Pain management in rheumatology research, training, and practice

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ABSTRACT

The Pain Management Task Force of the American College of Rheumatology published a report in 2010 highlighting pain management as a fundamental aspect of clinical practice, training and research. In the interim, the consideration of pain as a focus of attention of rheumatologists and rheumatology health professionals has become even more challenging than in 2010 because of the epidemic of opiate addiction and overdose death. The characterisation of categories of pain by mechanism (e.g., inflammation, joint degeneration, abnormalities of central pain processing) can help guide treatment. However, such categorisation can overlook the overlap of these processes and their interaction to create mixed pain states. Further complicating the assessment of pain, outcome measures in rheumatic disease often assess the degree of pain indirectly while concentrating on the quantification of inflammation. Non-inflammatory pain often persists despite treatment, highlighting the need for alternative analgesic therapies. Recommended therapies include acetaminophen, nonsteroidal anti-inflammatory drugs, and stimulators of the pain inhibitory pathway. Each of these non-opioid therapies has incomplete efficacy and potential toxicities that can limit their utility. Non-pharmacologic therapies can show efficacy that rivals or surpasses pharmacologic therapies in the control of pain and improving function in a variety of rheumatic disorders including chronic low back pain and fibromyalgia. A limitation of the use of these therapies is inadequate training and appreciation of their benefits. Furthermore, the supply of trained practitioners to provide non-pharmacological care and support patient efforts for self-management is often limited. Together, these considerations suggest the importance of a renewed effort to implement task force recommendations.

Introduction

In 2010, the Pain Management Task Force of the American College of Rheumatology (ACR) reported on their deliberations concerning pain as a critical consideration in the practice of rheumatologists and rheumatology health professionals (1). The Executive Committee of the ACR established the task force to increase the understanding of a rheumatologist's role in pain management and the place of pain in rheumatology research, training, and clinical practice agenda. The report contained recommendations to be considered by the ACR and the Association of Rheumatology Health Professionals (ARHP). (Table I) Since 2010, the Institute of Medicine published their report, *"Relieving Pain in America,"* which emphasised the need to tailor pain care to unique needs of the individual patient; the report also stressed the importance of inter-disciplinary care (2). Yet, in the last seven years, the recommendations of ACR Pain Management Task Force have had only limited implementation as has been true with recommendations of other organisations such as the Institute of Medicine. With the 2010 Task Force report in mind, this article is an update of the current status of the place of pain as a concern of the subspecialty of rheumatology.

Research and training aspects of pain management in rheumatic diseases

While the centrality of pain in rheumatic and musculoskeletal disease should make it a topic of overriding importance in the intellectual framework of rheumatology, research and training on pain are nevertheless often surrounded by uncertainty, ambiguity and even controversy. Furthermore, the role of the rheumatologist in pain management has become more complicated and problematic because of the national

Table I. Recommendations listed in the 2010 Pain Management Task Force Report.

1.	Treatment protocols for evidence based interventions
2.	Personalised medicine to identify specific polymorphisms that target therapeutic choices
3.	ACR therapeutic index for analgesics – overall effectiveness
4.	Clinical trial study design to allow different end points with adaptive design
5.	PROMIS (Patient reported outcome) development
6.	Continuation of the Pain Task Force
7.	Annual meeting educational offerings on pain
8.	Interrelationship with outside organisations interested in pain management (VA, NIH)
9.	Pain as part of the rheumatology trainee curriculum
10.	Patient educational materials

Table II. Sources of Pain in Rheumatic Disease*.

Mechanisms		
Inflammation	Damage	Pain processing and perception#
Rheumatoid arthritis	Osteoarthritis	Fibromyalgia
Psoriatic arthritis	Rheumatoid arthritis	TMJ disorder
Spondyloarthritis	Psoriatic arthritis	Rheumatoid arthritis
Osteoarthritis		Osteoarthritis Spondyloarthritis SLE

*The table presents a categorisation of clinical conditions in terms of mechanisms of pain that likely contribute to patient symptomatology and have been investigated in clinical studies. These conditions are listed as examples to emphasise that pain mechanisms are diverse and may interact in the individual patient.
#Includes peripheral and central sensitisation and related issues considered under the terminology of fibromyalgia. Also includes genetic polymorphisms related to neurophysiological pathways for pain.

concern about the frightening epidemic of opiate addiction and death. Specialties caring for patients with painful conditions therefore face special challenges as they establish research priorities and prepare their workforce to balance the personal needs of patients with the societal imperatives on a public health emergency.

