Disease control versus pain management in rheumatoid arthritis

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Current treatments for rheumatoid arthritis have improved our ability to suppress inflammation; however, for a significant proportion of patients they rarely give complete pain relief. To maximise function and quality of life in patients with rheumatoid arthritis, disease control and pain management should be viewed as two integrated but separate entities.

Key points

- **Pain management is a high priority for patients with rheumatoid arthritis.**
- **Disease control and pain management are two separate entities.**
- **Patients should be specifically questioned regarding the presence of pain rather than simply awaiting a spontaneous complaint.**
- **Early detection and suppression of inflammation may prevent chronic pain due to peripheral and central sensitisation.**
- **A multidisciplinary, multimodal approach combining education and nonpharmacological and pharmacological agents should be tailored to the individual patient.**

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A 48-year-old woman with anticyclic citrullinated peptide positive rheumatoid arthritis presents to your office for her regular review. Since commencing methotrexate, prednisone and a biological agent her inflammatory markers have now finally normalised and her joint swelling has subsided. You pleasingly remark that her disease now appears to be in remission and that she should continue her current treatments. A little despondently she replies, 'That's good news doctor, but why then do I still have pain?'

Rheumatoid arthritis (RA) is the most common inflammatory joint disease, affecting approximately 1.0% of the adult population worldwide,[1] including 450,000 people in Australia.[2] In recent times, we have become more adept at controlling inflammation with disease-modifying drugs and biological agents. However, despite treatment advances, pain continues to affect a substantial proportion of these patients (see example of a case scenario above). The magnitude of this problem was reported in a recent study of 2795 patients with RA, in whom 86% stated that their disease was 'somewhat to completely controlled'; however, 64% were not satisfied with their pain levels.[3]

It is well known that pain adversely impacts on function, psychological status, sleep and quality of life. Indeed, for some people, widespread pain may contribute more to their disability than structural joint damage. So if treatments have significantly improved, why do these patients with seemingly well-controlled disease continue to have pain, what is causing it and what can we do about it?

This article highlights the importance of proactively evaluating and managing pain in patients with RA, explores the mechanisms for why these patients have persistent pain and provides some practical guidance on how to approach this complex problem in the outpatient setting.

Pain mechanisms in RA

Historically, pain in patients with RA has been attributed solely to peripheral inflammation. However, persistent pain despite adequate control of inflammation indicates that there must be contributions from other pain pathways. In the past decade, we have seen extraordinary advances in the understanding of pain mechanisms at the molecular level. It is now clear that although peripheral tissue injury

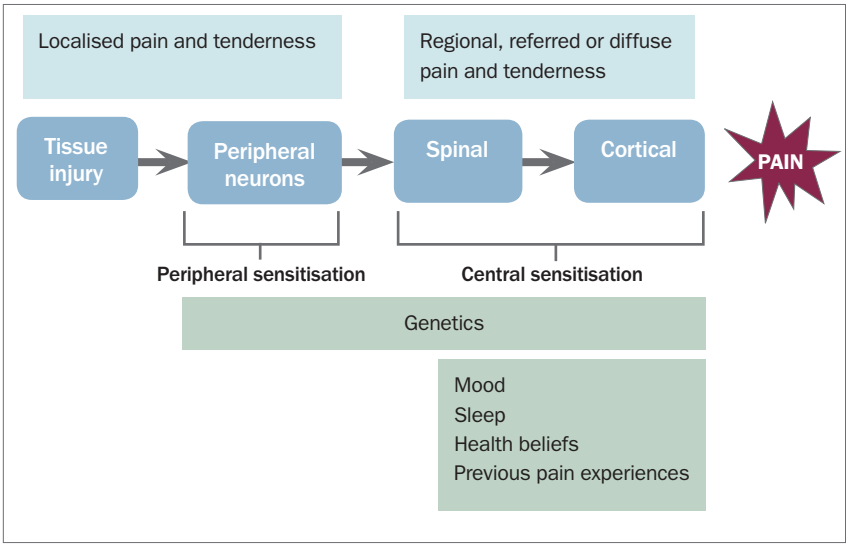


Figure 1. Mechanisms of pain in rheumatoid arthritis with different clinical manifestations (light blue) and effect modifiers (light green).

