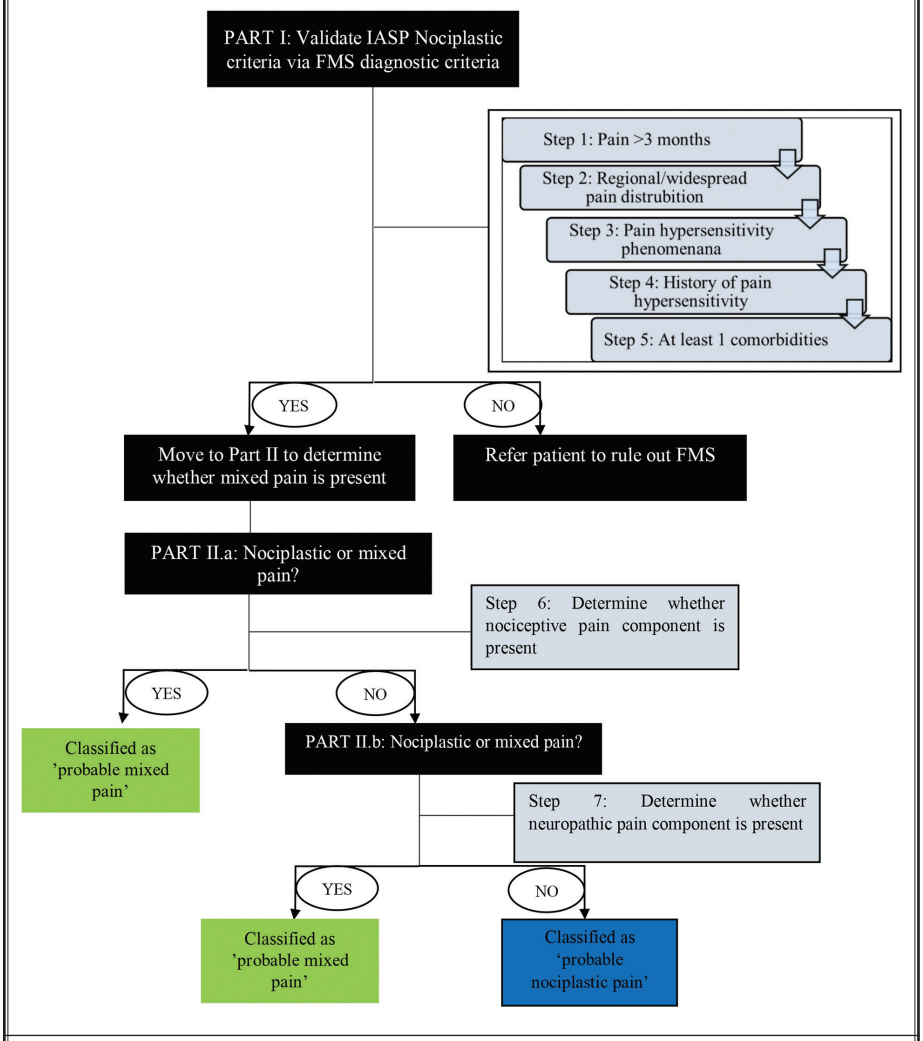

Fig. 2. *Clinical decision-making tree.*

Research Agenda

Further studies are needed to demonstrate the reliability and validity of the IASP's nociplastic and mixed pain criteria suggested in this novel approach for pain-phenotyping individuals with FMS. Clinical vignettes can be useful in serving this purpose (90). Clinical vignettes are brief scenarios describing the medical history and condition of actual cases, in which participants answer a series of open-ended or closed-ended questions (91). This technique allows multiple clinicians to assess individuals with FMS for nociplastic and mixed pain simultaneously, enabling an analysis of the intra- and interrater reliability and content validity of the IASP's clinical criteria.

Future studies might also evaluate the effectiveness of targeted treatment strategies, based on specific pain phenotypes determined with the IASP's clinical criteria in individuals with FMS. In this context, randomized controlled trials can be planned to evaluate outcomes such as pain, disease severity, quality of life, and health expenditures in treatment programs tailored to nociplastic and mixed pain phenotypes. The results of such studies may enable the incorporation of pain phenotype–specific treatment strategies in clinical guidelines for the management of FMS.

