Pain in rheumatoid arthritis: a critical review

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SUMMARY

Patients with rheumatoid arthritis (RA) are frequently afflicted by pain, which may be caused by joint inflammation (leading to structural joint damage) or secondary osteoarthritis, and may be increased by central sensitisation. Non-inflammatory pain may also confuse the assessment of disease activity, and so the aim of treatment is not only to combat inflammatory disease, but also relieve painful symptoms. In order to ensure effective treatment stratification, it is necessary to record a patients medical history in detail, perform a physical examination, and objectively assess synovitis and joint damage. The management of pain requires various approaches that include pharmacological analgesia and biological and non-biological treatments. Although joint replacement surgery can significantly improve RA-related pain, it may only be available to patients with the most severe advanced disease.

Key words: *Rheumatoid arthritis, Pain, Central sensitization, Analgesics.*

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INTRODUCTION

Rheumatoid arthritis (RA) is a common inflammatory joint disease that has a major impact on the quality of life, working productivity, and the use of healthcare resources (1, 2). RA patients usually declare that pain is their greatest problem and highest priority (3-5) as it causes psychological distress and sleep disturbances, and may even be a more important cause of disability than structural joint damage (6, 7). Pain is frequently considered a marker of inflammation, but there is only a weak correlation between the intensity of pain and measures of peripheral inflammation(8, 9); however, pain is associated with disease activity, and radiographic changes may be linked to future pain (10-13).

Inflammation causes pain, stiffness and progressive joint damage, but it is becoming increasingly possible to suppress it completely and ensure clinical remission (14), and long-term outcomes may be improved if this is rapidly achieved (15, 16). The results of clinical trials indicate that early intensive treatment with disease-modifying modifying anti-inflammatory drugs (DMARDs) and corticosteroids lead to better pain outcomes (17-20), especially when guided by the regular monitoring of disease activity. The effective suppression of inflammatory disease during the first years after a diagnosis of RA tends to decrease the level of pain, although it often does not completely disappear (21-24), and may subsequently increase once again.

The pain associated with RA may occur spontaneously or be evoked by gently moving a joint within its normal working range, and may even be felt in the apparently normal surrounding tissue. Referred pain syndromes have also been reported because the entity of symptoms does not

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necessarily correlate with the severity of the underlying disease, and symptoms may continue even in the absence of disease exacerbations (25, 26).

RA-related pain may be worsened by joint damage, which may be secondary to inflammatory disease or due to concomitant osteoarthritis (OA). Moreover, the prevalence of chronic, non-inflammatory pain syndromes such as fibromyalgia (FM) is higher among patients with RA than in the general population (27, 28). Patients with inflammatory arthritis and FM have higher levels of disease activity and a poorer quality of life than their counterparts without FM. Pain therefore not only affects patients directly, but also indirectly contributes to the psychological and social impact of RA, and the need for better analgesia remains an important issue (1, 2).

PAIN MECHANISMS IN RA

Causes of RA pain may vary between early and late disease, during and between inflammatory flares, and between different individuals.The inflamed synovium generates mediators such as prostaglandins and bradykinin and proinflammatory cytokines such as tumor necrosis factor alfa (TNF-α), interleukin-1 (IL-1), and IL-6 and nerve growth factor beta (NGF-β) which sensitize peripheral nerves contributing significantly to the generation and maintenance of pain (29-32).

The synovium is unlikely to be the only source of pain in RA, and sensory nerves are also localized to joint capsule, ligaments, the outer regions of menisci, subchondral bone, tendon sheaths, and muscles (29).

Articular cartilage and the inner two-thirds of the menisci are normally aneural, permitting normal pain-free weight bearing and joint movement.

Synovitis is associated with altered expression of neurotransmitters, such as γ-aminobutyric acid (GABA), substance P and calcitonin gene-related peptide (CGRP), and their corresponding receptors in the spinal cord (33, 34). Microglia and astrocytes within the spinal cord are activated to produce cytokines such as TNF-α, IL-1, and IL-6, which in turn facilitate pain transmission (35, 36). Enhanced descending activation and reduced descending inhibition may further increase nociceptive transmission (37-39).

Central sensitization may be more widespread than the innervation of the inflamed joint, resulting in reduced pain thresholds in adjacent tissues (1, 2, 40).

Widespread reductions in pain pressure thresholds have been associated with low mood and sleep disturbance (41, 42), features shared with FM. Indeed, approximately 8% of patients with RA may satisfy classification criteria for FM in cross-sectional surveys (43, 44). Application of FM classification criteria in RA may identify a subgroup of patients with the most abnormal pain processing, but may conceal a larger number of patients in whom similar pain mechanisms make an important contribution to their symptoms.

Pain in RA may be further exacerbated by joint damage, either secondary to inflammatory disease, or because of comorbid OA. This may be the case particularly in long-established disease.

