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# Unmet Needs in Spondyloarthritis: Understanding and Managing Chronic Pain

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***ABSTRACT.*** Among patients with axial spondyloarthritis (axSpA), persistent pain remains a critical unmet need. In this review, we discuss the prevalence of chronic pain and fibromyalgia in patients with axSpA and examine the existing knowledge on the pathophysiology of chronic pain in SpA, osteoarthritis, and rheumatoid arthritis. Finally, we discuss the specific unmet needs that must be addressed to improve long-term outcomes in axSpA, specifically those that will improve chronic pain in this patient population.

*Key Indexing Terms:* ankylosing spondylitis, pain, spondyloarthritis

## Introduction

Chronic pain is common among patients with axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) and contributes to substantial decrements in quality of life and physical function. Approximately 10% to 20% of patients with axSpA and/or PsA meet the criteria for fibromyalgia (FM), and opiates are still commonly used to treat chronic pain in axSpA (36%) and PsA (24%).[1-3] Separating nociplastic pain from axSpA disease activity is particularly challenging from history and physical examination alone. Although imaging can be helpful, there are shortcomings, including feasibility and cost. Insufficient pain control results in miserable patients, poor performance of outcome measures and therapies, and therapy cycling.

Strategies for managing and potentially preventing chronic pain in SpA remain a critical unmet need. Lessons from research investigating pathophysiology and management strategies for chronic pain in other conditions may provide insights that can be applied to SpA. At the Unmet Needs in Spondyloarthritis conference, held at the National Institutes of Health (NIH) Bethesda campus in September 2023, Drs. Yvonne Lee and Anne-Marie Malfait provided their perspectives from clinical rheumatoid arthritis (RA) research and basic osteoarthritis (OA) research, respectively. In this manuscript, we review the lectures provided and the unmet needs identified.

## Pathophysiology of pain and terminology

According to the International Association for the Study of Pain (IASP), pain is "an unpleasant sensory and emotional experience with, or resembling that associated with, actual or potential tissue damage."[4] The IASP categorizes pain into 3 broad, mechanistic categories: (1) nociceptive pain, (2) neuropathic pain, and (3) nociplastic pain. Nociceptive pain is pain resulting from activation of nociceptors during acute or threatened damage to nonneural tissue. Neuropathic pain is pain resulting from injury to the nervous system. Nociplastic pain is pain resulting from heightened pain sensitivity in the absence of obvious damage to nonneural or neural tissues.[5] Within the category of nociplastic pain, there are 2 overarching pathways: (1) bottom-up processes that reflect ascending pathways, which primarily facilitate pain; and (2) top-down processes that reflect descending pathways, which primarily inhibit pain. For definitions of various neurobiology terms, refer to Box 1.

*Pain.* Physiological pain is a protective mechanism that involves the detection of stimuli that have a potentially damaging effect on an organism. Pain-producing noxious stimuli are commonly mechanical, chemical, or thermal in origin and activate the peripheral nerve terminals of specialized sensory neurons that innervate tissues. These pain-sensing afferents are called nociceptors, and depolarization of their nerve terminals initiates the firing of action potentials that invade the dorsal root ganglia (DRG), where the cell bodies reside. Neurotransmitters such as glutamate, released from primary nociceptor terminals in the dorsal horn of the spinal cord, activate second-order neurons, which transmit the information to higher centers in the central

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*Box 1.* Glossary of neurobiology terms.[4]

**Allodynia:** A form of sensitization to pain in which a stimulus that does not normally provoke pain becomes painful.

**Central sensitization:** An increased responsiveness of nociceptors in the central nervous system to either normal or subthreshold afferent input resulting in hypersensitivity to stimuli.[4]

**Dorsal root ganglion:** A hub of neurons in the dorsal root of a spinal nerve. The cell bodies of sensory neurons are located here (part of the peripheral nervous system).

**Hyperalgesia:** A form of sensitization to pain in which the response to a painful stimulus is exaggerated.

**Nociceptor:** Pain-sensing afferent neurons. A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of sensing noxious stimuli such as chemicals, force, and temperature.

