Management of chronic pain in the rheumatic diseases with insights for the clinician

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***Abstract*:** Pain that accompanies musculoskeletal conditions should be regarded as an illness entity in its own right and deserves treatment in parallel with the management of the underlying condition. Recent understanding of the pathophysiology of rheumatic pain invokes interplay of the nociceptive mechanisms driven by local tissue factors and the neurogenic responses that sustain chronic pain. In line with other pain conditions, ideal treatment of rheumatic pain should be through a multimodal approach, integrating nonpharmacologic as well as pharmacologic treatments. In the light of this new concept of pain mechanisms, future pharmacologic treatment options may encompass a wider scope than the use of traditional analgesics and nonsteroidal anti-inflammatory drugs. There is currently limited experience for use of pharmacologic treatments that act primarily on neurogenic mechanisms in rheumatic conditions. Drug combination studies are lacking, but this strategy seems clinically reasonable to allow for an approach to treating pain from different mechanistic perspectives. An added advantage would be the opportunity to use lower doses of individual drugs and thereby reduce the side effect profile. Ideal pain management must also include attention to the important co-associates of pain such as effects on sleep, mood and energy, which all have an impact on the global burden of suffering. Although complete relief of pain is still an unrealistic objective, reasonable outcome goals for symptom relief should be accompanied with an improvement in function.

***Keywords*:** adjuvant, rheumatic pain, treatment

Introduction

Musculoskeletal pain can no longer be viewed as an isolated symptom [Fitzcharles and Shir, 2008]. The consequences of chronic pain, with their negative effect on sleep, mood and energy, carry equal importance regarding the global suffering of an individual patient and require attention [Goldenberg, 2010; Fitzcharles and Shir, 2008]. Any pharmacologic treatment intervention must be constantly re-evaluated to assess outcome on pain as well as the co-associates of pain, with the knowledge that pain relief may be counterbalanced by negative effects on sleep, mood and energy. The current best pain management will combine treatments that are nonpharmacologic as well as pharmacologic, with an emphasis on the understanding that treatments remain imperfect and that pain is seldom cured.

We now acknowledge that drug treatment alone is not an ideal solution for pain care, and disappointingly the pharmacological choices for pain management have been limited compared with the treatment advances seen for other medical conditions. In addition, enthusiasm for analgesic and anti-inflammatory drug treatments has been tempered in recent years because of the concern regarding adverse events [Crofford, 2010; Tannenbaum *et al.* 2006]. It is also noteworthy that a reduction of pain of only 30% is considered to represent effective relief of pain in both the clinical and research setting, still leaving patients with considerable ongoing symptoms. Effective management of pain therefore requires an integrated strategy taking into account the pathological process, psychosocial factors that affect the response to pain, and associated medical and pharmacologic considerations [Fitzcharles and Shir, 2008]. It is also necessary to constantly re-evaluate any treatment for efficacy and side effects, and ensure that outcome goals are appropriate and realistic. By paying

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attention to all of these factors the physician will be better equipped to develop a management plan that is tailored towards the unique needs of an individual patient.

In this review we highlight recent developments in the understanding of musculoskeletal pain from both the mechanistic as well as the clinical perspective, and apply this new knowledge to clarify treatment strategies. Although nonpharmacologic treatments constitute an important component of any pain management strategy, in this review we focus on current issues in the pharmacologic domain. This broadened perception of rheumatic pain will have implications regarding patient care in the coming years.

Emerging concepts in rheumatic pain

Musculoskeletal diseases causing pain are common, are increasing in frequency and represent a considerable burden to the individual and society [Helmick *et al.* 2008; Lawrence *et al.* 2008]. Lower-limb and spinal problems are most prevalent, especially with the aging of populations and poorer general health status related to obesity and sedentary lifestyles. Almost half of all persons over 65 years currently have some form of arthritis, with predictions that over a third of the general population will be affected by musculoskeletal complaints within the next two decades [Helmick *et al.* 2008; Hootman and Helmick, 2006]

