Review

Arthritis and pain

Current approaches in the treatment of arthritic pain

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Abstract

Current evidence suggests that although persistent arthritic pain is initiated and maintained by articular pathology, it is also heavily influenced by a range of other factors. Strategies for treating arthritic pain are therefore different from those adopted for acute pain. Although published guidelines offer general assistance, the complexity of underlying mechanisms requires that measures designed to relieve pain must take into account individual biological, psychological and societal factors. It follows that a combination of both pharmacological and non-pharmacological approaches offers the best opportunity for therapeutic success, although determining the effectiveness of such complex interventions remains difficult. Pharmacological therapy is often prolonged, and safety and tolerability issues become as important as efficacy over time.

Introduction

Arthritic pain is common and is associated with worse functional outcomes and poorer quality of life when compared with a range of other chronic conditions [1]. A bewildering array of guidelines and other evidence-based resources are available, but the variability of therapeutic responses can lead to frustration and disappointment for both patients and health professionals.

This review categorizes different pain states associated with arthritis and discusses the extent to which an understanding of underlying mechanisms can be used to inform the choice of analgesic therapy. Although a detailed and systematic evaluation of specific interventions is beyond the scope of the review, evidence for the utility of general approaches is presented. The limitations of current approaches to assessment and management are discussed along with the rationale for use of integrated care in patients with persistent pain.

Mechanisms of pain

Pain classification

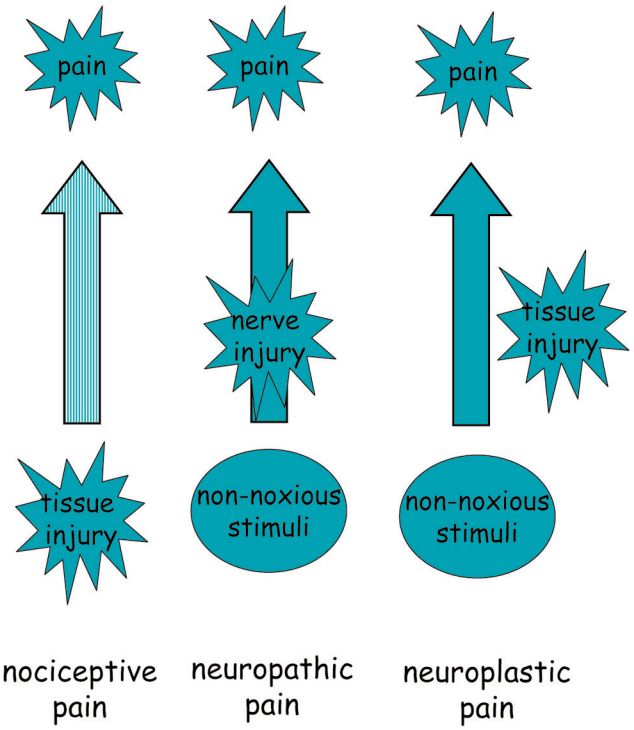
Traditionally, pain has been regarded as being either nociceptive (arising in response to tissue injury) or neuropathic (arising in response to nerve injury). Although this distinction has had some therapeutic utility, it has served to maintain the Cartesian concept of a fixed immutable pain system that faithfully transmits information from a site of injury to pain centres within the brain. Although this is largely true after acute injury, it is clear from epidemiological studies that in the presence of persistent disease a range of additional factors, often unrelated to the musculoskeletal system, serve to modify activity within pain (nociceptive) pathways.

Implicit in recent classification schemes is the notion that acute and chronic pain states are different and that functional changes within the nociceptive system are important in determining the signs and symptoms experienced by individuals with somatic disease [2]. Currently, four different pain states are recognized (Figure 1). The first of these, nociceptive pain, refers to those transient symptoms and signs that arise in response to acute injury and reflects the activation of specialized pain receptors (nociceptors) and corresponding activity in more central pathways. Under these conditions, symptoms broadly reflect the initiating stimulus or injury; treatment at a peripheral level is likely to be successful.