RA structural changes (erosions and joint space narrowing) are associated with greater pain, although they may explain only 2% of pain intensity after adjustment for other factors such as current disease activity (45).

Psychological factors contribute to the pain experience, and in addition, pain itself imposes a psychological burden. Psychological factors influence pain reporting in RA (46, 47), and high depression indices have been associated with greater RA pain (48).

The pain experience may be modified by beliefs about its causes and consequences, and expectations about prognosis and response to treatment.

The pain experience is complex and multifaceted, comprising both sensory and emotional components.

Despite the undoubted contribution of inflammation to RA pain, persistent pain despite adequate control of inflammation indicates contributions from multiple pain mechanisms (1, 2).

CLINICAL EXPRESSION OF PAIN IN RA

Pain is a major risk factor for a poor outcome. Patients with early RA who report high levels of bodily pain at the time of presentation are more likely to report greater disability after one year (49). Patients describe the severity, quality and periodicity of their joint pain in different ways. It is often described as "gnawing" or aching, which suggest nociceptive mechanisms directly mediated by inflammation or joint damage, but other descriptors such as "burning" or "shooting" are more characteristic of neuropathic pain and suggest possible nerve damage. Finally, the frequent descriptions of the more widespread pain associated with sleep disturbances, fatigue and mood (50) suggest abnormal central pain processing.

The 28-joint Disease Activity Score (DAS28) is frequently used to assess joint inflammation in randomised controlled trials (RCTs) and to guide treatment decisions in clinical practice (51). Intensive 'treat-to-target' regimens require treatment escalation in patients with active disease defined by their DAS28, and some national guidelines (such as those of the United Kingdom) restrict the use of biological to patients with a high score. However, the relationship between DAS28 and inflammatory disease activity is confounded by other factors (52). Although visual analogue scales (VAS) and tender joint counts certainly increase with inflammation, and are both closely related with reported bodily pain (53), they may also be increased by concomitant painful conditions such as OA, which usually affects the hands and knees (joints included in the DAS28), or by changes in pain processing such as central sensitisation, which coincides with joint inflammation and may make it difficult to interpret the DAS28 (54). For example, patients who fulfil the diagnostic criteria for both RA and FM report higher levels of pain (55) and have a higher DAS28 (56) than those with RA alone, which may indicate that central sensitisation or a painful comorbidity affects the scoring.

Two recent studies have found that pain significantly affects patients' assessments of RA disease activity. The first involved 7,028 patients from the Quantitative Standard Monitoring of Patients with RA (QUEST-RA) database receiving "usual care" at 83 centres in 30 countries (57), and showed that pain was the single most important determinant of patient global assessment. The second involved 646 RA patients starting methotrexate (MTX) treatment at an academic outpatient clinic, and found that pain explained 75.6% of the variability patient global assessment scores (58).

Although pain contributes less to physician global assessments, it was the fourth most important determinant of the physician global assessment in the QUEST-RA study, after swollen joint counts, the erythrocyte sedimentation rate, and tender joint counts (57), and second only to swollen joint counts in the physician global assessment of the MTX study (58), The fact that it was also one of the most significantly discordant variables between the patient and physician global assessments in both studies further underlines the importance of pain to patients and suggests that it is insufficiently considered by physicians.

PHARMACOLOGICAL MANAGEMENT OF RA-RELATED PAIN

The 3e (evidence, expertise, exchange) initiative, a 17-country collaborative project that promotes evidence-based practice in rheumatology, has recently published recommendations for the pharmacological management of pain in patients with inflammatory arthritis (59), many of which were based on a series of Cochrane database systematic reviews published in 2011-2012.

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to manage pain in RA patients, but are not appropriate for long-term disease control (60, 61); furthermore, although the early use of DMARDs is very important (62, 83), the significance of pain

to the patients means that they often take analgesics from the start of the disease. According to the European League Against Rheumatism (EULAR), symptomatic patients presenting with early arthritis should be treated with NSAIDs after their gastrointestinal, renal, and cardiovascular status has been carefully evaluated (64), whereas the British Society for Rheumatology (BSR) guideline for the long-term management of RA recommends the short-term use of a stepped approach combining NSAIDs with a proton pump inhibitor (64), and the National Institute for Health and Care Excellence (NICE) guideline suggests analgesics (e.g. paracetamol, codeine or fixed-dose combinations) as a means of reducing the need for long-term NSAID or cyclo-oxygenase (COX)-2 inhibitor treatment (64).