There are new and emerging concepts in the understanding of musculoskeletal pain from both the clinical as well as the scientific perspective. In the clinical domain it is increasingly appreciated that pain does not occur in isolation, but is often associated with cofactors such as sleep disturbance, fatigue and mood disorder. These associated symptoms contribute to poor health status, and if not recognized and addressed adequately will negatively affect pain management. Second, the original impression that musculoskeletal pain was purely nociceptive has been superseded by evidence of important neurogenic mechanisms operative in the setting of chronic pain [McDougall, 2006]. We acknowledge that there is still much to be learnt regarding pain mechanisms and that our current knowledge is preliminary. This broader concept of rheumatic pain mechanisms widens the spectrum of treatments beyond the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and simple analgesics, to eventually include medications beyond the paradigm of usual rheumatology care [Felson, 2001]. It is, however, unlikely that medication alone will solve the problem of chronic musculoskeletal pain in the near future.

Pain mechanisms in rheumatic conditions

Rheumatic pain was previously categorized as nociceptive, on the premise that the pain was related to inflammation or structural changes reflecting tissue damage. In contrast, neurogenic pain was believed to be associated with specific nerve damage. This distinct divide between nociceptive and neurogenic pain, particularly pertaining to arthritic disease, no longer exists, with clear evidence pointing to considerable overlap, and highlighting the role of neurogenic mechanisms [McDougall, 2006; Schaible and Grubb, 1993].

Acute pain appears to be an initiating event and driver for chronic pain. Inflammatory molecules produced at the local site initiate a response in the first-order somatosensory neuron which is relayed via the dorsal horn in the spinal cord to the brain [Kidd and Urban, 2001]. The neurogenic chemical mediators of pain include substance P and serotonin, both intrinsic to the neuron, nerve growth factor (NGF), which regulates the expression of neuropeptides, receptors and ion channels, and calcitonin gene reactive protein (CGRP) which induces vasodilatation and extravasation of fluid from capillaries [McDougall, 2006; Kidd *et al.* 2004; Schaible and Grubb, 1993]. This neuroactive and inflammatory milieu lowers the firing threshold of high-threshold nociceptors to mechanical, thermal or chemical stimuli, and a cycle of pain is set in motion. The success of the numerous NSAIDs in the last century can be attributed to the importance of these inflammatory mechanisms in rheumatic pain.

Joints structures are richly innervated with sensory neurons which are the initial messengers of the pain response [Kidd, 2006]. The simplistic concept of an uninterrupted pain message conveyed progressively to the somatosensory cortex is no longer tenable [Kidd and Urban, 2001]. The pain pathway as it applies to chronic rheumatic pain is more complex with evidence of modulation and sensitization at the dorsal horn, changes in the thalamus and higher centers, and effects mediated by descending inhibiting pathways [Gwilym *et al.* 2010; Baliki *et al.* 2008]. Molecules somewhat unfamiliar to the

rheumatologist such as norepinephrine, serotonin, endogenous opioids and cannabinoids play a modulating role in the pain experience [Basbaum and Fields, 1984].

Peripheral and central sensitization that occurs in the setting of a persistent pain stimulus contributes to pain chronicity [Coderre *et al.* 1993; Schaible and Grubb, 1993]. Under normal circumstances joint structures are not sensitive to strong pressure or even vigorous movement. In contrast, diseased joints that have been primed by inflammatory molecules, develop sensitivity to seemingly benign movements demonstrating a low threshold of activation, promoted by neurogenic inflammation [Schaible and Grubb, 1993]. Neurogenic inflammation in turn promotes the ongoing cycle of neuronal sensitization, perpetuates the inflammatory response and is now recognized as an integral part of inflammation.

Chronic pain in rheumatic diseases is a combination of pain arising from tissue destruction and mechanical changes to cartilage, bone and soft tissues and is sustained at least partly by activation of neurogenic mechanisms [McDougall, 2006]. Afferent neuronal pathways are influenced by descending neuron projections that synapse in the laminae of the dorsal horns [Gebhart, 2004]. Therefore, the excitability of neurons can be modulated by a variety of presynaptic and postsynaptic molecules such as opioids (μ, κ, δ) and receptor blockers at noradrenergic (α-1, α-2) and muscarinic sites. For these reasons, the management of chronic pain is more challenging and often less successful than that of acute pain.

