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Pain management in inflammatory arthritis

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Many people with inflammatory arthritis continue to experience high levels of pain even when receiving effective treatments. Chronic pain is a complex biological process that cannot be easily remedied with a single pill. A multimodal approach is required.

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Australian Rheumatology Association

Inflammatory arthritis (IA) affects up to 3% of the population and is characterised by pain, stiffness, loss of function and impaired quality of life.[1] It comprises diseases such as rheumatoid arthritis (Figure 1), psoriatic arthritis, reactive arthritis and spondyloarthropathies, and when treatment is successful IA is a satisfying condition to treat. There are many examples of the debilitated patient with polyarthritis who is revived with a pulse of steroid. Instant trust and often a smile can follow. Unfortunately, this is not always the case and for doctors and patients it can be frustrating when treatment fails to live up to the high expectations.

Some extraordinary developments in targeted biological therapy for patients with IA have occurred over the past decade. Indeed, for many patients with IA, when these therapies work, they really do work well. However, unfortunately the reality is that biological agents are costly, not all patients qualify for a rebate on the PBS, not all patients respond to treatment and those that do respond may still have ongoing pain. Despite these significant advances in treatment, it should

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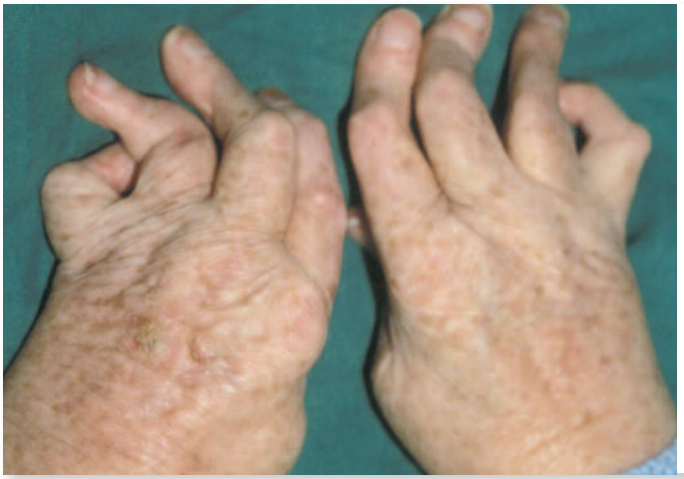

Figure 1. Deforming rheumatoid arthritis.

come as no surprise that patients with IA are reported to perceive pain as their predominant impairment[2] and pain management as one of their highest priorities.[3]

A case study of a woman with persistent knee pain is given in the box on this page.

CAUSES OF CHRONIC JOINT PAIN

One of the reasons for the lack of effective pain management is the paucity in our knowledge of what actually causes joint pain. The aetiology of pain in patients with IA is multifactorial and often

CASE STUDY. A 78-YEAR-OLD WOMAN COMPLAINING OF PERSISTENT KNEE PAIN

Case scenario

A 78-year-old woman with a 30-year history of erosive, deforming rheumatoid arthritis (RA) presented complaining of persistent pain in her right knee. She was known to have severe secondary osteoarthritis (Figure 2) but was not a suitable candidate for joint replacement therapy. The pain had been worsening for the past six months, was localised to the anteromedial aspect of the knee and was associated with mild swelling. She described the pain as a deep ache that was worse with weight-bearing and had now begun to limit her activities and disturb her sleep. The pain did not feel like her usual arthritis flare pain, she felt systemically well, had only 10 minutes of early morning stiffness and her other joints remained stable. She was taking methotrexate 20 mg weekly, folic acid 5 mg weekly, prednisone 5 mg daily and celecoxib 200 mg daily. On examination she had a body mass index of 31 kg/m^2 and walked unaided with an antalgic gait and had widespread tenderness to minimal pressure. There was a valgus deformity of the right knee with quadriceps wasting, a small effusion, medial joint line tenderness and marked crepitus.