Conclusion

FMS-related pain is commonly classified as nociplastic (61). It is believed that the primary mechanism underlying nociplastic pain is augmented central nervous system sensory processing with altered pain modulation (92,93). However, it has also been emphasized that some cases of FMS may present with a mixed pain phenotype involving nociceptive and/or neuropathic pain components. The current recommendations systematically summarize the methods that allow the pain phenotypes of individuals with FMS to be classified into nociplastic or mixed categories, based on potential nociceptive and neuropathic pain components. Identifying mixed pain types, with nociceptive and/or neuropathic pain components, will lay the groundwork for the implementation of more nuanced and individualized multimodal treatment approaches to achieve better treatment outcomes for people with FMS.

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Appendix 1: *Fibromyalgia Syndrome (FMS) Phenotyping - Case Study 1. A written informed consent form was obtained from the patient.*

Gender

Female

Age

53

Occupation

Grocery worker

Clinical History

Pain first began in her right shoulder in 2020. The MRI findings showed a partial rotator cuff tear. Subsequently, she underwent medical treatments, including exercise and corticosteroid injection therapy, but her shoulder pain did not improve. A month later, she began to feel widespread pain and stiffness in her entire back and both legs and arms. In 2021, MRI findings identified an L4-L5 lumbal disc herniation with possible mild nerve root compression, and she was prescribed NSAIDs and physiotherapy sessions. Those treatments helped temporarily, but widespread pain returned, along with symptoms of sleeplessness and fatigue. Laboratory tests did not reveal any evidence of rheumatoid arthritis or collagen disease. She was diagnosed with FMS by a physiatrist in early 2023.

Pain Duration

3 years

Pain Intensity

9/10 (Numeric Pain Rating Scale).

The patient's pain areas at the writing of this paper are shown in detail in Figure A1.

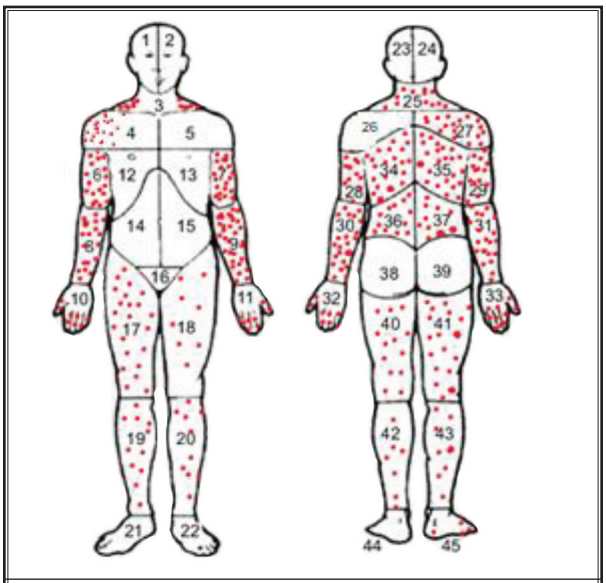

Figure A1. *Margolis Pain Diagram for patient 1.*

Clinical Assessment Findings

MRI findings:

In 2020: Partial Rotator cuff tear (right shoulder)

In 2021: Lumbal disc herniation with possible mild nerve root compression at L4-L5 level.

Msk Ultrasound findings:

In 2023: The thickness and calcification within the supraspinatus tendon

Physical Examination combined with MRI Findings

Painful arc was present at midrange of abduction on the right shoulder; Neer test was positive on the right side; tenderness was identified over the right Supraspinatus tendon area

* Quantitative Sensory Test: Positive static mechanical allodynia.
* Revised Fibromyalgia Impact Questionnaire (0-100): 62.16
* Quality of Life Scale(SF-12): Physical composite scores (24-56): 26.12 / mental composite scores (19-60): 48.32.
* Widespread pain index (WPI) score (0-19): 14
* Symptom severity scale (SSS) score (0-12): 7

Part 1: Confirming Nociplastic Pain

Step 1:

The patient reported persistent pain for 3 years. Hence the first criterion was met.

Step 2:

Pain was indicated in the following locations on the Margolis Pain Diagram (Figure A1): right arm (6,8,29,31), left arm (7,9,28,30), neck (3,25), back (34,35), right shoulder (27), right and left hand (10,11,32,33), lower back (36,37), right leg (17,19,41,43), left leg (18,20,40,42), right foot (45). The WPI score indicated widespread pain. Hence, the second criterion for the regional distribution of pain was fulfilled.