A clinical approach to rheumatic pain

The care of a patient presenting with musculoskeletal pain should begin with a comprehensive clinical assessment with attention to the characteristics of pain, psychosocial characteristics and risk management strategies that apply to any recommended treatment. An individual's response to a particular pain is influenced by factors such as genetic background, cultural and social environment, and psychological makeup [Lacroix-Fralish and Mogil, 2009]. Physicians must actively assess the severity of pain, gauge the effect on daily life, explore features commonly associated with pain, and offer management appropriate to the individual patient [Winfield, 2007]. Any strategy to manage pain must be patient centered and take into consideration all factors that uniquely apply to an individual patient. A stepwise approach for the clinician should be to first obtain a correct diagnosis and thereafter fully evaluate the pain complaint from the perspective of both pain as well as the co associated symptoms.

Correct diagnosis. A specific diagnosis of the musculoskeletal complaint is the first step to effective management. Although rheumatic conditions may be grouped into three broad categories of inflammatory, degenerative and soft tissue processes, there may be considerable overlap within an individual patient [Fitzcharles *et al.* 2010]. Examples include joint pain in a patient with long-standing inflammatory arthritis, where the pain is less inflammatory in nature and more related to the chronic changes of joint damage, or pain in osteoarthritis of the knee with the major pain arising in the anserine bursa outside the knee joint, or degenerative disc disease where the focus of pain complaint is mostly neurogenic due to spinal stenosis. In the setting of an inflammatory arthritis, the first goal of treatment must be to control the disease process, reduce the inflammatory activity and prevent chronic joint damage. Failure to address the global disease will result in continued and unremitting symptoms even with the best attention to pain.

The pain experience. Knowledge of the specific characteristics of the pain is vital. Not only should the location and intensity of pain be documented, but attention to timing, alleviating and aggravating factors is required. Some pain may occur only when changing position or after a prolonged period of immobility, whereas other pain may be most troublesome at night with associated disturbed sleep. The experience of pain as perceived by an individual is also specific to that person, with different individuals responding to the same pain differently due to factors such as genetic makeup, psychological status and previous pain experience [Lacroix-Fralish and Mogil, 2009; Sullivan *et al.* 2006]. Patients also innately cope with pain in different ways with some demonstrating better coping skills whereas others tend to catastrophize and amplify severity of symptoms.

Rheumatic pain is mostly low grade and unrelenting, sometimes aggravated by physical activity, and particularly disturbing when experienced at night during sleep. Pain in rheumatic conditions is subject to considerable variability and

fluctuation within an individual patient, and is influenced by environmental factors such as cold and damp weather conditions [Macfarlane *et al.* 2010]. A recent study has demonstrated up to 20% variation in osteoarthritis pain both within a week and from week to week [Hutchings *et al.* 2007]. Such usual fluctuations in pain levels would be sufficiently large to be considered clinically significant in a treatment efficacy study setting [Pham *et al.* 2004; Farrar *et al.* 2000]. It is also notable that pain level fluctuations correlated with changes in mood, sleep and quality of life, emphasizing the importance of pain [Hutchings *et al.* 2007; Wolfe *et al.* 2006]. Pain is not a symptom in isolation, but co-associates with sleep disturbance, mood changes including depression and anxiety, and fatigue [Winfield, 2007; Wolfe *et al.* 2006]. Although attention to these specific complaints has previously been out of the mainstream of rheumatologic practice, physicians and rheumatologists in particular will need to address these symptoms in order to achieve whole patient care.

I. Poor sleep, independent of mood status, has been associated with greater pain report in a population of chronic pain patients [Morin *et al.* 1998]. This added distress interferes with daily ability to function. Sleep disturbance may manifest in different ways such as difficulty falling asleep, interrupted sleep and awakening unrefreshed [Cole *et al.* 2007]. The cause of sleep disturbance may be multifactorial due to the presence of restless leg syndrome, inadequate pain control, underlying depression or simply poor attention to good sleep hygiene. Therefore, sleep disturbance should not immediately be treated with the prescription of a sleeping pill, but rather explored regarding its specifics and underlying causes. A few focused questions will help to clarify the characteristics of the sleep complaint and direct the physician to appropriate management.