Commentary: The initial differential diagnoses are quite broad and include osteoarthritis progression, RA flare, septic arthritis, crystal arthritis, stress fracture, avascular necrosis (AVN) and referred pain from the hip or back. This woman's history is more suggestive of mechanical rather than inflammatory pain; however, with mild swelling an inflammatory component to her symptoms needs to be excluded. A key piece of information is that this pain is different to the patient's usual RA flare pain, so RA is unlikely to be the cause. Although she feels systemically well, the history of progressive pain that is disturbing her sleep is a 'red flag' for more serious causes to be excluded. AVN, osteomyelitis and stress fracture should all be considered when the pain severity seems out of proportion to the clinical findings. Examination of the hip and back for irritability and reproduction of the knee symptoms can be helpful in identifying the source of the pain. The patient is not currently taking any paracetamol and this should be added early to her usual medications. Her widespread tenderness and poor sleep also suggest that a component of fibromyalgia may be present. Preliminary investigations should include measurement of baseline erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level to assess disease activity and a plain anteroposterior and lateral weight-bearing x-ray of the knees.

Case continued

Investigations in this woman showed the disease activity to be mildly elevated but stable with an ESR of 29 and a CRP level of 6.7.

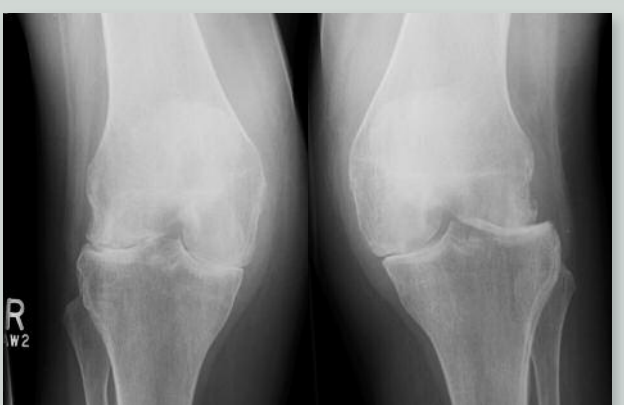

Figure 2. X-rays of the knees showing severe secondary osteoarthritis.

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difficult to assess. In the past decade, we have seen extraordinary advances in the understanding of pain mechanisms at the molecular level. However, there is still a long way to go. We know that pain receptors are located throughout the joint, having been identified in the capsule, ligaments, menisci, periosteum and subchondral bone. Therefore, damage at any of these sites can manifest as 'joint pain'.

Simplistically, to guide treatment, we often think of pain mechanisms as being inflammatory, mechanical, neuropathic or a combination of these. Recent evidence shows, however, that there is actually a complex interplay between the neural and immune systems, and that inflammatory cytokines influence both peripheral and central pain pathways.[4] As a consequence, many patients with IA manifest a generalised increase in pain perception and, in effect, become 'pain sensitised'. Untreated and undertreated pain also has a negative impact on sleep and mood, which are in turn associated with greater pain.[5] Hence, the patient becomes trapped in a self-perpetuating downward cycle that can be difficult to break.

BARRIERS TO PAIN MANAGEMENT

There are several barriers to pain management outlined in the box on page 54. An awareness of these is the first step to improving pain management in patients. Regardless of the underlying pathological process, the clinical evaluation of pain is always a challenge. There are many examples of patients with similar disease duration and severity who manifest very different degrees and phenotypes of pain. This is most likely explained by the concept that the experience of pain is uniquely influenced by factors other than the primary pathology, such as

CASE STUDY (continued)

There was no fracture or chondrocalcinosis (to suggest calcium pyrophosphate dihydrate disease) seen on the x-ray; however, there were severe tricompartmental osteoarthritic changes.

Commentary: The low-grade elevation in inflammatory markers needs to be interpreted in the context of the patient's disease, and input from her usual rheumatologist should be sought regarding any changes to the patient's disease-modifying antirheumatic drugs or the need for an MRI. An MRI is useful if there is a high suspicion of stress fracture, AVN, osteomyelitis or ongoing low-grade synovitis. A joint aspirate is always useful diagnostically and therapeutic cortisone injections can also be performed at the same time (if there is no concern regarding infection).

Case continued

The synovial fluid analysis showed a noninflammatory cell infiltrate with 1000 polymorphonuclear leucocytes, no crystals and was Gram stain and culture negative. An MRI showed no active synovitis, stress fracture, osteomyelitis or AVN. There was significant bone marrow oedema consistent with her severe osteoarthritis.