At present, rheumatologic conditions are often divided into three broad categories based on underlying pathogenesis and presumed etiology of pain. These categories include diseases of inflammation, both joint and systemic; diseases of joint degeneration and structural abnormality; and diseases of pain processing and perception. Table II provides examples of these conditions. While this categorisation is often used, it is an oversimplification that can obscure commonalities inherent in a more integrated and encompassing model of pain that can underpin a research agenda. The categorisation is further challenged by the dynamic nature of rheumatologic disease since the contributions of the different processes may fluctuate and vary over time; furthermore, distinguishing the contribution to symptoms of these processes is difficult in the absence of reliable laboratory biomarkers.

Rheumatoid arthritis (RA) provides a pertinent example of the manner in which a more narrow perspective based on simplified disease categorisation can affect thinking about aetiology and treatment. Along with stiffness and fatigue, pain is the primary symptom of RA. With the increasing effectiveness of biological and targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs and tsDMARDs), remission is a realistic goal of many patients, with the often dramatic response of patients to DMARDs suggesting that inflammation may suffice to explain the symptoms of RA pain. Interestingly, questions in at least some of commonly used outcome measures to assess remission do not directly ask about pain. Rather, the questions relate to concepts such as "general health" and "disease activity" and include assessments such as "Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?" In routine patient care, the utilisation of formal outcome measures appears limited, suggesting that decision-making is based on other clinical assessments. Since the effective agents to treat RA inflammation are directed at the immune system, the success with treat-to-target approaches would suggest that inflammatory mediators represent the relevant pain drivers in this condition. Indeed, current treatment paradigms suggest that, if a particular DMARD is not effective, then a switch to an agent with another mode of action should be considered (3). As shown in clinical trials of new agents, those severely affected by RA may receive as many as five different DMARDs over the course of their disease and still display persistent disease activity. If a single DMARD is not effective, then combination therapy is often utilised and many patients simultaneously receive agents targeting different immune pathways. Examples would include triple therapy with methotrexate, sulfasalazine and hydroxychloroquine or the combination of methotrexate, a TNF blocker and low dose prednisone. This approach makes sense if the inflammation is predominant if not only driver of pain.

If pain in some patients, however, reflect the effects of damage or central and peripheral sensitisation, then a focus only on inflammation would limit certain types of investigation and the application of a more multi-disciplinary approach to pain management (4, 5). In the study of osteoarthritis (OA), research on the effects of sex, race and ethnic group and age has provided important insight into the basis of symptomatology (6, 7); perhaps, unfortunately, these topics have received far less attention in the study of RA even though patient demographics can affect pain perception and processing as well as inflammation. In this regard, low education level has been associated with high levels of pain. Correspondingly, if pain from inflammation is viewed primarily as an acute effect on inflammatory mediators on pain transmission, then

long-term effects of chronic inflammation on central as well as peripheral sensitisation may not be appreciated. In this regard, just as different cytokines can induce distinct and characteristic types of immune responses (*e.g.* Th1, Th2 and Th17 cell responses) or endophenotypes, these mediators may differ in the manner in which they shape and modulate pain processes.

In RA, inflammation provides an important mechanism to account for pain although damage and distress may also contribute. In osteoarthritis (OA), the role of inflammation has been less clear. OA is often considered to be a non-inflammatory condition provoked by cartilage breakdown and resulting mechanical imbalance. Inflammation often follows degeneration and damage, however, suggesting that inflammation also impacts on pathogenesis and that, in OA, cytokines may contribute to pain as well as disease progression. Despite the relevance of these cytokines to pathogenesis, delineating their role may be more difficult in the setting of OA then RA because of their magnitude and local action, necessitating the analysis of synovial fluid rather than blood. Nevertheless, the recognition that certain cytokines as well as pathways of inflammation may drive pain in OA can expand the conceptualisation of disease and lead to new research approaches to elucidate the origin of pain in this common condition (8, 9-11).