II. A second important complaint commonly associated with pain is mood disturbance [Smith and Zautra, 2008]. Depression is commonly associated with all chronic pain, and may be an exacerbation of a pre-existing depressive condition, or may be a response to inadequately managed pain. Similarly, anxiety is a common symptom that may be masked, but could in turn aggravate pain. Depending upon the underlying personality of the individual, mood disturbance may play a role of greater or lesser importance for an individual patient.

III. Fatigue is commonly present to some degree in almost all patients with chronic pain [Uutela *et al.* 2008]. The concept that fatigue may be physical or central deserves comment, although clinical differentiation is less clear. Patients with central fatigue may complain more commonly of cognitive impairment and memory problems, whereas those with physical fatigue report tiredness and need for sleep. Fatigue is subjective, solely measured by patients' report and is likely the most challenging symptom to address in patients with chronic pain. Some causes of fatigue may include inadequate control of the underlying systemic disease, adverse effects of medications including analgesics or adjuvants, or a symptom of depression.

Treatment overview

Effective pain management for the rheumatology patient is not simply the prescription of an analgesic pill. Pain treatment should take into account symptoms that co-associate with pain, and proceed in parallel with the best management of the underlying rheumatologic process. The passive attitude of modern society regarding healthcare issues, with patients looking to pharmacologic treatments as a solution to most problems, should be superseded by active patient participation in healthcare management. In the absence of a 'gold standard' of treatment, a multimodal approach, incorporating nonpharmacologic as well as pharmacologic treatments, and tailored to the individual patient needs is ideal [Cooper *et al.* 2003]. Outcome for any treatment should not only be measured as pain relief, but also as an improvement in function.

Although a comprehensive review of nonpharmacologic treatments is beyond the scope of this article, we stress the importance of these strategies which should be the first step in the management of chronic pain in the rheumatic diseases. Reassurance and simple explanation is required for all patients. Alleviating fear, encouraging the use of self-help and coping measures and paying attention to the co-associates of pain are as important as specifically addressing pain. Psychological considerations play an increasingly important role with promotion of coping strategies and encouragement for the patient to take responsibility for health status [Keefe *et al.* 2010, 2008]. Cognitive behavioral therapy,

biofeedback, meditation and mindfulness training, relaxation therapy and others are specific techniques that have been shown to be useful in rheumatic pain. Physical activity in almost any form is vital for global health in all patients with musculoskeletal complaints. Exercise has many beneficial effects on both the physical and mental status in patients with chronic pain [Keysor and Brembs, 2011]. Activation of descending inhibitory mechanisms is believed to be the mechanism of action for pain relief for many of these treatments. Other interventions that may be useful include local corticosteroid injections into joints and soft tissues and finally surgical intervention with joint replacement for severe damage of hips and knees.

Adherence to any treatment recommendation is clearly an important component for a favorable outcome. It is well recognized that patients with chronic pain and rheumatic diseases in particular adhere poorly to prescribed medications [Harrold and Andrade, 2009]. There is, however, limited information regarding methods to improve this poor adherence. In contrast, self-management techniques as well as supervised exercise programs, whereby patients develop responsibility for their health status, have shown positive effects in adherence to exercise strategies [Jordan *et al.* 2010; Brand, 2008].

As rheumatic pain is no longer believed to be entirely dependent upon the inflammatory prostaglandin cascade, or effectively treated with opioids only, other drug treatment modalities may offer an advantage. When choosing a drug treatment, the ideal agent would address both pain as well as at least another co symptom such as sleep disturbance or mood disorder. There is also limited information regarding combination pharmacotherapy in musculoskeletal pain, although this is likely practiced in the clinical setting with hope of reducing side effects due to higher doses of individual drugs and approaching pain from a number of angles. A good practice should be the use of lowest dose of medication for the shortest time possible in order to reduce drug-related side effects.