Commentary: These results are most consistent with pain occurring secondarily to osteoarthritis. Being a single joint, the best treatment option would be an intra-articular corticosteroid injection. However, this will be of temporary benefit and without definitive treatment (joint replacement) the patient is likely to have ongoing pain. Nonpharmacological strategies including education, walking aids, heat packs, transcutaneous electrical nerve stimulation (TENS) and gentle exercise to aid muscle strength and weight loss will be helpful. Bracing may also improve stability of the joint and input from a physiotherapist and occupational therapist should be sought. Glucosamine and fish oil may also be considered but are unlikely to make a significant difference.

Case continued

She returned one month later and stated that her knee pain was moderately improved but she still had widespread pain and was not sleeping. Despite the improvement in her knee pain, she was reluctant to exercise, had become withdrawn and was feeling tired all the time. She had been taking paracetamol 3 g daily and celecoxib 200 mg daily. There was no evidence of inflammation in her knee but she had marked quadriceps wasting. She wanted to know what else she could do for pain relief.

Commentary: In addition to her knee pain she has symptoms that are suggestive of fibromyalgia and it is likely her pain threshold has been further reduced by her poor sleep and possible coexistent low mood. Stronger opioid analgesics are unlikely to improve these symptoms and should be avoided. The patient's beliefs about the cause of her pain and her reluctance to exercise should be explored further. A gentle exercise and quadriceps-strengthening program may improve her muscle mass, joint stability, falls risk and possibly sleep. Regular review with the patient and referral to a physiotherapist for a modified exercise program with achievable goals may reduce some of the patient's anxiety regarding exercise. Having a plan of what to do if her pain gets worse (e.g. use of a TENS machine, hot and cold packs or codeine [for knee pain]) would also be useful. After ensuring that the patient's vitamin D level was optimised, in addition to exercise, a trial of a low-dose antidepressant for her fibromyalgia (off-label use) could also be considered. If her mood symptoms were significant and no progress was made, consideration of input from a psychologist or psychiatrist may be warranted.

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BARRIERS TO EFFECTIVE PAIN MANAGEMENT

Patient
- Reluctance to report pain to physicians
- Reluctance to take more 'pills'
- Lack of education regarding available pain therapies
- Fear of side effects or drug addiction
- Fear of masking the disease
- Compromised cognitive function secondary to certain pain medications

Physician
- Focused on disease management, not pain
- Inadequate training and knowledge of pain management
- Inadequate assessment of pain
- Time constraints of a busy practice
- Concern about scrutiny from regulatory agencies

Healthcare system
- Low priority of pain management
- Cost of medications
- Limited access to allied health services
- Lack of pain management clinics

IMPORTANT ELEMENTS OF THE PAIN HISTORY

- Characteristics of the pain
- Impact of the pain on the patient (e.g. physical, psychosocial, role functioning, work, etc)
- Prior treatments for the pain
- Physical functioning
- Mood and psychological well-being
- Sleep and energy levels
- Premorbid and comorbid medical and psychiatric conditions
- Comprehensive medication history
- Social support structures

psychological status, past pain experience, cultural background, environment and genetics of the individual. In the end, pain evaluation often requires the clinician to make a clinical judgement taking into account all these factors in a limited time frame, and without an objective test or laboratory measure. Important aspects of the pain history that should be explored are shown in the box on this page.

APPROACH TO PAIN MANAGEMENT

It is important to remember that the goals of treatment are not only to reduce pain, but also to improve function and quality of life. A patient-centred integrated approach involving the GP, rheumatologist and other allied health professionals is therefore likely to offer the best overall outcome. Patients with IA should have a chronic disease care plan to enable them to access a Medicare rebate for these additional services.

When considering an overall treatment strategy many aspects such as the patient's underlying disease, pain characteristics, age, comorbidities, social supports, coping strategies and health beliefs should be taken into account. Factors that will affect the likelihood of compliance, such as patient preference, cost of medications, the frequency and complexity of the regimen, route of administration and tolerability of the regimen, should also be considered. A combination of both pharmacological and nonpharmacological approaches usually offers the best opportunity for therapeutic success (see the boxes on page 55).