**Peripheral sensitization:** Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields.

nervous system (CNS). Nociceptive signals are ultimately perceived as pain in the brain.[6]

*Sensitization.* The normal processing of pain is substantively altered in response to pathology. In many instances, such as in inflammation or tissue injury, pain pathways become sensitized so that stimuli that were previously innocuous now trigger painful responses. This clinically manifests as allodynia and hyperalgesia, as assessed by quantitative sensory testing (QST).[7,8] Nociceptors express receptors for inflammatory mediators, including G-protein coupled receptors; tropomyosin receptor kinase A (TrkA), which is the high affinity receptor for nerve growth factor (NGF); cytokine receptors; and Toll-like receptors. Hence, intraarticular injection of NGF, cytokines (tumor necrosis factor [TNF], interleukin [IL]-6, IL-1β, IL-17), chemokines (chemokine ligand 2 [CCL2]), or aggrecan fragments produce sensitization to mechanical stimuli in healthy rodents.[9] Different inflammatory mediators might drive pain in different conditions. For example, antibodies neutralizing traditional proinflammatory cytokines, including IL-1 and TNF, have had pronounced effect on pain in inflammatory arthritides, but not in OA.[10] Antibodies that block IL-17A relieve pain in people with SpA and PsA but do not show consistent analgesic benefit in people with RA.[11]

*Structural neuroplasticity.* Joints are densely innervated with nociceptors, with unmyelinated free nerve endings present in the joint capsule, synovium, subchondral bone, fat pads, and insertion sites of tendons and ligaments. In the course of arthritis, the normal nociceptive innervation of the joints is profoundly altered. In OA, for example, osteochondral channels breaching the tidemark between the subchondral bone and the articular cartilage contain blood vessels and sensory neurons.[12] In human OA knees, the presence of calcitonin gene-related peptide (CGRP)-immunoreactive nociceptors in these channels is associated with pain, as in a rat OA model.[13] This nerve growth into joint structures exposed to high mechanical loads may render them sensitive to mechanical stimulation, resulting in pain. Further, in human OA and in rodent models, sprouting of nociceptors has been described in the synovium, the meniscus, and in osteophytes.[14,15] Ongoing work is trying to identify mediators that regulate this neuronal growth in arthritis, since they may provide novel targets for joint pain.[16]

*Neuroimmune contributions to pain.* Neuroinflammation in arthritis is an emerging field, and it is becoming increasingly clear that joint inflammation and joint damage have a profound effect on the nervous system. In an arthritic joint, innervating nociceptors interact with tissue resident cells and infiltrating immune cells, and this crosstalk is a critical driver and modifier of chronic pain. Immune cells can release mediators that either directly activate or sensitize nociceptors, and immune cells can be targeted for achieving analgesia. For example, macrophage depletion can reduce pain in experimental models of arthritis.[17] Further, autoantibodies can form immune complexes with type II collagen in arthritic mice, and these complexes act on Fcγ-receptor I expressed by neurons, resulting in pain.[18] Neuroimmune interactions can also occur within the nervous system. Macrophage infiltration of DRGs and activation of dorsal horn microglial cells (the resident macrophages of the CNS) are important regulators of pain in chronic diseases, as has been described in experimental models of OA and RA.[19] It can be expected that unraveling the precise nature of these cellular interactions in the joint and at different levels of the neuraxis may result in targeted, disease-specific therapies.

## Mechanistic studies of pain in RA and OA

Mechanistic studies into joint pain have focused largely on OA and RA.[8] It is unknown at this time how mechanisms underlying pain may overlap or differ between different types of rheumatic diseases. For example, OA, historically considered a mechanically driven degenerative disease with low-level inflammation, and RA, an inflammatory autoimmune disease that also affects young people, are driven by very different peripheral triggers in the joint and/or systemically, and it is unknown how these triggers may differentially engage pain pathways. All these issues can now be tackled by a variety of new techniques that bring

together the disciplines of neuroscience and arthritis research—an approach that has been sorely lacking. This interdisciplinary approach has started to reveal important facts about the molecular characteristics of joint-innervating nociceptors and their central connections. Such techniques include (1) the development of sophisticated animal models of arthritic/musculoskeletal (MSK) disease with clear translational applicability; (2) the development of clinically relevant behavioral tests for MSK pain; (3) single-cell transcriptomics and related techniques designed to elucidate the molecular characteristics of populations of joint nociceptors; (4) genetic techniques that allow the identification of populations of neurons through the expression of fluorescent markers, allowing their anatomical characterization assisted by clearing methods; (5) in vivo calcium imaging and related methods for assessing the physiological functioning of relevant pain pathways in MSK diseases; and (6) increasingly sophisticated imaging, including clearing-enabled light sheet microscopy as a novel method for 3-D mapping of sensory innervation.[20]