Traditional analgesic treatments revisited

Evidence-based treatment for pain management has mostly focused on the use of analgesics and NSAIDs. For centuries anti-inflammatory treatments have been the mainstay of rheumatic disease medicinal management. Hippocrates wrote of the bitter powder from the willow bark that could ease rheumatic aches and pains. Salicin from the willow led to the development of salicylic acid and eventually the variety of NSAIDs which constitute the modern-day rheumatology pharmacopoeia [Vonkeman and van de Laar, 2010]. The medicinal effects of opioids have also been known for centuries, with first recorded analgesic effects recorded in the writings of Theophrastus in the third century BC.

Acetaminophen. Acetaminophen remains the most commonly used analgesic for the management of musculoskeletal pain, although there seems to be patient preference for use of NSAIDs [Kroenke *et al.* 2009; Towheed *et al.* 2006]. Until the advent of the selective cyclooxygenase (COX) inhibitors, acetaminophen was the gold standard for pain management in the arthritic diseases. Owing to concerns regarding adverse effects of the NSAIDs, acetaminophen may once again become an important analgesic for patients with rheumatic diseases. The safety profile of acetaminophen in doses below 2000 mg a day remains acceptable, but there are risks of liver toxicity when higher doses are used for prolonged periods, or in the setting of liver or renal dysfunction [Guggenheimer and Moore, 2011; Fitzcharles *et al.* 2010; Fored *et al.* 2001]. Acetaminophen combined with other agents such as codeine or tramadol may be an added risk for acetaminophen overdose when patients continue to use additional over the counter medication.

The mechanism of action of acetaminophen is becoming clearer. There is an effect on COX-1 and COX-2 enzymes in the brain, impact upon neurogenic inflammation and a recently identified action on the endocannabinoid system. A metabolite of acetaminophen, when compounded with arachidonic acid, blocks reuptake of endogenous cannabinoids in brain and spinal cord of animals [Bertolini *et al.* 2006; Hogestatt *et al.* 2005]. This latter effect may better explain antipyretic and analgesic actions of this agent. Other brain and nervous system potential targets for acetaminophen include the third isoform COX-3, effect on serotonergic mechanisms, and impact on neurogenic inflammation [Chandrasekharan *et al.* 2002]. Peripheral inhibition of COX-1 and COX-2 enzymes is unlikely to result in appreciable clinical anti-inflammatory effect, although a recent study has demonstrated reduced synovial effusion in osteoarthritis of the

knee equivalent to the effect achieved by standard doses of NSAIDs [Brandt *et al.* 2006].

NSAIDs. Traditional NSAIDs and COX-2 selective inhibitors have played an important role in pain management, especially in the setting of inflammation, but with increasing recommendations for limited use [Bjordal *et al.* 2004]. These agents are now recognized to be associated with serious adverse effects on the gastrointestinal tract, kidneys, liver and cardiovascular system, and any use in now recommended to be at the lowest dose required and for the shortest period of time [Trelle *et al.* 2011; Vonkeman and van de Laar, 2010; Soni *et al.* 2009; White *et al.* 2007; Tannenbaum *et al.* 2006; Bjordal *et al.* 2004].

Topical applications of NSAIDs provide an attractive alternative to oral treatments for patients with musculoskeletal conditions [Taylor *et al.* 2011; Massey *et al.* 2010]. There is evidence for good tissue levels of the applied drug, and reduced systemic effects on account of low plasma levels of drug [Mason *et al.* 2004; Dominkus *et al.* 1996]. Topical diclofenac performed as well as ingested diclofenac in a recent study of osteoarthritis of the knee [Tugwell *et al.* 2004]. It is notable that the effect of topical NSAIDs is of short duration only [Mason *et al.* 2004]. Other agents such as capsaicin or amitriptyline have been used topically in some chronic pain conditions, in animals and humans, but their role in rheumatic pain has yet to be illustrated [Lynch *et al.* 2005].