NONPHARMACOLOGICAL STRATEGIES

Education

Patient education is an essential part of the pain management program and gives patients a sense of control over their situation. All educational activities should be sensitive to culture, ethnicity and the values and beliefs of individual patients and their families. Validating the patient's pain, setting realistic goals (e.g. reducing rather than completely removing pain), addressing the patient's fears and misconceptions, and having an action plan for 'bad days' can reduce anxiety levels and the frequency of subsequent medical reviews. Written information to explain the diagnosis, cause(s) of pain and reinforce the management strategy is also very helpful. Patient information sheets are available on the Australian Rheumatology Association website and are a useful patient resource.[6]

Exercise

Exercise is particularly useful in patients who have muscle wasting, are overweight or have fibromyalgia. With regular exercise, muscle tone is maintained, musculoskeletal structures are stabilised and regenerative processes are stimulated. Additional benefits include the production of natural analgesics (endogenous opioids), improved mental health and sleep, weight loss and reduced cardiovascular risk. Although concerns about causing further damage to joints are often voiced, patients should be reassured that provided trauma is avoided, physical activity within reasonable limits will not cause harm. For painful joints, nonweight-bearing activities such as hydrotherapy and cycling are useful starting points and a physiotherapist should be involved when possible.

Counselling/cognitive behavioural therapy

Chronic pain is often associated with psychological disorders such as anxiety and depression. These patients should be identified, treated and referred for further evaluation when necessary. For many patients, counselling and regular review by their GP may be all that is required. However, if this fails, cognitive behavioural therapy (CBT) can be a useful adjunctive management tool. CBT can be broadly defined as interventions that

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change behaviour, thoughts or feelings to help patients experience less distress and enjoy more satisfying and productive daily lives. Patients learn to identify and change dysfunctional beliefs and attitudes that adversely affect their ability to cope with pain. Interestingly, CBT and stress management training have been shown to decrease inflammation as well as pain, which may also help with control of the underlying disease.

Other

Other nonpharmacological interventions frequently used by patients include joint assistive devices, hot and cold therapy, ultrasound, relaxation, meditation, hypnosis, acupuncture, massage and transcutaneous electrical nerve stimulation (TENS). Although these interventions still require formal evaluation in high-quality trials, they appear to have favourable risk–benefit profiles. Smoking is associated with erosive joint disease and a decrease in response to disease-modifying anti-rheumatic drugs (DMARDs), so facilitating smoking cessation will aid control of the disease and resultant articular pain.

PHARMACOLOGICAL STRATEGIES

The first question to address when treating the patient with IA is whether there is an inflammatory component to the pain. For the patient with a clear flare of disease with tender swollen joints, early morning stiffness and raised inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] level), 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 of patients with IA.

In the setting of long-standing inflammatory disease, the presence of active inflammation can be more difficult to assess. Established articular changes with associated structural deformity make the assessment of synovitis more difficult. Doppler ultrasound has recently also shown that the ESR and CRP level may not be sensitive enough to detect persistent low-grade disease activity. After consideration of a patient's comorbidities and discussion with their treating rheumatologist, sometimes a short course of a corticosteroid (seven to 10 days) can help to rule out ongoing active inflammation as a contributor to the patient's pain. It is emphasised, however, that systemic glucocorticoids are not generally recommended for the routine management of pain in patients with IA (in the absence of signs and symptoms of inflammation). The choice, dose and duration of immunosuppressive therapy needs to be individualised to the patient and should be discussed with their treating rheumatologist.

Available in a standard or concentrated preparation, fish oil possesses anti-inflammatory properties and may be a useful adjunctive therapy in patients with persistent inflammation. However, to achieve this, current evidence suggests that fish oil needs to be taken in high doses (≥2.7 g of omega-3 [eicosapentaenoic acid plus docosahexaenoic acid] daily), which are often not well tolerated. Doses of more than 7 g of omega-3 fats per day may increase a patient's risk of bleeding.

TREATMENT OF PATIENTS WITH A SUSPECTED INFLAMMATORY CAUSE OF PAIN

An inflammatory cause of pain is suspected in patients who present with early morning stiffness, increased inflammatory markers and joint swelling.