1. Red flags and diagnoses to consider excluding when assessing pain in rheumatoid arthritis (RA)

Red flags
Night pain
Acute severe pain different to usual RA pain
Neurogenic pain or claudication
History of significant trauma
Single hot and swollen joint
Focal or diffuse muscle weakness
Constitutional signs and symptoms (e.g. fever, weight loss, malaise)
Rash

Red flag diagnoses
Infection
Malignancy
Vasculitis
Stress fracture
Avascular necrosis

is important for the initiation and maintenance of joint pain, more central changes to pain processing become equally important with time. An overview of pain processing in people with RA and how it is influenced is shown in Figure 1.

Acute inflammation and structural damage

With early RA, acute synovial inflammation leads to the generation of mediators such as bradykinins, prostaglandins, tumour necrosis factor-α, interleukin-1 and interleukin-6. These mediators can induce acute pain by directly activating sensory nerves known to be present in the synovium, joint capsule, tendon sheaths, ligaments, menisci (outer regions), subchondral bone and muscles.[4] Over time, structural joint damage, either secondary to inflammatory disease or because of comorbid osteoarthritis, may also contribute to pain levels in these patients. Joint erosions may expose subchondral nerves to activating and sensitising factors,[5] and abnormal joint mechanics may lead to the presence of painful bone marrow lesions[6] and abnormal sensory nerve growth into both articular cartilage and the normally aneural inner two-thirds of the meniscus.[7] Pain due to these mechanisms will typically be localised to the affected joints.

Peripheral and central sensitisation

In early disease, the extent of an individual's joint inflammation seems to correlate well with their level of pain. However, this is not the case in people with longer disease duration, and is likely explained by both peripheral and central sensitisation that occurs with more chronic tissue injury.[8] Peripheral sensitisation may occur in patients with RA if there is chronic activation of joint sensory fibres by mediators of inflammation. Once this occurs, peripheral nerves may 'fire' pain signals even with mechanical stimuli that are normally innocuous. Hence, a patient in remission with no evidence of inflammation may still complain of pain or discomfort during light joint palpation, weight bearing or range of motion exercises. This pain does not signify ongoing tissue injury. It is important to explain this concept to patients who often instinctively immobilise their painful joints, which may lead to further muscle and tendon atrophy, abnormal joint mechanics, instability and ironically more pain.

Similarly, with chronic disease, central sensitisation may occur at the spinal and cortical levels. Processing of pain centrally is influenced by both excitatory inputs and descending inhibitory controls. Examples of excitatory inputs resulting from chronic synovitis include altered expression of neurotransmitters, neuromodulators and their receptors.[9] Over time, patients with chronically active RA may develop 'hyper-excitable' spinal neurons and therefore experience enhanced pain perception both at the initial site of injury, as well as in normal tissues both nearby and removed from the primary site of inflammation.[10] This enhanced and aberrant pain perception again does not signify ongoing tissue injury. It may, however, be further compounded by reduced descending inhibition, which can occur with disturbances in a patient's mood and sleep, as well as a variety of other psychosocial, cultural and environmental factors. These patients commonly describe more widespread pain and up to 20% may fulfil the classification criteria for fibromyalgia.[11,12]

Evaluation of pain in RA

When approaching the diagnostic challenge of pain in a patient with RA it is useful to think about the diverse underlying mechanisms, such as inflammation, structural damage, and alterations in peripheral and central pain processing. Patients should be specifically questioned regarding the presence of pain rather than simply awaiting a spontaneous complaint. Causes of pain in people with RA may vary between early and late disease, and during and between inflammatory flares. As is standard in the evaluation of patients with painful conditions, a thorough history and physical examination should focus on onset,

pattern, duration, location, intensity and characteristics of the pain, as well as any aggravating or relieving factors. Patients with RA are also at increased risk of infection, malignancy and complications from their treatments so 'red flags' should be sought and immediately investigated (Box 1). It is also important to ask patients about sleep, fatigue, psychiatric comorbidity (predominantly mood disturbance and anxiety) and functional impairments because these will be important to address in the overall management strategy.

A quantitative measurement of pain can be useful to record the magnitude, frequency and response to treatment. Simple examples that can be used in the clinic setting include Visual Analogue and Numerical Rating Scales (Box 2).