While peripheral and central sensitisation may contribute to symptoms in inflammatory arthritis as well as OA, the study of sensitisation has dominated research on fibromyalgia. The nervous and immune systems are not separate universes, however, but rather have extensive interactions (12). Thus, cytokines may contribute to symptomatology in at least some patients with fibromyalgia while fibromyalgia may develop in the context of inflammatory arthritis (13, 14). Elucidating the links between inflammation and central and peripheral sensitisation would thus seem to be a highly relevant area of inquiry that can better fit fibromyalgia in the framework of rheumatology. In this regard, determining the relationship between depression and other neuropsychiatric diseases with fibromyalgia (as well as inflammatory arthritis and OA) represents another important research priority as the concept of multi-morbidity expands and underpins more holistic and interdisciplinary therapy.

At the time of the first report of the ACR Pain Management Task Force, studies of genetics were just beginning to provide new insights into the etiology of pain and its experience in different diseases. The number of genes involved with pain is very large and likely total several hundred. Among these genes, enzymes involved with metabolism of mediators (catechol-O-methyltransferase or COMT) and voltage-gated sodium channels both have properties potentially relevant to differences among patients in pain experience. Research on these systems has helped delineate inherited pain disorders such as inherited primary erythromyalgia and familial episodic pain syndrome.

Delineating their role in disease like RA or OA, however, remains a challenge given their clinical complexity, the coexistence in the individual patient of different pain processes (*e.g.,* inflammation, damage and central sensitisation) and the impact of therapy (15). In contrast, in fibromyalgia where central sensitisation is more prominent and inflammation much less so, the likelihood of detecting the contribution of genetic factors seems greater. Hopefully, research will continue to define approaches to understand the genetic underpinning of pain so that they can be relevant in the full spectrum of painful conditions treated by rheumatologists. This endeavour will also entail the development of more sophisticated clinical tools so that the types of pain that patient's experience (*e.g.,* pain from inflammation and damage in RA, rest pain *vs.* pain on activity in OA) can be better analysed. It is even possible that genetic contributions vary with the joint(s) affected.

Pain should be one of the most exciting areas in rheumatologic research as well as the most frequent topics of training and education. Nevertheless, offerings at national meeting remain limited as do publications in major rheumatologic journals. The number of rheumatologic investigators who explore pain mechanisms is also small. A number of factors can account for this situation, and will need attention if rheumatology is to advance optimally in the future. One important factor relates to the inherent complexity of analysing pain in a condition such as RA where inflammation and damage are prominent and may vary dynamically over the course of disease. Similarly, the intensity and quality of pain also vary in the course of OA as damage and secondary inflammation occur. For an investigator wishing to study pain, these are very complicated systems especially in studies trying to relate to endophenotype to genetics. In this regard, the translation of new understanding of pain mechanisms into therapy has been slow and often uncertain for rheumatologic disease. Clinical conditions outside the scope of rheumatology (*e.g.* neurology) may be more amenable for revealing these relationships and allowing their translation into new treatment.

A second factor for the comparatively low attention to pain in rheumatology is practical and relates to the time and attention needed to treat chronic pain especially using interdisciplinary and multidisciplinary approaches. Given the shortage of rheumatologists, providers have to adapt their practices to work at high volume. Patients with chronic pain can consume considerable time especially now with the current difficulties with prescription of opiates and the attendant worries about their possible overuse and abuse even in patients for whom they are indicated. Because of the development of palliative care and pain medicine as clinical specialties, rheumatologists can refer patients to these providers; as a result, they have options for the treatment of their patients with severe pain that reduce their direct involvement in prescription or utilisation of certain medications or modalities. While the referral of patients to pain specialists can facilitate certain aspects of care, such a situation can separate consideration of pain from other symptoms in a setting of complex, multisystem disease and limit scientific advance. The ACR Pain Management Task Force represented an important step to encour-

age inquiry into pain and build a framework for its understanding across the spectrum of rheumatic disease. While almost a decade has passed since the creation of the Task Force, its work has just begun and remains as vital now as ever to keep pace with the growing demands of care for those patients who have not yet benefited from modern armamentarium of rheumatologic therapy.