However, the use of analgesics in RA is often only indirectly supported as the evidence comes from RCTs involving patients with other conditions, and publication biases may conceal some findings of inefficacy in arthritis. Furthermore, although paracetamol is readily available, there is little RCT-based evidence supporting its use (65-69), and the trials have often used it in combination with another analgesic of a different class. Paracetamol is often a component of combined products, and one potential concern is that they may mask the patient's cumulative paracetamol intake, which should not exceed four grams in healthy adults. On the other hand, typical paracetamol-containing products include opioid combinations (codeine, tramadol, oxycodone, etc.), which may actually be opioid sparing because they provide effective analgesia at lower opioid doses than single opioids (89), and it has been demonstrated that the fixed-dose combination of tramadol and paracetamol leads to synergistic benefits (70, 71).

Nevertheless, it does seem to offer some short-term analgesic benefit and, in combination with a COX inhibitor, may be more effective than either alone, although there is no evidence that this maintained in the long term.

A systematic review (72) of 11 randomised or quasi-RCTs comparing opioids with placebo or an active analgesic has concluded that the evidence in favour of the use of weak opioids (codeine, dextropropoxyphene, pentazosine, tilidine and tramadol) is itself weak. Furthermore, the risk ratio for study withdrawal due to the frequent side effects of constipation, dizziness, nausea and vomiting between the opioid- and placebo-treated participants was 2.7, and the use of opioids may also lead to opioid-induced hyperalgesia, which is associated with heightened pain sensitivity and increased clinical pain intensity. Consequently, it is generally recommended that long-term opioid prescriptions should be minimised and, when opioids are necessary, their use should be regularly and carefully monitored (73-78).

A Cochrane systematic review found that the evidence in favour of using neuromodulators to treat RA-related pain was also weak (79), although it only considered four small randomised, placebo-controlled trials: two of nefopam (a centrally acting analgesic used in Europe but not the United States), one of topical capsaicin, and one of oro-mucosal cannabis. The authors concluded that topical capsaicin could be considered as adjuvant therapy for RA-related pain (80). Other potential adjuvant treatments options for pain in inflammatory arthritis recommended by the 3e initiative are gabapentin and pregabalin, although it should be remembered that these recommendations are mainly based on their efficacy in studies of pain in FM, a non-inflammatory, chronic widespread pain condition (81, 82).

Biological therapies (83-85), are reserved for patients with the most advanced or severe disease, whereas disease control in the majority of patients depends on glucocorticosteroids and traditional DMARDs such as MTX (86, 87). Glucocorticosteroids and DMARDs reduce RA-related pain, but the analgesic effects of the former may only last for three months (88, 89). The early suppression of inflammatory disease activity is not only important to reduce pain in the short term because delaying the introduction of DMARDs is associated with

worse pain 12 months after presentation. Finally, DMARD combinations may be more effective than monotherapy

It must also be remembered that inflammation is only one component contributing to the pain experienced by many arthritic patients, and incomplete symptomatic relief is frequent even when there is other evidence of inflammatory control such a reductions in swollen joint counts, the levels of acute-phase reactants, and ultrasound findings of synovitis. These clinical observations and the often slow action of disease-modifying treatments mean that alternative strategies are necessary. Although adequate analgesia may have a positive effect on disease activity scores by reducing joint tenderness and improving patient-reported general health, it is necessary not to mistake this for the suppression of the underlying disease.

Tricyclic antidepressants (TCAs such as amitriptyline, dothiepin and imipramine) inhibit serotonin and norepinephrine reuptake and neuronal sodium channels (90), but it is believed that the differences in the antinociceptive effects of the various TCAs are substantially due their non-serotoninergic properties. The results of clinical trials of TCAs have led to equivocal results in RA patients (91). A Cochrane systematic review of eight RCTs comparing antidepressant therapy with placebo or an active intervention found insufficient evidence to recommend its use to treat RA-related pain (91), whereas the 3e recommendations include TCAs as a potential adjuvant treatment for patients with inflammatory arthritis (59), although it was specifically noted that the still-incomplete data mean that they should only be considered for a subset of patients. Nevertheless, TCAs offer RA patients significantly more pain relief than placebo (91-93), and their use has become so widespread that it has been proposed that, like anticonvulsants, they should be considered "pain-modifying drugs" .

The current stratification of analgesic treatment is based on potency or sequential trials, beginning with the least expensive, low- risk treatments. However, individual failures of analgesic or anti-inflammatory therapy may indicate that other pain mechanisms are involved, and that patients may benefit more if stratified care is based on the careful evaluation of the contributions of inflammation, joint damage and central sensitisation.

The multi-dimensional nature of RA and most other chronic pain indications suggests that a combined approach to analgesia may be more appropriate, and findings of the 23 studies published so far have been summarised in a recent Cochrane systematic review (94). No meta-analysis was made because of the heterogeneity of these studies, but 18 reported no significant difference in a standardised pain outcome between the monotherapy and combination therapy groups: however, it is unclear whether these results can be generalised.