**Management of noninflammatory pain in patients with RA**

Pain often persists among patients with rheumatic diseases, even when it appears that they have little or no peripheral or systemic inflammation. Research among patients with RA found that 12% of patients who are in long-term Disease Activity Score in 28 joints (DAS28) remission reported clinically important pain at levels ≥ 4/10.[21] Whereas sleep problems, fatigue, and disability were strongly associated with pain intensity, measures of inflammation and joint damage were not significantly associated with pain intensity.

In these situations, there is significant heterogeneity in how rheumatologists manage, or do not manage, pain. Rheumatologists are generally not trained in managing chronic pain. In 2010, the American College of Rheumatology (ACR) convened the Pain Management Task Force.[22] The task force conducted surveys and in-person and telephone meetings to understand how rheumatologists view their role in pain management. They discovered that most rheumatologists were not taught how to assess or treat pain during training. As such, most approached pain by focusing on treatments to decrease joint inflammation, as opposed to directly assessing and treating pain itself. Opioid use rates of patients of healthcare providers involved in the CorEvitas RA registry ranged from 0% to 70%.[23] Of note, recent clinical trial data also indicate that opioids are not effective for managing MSK pain.[24]

**Assessments to phenotype pain**

To comprehensively phenotype pain, it is necessary to include a broad array of assessments. Since pain is multifactorial and modulated by individual experiences and characteristics, it is critical that assessments include validated patient-reported outcomes of pain and pain-related concepts. To facilitate data sharing and enable combining and comparing data from different studies, the NIH Helping to End Addiction Long-term (HEAL) Initiative supports a Common Data Elements Program, which includes 10 core pain domains, including pain intensity, pain interference, physical functioning, sleep, pain catastrophizing, depression, anxiety, global satisfaction with treatment, substance use, and quality of life. Recommended questionnaires for each of these domains are provided for adult acute pain, adult chronic pain, and pediatric acute and chronic pain.[25]

Building upon this foundation, clinical studies examining mechanisms of pain should also consider including QSTs such as pressure algometry to assess pain sensitivity at articular and nonarticular sites. In addition, dynamic QST paradigms, such as temporal summation and conditioned pain modulation, provide information on the ascending pain facilitatory pathways and descending inhibitory pain pathways, respectively. Details regarding structural and functional brain pathways can also be obtained through neuroimaging.

**Key questions and unmet needs in RA**

One of the key areas of unmet need involves understanding factors that can identify patients who are most likely to respond to specific treatments. As noted earlier, most rheumatologists focus on treating pain by treating inflammation. Thus, the first question is, how can patients who are unlikely to respond to disease-modifying antirheumatic drugs (DMARDs) be identified? Our research has shown that QST assessments predict treatment response to DMARDs in patients with RA. Specifically, baseline abnormalities in conditioned pain modulation, indicative of impaired descending inhibition, were significantly associated with lower odds of achieving a good response to DMARDs.[26] In addition, abnormalities in combinations of pathways (eg, both temporal summation, indicating enhanced pain facilitation, and conditioned pain modulation, indicating inefficient pain inhibition) were associated with the lowest rate of DMARD response (22% vs 53% among those without abnormalities in either temporal summation or conditioned pain modulation). Using a data-driven approach, we found that the association between QST measures and RA disease activity after treatment was moderated by the level of disease activity prior to initiation of the new DMARD.[27] Among patients with baseline low/moderate disease activity, low knee pressure pain thresholds (a measure of peripheral sensitization) were most predictive of poor DMARD response, whereas among patients with high baseline disease activity, low conditioned pain modulation (a measure of inefficient pain inhibition) was most predictive of poor DMARD response.