Opioid analgesics. Opioid medications offer the best available pharmacologic analgesia for almost any pain, with use limited by immediate side effects as well as concerns for long-term safety [Chou *et al.* 2009]. The human opioid system comprises a number of endogenous molecules, with three classes of receptors, μ, κ and δ, distributed throughout the periphery and the central nervous system. Endogenous opioids are released in response to pain, but also following exercise and mediate the placebo response [Pollo and Benedetti, 2008; Goldfarb and Jamurtas, 1997]. Activation of all three receptors results in the closure of voltage-gated calcium channels, with reduced calcium influx and reduction in neurotransmitter release.

Although most commercially available opioids are μ-opioid receptor agonists, individual patients may respond differently to specific opioid preparations. This may be due to variability in receptor responsiveness for a number of reasons including genetic variation in coding for the individual receptor, type and duration of pain, and also previous treatments. Traditionally it is recommended that treatment be initiated with the weaker opioid agonists such as codeine or tramadol, before moving to the stronger opioids, but without any convincing evidence. It should also be remembered that the analgesic properties of codeine are dependent upon its conversion to morphine via the cytochrome P450 isoenzyme 2D6 [Chen *et al.* 1988]. As this isoenzyme demonstrates considerable polymorphism, there are individuals who lack the ability to metabolize codeine to an active analgesic form. Rheumatologists most commonly use opioids in the management of osteoarthritis pain of weight-bearing joints, and for treatment of low back pain, although a recent review recommends that adverse effects outweigh the benefits [Nuesch *et al.* 2009]. Although slow acting preparations are suggested for long-term use, there is scanty evidence to support this claim [Chou *et al.* 2009].

The progressive increase in prescription of opioids has seen a parallel increase in their use as drugs of abuse [Crofford, 2010; Manchikanti *et al.* 2010; Okie, 2010; Hartung *et al.* 2007]. Of increasing concern are the increased deaths associated with overdose of opioids, usually in younger individuals, often receiving prescription opioids and usually combined with other agents such as alcohol or benzodiazepines. The American Pain Society published guidelines for the safe and effective use of opioids in chronic pain patients in 2009 [Chou *et al.* 2009]. The tone of these guidelines is cautious. Physicians should practice responsible prescribing behaviors, pay attention to physical and psychosocial aspects of patient care, and constantly re-evaluate the efficacy and side effect profile of any prescribed medications.

An opioid with more than one analgesic mechanism presents an attractive treatment option. Currently, there are two synthetic opioids, tramadol and tapentadol whose analgesic mechanisms are not limited to effect on opioid receptors only [Hersh *et al.* 2010; Nuesch *et al.* 2009; Cepeda *et al.* 2007]. The parent compound tramadol has serotonin and norepinephrine effects, whereas tapentadol has effects on noradrenergic receptors. Tramadol is predominantly metabolized in the liver via the cytochrome-P450 (CYP)

isoenzyme 2D6, similar to codeine, whereas tapentadol is metabolized to a nonactive component via hepatic glucuronidation resulting in fewer drug–drug interactions. Both agents have demonstrated efficacy in the management of musculoskeletal pain, with generally improved tolerability compared to the traditional opioids. The use of these agents could be recommended for pain relief as a step up from acetaminophen, and prior to the use of more potent opioid analgesics.

Nontraditional analgesic agents

Adjuvant drugs may be defined as agents whose primary function is not pain relief, but have pain modulatory effects as an associated feature [Portenoy, 2000]. Although initially used in the management of neuropathic pain, they have been shown to have effect in fibromyalgia, with increasing interest in their use in other painful musculoskeletal conditions. The two classes of drugs that have been most studied for analgesic effects are the antidepressants and anticonvulsants. We suggest that the latter terminology should be replaced with the term 'pain modulator' in order to avoid confusion for a patient regarding the reason for a particular prescription.

Pain modulators affecting sensitization. Drugs affecting sensitization were initially used as anticonvulsants. These agents act as neuromodulators by their propensity to reduce neuronal excitability [Rogawski and Loscher, 2004]. Although their precise mechanism of analgesia is not totally clear, they may diminish pain through site-specific effects on voltage-gated ion channels, ligand-gated ion channels, receptors of glutamate and N-methyl-D-aspartate (NMDA), as well as receptors for GABA and glycine.