- Send the patient for rheumatologist review
- Trial the use of paracetamol and/or an NSAID
- If this is unsuccessful, trial a different NSAID
- Try a short trial (7 to 10 days) of low-dose prednisone
- Consider using an alternative disease-modifying agent

TREATMENT OF PATIENTS WITH RESIDUAL NONINFLAMMATORY PAIN: A MULTIMODAL APPROACH

Nonpharmacological agents

- Patient education
- Fish oil ≥2.7 g/day
- Glucosamine
- Vitamin D3 if levels <80 nmol/L
- Massage/acupuncture
- Exercise program/hydrotherapy
- Orthoses/splints
- Transcutaneous electrical nerve stimulation (TENS) machine
- Psychological support cognitive behavioural therapy
- Relaxation

Pharmacological agents

Mild pain

- Paracetamol 2 to 4 g/day*
- Topical or oral NSAID**

Moderate pain

- Consider adding codeine or tramadol

Severe pain

- Consider adding transdermal buprenorphine, oxycodone, transdermal fentanyl or morphine

Adjuvant agents

- Topical capsaicin 0.025%
- If component of fibromyalgia present, consider use of amitriptyline†, duloxetine†, gabapentin† or pregabalin† (off-label uses)
- If neuropathic pain present, consider use of amitriptyline† (off-label use), gabapentin† or pregabalin†
- If depression or anxiety is significant, suggest psychiatric review regarding optimal agent

* Reduce dose in elderly, caution in patients with liver disease.
** Caution in patients with cardiovascular, renal or gastrointestinal disease.
† Watch for interaction with tramadol.

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TABLE. ANALGESIC OPTIONS AND SIDE EFFECT PROFILES

Agent	Starting doses	Limitations
Simple analgesics		
Paracetamol	2 to 4 g/day	Generally safe, but care should be taken in patients with liver or renal disease; watch total dosage with combination pills
Glucosamine	1500 mg/day	High cost; data regarding efficacy are limited, care should be taken in patients with bleeding disorders or in those taking blood-thinning medications
Fish oil	2.7 g/day or more	Bad taste; high cost; data regarding efficacy are limited
Weak opioids		
Codeine	30 to 60 mg/day	Causes nausea and constipation
Tramadol	50 to 100 mg/day	Causes dizziness, nausea and constipation; care should be taken when coprescribed with selective serotonin reuptake inhibitors
Strong opioids		
Oxycodone	2.5 to 5 mg	Cause dizziness, headaches, nausea, constipation, respiratory depression and somnolence; have the potential for tolerance and addiction
Buprenorphine	5 mg patch weekly	
Morphine	10 mg/day	
Fentanyl patch	12.5 µg/hour every three days	
Adjuvants		
Capsaicin 0.025%, topical*	Apply four times a day	Causes local burning and skin irritation
Amitriptyline*§	10 to 25 mg/day	Causes dizziness, somnolence, dry mouth and constipation
Fluoxetine*§	20 mg/day	Causes nausea, somnolence, dry mouth and sexual dysfunction
Duloxetine†	30 to 60 mg/day	Causes dizziness, somnolence and dry mouth
Gabapentin‡	300 to 900 mg/day	High cost; causes dizziness, somnolence, swelling and ataxia
Pregabalin‡	150 mg/day	High cost; causes dizziness, somnolence, swelling and ataxia

* Off-label use.
† Off-label use unless used for the treatment of patients with diabetic neuropathic pain.
‡ Off-label use unless used for the treatment of patients with neuropathic pain.
§ Not listed on the PBS for pain management.

After the inflammatory component of IA has been minimised, treatment goals shift to being similar to those for patients with secondary osteoarthritis. In the patient with persistent pain despite having well-controlled IA, a general stepwise approach is used. A summary of the agents and their common side effects to be considered is shown in the Table. In general, use of more than one drug with the same mode of action is likely to increase the risk of adverse effects and should be avoided. Severe vitamin D deficiency is also known to cause arthralgias and myalgias and deficiency should be treated as a reversible cause of pain (aiming for vitamin D levels of more than 80 nmol/L). It should be noted that not all patients with pain are responsive to pharmacological treatments; once a treatment has been initiated, it is important to monitor its efficacy to justify continuation of that treatment.