The second question is, if DMARDs are unlikely to improve pain, what specific treatments are most likely to improve pain in an individual patient? Small studies in other chronic pain conditions suggest that QST measures of pain facilitation and pain inhibition can predict response to medications, such as duloxetine and pregabalin, which target specific CNS pathways.[28,29] Few data exist in patients with systemic inflammatory arthritis. Our research group conducted a randomized blinded crossover trial of milnacipran, a serotonin-norepinephrine reuptake inhibitor, for the treatment of pain in patients with RA.[30] Among the total study population (participants with RA and widespread pain), the change in pain intensity during treatment with milnacipran did not differ from the change in

pain intensity during treatment with placebo. However, among participants with well-controlled peripheral inflammation (≤ 1 swollen joint), treatment with milnacipran was associated with significant improvements in pain intensity compared to placebo. These results underscore the importance of carefully phenotyping patients and considering different pain phenotypes (eg, inflammatory vs noninflammatory pain) when making treatment decisions.

Another key area of unmet need is identifying factors that lead to the development of chronic pain unresponsive to DMARD treatment. Chronic pain, once established, is difficult to treat. Understanding factors that predict the development of chronic pain would be the first step toward developing interventions to prevent chronic pain. Several lines of evidence suggest that systemic inflammatory arthritis predisposes to the development of FM, the prototypical nociplastic pain condition. First, multiple studies have shown that patients with systemic inflammatory arthritis have a higher prevalence of FM than the general population.[31] In a study using data from the Canadian Early Arthritis Cohort (CATCH), we determined that the incidence of developing FM was highest during the first year after inflammatory arthritis diagnosis.[32] Subsequent analyses in the same cohort showed that poor sleep, high pain intensity, and disability were significantly associated with pain 1 year later.[33] The association between poor sleep and subsequent pain intensity was replicated in the Central Pain in Rheumatoid Arthritis (CPIRA) cohort, which included patients with established disease starting a new DMARD for treatment of active RA.[34] Of note, the relationship between poor sleep and subsequent pain intensity was partially mediated by QST assessments of pain sensitization, indicating that poor sleep may affect pain intensity by altering neurobiological pathways associated with pain sensitivity. However, QST assessments of pain sensitization accounted for only 10% to 19% of the effect, suggesting that poor sleep also works through other pathways not yet measured.

In addition to poor sleep, others have postulated that high systemic inflammation may prime individuals for developing chronic nociplastic pain. In a cross-sectional, neuroimaging study of patients with RA, stratified by presence of concomitant FM, the erythrocyte sedimentation rate (ESR) was significantly associated with functional connectivity between the left inferior parietal lobule and medial prefrontal cortex and between the left inferior parietal lobule and anterior cingulate cortex among patients with RA and concomitant FM, but not among those with RA only.[35] The left inferior parietal lobule and medial prefrontal cortex are part of the default mode network, and the anterior cingulate cortex is part of the salience network. Abnormalities in connectivity between these networks have been observed in other chronic pain conditions.[36-38] The association between ESR and abnormalities in connectivity between these networks supports the hypothesis that differential brain responses to systemic inflammation may influence whether patients with RA transition from acute episodes of inflammatory pain to a chronic nociplastic pain state. Longitudinal studies are needed to provide further evidence for this hypothesis.

**Pain in SpA**

Targeted immunomodulatory therapies, such as biologics targeting TNF and the IL-23/IL-17 axis, have transformed the treatment landscape for SpA. However, many people continue to experience distressing chronic pain.[39] The discordance between inflammation and pain is a major hindrance in the development of efficacious and safe analgesic therapies and reflects our incomplete understanding of the biology of pain in inflammatory arthritis.

As discussed in the section on RA, many patients with RA exhibit characteristics consistent with aberrant pain processing. Fewer studies of pain in patients with SpA have been published. These studies support a relatively high prevalence (11-21%) of FM among patients with SpA.[2,40,41] Studies examining pain mechanisms using QST, however, have been conflicting, with some studies showing similar or higher pain thresholds in patients with SpA compared to healthy controls.[42-44] Of note, most of these studies were small and were performed before widespread use of biologic DMARDs for treatment of SpA. In addition, results may have been confounded by other differences in the groups (eg, sex).