Effective treatment stratification requires a full assessment of pain mechanisms by clinical history and examination, as well as objective assessment of synovitis and joint damage. An approach to the diagnosis and subsequent management of pain in patients with RA is shown in the flowchart on page 22. When assessing the location of pain, the first distinction to consider is whether the pain is predominantly at a joint or nonjoint site. If the pain is in a joint, it is important to consider whether the joint affected is one typically affected by the patient's RA (Figure 2). For example, new pain in the carpometacarpal, lower back or distal interphalangeal joints is not typical of RA and more likely to be due to osteoarthritis.

If the pain is joint specific, the next important distinction to make is whether there is a component of inflammation present. This is a more difficult question to answer due to the poor sensitivity of our ability to detect 'subclinical inflammation' with clinical examination and inflammatory markers (erythrocyte sedimentation rate and C-reactive protein). Be mindful that a patient with no obvious swelling and normal inflammatory markers may still have a component of inflammation present. If uncertain, input from the patient's rheumatologist should be sought. Newer imaging modalities such as power doppler ultrasound and MRI are increasingly being used by rheumatologists to detect low-grade inflammation when other modalities have failed. MRI can also be helpful in assessing structural damage and in excluding more sinister causes for the patient's pain such as avascular necrosis, infection, malignancy or stress fracture.

If there is no evidence of inflammation, consider whether there is structural damage (erosions), joint instability (muscle wasting, ligamental laxity) or coexisting osteoarthritis present. For non-joint-specific pain the main differentiation to consider is whether the pain is widespread or localised.

Management

Due to the complexity of underlying pain mechanisms in patients with RA, measures designed to relieve pain should take into account individual, biological, psychological and societal factors. Factors that affect the likelihood of compliance, such as the frequency, tolerability and complexity of the regimen, should be considered and any other barriers to effective pain management actively explored. In general, a combination of both pharmacological and nonpharmacological approaches

2. Visual Analogue and Numerical Rating Scales

The simple pain Numerical Rating Scale (NRS) and Visual Analogue Scale (VAS) can be used to monitor pain and its response to treatment. Adding similar simple scales for concurrent symptoms such as fatigue, sleep difficulty, and depression can also assist in evaluating the multiple symptoms associated with pain.

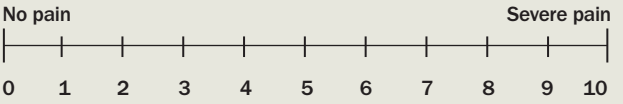
Numerical Rating Scale

On a scale of 0 to 10, where 0 = no pain at all and 10 = very severe pain, how much pain have you had in the last month, on average, from your arthritis?

Numerical rating scale (0–10) _____

Visual Analogue Scale (VAS)

Please mark on the scale below how much pain have you had in the last month, on average, from your arthritis?