In contrast, neuroplastic pain (also called inflammatory pain) occurs in response to more persistent tissue injury and is the most common pain state associated with musculoskeletal disease [3]. It arises as a result of mediators released from damaged tissues acting to increase the excitability of the nociceptive pathway and has the effect of making everyday

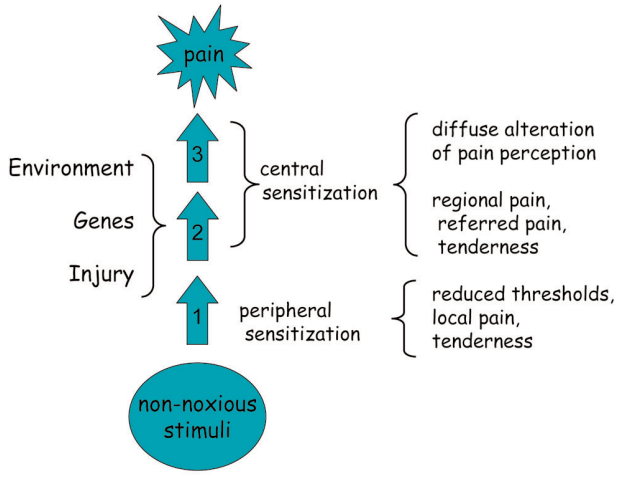
coxibs = cyclooxygenase inhibitors; IL = interleukin; NSAID = non-steroidal anti-inflammatory drug; OA = osteoarthritis; RA = rheumatoid arthritis; RCT = randomized controlled trial; TENS = transcutaneous electrical nerve stimulation; TNF = tumour necrosis factor.

Figure 1



Classification of pain. Nociceptive pain is triggered by tissue injury and activates unmodified nociceptive neurons (light arrow) inducing acute pain. In contrast, normally innocuous stimuli produce pain in neuropathic and neuroplastic conditions in consequence of sensitized nociceptive pathways (dark arrows). Note: Idiopathic pain omitted from figure. (Adapted from [3].)

Figure 2



Causes and consequences of neural plasticity. Although tissue injury or inflammation can trigger nociceptor sensitization in peripheral neurons (1), other somatic, psychological and environmental influences are likely to determine the magnitude of any subsequent change as a result of modulation of activity at spinal (2) or cortical (3) levels. (Adapted from [3].)

activities such as standing or walking painful. Effective therapy requires that attention be directed to both the originating injury and those additional factors (see below) that influence nociceptive activity.

Third, neuropathic pain occurs in the presence of nerve injury, as might occur in association with carpal tunnel syndrome or after lumbar disc prolapse. Ectopic expression of ion channels, receptors and related phenomena occur in both injured and neighbouring non-injured neurons, with resultant regional pain hypersensitivity and sensory disturbance.

There is currently debate as to the origins of a fourth pain category, idiopathic pain, which covers such medically unexplained disorders as fibromyalgia syndrome, irritable bowel syndrome and tension headache. In all of these disorders, evidence for peripheral pathology is minimal and symptoms are considered to reflect disordered pain processing at more central levels.

Arthritic pain

At a local level, mediators released from synovium, bone or other tissues will induce the sensitization of articular pain receptors. The clinical correlate of sensitization at this peripheral level is that musculoskeletal symptoms will be localized, with a relatively close relationship to mechanical stimuli such as walking or standing (Figure 2). Treatment with systemic or topical therapies designed to reduce inflammatory mediators might be expected to have a beneficial effect, which is in accord with clinical experience [4].

In chronic conditions such as osteoarthritis (OA) or rheumatoid arthritis (RA), neural sensitization will not be confined to the periphery. The finding of increased areas of punctate hyperalgesia in patients with RA after topical application of capsaicin is in accord with increased excitability of spinal neurons in this condition [5]. Clinically, this leads to enhanced pain perception at the site of injury, as well as to the development of pain and tenderness in normal tissues both adjacent to and removed from the primary site.

Spinal nociceptive processing in arthritic patients is under the influence of descending inhibitory controls and inputs from other somatic structures [6]. Both previous pain episodes and genetic factors are also likely to influence activity. The multiplicity of mediators involved provides an opportunity for therapeutic intervention, and many of the commonly used therapeutic strategies including acupuncture, transcutaneous electrical nerve stimulation (TENS) and pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs) and the weaker opioid drugs are likely to be exerting an effect at this level.