Step 3:

Signs of static mechanical allodynia and hypersensitivity were detected via quantitative sensory testing at the most painful body regions. Therefore, this criterion was met. Since all the criteria in the first three steps were met, the patient was characterized as "probable nociplastic pain." Next, we proceeded to step 4 and 5 to confirm "probable nociplastic pain."

Step 4:

During the interview, she reported hypersensitivity to mechanical pressure while sitting on a chair for extended periods of time. She also indicated that walking and housework led to increased pain (hypersensitivity to movement). Therefore, the criterion for pain hypersensitivity was met.

Step 5:

In this step, the presence of other comorbid symptoms, in addition to pain, were assessed. The patient stated that she experienced sleeplessness and fatigue with frequent night awakenings and her high WPI score indicated these and additional comorbid symptoms. Since these criteria were met, it was confirmed that the patient had "probable nociplastic pain." The remaining two steps were performed to differentiate between nociplastic pain and a mixed pain type.

Part 2: Assessing the Presence of Mixed Pain

Step 6:

The patient's clinical history identified a partial rotator cuff injury to her right shoulder three years previously. A current physical examination found localized tenderness in the right supraspinatus tendon, suggesting that the rotator cuff had not healed properly. Painful arc was present at the midrange of abduction on the right shoulder; Neer test was positive on the right side. Following the positive physical examination findings, an ultrasound scan of the right shoulder indicated calcification within the supraspinatus tendon. Because a nociceptive pain source was identified, the criterion in Step 6 was met and the pain symptoms were (partly) attributable to a nociceptive pain component. The clinicians then proceeded to step 7 to examine the likelihood of a neuropathic pain component.

Step 7:

The patient was diagnosed with "lumbar disc herniation with possible nerve root compression" in 2021. Hence, the first step of NeuPSIG criteria for neuropathic pain was met. Although MRI findings supported the nerve root compression at L4-L5 level, pain distribution in the lower limbs was not consistent with her diagnosis. Pain was reported in both legs, without any paraesthesia or hypoesthesia during sensory examination, so the pattern was not determined to be neuroanatomically plausible for a nerve root compression at L4-L5. Therefore, a neuropathic pain component was excluded for this case.

Altogether, case 1 can be classified as having "mixed pain (nociplastic and nociceptive pain)".

Appendix 2: *Fibromyalgia Syndrome (FMS) Phenotyping - Case Study 2. A written informed consent form was obtained from the patient.*

Gender

Female

Age

53

Occupation

Recycling Worker

Clinical History

Sharp left leg pain began in 2015. Following a physical examination and MRI, she was diagnosed with a lumbar disc herniation with possible nerve root compression and prescribed medications (NSAIDS and muscle relaxers) and a home exercise program. The pain initially subsided but then returned 3 months later. Over time, the leg and back pain got worse, spreading into the neck, upper back, and left scapular region. A second MRI in early 2021 revealed that the nerve root compression had not healed and degenerative changes had gotten worse. She began to report diffuse tenderness to relatively light touch around this time. Additional laboratory tests and imaging did not reveal any evidence of disease except some degenerative changes in the lumbar spine. She was diagnosed with FMS in lately 2021.

Pain Duration

8 years

Pain Intensity

8/10 (Numeric Pain Rating Scale).

The patient's current pain areas are shown in detail in Figure A2.

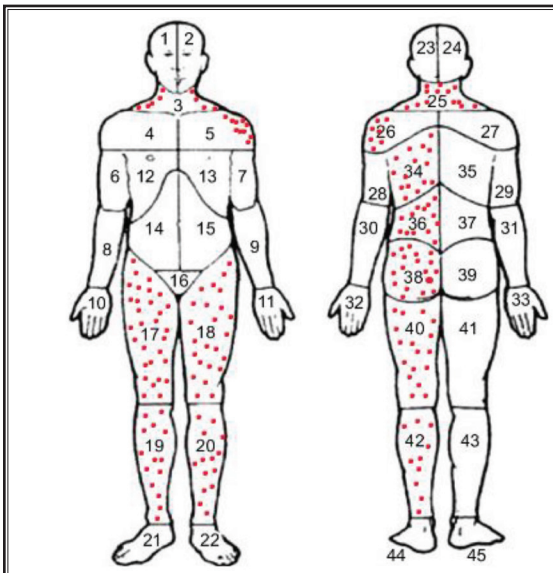

Figure A2. *Margolis Pain Diagram for patient 2.*

Clinical Assessment Findings

***MRI findings**

In 2015: A lumbal disc herniation with possible mild nerve root compression at the L5-S1 level.