Previous neuroimaging studies have reported structural and functional changes in the brains of patients with SpA compared to those of healthy controls.[45-47] For example, a neuroimaging study of 20 patients with SpA showed that functional connectivity between the default mode and salience networks (brain regions altered in patients with chronic pain) was significantly correlated with the Bath Ankylosing Spondylitis Disease Activity Index.[48] A subsequent study showed that moment-to-moment brain activity in the default mode and salience networks was altered in 56 patients with SpA compared to 62 healthy controls.[49] These alterations were associated with average pain intensity and the strengths of these associations differed between men and women with SpA. Other neuroimaging studies have also reported differences in functional connectivity between men and women with SpA, which may be moderated by chronic pain.[50,51]

Although there is frequently a disconnect between inflammation and patient-reported pain in patients with long-standing SpA, uncontrolled inflammation during the early stages of SpA may be associated with the development of nociplastic pain. A large study of patients with axSpA in the British Society for Rheumatology Biologics Register reported that high disease activity and widespread pain predicted the development of FM, whereas low disease activity, absence of widespread pain, and starting a TNF inhibitor predicted resolution of FM.[52] These results are intriguing because they suggest that early, aggressive treatment may prevent the development of chronic, treatment-recalcitrant nociplastic pain.

Overall, however, there remains a lack of in-depth clinical and translational studies exploring mechanisms of pain in subjects with SpA. There is also no information on pain-related behaviors and concomitant changes in sensory neurons in preclinical models of SpA. Unraveling these mechanisms will require studies in relevant experimental models, with a comprehensive description of neuronal pathways and nociceptor

innervation in the affected joints, both in animal models and in human tissues. It can be expected that recently developed omics approaches, such as spatial transcriptomics, and sophisticated bioinformatics analyses will lead to detailed mapping of the cellular environment in joint tissues of different forms of arthritis. These approaches will likely enable identification of key elements in the communication process between neurons and the joint environment, thus aiding the identification of new targets for pain.

### Unmet needs in the pathophysiology and management of pain in SpA

Increasingly, research in sophisticated animal models and in human subjects is revealing disease-specific pathways underlying pain associated with rheumatic diseases. In the course of chronic disease, the nervous system undergoes tremendous functional, molecular, and anatomical neuroplasticity in a disease-specific, time-dependent, and sex-dependent manner. Cellular crosstalk between neurons and joint resident cells/immune cells modify pain pathways at all stages of disease, as does neuroimmune crosstalk in the nervous system. Although this complexity offers challenges that will require in-depth and sophisticated approaches to unravel (Box 2), it also offers tremendous opportunities for targeted interventions and the development of novel therapies. The field of pain research in SpA is in its infancy, but the availability of animal models, strong clinical research, and increasingly advanced techniques to interrogate the pathways involved will enable rapid progress in the field.

### Conclusion

The accurate assessment and management of chronic pain in patients with systemic inflammatory arthritis is an area of significant unmet need. Critical knowledge gaps exist in identifying patients whose pain will not resolve with appropriate immunomodulatory therapies; determining which patients are most likely to respond to targeted pharmacologic interventions for pain; understanding the specific mechanisms underlying nonpharmacologic treatments for pain, particularly those directed at improving sleep; and identifying the underlying pathways linking acute peripheral inflammation to CNS changes associated with chronic pain.

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*Box 2.* Unmet needs and unanswered questions in axSpA.[4]

- Understand which mechanisms of pain are at play in SpA and how to distinguish among them.
- Examine the pathophysiology of neuroplasticity in experimental models and in the joints of patients with SpA.
- Identify patients who have fibromyalgia only vs axSpA only, vs the overlap of both conditions.
- Develop study designs and methods for interpreting outcomes in those studies that account for a large proportion of our patients having centralized pain.
- Develop an approach for assessing and treating pain in our patients with axSpA.
- Test nonpharmacologic management options in SpA and understand their role in a comprehensive management plan.
- Understand the effect of social determinants of health on chronic pain and the implications for management.

axSpA: axial SpA; SpA: spondyloarthritis.

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