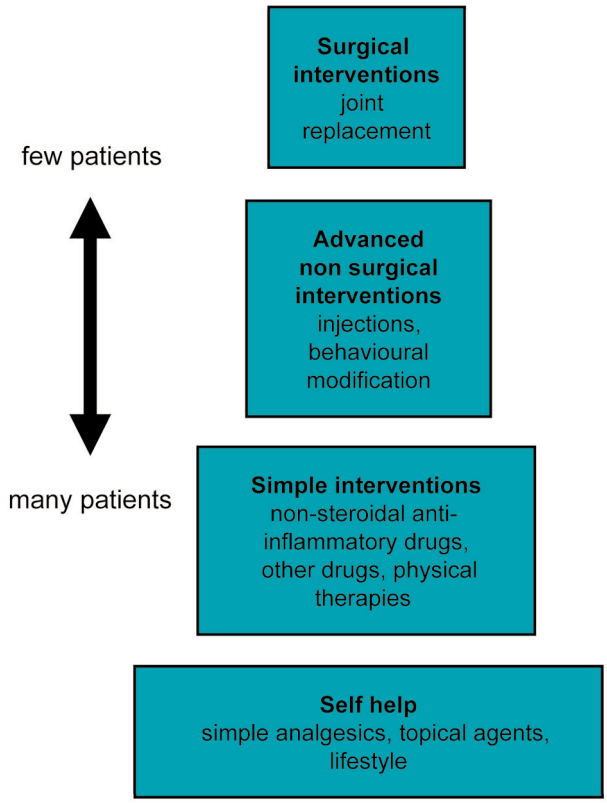
Psychological and social factors have been shown to be the most important predictors of both the presence and severity

of pain in a range of disorders including RA, OA and persistent low back pain. It seems logical to assume, but remains unproven, that these external factors modulate nociceptive processing at a supraspinal or cortical level [7]. The overall effect is to enhance pain perception and to increase pain reporting and behavioural change, including disability.

Reliance on peripherally or spinally active therapies alone is unlikely to prove successful in those patients with more general symptoms arising from central sensitization. Prostanoid and opioid receptors are constitutively expressed in cortical tissues, and the relevant therapeutic agents are undoubtedly exerting an effect at this level. Nevertheless, additional measures often using non-pharmaceutical approaches, including education and cognitive behavioural therapy, may be required.

Despite the progress that has been made over the past several decades to define key pain processes, the need remains to translate this knowledge into better assessment techniques and more effective pain therapy. Attempts to devise mechanism-based approaches to therapy have met with mixed success, in part as a result of lack of clinical techniques by which to define specific nociceptive processes. Quantitative sensory tests and cortical imaging can be used to quantify central changes associated with articular pathology but are not suitable for more general clinical use. In practical terms, the duration of symptoms is important: the likelihood of a significant central component increases with time. Referred pain and tenderness away from the site of joint pathology are suggestive of a neuroplastic pain state, whereas radicular pain is inevitably associated with neuropathic syndromes.

Figure 3



Principles for the management of osteoarthritis: a suggested sequential pyramidal approach to symptom management. (Adapted from [49].)

General approaches to pain management

Clinical guidelines

Published goals for the management of both OA and RA include the prevention or amelioration of joint damage, the prevention of loss of function, and the reduction of pain [8,9]. In the absence of complete remission, it is suggested that longitudinal plans for pain management take into account adverse effects and costs, as well as the patient's risk factors, co-morbid conditions and preferences [9].

Guidelines are increasingly used in a range of settings to promote effective multidisciplinary health care (Figure 3). Although clinical guidelines for the management of arthritic pain have been published, their development has been hampered by often insufficient, or frankly contradictory, evidence [8,9]. As outlined in the previous section, persistent joint pain arises in response to a range of different factors, and it has proved difficult to adapt evidence obtained from often tightly controlled research trials to more general clinical settings.

A further problem has been the paucity of techniques by which the effects of analgesic intervention can be monitored. In practice, although the assessment and integration of available information by an individual health professional might be of high quality, it often proves difficult to systematically quantify the effects of any subsequent intervention. Pain is a subjective experience, and although pain intensity can be monitored with visual analogue scales, other aspects of the pain experience have proved more difficult to capture. Instruments such as the McGill pain questionnaire purport to measure these other domains but have been used mostly for research purposes.

Education and behavioural change

Patient education has been recommended as a fundamental component of arthritic pain management; however, objective evidence for efficacy remains poor. Systematic reviews report few well-designed randomized controlled trials (RCTs) of education alone [10]. In contrast, more substantial evidence exists for the efficacy of lifestyle modification, particularly exercise and weight reduction [11].

Several systematic reviews evaluating aerobic and strengthening exercises have demonstrated clear benefits with regard

to both pain reduction and improved function in people with knee and hip OA [12]. Weight loss also reduces OA-associated knee pain in overweight individuals and improves physical activity, especially when combined with regular exercise [13]. Measures that maintain adherence to a regime, such as keeping a personal diary or social support from friends, are thought to improve long-term outcome [11]. Braces and orthotics can also be effective, although evidence for the efficacy of these measures has yet to be fully established in clinical trials.