NON-PHARMACOLOGICAL TREATMENT OF RA-RELATED PAIN

Non-pharmacological pain management can be important because chronic pain acceptance, coping skills and self-efficacy contribute to the quality of life of RA patients, and psychological interventions such as cognitive behavioural therapy may also help (95-98). A better understanding of pain mechanisms can limit catastrophic thoughts concerning the meaning of pain, and combined psychological and pharmacological strategies can facilitate pain control. In some cases cognitive therapy may be an effective treatment for RA and need not necessarily include behavioral strategies (99, 100).

Patients with RA who have moderate disease activity and limited joint erosions may benefit from short-term exercise including aerobic capacity and dynamic strength training. Short-term, land-based aerobic exercise is likely to improve aerobic capacity immediately following the intervention but may not affect muscle strength or functional ability. Short-term and long-term, land-based aerobic and strength training may improve aerobic capacity and muscle strength. Exercise also does not appear to produce any negative effects with respect

to increased pain or disease activity (101). Resistance exercise in RA is safe, and the improvement in most outcomes was statistically significant and possibly clinically relevant for RA pain and disability (102).
In the case of patients with severe, unremitting pain localised to a single joint, joint replacement surgery can offer substantial relief (103-105). The underlying reasons for this are not fully understood, but may include the physical protection of subchondral nerves or the avoidance of the development of synovitis from an origin in the articular cartilage.

CONCLUSIONS

Rheumatoid arthritis is a frequent and chronic painful condition affecting the synovial joints. Current treatments concentrate on suppressing inflammation, but rarely provide complete pain relief. Pain is not only an important outcome for RA patients, but also aggravates disability and psychological distress. RA-related pain may be mediated by mechanisms such as inflammation, structural damage or altered central pain processing, and a better understanding of the different contributions of these mechanisms should lead to more effective treatment targeting as well as the development of new and more efficacious treatments with fewer side effects. The two most important advances in the treatment of arthritic pain over the last 40 years have been the introduction of total joint replacement surgery into routine clinical practice, and the more recent development of biological therapies that suppress the underlying inflammatory disease (1, 2). Both have improved the quality of life of large numbers of patients, but both are now associated with substantial healthcare expenditure. Furthermore, 15% of the patients undergoing total knee replacement surgery may continue to experience persistent and disabling pain, and up to 25% of those receiving anti-TNF therapy for presumed active RA receive no meaningful benefit. RA treatments targeting inflammatory mechanisms not only relieve pain by suppressing synovitis, but may also reduce central sensitisation by modulating neuroimmune interactions in the central nervous system: they should therefore be offered together with pharmacological and non-pharmacological treatments for RA-related pain in order to optimise both short- and long-term outcomes (106).

REFERENCES

1. Walsh DA, McWilliams DF. Pain in rheumatoid arthritis. Curr Pain Headache Rep. 2012; 16: 509-17.
2. Lee YC. Effect and treatment of chronic pain in inflammatory arthritis. Curr Rheumatol Rep. 2013; 15: 300.
3. Heiberg T, Kvien TK. Preferences for improved health examined in 1024 patients with rheumatoid arthritis: pain has highest priority. Arthritis Rheum. 2002; 47: 391-7.
4. Taylor P, Manger B, Alvaro-Gracia J, Johnstone R, Gomez-Reino J, Eberhardt E, et al. Patient perceptions concerning pain management in the treatment of rheumatoid arthritis. J Int Med Res. 2010; 38: 1213-24.
5. Minnock P, FitzGerald O, Bresnihan B. Women with established rheumatoid arthritis perceive pain as the predominant impairment of health status. Rheumatology. 2003; 42: 995-1000.
6. Kvien TK. Epidemiology and burden of illness of rheumatoid arthritis. Pharmacoeconomics. 2004; 22: 1-12.
7. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis Care Res. 2012; 64: 206-14.
8. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in the perception of rheumatoid arthritis disease activity. Arthritis Rheum. 2012; 64: 2814-23.
9. Courvoisier N, Dougados M, Cantagrel A, Goupille P, Meyer O, Sibilia J, et al. Prognostic factors of 10-year radiographic out- come in early rheumatoid arthritis: a prospective study. Arthritis Res Ther. 2008; 10: R106.
10. Odegard S, Finset A, Mowinckel P, Kvien TK, Uhlig T. Pain and psychological health status over a 10-year period in patients with recent onset rheumatoid arthritis. Ann Rheum Dis. 2007; 66: 1195-201.
11. Sokka T, Kankainen A, Hannonen P. Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores. Arthritis Rheum. 2000; 43: 386-9.