Clinical aspects of pain management in rheumatic disease

Pharmacologic therapies

In 2010, the American Pain Society labelled pain as the "fifth vital sign." The consequences of that designation resulted in a heightened measurement of pain in patient care, primarily through documentation with visual analogue scales; these scales are subjective, however, and can be difficult to apply to symptoms to produce quantitative information. As suggested in the Task Force report, PROMIS (Patient Reported Outcome Measures Information System) has developed an increasingly sophisticated means of measuring a variety of health outcomes including pain. Pain VAS scales distinguish active from control treatment in RA clinical trials at a higher level of significance than ESR, CRP, or tender joint counts. In addition to visual analogue scales, proper assessment of pain measures effects on interference, function, sleep, mood and fatigue. Furthermore, in the clinical arena, effective treatment of pain was required with possible physician sanctions by State Medical Societies for undertreatment based on subjective scales. The unintended result on this focus on treatment of pain was the increased prescription of opioid analgesics, as opposed to the multimodality team approach suggested in the 2010 report. A marked increase in opioid prescriptions has occurred in the United States, with 2 million Americans being addicted and with 15 million misusing these medications (16). The Surgeon General called on physicians to be mindful of their choice of pain therapy to consider non-opioid pain-treatment alternatives (17). The predicament for the clinical rheumatologist is that pain remains a prime manifestation of rheumatic disorders. For example, the hallmark symptom of osteoarthritis, our most common rheumatic disease, is pain. That symptom contributes to functional limitations and reduced quality of life (18). Causes of pain in rheumatic disorders have not been fully elucidated but, as discussed, are likely to be complex and vary among individuals as well as stage of disease. For example, the sources of pain in osteoarthritis are multiple, involving most structures of the joint, surrounding muscle, tendons, and ligaments, as well as the peripheral and central nervous systems (19).

Drug and interventional therapies, including peripheral joint injections, for musculoskeletal pain is limited and only partially effective. Acetaminophen is recommended as an analgesic since it has fewer toxicities compared to other drug therapies when used at the lower recommended 2000 mg daily dose. Unfortunately, acetaminophen is ineffective for low back pain, a common musculoskeletal symptom, and is minimally effective for osteoarthritis (20). Non-steroidal anti-inflammatory drugs (NSAIDs) are analgesic and anti-inflammatory and are a mainstay of rheumatic disease therapy (21). However, their efficacy is not consistent to be useful in most if not all rheumatic disorders. For example, their utility in spinal pain is not large enough in many instances to result in a consistent, clinically significant improvement in pain (22). NSAIDs are associated with gastrointestinal, cardiovascular, and renal toxicities which limit their utility in the elderly population who are at greatest risk for back pain and osteoarthritis (23).

Opioids are considered to be effective analgesics for acute pain but are associated with a number of limitations as the ideal analgesic. In the setting of an increased number of opioid overdoses and misuse of prescribed opioids, the CDC published a guideline for prescribing opioids for chronic pain (24). The report noted that most clinical trials of opioids are 6 weeks or less in duration and do not offer data on benefits and risks with chronic usage. The guideline recommends that use of opioids only if the expected benefits of both pain and function are anticipated to outweigh risks to the patients. Opioids are to be used in combination with non-pharmacologic and non-opioid pharmacologic therapy. While it would be ideal to have no rheumatic disease patients on opioids, that is not the current situation. In a practice of one of the authors, 15% of patients are taking long-term opioid therapy in the setting of chronic pain associated with disabling arthritis. The pressure for clinical physicians to carefully monitor patients and decrease and eliminate opioid therapy will become the expected norm.