A small proportion of patients with identifiable musculoskeletal pathology experience extreme and widespread symptoms, often associated with recognizable behavioural changes indicative of a chronic pain syndrome. These individuals may benefit from psychological/cognitive-behavioural therapies as part of a multidisciplinary strategy. Accumulating evidence attests to the efficacy of these approaches in such patients and is reviewed elsewhere [14].

Pharmacological therapies

Paracetamol (acetaminophen)

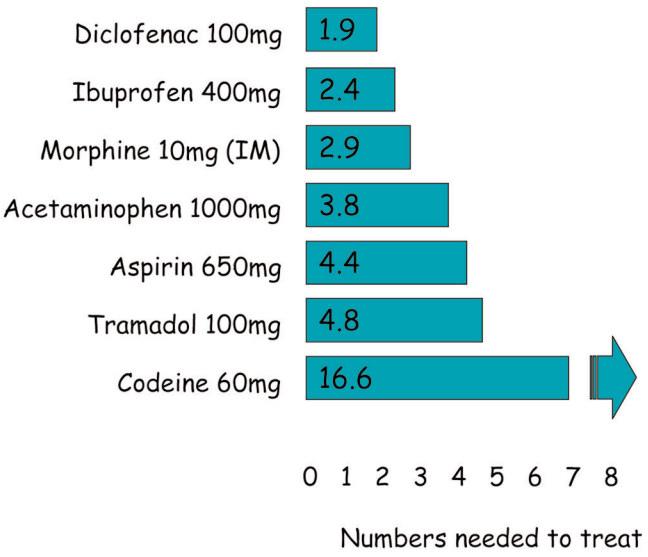
This drug has been used for over 100 years; however, its mechanism of action remains uncertain [15]. Currently, it has no known endogenous binding sites, but various claims have been made about inhibition of central cyclooxygenase activity, inhibition of *N*-methyl-D-aspartate receptor activity, and stimulation of descending inhibitory pathways [16].

Paracetamol is effective in many arthritic conditions and across all age groups. It has been recommended as the oral analgesic of choice for mild to moderate pain in OA [17] and is generally well tolerated in osteoarthritic patients for periods of up to 12 months [18]. In general, paracetamol has a good tolerability profile and overall safety record, although recently the frequency of use has been reported to be independently associated with a moderate increase in the risk of incident hypertension [19].

Tramadol

Tramadol is a central-acting oral analgesic that has a unique dual mechanism of action involving both a weak μ-agonist action as well as inhibition of the reuptake of noradrenaline (norepinephrine) and serotonin. It has received widespread approval for use in both moderate and severe pain and has found use as adjunctive therapy for arthritic pain [20]. Tramadol combines favourably with paracetamol and permits a decrease in the use of NSAIDs without compromising analgesia [21]. Use of the drug is limited in a significant proportion of patients as a result of toxicity, with the most commonly reported side effects being dizziness, nausea and constipation [22]. Care should be taken with the concomitant use of serotonin-selective reuptake inhibitors because of potential elevation of basal serotonin levels, with associated risks of seizures and/or serotonin syndrome [23].

Figure 4



Oxford league table of commonly used analgesics in acute pain. Numbers needed to treat for 50% pain relief over 4 to 6 hours are shown. Note that no comparable data exist for analgesia for chronic musculoskeletal pain. (Adapted from [50].)

Non-steroidal anti-inflammatory drugs

The primary anti-inflammatory and antinociceptive effects of NSAIDs have been linked to an inhibitory effect on cyclo-oxygenase enzymes and a subsequent decrease in inflammatory prostaglandins such as PGE_2 and prostacyclin. There is some evidence for a dissociation between the anti-inflammatory and antinociceptive effects, in keeping with both peripheral and central sites of action [24].

NSAIDs have been shown to be highly effective for treating acute pain (Figure 4) and remain one of the principal pharmacological agents for treating arthritic pain [25]. Published guidelines and expert opinion are divided over the relative roles of NSAIDs versus paracetamol as first-line analgesic therapy for arthritic conditions. A recent meta-analysis of 15 RCTs involving 5,986 participants concluded that NSAIDs were superior to paracetamol for improving knee and hip pain in OA; however, the effect size for both treatments was modest [26]. NSAIDs are also widely used for symptomatic therapy for RA, although similarly modest effects are observed [27].