12. Sarzi-Puttini P, Fiorini T, Panni B, Turiel M, Cazzola M, Atzeni F. Correlation of the score for subjective pain with physical disability, clinical, and radiographic scores in recent onset rheumatoid arthritis. BMC Musculoskelet Disord. 2002; 3: 18.
13. McWilliams DF, Zhang W, Mansell JS, Kiely PD, Young A, Walsh DA. Predictors of change in bodily pain in early rheumatoid arthritis: an inception cohort study. Arthritis Care Res (Hoboken). 2012; 64: 1505-13.
14. Schipper LG, Fransen J, den Broeder AA, Van Riel PL. Time to achieve remission determines time to be in remission. Arthritis Res Ther. 2010; 12: R97.
15. Finckh A, Choi HK, Wolfe F. Progression of radiographic joint damage in different eras: trends towards milder disease in rheumatoid arthritis are attributable to improved treatment. Ann Rheum Dis. 2006; 65: 1192-7.
16. Soubrier M, Lukas C, Sibilia J, Fautrel B, Roux F, Gossec L, et al. Disease activity score-driven therapy vs routine care in patients with recent-onset active rheumatoid arthritis: data from the GUEPARD trial and ESPOIR cohort. Ann Rheum Dis. 2011; 70: 611-5.
17. Atzeni F, Sarzi-Puttini P. Rheumatoid arthritis: why wait? Explaining delays in seeking therapy for early arthritis. Nat Rev Rheumatol. 2012; 8: 190-1.
18. Andersson ML, Svensson B, Bergman S. Chronic widespread pain in patients with rheumatoid arthritis and the relation between pain and disease activity measures over the first 5 years. J Rheumatol. 2013; 40: 1977-85.
19. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ten Wolde S, Han KH, van Krugten MV, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. Arthritis Rheum. 2007; 56: 2129-34.
20. Wolfe F, Michaud K. Assessment of pain in rheumatoid arthritis: minimal clinically significant difference, predictors, and the effect of anti-tumor necrosis factor therapy. J Rheumatol. 2007; 34: 1674-83.
21. Wiles NJ, Scott DG, Barrett EM, Merry P, Arie E, Gaffney K, et al. Benchmarking: the five year outcome of rheumatoid arthritis assessed using a pain score, the Health Assessment Questionnaire, and the Short Form-36 (SF-36) in a community and a clinic based sample. Ann Rheum Dis. 2001; 60: 956-61.
22. Rupp I, Boshuizen HC, Roorda LD, Dinant HJ, Jacobi CE, van den Bos G. Course of patient-reported health outcomes in rheumatoid arthritis: comparison of longitudinal and cross-sectional approaches. J Rheumatol. 2006; 33: 228-33.
23. Roche PA, Klestov AC, Heim HM. Description of stable pain in rheumatoid arthritis: a 6 year study. J Rheumatol. 2003; 30: 1733-8.
24. Gerecz-Simon EM, Tunks ER, Heale JA, Kean WF, Buchanan WW. Measurement of pain threshold in patients with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and healthy controls. Clin Rheumatol. 1989; 8: 467-74.
25. Atzeni F, Cazzola M, Benucci M, Di Franco M, Salaffi F, Sarzi-Puttini P. Chronic widespread pain in the spectrum of rheumatological diseases. Best Pract Res Clin Rheumatol. 2011; 25: 165-71.
26. Wolfe F. Fibromyalgianess. Arthritis Rheum. 2009; 61: 715-6.
27. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011; 38: 1113-22.
28. Lee YC, Chibnik LB, Lu B, Wasan AD, Edwards RR, Fossel AH, et al. The relationship between disease activity, sleep, psychiatric distress, and pain sensitivity in rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther. 2009; 11: R160.
29. Konttinen YT, Tiainen VM, Gomez-Barrena E, Hukkanen M, Salo J. Innervation of the joint and role of neuropeptides. Ann N Y Acad Sci. 2006; 1069: 149-54.
30. Schaible HG, Ebersberger A, Von Banchet GS. Mechanisms of pain in arthritis. Ann N Y Acad Sci. 2002; 966: 343-54.
31. Raychaudhuri SP, Raychaudhuri SK, Atkuri KR, Herzenberg LA, Herzenberg LA. Nerve growth factor: a key local regulator in the pathogenesis of inflammatory arthritis. Arthritis Rheum. 2011; 63: 3243-52.
32. Schaible HG, von Banchet GS, Boettger MK, Brauer R, Gajda M, Richter F, et al. The role of proinflammatory cytokines in the generation and maintenance of joint pain. Ann N Y Acad Sci. 2010; 1193: 60-9.
33. Benemei S, Nicoletti P, Capone JG, Geppetti P. CGRP receptors in the control of pain and inflammation. Curr Opin Pharmacol. 2009; 9: 9-14.
34. Brenn D, Richter F, Schaible HG. Sensitization of unmyelinated sensory fibers of the joint nerve to mechanical stimuli by interleukin-6 in the rat: an inflammatory mechanism of joint pain. Arthritis Rheum. 2007; 56: 351-9.
35. Zhang L, Berta T, Xu ZZ, Liu T, Park JY, Ji RR. TNF-alpha contributes to spinal cord synaptic plasticity and inflammatory pain: distinct role of TNF receptor subtypes 1 and 2. Pain. 2011; 152: 419-27.
36. Watkins LR, Maier SF. Beyond neurons: evidence that immune and glial cells contrib-