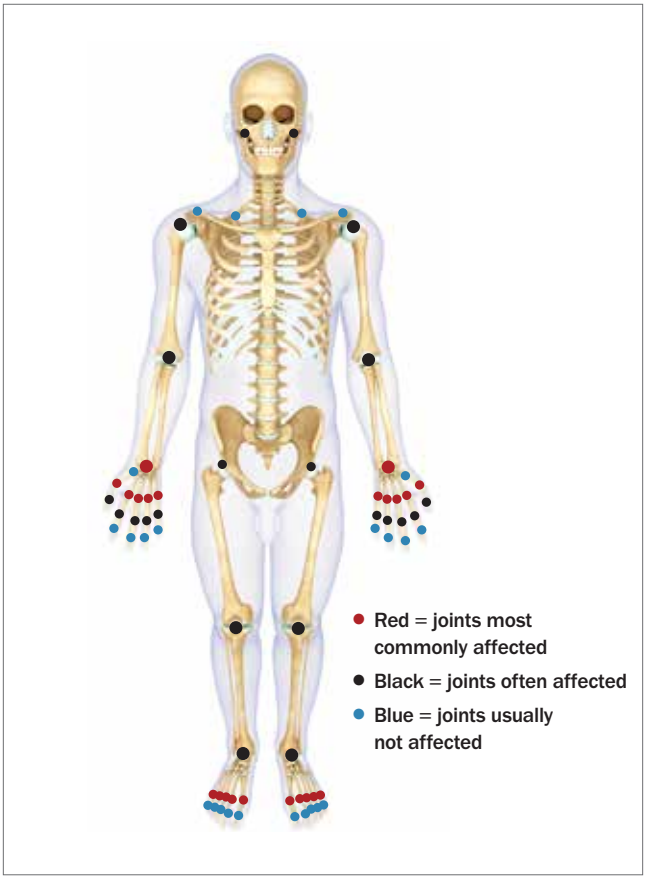
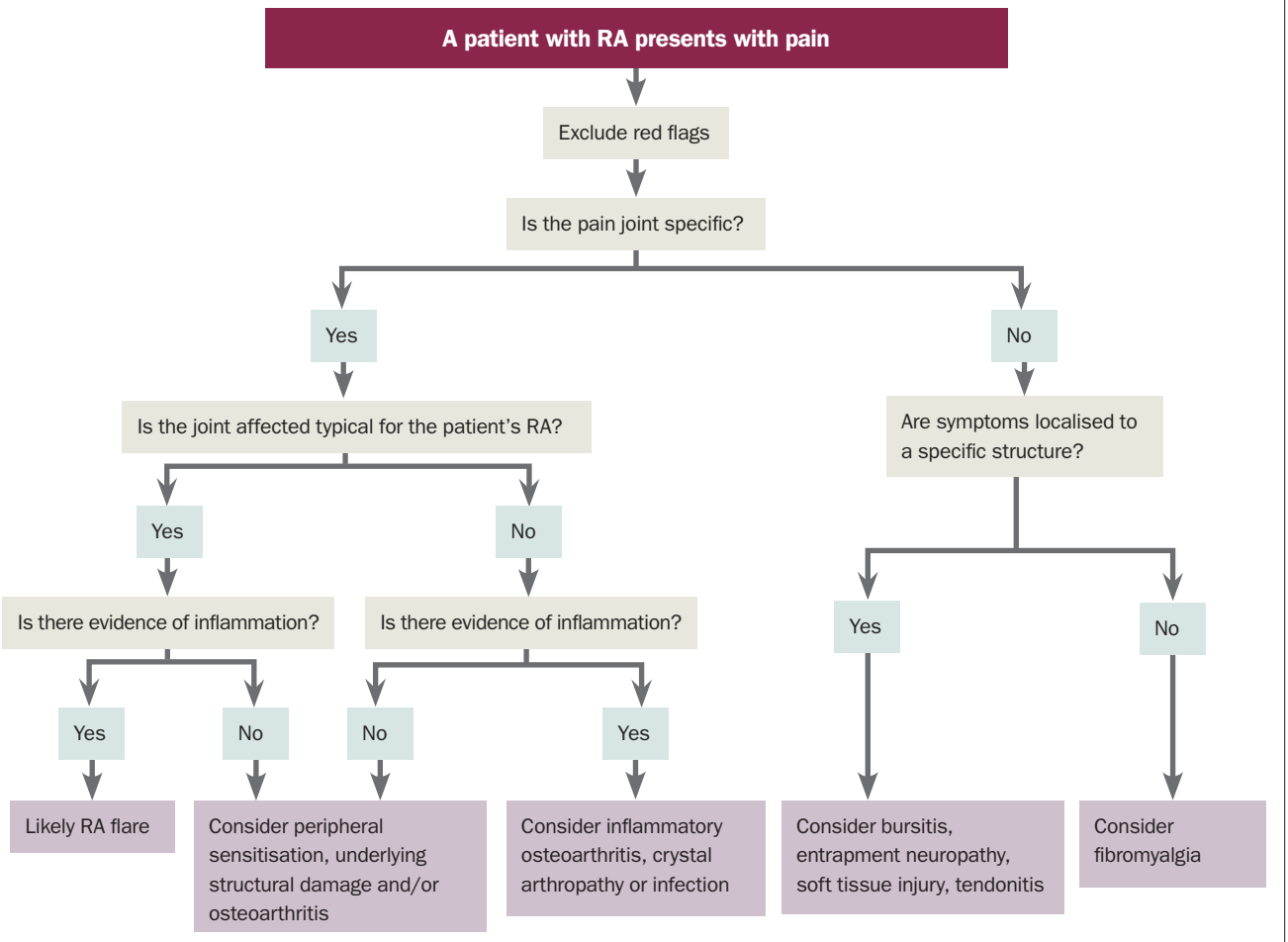


Figure 2. Joints affected in people with rheumatoid arthritis.

Approach to the diagnosis of pain in patients with rheumatoid arthritis*



* Patients may at times have symptoms suggestive of multiple pathways being present.
Abbreviation: RA = rheumatoid arthritis.

offers the best opportunity for therapeutic success (Box 3).