Concerns about the toxicity of NSAIDs have become more prominent in recent years. Gastrointestinal events, including perforation, ulceration and bleeding, are well documented and a considerable literature is available for review [28]. Other well recognized problems include oedema and renal insufficiency; however, the development of cyclooxygenase inhibitors (coxibs) has highlighted additional cardiovascular risks associated with these agents.

International regulatory authorities including the US Food and Drug Administration and the European Medicines Agency have issued warnings on the use of coxibs in patients with increased cardiovascular risk and for long-term use, recommending using the lowest effective dose for the shortest duration. With evidence that both the traditional non-selective NSAIDs and coxibs are associated with cardiovascular adverse events, the broader cardiovascular warning from the US Food and Drug Administration covers the whole class of anti-inflammatory analgesics.

Opioids

The long-term use of stronger opioids in chronic musculoskeletal conditions remains controversial [29]. Three subclasses of opioids receptor have been described – the μ-, δ- and κ-opioid receptors – with a widespread distribution throughout both the central and peripheral nervous systems. Agonists for the μ-receptor display the best analgesic activity but also the highest abuse potential.

There is a relative paucity of evidence to support the isolated use of weaker opioids such as codeine for chronic arthritic pain [30], but these agents are devoid of serious organ-damaging effects and when combined with paracetamol may well be clinically safe for long-term therapy [31].

In those arthritic patients for whom NSAIDs are contra-indicated or for whom combined therapy is ineffective, the use of stronger opioids may have a limited role [32]. A systematic review of 15 RCTs involving 1,025 patients with chronic non-malignant pain found a mean decrease in pain intensity in most studies of at least 30%, with a comparable effect size in both neuropathic and musculoskeletal pain [29]. Recent developments in oral and transdermal sustained-release formulations have increased the safety and utility of strong opioid therapy. Transdermal fentanyl has been shown to be effective in reducing pain scores and improving function in patients with knee and hip OA [33].

In practice, toxicity issues remain a problem; the most commonly reported opioid side effects are constipation, nausea and somnolence [29]. Concerns over abuse potential remain, although patient education and informed consent, exercise, complementary medicine and the use of a controlled-substance agreement increase the likelihood of patient compliance with treatment guidelines, as well as improving functional capacity and quality of life [34].

Antidepressants

The antinociceptive action of antidepressants is independent of their effect on depression and occurs at lower doses and after a shorter duration of treatment [35]. Tricyclic antidepressants have the best antinociceptive efficacy and act to inhibit uptake of noradrenaline and serotonin, although other actions have been reported.

The main antinociceptive indication for tricyclic antidepressants is for neuropathic pain, although they have beneficial effects in patients with fibromyalgia as well as back pain. More modest effects have been noted in RA [36]. For the most part, these agents remain useful as adjuvant therapy and are not considered front-line analgesic agents in most musculoskeletal disorders.

Anti-cytokine therapies

Cytokines released from immune cells as part of the inflammatory cascade, including IL-1, IL-8 and TNF-α, are hyperalgesic agents as a result of their ability to stimulate the production and release of other pro-inflammatory agents such as bradykinin. Direct effects on primary nociceptors during inflammatory states may also be clinically relevant. Agents that suppress the production or actions of TNF-α have been shown to have potent analgesic activities in clinical trials in patients with various rheumatic diseases, although whether there is a dissociation between the anti-inflammatory and analgesic effects remains to be seen.

Combination analgesics

The relative failure of single pharmacological therapy to relieve chronic musculoskeletal pain has encouraged the use of combination therapy [37]. Combinations of paracetamol plus codeine are widely used although objective evidence for efficacy is limited by the paucity of clinical trials. Adverse events limit widespread applicability, although titration of the dose against effect is useful in overcoming these problems [38]. More robust evidence supports the use of combinations of paracetamol plus tramadol [37]. Other clinically useful strategies include NSAID plus tramadol or NSAID plus weak opioid, although there are far fewer adequately designed RCTs to provide objective support for these approaches.