ute to pathological pain states. Physiol Rev. 2002; 82: 981-1011.
37. Richter F, Natura G, Loser S, Schmidt K, Viisanen H, Schaible HG. Tumor necrosis factor causes persistent sensitization of joint nociceptors to mechanical stimuli in rats. Arthritis Rheum. 2010; 62: 3806-14.
38. Bekkelund SI, Mellgren SI, Proven A, Husby G. Quantified neurological examination with emphasis on motor and sensory functions in patients with rheumatoid arthritis and controls. Br J Rheumatol. 1996; 35: 1116-21.
39. Leffler AS, Kosek E, Lerndal T, Nordmark B, Hansson P. Somatosensory perception and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from rheumatoid arthritis. Eur J Pain. 2002; 6: 161-76.
40. Huskisson EC, Hart FD. Pain threshold and arthritis. Br Med J. 1972; 4: 193-5.
41. Covic T, Tyson G, Spencer D, Howe G. Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors. J Psychosom Res. 2006; 60: 469-76.
42. Drewes AM, Svendsen L, Taagholt SJ, Bjerregard K, Nielsen KD, Hansen B. Sleep in rheumatoid arthritis: a comparison with healthy subjects and studies of sleep/wake interactions. Br J Rheumatol. 1998; 37: 71-81.
43. Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Fitzgerald JD, Ranganath VK, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep. 2012; 35: 537-43.
44. Nicassio PM, Ormseth SR, Kay M, Custodio M, Irwin MR, Olmstead R, et al. The contribution of pain and depression to self-reported sleep disturbance in patients with rheumatoid arthritis. Pain. 2012; 153: 107-12.
45. Khanna D, Ranganath VK, Fitzgerald J, Park GS, Altman RD, Elashoff D, et al. Increased radiographic damage scores at the onset of seropositive rheumatoid arthritis in older patients are associated with osteoarthritis of the hands, but not with more rapid progression of damage. Arthritis Rheum. 2005; 52: 2284-92.
46. Hagglund KJ, Haley WE, Reveille JD, Alarcon GS. Predicting individual differences in pain and functional impairment among patients with rheumatoid arthritis. Arthritis Rheum. 1989; 32: 851-8.
47. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. Nat Rev Rheumatol. 2011; 7: 216-24.
48. Hewlett S, Sanderson T, May J, Alten R 3rd, Bingham CO, Cross M, et al. "I'm hurting, I want to kill myself": rheumatoid arthritis flare is more than a high joint count - an international patient perspective on flare where medical help is sought. Rheumatology (Oxford). 2012; 51: 69-76.
49. Rupp I, Boshuizen HC, Dinant HJ, Jacobi CE, van den Bos GA. Disability and health-related quality of life among patients with rheumatoid arthritis: association with radiographic joint damage, disease activity, pain, and depressive symptoms. Scand J Rheumatol. 2006; 35: 175-81.
50. Nicassio PM, Wallston KA. Longitudinal relationships among pain, sleep problems, and depression in rheumatoid arthritis. J Abnorm Psychol. 1992; 101: 514-20.
51. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995; 38: 44-8.
52. van der Heijde DM, van't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, van de Putte LB. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis. 1992; 51: 177-81.
53. Leeb BF, Andel I, Sautner J, Nothnagl T, Rintelen B. The DAS28 in rheumatoid arthritis and fibromyalgia patients. Rheumatology (Oxford). 2004; 43: 1504-7.
54. Pollard LC, Kingsley GH, Choy EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. Rheumatology (Oxford). 2010; 49: 924-8.
55. Dhir V, Lawrence A, Aggarwal A, Misra R. Fibromyalgia is common and adversely affects pain and fatigue perception in North Indian patients with rheumatoid arthritis. J Rheumatol. 2009; 36: 2443-8.
56. Ranzolin A, Brenol JC, Bredemeier M, Guarienti J, Rizzatti M, Feldman D, et al. Association of concomitant fibromyalgia with worse disease activity score in 28 joints, health assessment questionnaire, and short form 36 scores in patients with rheumatoid arthritis. Arthritis Rheum. 2009; 61: 794-800.
57. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther. 2009; 11: R7.
58. Kiely P, Walsh D, Williams R, Young A. Outcome in rheumatoid arthritis patients with continued conventional therapy for moderate disease activity - the early RA network (ERAN). Rheumatology (Oxford). 2011; 50: 926-31.
59. Whittle SL, Colebatch AN, Buchbinder R, Edwards CJ, Adams K, Englbrecht M, et al.