Drug therapies directed at the pain inhibitory pathways in the central nervous system have benefits in some patients with osteoarthritis. Selective serotonin and norepinephrine reuptake inhibitors have demonstrated efficacy in decreasing pain in osteoarthritic joints and chronic low back pain compared to placebo (25, 26). However, this category of drug is associated with toxicities manifest as nausea, xerostomia, fatigue, diarrhoea, hyperhidrosis, and dizziness. In older populations, these toxicities limit the number of individuals who are tolerant of these drugs.

A new drug class with a different mechanism of action is the one consisting of antibodies directed at nerve growth factor (27). Nerve growth factor (NGF) is a key regulator of nociceptive sensitisation after tissue injury (28). Antibodies directed against NGF have shown significant improvement in clinical trials for significant decrease in pain in osteoarthritis and chronic low back pain (29, 30). While this category of pain therapy shows promise, the ideal dose of these antibodies remains to be determined. Higher doses of antibody may be associated with neurologic symptoms including paresthesias (31). Concomitant use with NSAIDs may predispose to rapidly progressive osteoarthritis and joint replacement. These agents have not been approved by the Food and Drug Administration for clinical use.

Non-pharmacologic therapies

The 2010 Task Force report recognised the importance of non-pharmacologic interventions for the treatment of musculoskeletal pain (1). A partial list of

these interventions includes patient education, physical and occupational therapy, nutrition and weight control, physical activity, behavioural therapies including cognitive-behavioural therapy, and self-management strategies. Many health professionals who offer these services are members of the Association of Rheumatology Health Professionals (ARHP). The ARHP has promoted education of pain management in many ways including through its choice of topics at its Clinical Focus Course and many other symposia offered at the ACR/ARHP Annual Meeting. The ARHP also offers extensive online education such as the Advanced Rheumatology Course where Module 13 specifically addresses an interdisciplinary approach to pain management.

Recent clinical trials, systematic reviews and meta-analyses documenting the benefits of non-pharmacologic therapies have been added to the medical literature. The magnitude of the improvements is to such a significant degree that some are included in ACR guidelines for treatment. For example, a strong recommendation is given for physical therapy in patients with ankylosing spondylitis in the ACR 2015 treatment recommendations (32). Overall, the data are extensive and thus beyond the scope of this article; only a few examples will therefore be provided. In rheumatoid arthritis, systematic reviews have indicated that occupational therapy interventions such as therapeutic exercise, patient education through joint protection and splinting are well supported (33). Chronic low back pain patients who participate in a yoga or physical therapy programs are 22% less likely to use pain medicine compared to those who receive education alone. Improvements are maintained when re-evaluated at a year (34). Cognitive behavioural therapy and mindfulness-based stress reduction can improve function in individuals with chronic low back pain to a greater degree when compared to usual care that includes drug therapy (35). Similarly, for fibromyalgia, Acceptance and Commitment Therapy (ACT) was shown to be more effective than pharmacological therapy (combined therapy of pregabalin and duloxetine) (36). The American College of Physicians has published a clinical practice guideline for acute, subacute, and chronic low back pain where non-pharmacologic therapies like, exercise, progressive relaxation, tai chi, yoga, and cognitive behavioural therapy are recommended prior to the start of pharmacologic therapy (37).

A unifying theme across studies and guidelines is the importance of tailored and interdisciplinary care in the management of pain. Yet, numerous barriers still exist that limit access to these effective therapies. To name just a few, Medicare therapy caps in the case of physical and occupational therapy (*i.e.,* H.R. 807, *The Medicare Access to Rehabilitation Services),* availability of trained providers and adequate reimbursement in the case behavioural interventions, and health professional training programmess, including medical schools, offer inadequate education in regard to pain management.

Conclusions

The topic of pain and its treatment remains an area of research and clinical importance. Our understanding of pain mechanisms is increasing but remains incomplete. Pain treatments remain inadequate in efficacy and associated with a variety of toxicities. Despite this situation, rheumatologists continue to treat patients with painful rheumatic disorders on a daily basis. The specialty of rheumatology, through its professional organisations ACR and ARHP should remain at the forefront of advances in the elucidation of pain and its effect on patients with rheumatic diseases. The ACR and ARHP should be committed to supporting pain research and informing its membership, including trainees, about advances in this field.

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