Mild pain

Depending on the individual, paracetamol, NSAIDs or a combination of both should be considered before using more potent analgesics. The daily dose of paracetamol should not exceed 4 g if there is a history of liver disease or the patient is elderly. Several selective and nonselective NSAIDs are available and switching agents should be considered if insufficient analgesia is achieved after a few weeks. This is because the failure of one NSAID does not predict failure of all NSAIDs. The combination of these agents with methotrexate is generally considered to be safe.

It is well known that the use of selective and nonselective NSAIDs are associated with an increased risk of cardiovascular events in the general population. Naproxen appears to have the least potential to increase the risk of cardiovascular disease, although there are limited data available that evaluate the magnitude of this risk in patients with IA. As a guide, in patients with IA and pre-existing gastrointestinal, hypertension, cardiovascular or renal disease, paracetamol should be used as first-line treatment. If required, NSAIDs including coxibs should be used with caution at the lowest effective dose and for the shortest time, monitoring for adverse events carefully. If NSAIDs are needed in patients with high

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KEY POINTS FOR GPS

- Pain management is a high priority for patients with inflammatory arthritis.
- A multimodal approach should be tailored to an individual patient's needs.
- All patients with inflammatory arthritis and chronic pain should have an action plan for 'bad days'.
- Systemic glucocorticoids are not recommended for the management of pain in the absence of inflammation.
- Patients should be reviewed regularly and ineffective therapies discontinued if therapeutic goals are not achieved.

gastrointestinal risk, the use of selective COX-2 inhibitors is preferential and the concurrent prescription of a proton pump inhibitor is also recommended.

Moderate pain

If paracetamol and NSAIDs provide inadequate relief, a weak opioid such as codeine or tramadol may be added. They combine favourably with paracetamol; however, use is limited by side effects such as dizziness, nausea and constipation. It should be remembered that 5 to 10% of the population are slow metabolisers, and are unable to synthesise enough morphine from codeine or convert tramadol to its active metabolite to produce an analgesic effect. Care should be taken to avoid the concomitant use of selective serotonin reuptake inhibitors and tramadol.

Severe pain

The role of long-term opioid therapy for patients with persistent nonmalignant pain continues to be controversial. However, it is reasonable to consider the use of these drugs in patients in whom the above combined treatment strategies are contraindicated or have failed and there is pain-related impairment of function and quality of life. An example would be a patient with refractory pain who requires, but is not a candidate for, joint replacement surgery. Stronger agents to consider include transdermal buprenorphine, oxycodone and occasionally transdermal fentanyl or morphine. Concerns regarding tolerance, addiction and the commonly reported side effects of constipation, nausea and somnolence limit the use of opioids. If used, a laxative should be coprescribed, although a newer preparation combining oxycodone plus naloxone is now available and has been designed to reduce opioid-induced constipation.

Safe and effective prescribing of opioids on a long-term basis requires skills in both opioid pharmacotherapy and risk assessment and management. Patients receiving these agents should be regularly reassessed for the attainment of therapeutic goals, adverse effects and responsible medication use. A contract with the patient regarding a definitive trial period should be discussed and a gradual withdrawal plan instigated if the aspired benefits have not been achieved.

Adjuvant agents

Adjuvant agents are not recommended as analgesic options in isolation, but can be considered at any time as part of a comprehensive pain management strategy. Despite a lack of data in patients with IA, if there is a significant element of either fibromyalgia or neuropathy (where there is good efficacy data), it is reasonable to trial an antidepressant (off-label use), such as amitriptyline or duloxetine or one of the newer, more costly neuromodulating agents, such as gabapentin or pregabalin (Table). A low dose should be initiated and slowly increased according to efficacy and adverse effects, knowing that therapeutic benefits are often slow to develop. For patients with troublesome joints, topical capsaicin may be tried, although about 30% of patients are unable to tolerate the local burning sensation. There is no evidence to support the use of muscle relaxants as analgesics in patients with IA.

CONCLUSION

Pain management is a high priority for patients with IA and even small decreases in the severity of pain can positively influence a patient's well-being (see the key points box on this page). Currently, there are no guidelines because of a lack of published studies in this patient population. For patients with persistent joint pain, a multidisciplinary approach combining education, nonpharmacological and pharmacological interventions should be tailored to the individual's risk–benefit profile. MT

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COMPETING INTERESTS: None.

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