Multinational evidence-based recommendations for pain management by pharmacotherapy in inflammatory arthritis: integrating systematic literature research and expert opinion of a broad panel of rheumatologists in the 3e initiative. Rheumatology (Oxford). 2012; 51: 1416-25.
60. di Munno O, Sarchi C. Effectiveness of tolmetin in rheumatoid arthritis: evaluation by means of a new method. Methods Find Exp Clin Pharmacol. 1982; 4: 203-6.
61. Sarzi-Puttini P, Atzeni F, Lanata L, Bagnasco M. Efficacy of ketoprofen vs. ibuprofen and diclofenac: a systematic review of the literature and meta-analysis. Clin Exp Rheumatol. 2013. [Epub ahead of print].
62. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum. 2002; 46: 347-56.
63. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology. 2004; 43: 906-14.
64. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010; 69: 964-75.
65. National Health Institute for Health and Care Excellence (NICE). Rheumatoid arthritis - the management of rheumatoid arthritis in adults. Clinical guidelines, CG79 - Issued: February 2009. London: HMSO; 2009.
66. Wienecke T, Gotzsche PC. Paracetamol vs nonsteroidal anti-inflammatory drugs for rheumatoid arthritis. Cochrane Database Syst Rev. 2004; 1: CD003789.
67. Seideman P, Melander A. Equianalgesic effects of paracetamol and indomethacin in rheumatoid arthritis. Br J Rheumatol. 1988; 27: 117-22.
68. Marks JL, Colebatch AN, Buchbinder R, Edwards CJ. Pain management for rheumatoid arthritis and cardiovascular or renal comorbidity. Cochrane Database Syst Rev. 2011; (10): dCD008952
69. Seideman P. Additive effect of combined naproxen and paracetamol in rheumatoid arthritis. Br J Rheumatol. 1993; 32: 1077-82.
70. Lee EY, Lee EB, Park BJ, Lee CK, Yoo B, Lim MK, et al. Tramadol 37.5 mg/acetaminophen 325 mg combination tablets added to regular therapy for rheumatoid arthritis pain: a 1-week, randomized, double-blind, placebo-controlled trial. Clin Ther. 2006; 28: 2052-60.
71. Richards BL, Whittle SL, Buchbinder R. Muscle relaxants for pain management in rheumatoid arthritis. Cochrane Database Syst Rev. 2012; 1: CD008922.
72. Whittle SL, Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev. 2011; 11: CD003113.
73. Zuccaro SM, Vellucci R, Sarzi-Puttini P, Cherubino P, Labianca R, Fornasari D. Barriers to pain management: focus on opioid therapy. Clin Drug Investig. 2012; 32: 11-9.
74. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010; 1: CD006605.
75. Atlas LY, Whittington RA, Lindquist MA, Wielgosz J, Sonty N, Wager TD. Dissociable influences of opiates and expectations on pain. J Neurosci. 2012; 32: 8053-64.
76. Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011; 3: 7-4.
77. Labianca R, Sarzi-Puttini P, Zuccaro SM, Cherubino P, Vellucci R, Fornasari D. Adverse effects associated with non-opioid and opioid treatment in patients with chronic pain. Clin Drug Investig. 2012; 32: 53-63.
78. Crofford LJ. Adverse effects of chronic opioid therapy for chronic musculoskeletal pain. Nat Rev. 2010; 6: 191-7.
79. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database Syst Rev. 2012; 1: CD008921.
80. Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, et al. Treatment of arthritis with topical capsaicin: a double-blind trial. Clin Ther. 1991; 13: 383-95.
81. Ogawa S, Satoh J, Arakawa A, Yoshiyama T, Suzuki M. Pregabalin treatment for peripheral neuropathic pain: a review of safety data from randomized controlled trials conducted in Japan and in the west. Drug Saf. 2012; 35: 793-806.
82. Siler AC, Gardner H, Yanit K, Cushman T, McDonagh M. Systematic review of the comparative effectiveness of antiepileptic drugs for fibromyalgia. J Pain. 2011; 12: 407-15.
83. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014; 73: 492-509.
84. Emery P. Optimizing outcomes in patients