In 2021: Intense zygapophyseal edematous changes in the lumbar spine and a disc herniation with possible moderate nerve root compression at L5-S1 level.

* Physical Examination combined with the MRI Findings: Pain with palpation in both the lower lumbar segments (during PA glides) and along the left sciatic nerve pathway; pain in prone and restricted body positions; pain with specific movements (including lumbar extension); positive straight leg raise and Slump tests on the left side; normal reflexes and myotomes.
* Quantitative Sensation Test: Positive static and dynamic mechanical allodynia were identified in the lower and upper back, and neuroanatomically plausible paraesthesia was identified in the L5-S1 dermatomes.
* Revised Fibromyalgia Impact Questionnaire (0-100): 62.66
* Quality of Life Scale (SF-12): Physical composite scores (24-56): 32.54/ mental composite scores (19-60): 45.69
* Widespread pain index (WPI) score (0-19): 8
* Symptom severity scale (SSS) score (0-12):9

Part 1: Confirming Nociplastic Pain

Step 1:

The patient reported persistent pain for 8 years. Hence the first criterion was met.

Step 2:

Pain was indicated in the following locations on the Margolis Pain Diagram (Figure A2): neck region (3,25), left shoulder regions (5,26), left scapula region (34), left lumbar region (36), left hip region (38), left hind leg regions (18,20,40,42), right front leg regions are (17,19). The WPI score indicated widespread pain. Hence, the second criterion for regional distribution was fulfilled.

Step 3:

Both static and dynamic mechanical allodynia were found around the lower and upper back. Therefore, this criterion was met. At this stage of the clinical decision-making process, the patient can be characterized as "probable nociplastic pain," since all the criteria in the first three steps were met. Next, we proceeded towards step 4 and 5 to confirm "possible nociplastic pain."

Step 4:

She reported hypersensitivity to heat/cold and touch. Extremely hot and cold weather and hot showers aggravated her symptoms. Even relatively light contact with people (such as hugging) caused pain. Therefore, the hypersensitivity criterion is met.

Step 5:

In this step, the presence of comorbidity was assessed. As indicated by the SSS, she reported sleep disturbance, memory loss, and fatigue, especially in summer and winter. In this case, the criterion for the presence of symptom comorbidities was met. At this stage, the patient was classified as having "probable nociplastic pain" type. The remaining two steps proceeded to differentiate between nociplastic pain and mixed pain types.

Part 2: Assessing the Presence of Mixed Pain

Step 6:

Reviewing the patient's clinical history, it was seen that an initial diagnosis of lumbar disc herniation with nerve root compression was made. Both previous and current MRI findings indicated intensive zygapophyseal edematous changes in the lumbar spine with L5-S1 nerve root compression that could have been sources of nociception around the lower back region. In addition, physical examination findings (painful palpation of lower lumbar segments during PA glides and restricted end-of movement in lumbar extension) were consistent with the MRI findings. The criterion in Steps 6 was met and the pain symptoms were (partly) attributable to the nociceptive pain component. The clinicians proceeded to step 7 to examine the likelihood of a neuropathic pain component.

Step 7:

Based on the results of her MRI and physical exam in step 6, the first step of NeuPSIG criteria for neuropathic pain was met. The Margolis Pain Diagram (Figure A2) indicated that her symptoms followed a neuroanatomically appropriate distribution. Therefore, the second step of NeuPSIG criteria for neuropathic pain was met. During the sensory examination, the patient reported paraesthesia, including numbness, tingling and "pins and needles," throughout the L5-S1 dermatoma. Hence all criteria in Steps 7 were met and the pain symptoms were (partly) attributable to a neuropathic pain component as well.

Altogether, case 2 can be classified as having "mixed pain (nociplastic, nociceptive and neuropathic pain)".