Additional approaches

Topical therapy

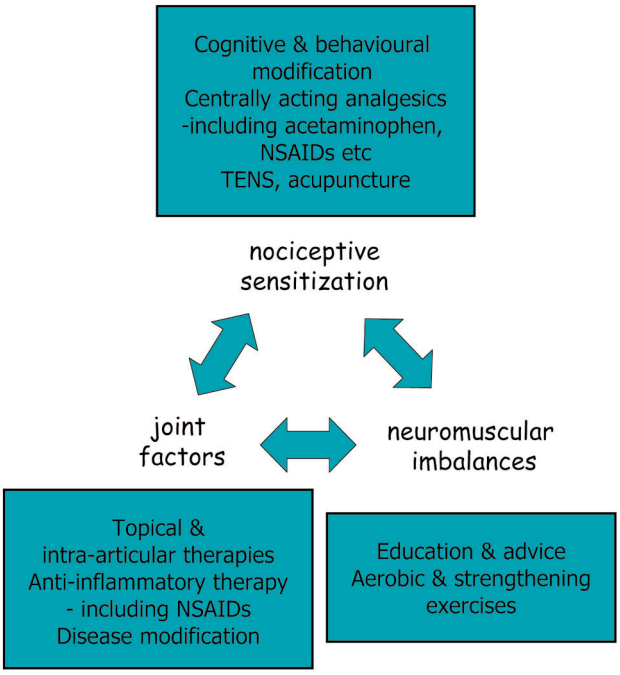
Topical NSAIDs have a proven efficacy across a range of musculoskeletal disorders with fewer side effects than oral therapy [4]. Although used primarily for neuropathic conditions, systemic reviews also support the use of topically applied capsaicin. A limited number of trials report benefit in OA, with around one-third of patients reporting local adverse events, usually burning discomfort at the site of application [39].

Intra-articular injections and other local therapies

Intra-articular steroid injections are widely used to control symptoms in both OA and inflammatory conditions. The duration of symptom relief may be relatively short in OA, with effects lasting only a few weeks [40], although longer responses may occur in RA. Concerns over effects on cartilage have been partly allayed by studies suggesting no long-term deleterious events from such therapy [41].

Intra-articular hyaluronic acid (hyluronan) is a high-molecular-mass polysaccharide with a multiplicity of biological actions

Figure 5



Multimodal therapy for the management of arthritic pain with a mechanism-based approach. Note the lack of a hierarchical system with potential for synergistic interactions between therapeutic options in different boxes.

that has gained favour for symptomatic therapy in OA. Symptomatic benefits may be similar to intra-articular steroids, although the onset of action is delayed, with effects lasting up to 12 months [42]. Glucosamine and chrondroitin sulphate have enjoyed striking popularity for the treatment of OA; they received favourable early reports, but a more recent large-scale trial failed to show benefit over placebo [43].

Acupuncture

A large proportion of patients with arthritic pain seek help from complementary or alternative sources, with acupuncture being a popular choice. Recent individual RCTs have reported conflicting results [44] in patients with arthritic pain, although a couple of systematic reviews provided generally favourable support with symptomatic benefits over both sham acupuncture and placebo [45]. Overall, acupuncture has a good safety record with few reports of serious adverse effects, and it retains a place in the symptomatic management of patients with arthritis.

Transcutaneous electrical nerve stimulation

TENS has an established general role in the treatment of chronic pain, although there have been few studies assessing the efficacy of the technique for arthritic pain. Underlying mechanisms of action remain unclear, but in studies of experimental joint inflammation TENS reduces spinal stimulatory neurotransmitters (glutamate and aspartate) and at the same time activates modulatory opioid, serotonin and/or muscarinic receptors to reduce pain behaviours [46]. In clinical studies, TENS has been found to be as effective as exercise and better than placebo for controlling arthritic pain, although combination approaches produce the most favourable result [47].

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Arthritis and pain
edited by Jason McDougall.

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Conclusion

The mechanisms of chronic pain differ from those of acute pain. Although peripheral tissue injury is undoubtedly important for the initiation and maintenance of arthritic pain, more central factors, involving changes to pain pathways, become equally important with time. Strategies for treating arthritic pain need to embrace this reality and will necessarily involve multimodal therapy with both pharmacological and non-pharmacological measures (Figure 5). Despite the theoretical advantages, there is a paucity of objective clinical evidence to show the benefits of using an integrated approach for analgesia in persistent joint pain. Designing and evaluating complex interventions to improve health care pose a considerable challenge and require a substantial investment of time and financial resource [48] but nevertheless remain a key priority for clinical research into musculoskeletal disease.

Competing interests

RML has received lecture and consultancy fees from Pfizer, GlaxoSmithKline, and performed sponsored research on behalf of Astra Zeneca, Pfizer, Jannsen-Cilag, Johnson and Johnson and Grunenthal. BLK has received lecture and consultancy fees from Pfizer and performed sponsored research on behalf of Astra Zeneca, Napp and Nycomed.

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