The second-generation anticonvulsants, of which gabapentin and pregabalin are the best studied, are generally better tolerated due to fewer adverse events compared with the first-generation molecules (e.g. carbamazepine). Gabapentin and pregabalin are similar in their sites of action and pharmacological profile, with pregabalin showing more potency. They are well absorbed after oral administration, have good bioavailability, and are excreted unchanged by the kidneys. Although relatively safe, their use could be associated with side effects or drug interactions and their daily dose should be adjusted in the presence of renal impairment [Randinitis *et al.* 2003]. There is no recommended dose of gabapentin in chronic pain but doses in the range 2400–3600 mg/day have been routinely used in patients with neuropathic pain. In contrast, the maximal recommended daily dose of pregabalin is 600 mg.

Although mainly indicated for treating neuropathic pain both gabapentin and pregabalin have been excessively used off-label with anecdotal reports of efficacy in other painful conditions. Both medications may have a role in rheumatic pain: gabapentin has reduced pain behaviors in an acute arthritis model in the rat and was beneficial in osteoarthritis of the hip [Houghton *et al.* 1998]. In a recent meta-analysis pregabalin, but not gabapentin, showed benefit for pain relief in patients with fibromyalgia [Tzellos *et al.* 2010].

Pain modulators affecting descending inhibitory pathways. Antidepressant medications affect pain independently of their impact on mood, with pain relief occurring as early as 2 weeks following initiation of treatment [Chan *et al.* 2009; Perrot *et al.* 2008; Bannwarth, 2005; Lynch, 2001]. Although mostly studied in fibromyalgia, there is evidence for effect in other rheumatic conditions where analgesics and NSAIDs are not sufficiently effective [Perrot *et al.* 2008]. The major mechanism of action is to affect descending pain inhibitory pathways in the brain stem and spinal cord mediated by norepinephrine and serotonin. Other effects may include impact on opioid mechanisms, ion channels, NMDA channels, and even inflammation.

The best studied in this group are the older tricyclic antidepressants. Amitriptyline and its metabolite nortriptyline have shown best efficacy in the treatment of pain syndromes, especially fibromyalgia, but with modest effect that tends to wear off over time [Chan *et al.* 2009]. Possessing a nonselective effect on cholinergic and muscarinic receptors is the main drawback of these agents, with the additional troublesome side effect of sedation and weight gain. The selective serotonin reuptake inhibitors (SSRIs) have however failed to show a consistent analgesic effect [Jung *et al.* 1997].

The development of new antidepressant agents with reduced side effect profile holds promise for the management of rheumatic pain. These agents termed selective serotonin and norepinephrine reuptake inhibitors (SNRI) bind

primarily to norepinephrine and serotonin receptors, with less of an effect on other receptors. Included in this group are venlafaxine, duloxetine and milnacipran. It is also possible that agents that affect the dopaminergic system, such as bupropion may have some effect on pain modulation.

The SNRIs vary in selectivity as well as binding affinity for their receptors, factors that may have an influence on efficacy, tolerability and drug interactions. Milnacipran demonstrates a higher selectivity for the norepinephrine *versus* the serotonin receptor compared with other agents such as amitriptyline, duloxetine and venlafaxine, and also has a higher affinity for this receptor than for other agents in this class [Vaishnavi *et al.* 2004]. Metabolism, which has effects on drug interactions, is also different with duloxetine metabolized by the cytochrome P-450 enzyme, whereas milnacipran is primarily excreted by the kidney unchanged. Both duloxetine and milnacipran have been approved by the FDA for treatment of fibromyalgia, and duloxetine has an added indication for the treatment of chronic pain including low back pain. Since patients with rheumatic pain often present with associated fibromyalgia symptoms use of this group will likely increase in the future.

The cannabinoids. Cannabinoids used for medical purposes evoke strong emotional responses from the medical community and patients alike. Whether these agents will truly have a role in the management of chronic musculoskeletal pain is yet to be determined. In view of the important psychoactive effects that accompany use of cannabinoids, caution should be exercised regarding any medical recommendations [Campbell *et al.* 2001]. Although well-controlled studies in pain conditions that are not primarily neurological are lacking, anecdotal reports are sufficiently positive to justify formal scientific study.