Appendix 3. *Fibromyalgia Syndrome (FMS) Phenotyping - Case Study 3. A written informed consent form was obtained from the patient.*

Gender

Female

Age

42

Occupation

Nursery Teacher

Clinical History

After her father's death in 2021, the patient was diagnosed with major depressive disorder. She reported sadness, frequent crying, low motivation, difficulty getting out of bed in the morning, generalized pain, and fatigue, irrespective of rest. Over time, other symptoms developed, including severe stomachache, lower back pain, restless legs, and morning stiffness. Her symptoms were generally worse when not working, including weekends and summer breaks. She underwent extensive medical testing, including blood work, colonoscopy, MRI, and CT, but no evidence of pathology was revealed. She was diagnosed with FMS in late 2022.

Pain Duration

2 years

Pain Intensity

7/10 (Numeric Pain Rating Scale).

The patient's current pain areas are shown in detail in Figure A3.

Clinical Assessment Findings

* Quantitative Sensory Test: Positive static mechanical allodynia.
* Revised Fibromyalgia Impact Questionnaire (0-100): 67.37
* Quality of Life Scale(SF-12): Physical composite scores (24-56): 42.53 / mental composite scores (19-60): 36.28.
* Widespread pain index (WPI) score (0-19): 8
* Symptom severity scale (SSS) score (0-12): 9

Part 1: Confirming Nociplastic Pain

Step 1:

The patient reported persistent widespread pain for 2 years. Hence the first criterion was met.

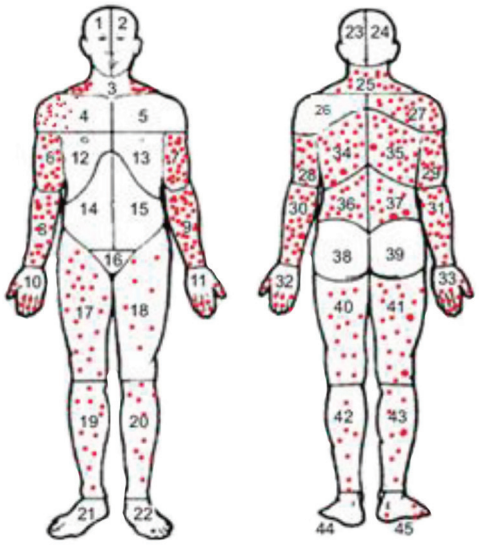

Figure A3. *Margolis Pain Diagram for patient 3.*

Step 2:

Pain was indicated in the following locations on the Margolis Pain Diagram (Figure A3): neck (3,25), upper back (34,35), lower back (36,37), belly (14,15,16), left shoulder (26), right leg (17,19,41,43), left leg (18,20,40,42)), right foot (22,45) and left foot (21,44). The WPI score indicated a widespread pain pattern. Hence, the second criterion for regional distribution was fulfilled.

Step 3:

Static mechanical allodynia was confirmed in her upper and lower back (her most painful regions). Therefore, the hypersensitivity criterion was met. At this stage of the clinical decision-making process, the patient can be characterized as having "possible nociplastic pain." Next, we proceeded toward steps 4 and 5 to confirm "probable nociplastic pain."

Step 4:

She reported that prolonged sitting at work was unpleasant (hypersensitivity to pressure) and any physical activity aggravated her symptoms (hypersensitivity to movement). Therefore, the criterion for pain hypersensitivity was met.

Step 5:

In this step, the presence of comorbid symptoms, in addition to pain, was assessed. The patient reported

sleeplessness, fatigue, memory loss, and sometimes concentration problems. It was noted that these are common symptoms of both FMS and major depressive disorder and that these disorders are frequently coexisting. She also suffered from restless legs, morning stiffness, and constipation most weeks, which was associated with increased stomach pain. Since this criterion was met, it was confirmed that the patient had "probable nociplastic pain." Next, the remaining two steps differentiated between nociplastic pain and mixed pain.

Step 6:

Because no evidence of pathology was revealed from extensive medical testing, a nociceptive pain component was excluded. The clinicians then proceeded to step 7 to examine the likelihood of the neuropathic pain component.

Step 7:

Previous imaging and physical examination results found no history of neurological lesions or diseases. In addition, she did not report a plausible neuropathic pain pattern. Therefore, a neuropathic pain component was excluded.

Altogether, case 3 can be classified as "predominantly nociplastic pain."