To reduce the chance of peripheral and central sensitisation occurring and to improve long-term outcomes for patients with RA, early recognition of joint inflammation and referral of the patient to a rheumatologist for aggressive suppression of inflammation is vital. For patients with obvious inflammation, short-term courses of oral corticosteroids or NSAIDs can be useful. Similarly, intra-articular corticosteroids can be used by experienced clinicians to treat individual joints.

For residual, noninflammatory pain a stepwise approach commencing with simple analgesics and a variety of nonpharmacological strategies suited to the patient are recommended. Realistic goal setting for both pain and functional outcomes, as well as regular evaluation for a therapeutic response, will help determine if escalation of treatment is required. Knowing if patients have structural damage or coexistent osteoarthritis present will help inform treatment strategies. If patients with significant joint damage have severe, localised pain, joint replacement surgery can offer substantial relief and appropriate referral should be made as required. Patient education regarding the disease, mechanisms of pain, multimodal treatment strategies and 'bad day' management is a fundamental part of any pain management program. Improved understanding of pain mechanisms can limit catastrophic thoughts about the meaning of pain, facilitate a sense of control and reduce anxiety about causing further joint damage with activity.[13] Healthy lifestyle habits such as smoking cessation, sleep hygiene, adequate exercise and weight control should be encouraged. Exercise is particularly useful in patients who have muscle wasting, are overweight or have fibromyalgia. Low-impact land exercise (e.g. stationary cycling, walking) or pool-based exercise of low to moderate intensity are preferential for people with painful joints.

In people with a significant component of fibromyalgia, adjuvant agents (e.g. amitriptyline, pregabalin, duloxetine and gabapentin [all off label for fibromyalgia]), in addition to an exercise program and cognitive behavioural therapy, can be tried (see Box 3). In people with a significant mood disturbance, consideration of referral to a psychiatrist may be warranted. Low mood may be a consequence of pain, but may also contribute to its distressing quality and impair facility to cope with pain.

3. A multimodal approach for pain management in rheumatoid arthritis

Joint inflammation present (early morning stiffness >30 mins, raised ESR/CRP, joint swelling)

Consider referral of patient to, or discussion with, a rheumatologist regarding:

- adding an NSAID* (if no contraindications)
- a trial of a different NSAID
- a short trial (7 to 10 days) of low dose prednisone
- rheumatologist review of modification of DMARDs

For residual noninflammatory joint pain use a multimodal approach

Nonpharmacological strategies

Patient education
Exercise program/hydrotherapy
Fish oil
Orthoses/splints
Transcutaneous electrical nerve stimulation machine
Massage/acupuncture
Psychological support
Cognitive behavioural therapy
Mindfulness, meditation, relaxation
Web based self-management program

Pharmacological strategies

Mild pain

Paracetamol

Moderate pain

Structural damage/osteoarthritis

Local corticosteroid injection if appropriate
Add NSAID/trial different NSAID
Add codeine or tramadol
Intra-articular hyaluronic acid

No structural damage/osteoarthritis

Consider adding adjuvant therapies

Severe pain

Consider referral of patient to rheumatologist or pain management specialist

Structural damage/osteoarthritis

Refer for joint replacement if appropriate
Add opioid (transdermal buprenorphine, oxycodone, transdermal fentanyl, morphine) with aperient
Add topical capsaicin (off-label use)

No structural damage/osteoarthritis

Re-evaluate 'red flags'
Consider adding adjuvant therapies

Adjuvant therapies

If the patient has significant component of fibromyalgia or neuropathic pain:

Consider adding:

- amitriptyline (off-label use)†
- pregabalin†
- duloxetine†§
- gabapentin†

* Caution in patients with cardiovascular, renal or gastrointestinal disease.
† Watch for interaction with tramadol.
† Off-label use unless used for the treatment of patients with neuropathic pain.
§ Off-label use unless used for the treatment of patients with diabetic neuropathic pain.
Abbreviation: DMARDs = disease modifying antirheumatic drugs.

Summary

Although current treatments for RA have improved our ability to suppress inflammation, they rarely afford complete pain relief. When caring for patients with RA it is therefore important to consider disease control and pain management as two separate entities. After sinister causes are excluded, multimodal treatment strategies should be tailored to the individual patient's needs and should aim to suppress inflammatory disease, relieve pain symptoms, and improve function and quality of life. PMT

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