with rheumatoid arthritis and an inadequate response to anti-TNF treatment. Rheumatology. 2012; 51: v22-30.
85. Kirwan JR, Hallgren R, Mielants H, Wollheim F, Bjorck E, Persson T, et al. A randomized placebo controlled 12 week trial of budesonide and prednisolone in rheumatoid arthritis. Ann Rheum Dis. 2004; 63: 688-95.
86. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, West-hovens R, van Denderen JC, et al. Randomized comparison of combined step-down prednisolone, methotrexate, and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997; 350: 309-18.
87. Steiman AJ, Pope JE, Thiessen-Philbrook H, Li L, Barnabe C, Kalache F, et al. Non-biologic disease-modifying antirheumatic drugs (DMARDs) improve pain in inflammatory arthritis (IA): a systematic literature review of randomized controlled trials. Rheumatol Int. 2013; 33: 1105-20.
88. Radner H, Ramiro S, Buchbinder R, Landewe RB, van der Heijde D, Aletaha D. Pain management for inflammatory arthritis (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and other spondylarthritis) and gastrointestinal or liver comorbidity. Cochrane Database Syst Rev. 2012; 1: CD008951.
89. Richards BL, Whittle SL, Buchbinder R. Antidepressants for pain management in rheumatoid arthritis. Cochrane Database Syst Rev. 2011; 11: CD008920.
90. Sarzi-Puttini P, Cazzola M, Boccassini L, Ciniselli G, Santandrea S, Caruso I, et al. A comparison of dothiepin versus placebo in the treatment of pain in rheumatoid arthritis and the association of pain with depression. J Int Med Res. 1988; 16: 331-7.
91. Caruso I, Sarzi-Puttini PC, Boccassini L, Santandrea S, Locati M, Volpato R, et al. Double-blind study of dothiepin versus placebo in the treatment of primary fibromyalgia syndrome. J Int Med Res. 1987; 15: 154-9.
92. Ramiro S, Radner H, van der Heijde D, van Tubergen A, Buchbinder R, Aletaha D, et al. Combination therapy for pain management in inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database Syst Rev. 2011; (10): CD008886.
93. Keefe FJ, Affleck G, Lefebvre JC, Starr K, Caldwell DS, Tennen H. Pain coping strategies and coping efficacy in rheumatoid arthritis: a daily process analysis. Pain. 1997; 69: 35-42.
94. Keefe FJ, Caldwell DS, Martinez S, Nunley J, Beckham J, Williams DA. Analyzing pain in rheumatoid arthritis patients. Pain coping strategies in patients who have had knee replacement surgery. Pain. 1991; 46: 153-60.
95. Knittle K, Maes S, de Gucht V. Psychological interventions for rheumatoid arthritis: examining the role of self-regulation with a systematic review and meta-analysis of randomized controlled trials. Arthritis Care Res. 2010; 62: 1460-72.
96. Knittle KP, De Gucht V, Hurkmans EJ, Vlieland TP, Peeters AJ, Ronday HK, et al. Effect of self-efficacy and physical activity goal achievement on arthritis pain and quality of life in patients with rheumatoid arthritis. Arthritis Care Res. 2011; 63: 1613-9.
97. Sharpe L, Schrieber L. A blind randomized controlled trial of cognitive versus behavioral versus cognitive-behavioral therapy for patients with rheumatoid arthritis. Psychother Psychosom. 2012; 81: 145-52.
98. John H, Hale ED, Treharne GJ, Kitas GD, Carroll D. A randomized controlled trial of a cognitive behavioural patient education intervention vs a traditional information leaflet to address the cardiovascular aspects of rheumatoid disease. Rheumatology (Oxford). 2013; 52: 81-90.
99. Iversen MD, Brandestein JS. Do dynamic strengthening and aerobic capacity exercise reduce pain and improve functional outcomes and strength in people with established rheumatoid arthritis? Phys Ther. 2012; 92: 1251-7.
100. Baillet A, Vaillant M, Guinot M, Juvin R, Gaudin P. Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2012; 51: 519-27.
101. Liu SS, Buvanendran A, Rathmell JP, Sawhney M, Bae JJ, Moric M, et al. A cross-sectional survey on prevalence and risk factors for persistent postsurgical pain 1 year after total hip and knee replacement. Reg Anesth Pain Med. 2012; 37: 415-22.
102. Clarke H, Woodhouse LJ, Kennedy D, Stratford P, Katz J. Strategies aimed at preventing chronic post-surgical pain: comprehensive perioperative pain management after total joint replacement surgery. Physiother Can. 2011; 63: 289-304.
103. Calder JD, Ashwood N, Hollingdale JP. Survivorship analysis of the "Performance" total knee replacement-7-year follow-up. Int Orthop. 1999; 23: 100-3.
104. Cherubino P, Sarzi-Puttini P, Zuccaro SM, Labianca R. The management of chronic pain in important patient subgroups. Clin Drug Investig. 2012; 32: 35-44.
105. Sarzi-Puttini P, Vellucci R, Zuccaro SM, Cherubino P, Labianca R, Fornasari D. The appropriate treatment of chronic pain. Clin Drug Investig. 2012; 32: 21-33.
106. Smith HS, Smith AR, Seidner P. Painful rheumatoid arthritis. Pain Physician. 2011; 14: E427-58.