There are a number of factors relevant to the rheumatic diseases that pertain to the cannabinoid system. Cannabinoid receptors are distributed throughout the nervous system, and also in the periphery at sites which include the skin, joint tissue and cartilage. The CB1 receptor is mostly associated with neural tissue, whereas the CB2 receptor is found on immunologic cells as well as chondrocytes and osteoclasts. Endocannabinoid molecules are produced by breakdown of phospholipids, and may constitute the endogenous anti-inflammatory pathway [Cravatt and Lichtman, 2004]. Inflammatory pain in the rat model has been attenuated by activation of CB1 and CB2 receptors [Elmes *et al.* 2005], and activation of cannabinoid receptors results in inhibition of pain mechanisms [Pertwee, 2001]. With effects on inflammation, pain and even joint damage, the cannabinoids may have potential for management of rheumatic diseases. The importance of this system with receptors both ubiquitous and widespread is yet to be fully appreciated.

Possible future treatments. An important culprit in perpetuation of chronic pain is believed to be activation of the NMDA receptor. Drugs with NMDA receptor blocking activity include ketamine, dextromethorphan, amantadine, memantine and methadone [Noppers *et al.* 2010; Shah and Diwan, 2010; Kleinbohl *et al.* 2006]. An ideal pain modulator for chronic pain would be a molecule with the ability to block this receptor, but to date there have been no studies testing any of these agents in patients with rheumatic pain. Ketamine may also function to reduce opioid tolerance in patients on opioids by blocking the NMDA receptor, resulting in lowered doses of opioids. The clinical trials of combination opioids and ketamine, however, show mixed results.

There has been recent interest in the use of antiparkinson drugs in the treatment of fibromyalgia. It is theorized that a relative deficiency of dopamine may be a factor in fibromyalgia and possibly other pain conditions. A recent small study of the use of the dopaminergic drug pramipexole in fibromyalgia has reported improvement in symptoms of pain [Holman and Myers, 2005]. An important limitation to the use of this category of drugs is gastrointestinal intolerance, excessive daytime sleepiness and inability to reach adequate dosage of drug.

This greater understanding of mechanisms and modulation of pain will hopefully lead the way to the development of more targeted and specific pain therapies. Important targets for pain modulation could be specific neural electrolyte channels, expanded use of NSAIDs, opioids, α-2 agonists for modulation of excitatory and inhibitory neuronal activity and local anesthetics for suppression of electrical impulses [Dray, 2008]. Identification of opioid, α-2 and prostaglandin receptors in the spinal cord as well as inflamed

tissues argues in favor of the administration of molecules targeting these receptors at the local site. Administering drugs that promote spinal inhibitory mechanisms such as α-2 agonists may modify the consequences of disinhibition. Therefore, we may look forward to a broader scope of pharmacologic treatments for rheumatic pain in the future.

Conclusion

Rheumatic pain will affect most people during their lifetime with alarming escalating prevalence in the elderly. Similar to other chronic pain, poorly controlled rheumatic pain has an impact on wellbeing and global health with consequences on daily function, sleep, energy and mood, independent of the underlying disease process. Pain should therefore be considered an independent disease entity, carrying the same importance as the underlying rheumatic disease. Although the clinical evaluation of pain still remains subjective, progress has been made in the understanding of chronic pain mechanisms. This new knowledge sets the stage for consideration of treatment modalities outside the conventional analgesic paradigm.

In this scientifically enlightened setting, optimal pain management for the rheumatic patient will be multimodal, with greater incorporation of nonpharmacologic interventions. The current pharmacologic treatments are able to address chronic rheumatic pain from different perspectives, taking into account new knowledge of the molecular mechanisms of pain. These treatments however remain suboptimal for many patients, are generally nonspecific and are still associated with a myriad of unacceptable side effects. Although patients should no longer be expected to endure uncontrolled pain, they should be encouraged to become active participants in their healthcare management and demonstrate a willingness to achieve better health. Although rheumatic pain remains a challenge, recent developments regarding understanding of pain mechanisms and application of newer treatment strategies is encouraging and will hopefully benefit patient care.

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