Acute and chronic musculoskeletal pain

Pharmacological management

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A multimodal, multidisciplinary approach is required when managing patients with musculoskeletal pain. Nonopioid analgesics should be trialled first and opioids then used with caution.

Musculoskeletal pain is a major burden on the psychosocial and physical wellbeing of an individual. In 2015, musculoskeletal conditions were the most common chronic disorders in Australia and were largely managed in the primary care setting. According to self-reported estimates in 2011 to 2012, 28% or 6.1 million people in Australia experienced chronic musculoskeletal conditions, mainly arthritis.[1] Of these, 14% had back pain, 8% chronic osteoarthritis (OA), 3% osteoporosis and 2% rheumatoid arthritis. Previous estimates have suggested that $5.7 billion was spent on patients with chronic musculoskeletal problems in Australia from 2008 to 2009. This included the costs of pharmacological treatments and joint replacements.[1]

Musculoskeletal pain is caused by conditions of the bones, muscles and their attachments (i.e. tendons, ligaments and connective tissues), and arthritis (i.e. joints).[1,2] These conditions range in time frame from sudden-onset and short-lived problems to life-long chronic disorders. Consequences of the pain include loss of dexterity and mobility, which explains why musculoskeletal conditions are the most common cause of disability.[2]

It is estimated that 20% of primary care visits are due to musculoskeletal disorders, and many practitioners feel uncomfortable managing patients with common problems associated with these conditions.[3] The issues of managing affected patients are further compounded by the fact that most are elderly with significant comorbidities and increased risk of adverse effects of medications. Most importantly, thorough clinical assessment and investigations for underlying medical disease or chronic inflammatory conditions should be performed to avoid missing other diagnoses or stereotyping patients.[4]

Common approaches to managing patients with musculoskeletal pain include several pharmacological and nonpharmacological treatments, including pharmacotherapy, surgery, injections, physical therapy, psychological approaches such as

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KEY POINTS

- Musculoskeletal pain is common and has significant consequences for affected patients and society as a whole.
- Musculoskeletal pain is not purely nociceptive; peripheral inflammation and central sensitisation processes, as well as neuropathic components, contribute.
- Management of patients with these conditions should be multimodal and multidisciplinary, not rely on pharmacological approaches alone, and follow principles of chronic disease management aiming for improved function.
- Nonopioid analgesics, in particular NSAIDs, play an important role in the pharmacological management of patients with these conditions.
- Opioids should be used with caution and only after careful consideration in patients with musculoskeletal pain; tramadol, buprenorphine and tapentadol may be preferable here.
- Adjuvants such as anticonvulsants (e.g. pregabalin) and antidepressants (e.g. duloxetine) may play a previously underestimated role in the management of patients with musculoskeletal pain.

hypnosis, relaxation and cognitive behavioural therapy, and complementary or alternative medicines. Improved understanding of pain physiology and the underlying neurobiology has improved patient outcomes through the development of new approaches, better analgesics and more advanced delivery techniques.

Mechanisms of pain

Early concepts focused on degenerative wear and tear of the musculoskeletal elements as the main underlying mechanism of musculoskeletal pain, with inflammatory factors leading to peripheral sensitisation. However, more recent data suggest that central sensitisation and, in particular, neuropathic elements also play a significant role in the background of musculoskeletal pain.[5]

For example, it is widely accepted that in the joint, peripheral unremitting inflammatory reactions cause peripheral sensitisation, especially after an acute injury. Different types of mechanoreceptors in the joint, including polymodal type IV receptors, are involved in local sensitisation as seen in inflammatory conditions.[6] Furthermore, subsequent central neuronal plasticity causes perpetuation of pain; this process is now commonly called central sensitisation.[7] Functional MRI studies (fMRI) and psychophysical quantitative sensory testing (QST) confirm that increased activity in the central nervous system is associated with skin stimulation in patients with chronic OA.[6,8] Pain signal amplification in the central nervous system augments pain perception leading to allodynia (non-noxious stimuli perceived as pain) and hyperalgesia (heightened response to painful stimuli). Clinically, patients with

dominant features of central sensitisation experience disproportionate pain, fatigue, cognitive impairment and other somatic symptoms such as sleep deprivation, stress and anxiety. Features of central sensitisation can be identified by the use of the Central Sensitisation Inventory, which can then guide clinicians in selecting the most appropriate therapeutic approaches.[9] Similarly, components of neuropathic pain can be identified using screening questionnaires, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale, the Douleur Neuropathique 4 (DN4) or the painDETECT questionnaire.[10]

Nonopioid analgesics

Paracetamol

Paracetamol has no specific endogenous binding sites, hence the continuous debates surrounding its mechanisms of action.[11] It seems to exert effects centrally, possibly via direct and indirect cyclo-oxygenase inhibition; the activation of spinal serotonergic and endocannabinoid systems also appears to be involved in its analgesic effect.

When used by patients with acute postoperative pain, paracetamol is an effective analgesic, with an NNT50% in the range of 3.6; that is, 3.6 patients need to be treated to achieve 50% pain reduction involving one patient compared with placebo.[12] However, the results are much more disappointing in patients with musculoskeletal pain conditions. A large randomised trial in patients with acute back pain showed no benefit of regular or on-demand paracetamol on pain relief and time to recovery compared with placebo.[13] Similarly, a meta-analysis of paracetamol use in patients with chronic low back pain showed no beneficial effect on pain, function or quality of life.[14] In the same meta-analysis, paracetamol improved pain and disability in patients with OA of the hip and knee; however, although the effects were statistically significant, they were too small to be clinically important. These disappointing findings were confirmed in another network meta-analysis of pharmacological interventions in patients with OA of the knee; of all interventions analysed, paracetamol showed the poorest improvement, the only one that was not clinically meaningful.[15] Although this does not mean that paracetamol may not be useful in patients who respond well to it,[16] it leads to a reconsideration of most previous guidelines emphasising the role of paracetamol as first-line treatment in the setting of acute and chronic musculoskeletal pain.

Paracetamol combined with an NSAID is superior to either compound alone; this has been shown in particular for the combination of paracetamol and ibuprofen, available commercially.[17,18] Similarly, the combinations of paracetamol with a weak opioid such as codeine or tramadol are more effective than paracetamol on its own, shown mostly in patients with acute postoperative pain.[19,20] There are also some data on the efficacy of paracetamol and tramadol combinations in patients with chronic musculoskeletal pain.[21]

Systemic NSAIDs

The biological stress response that occurs after a trauma or surgery generates chemical mediators such as prostaglandins, which contribute to acute pain and its morbidities. A low-grade local or systemic inflammation may persist, explaining the more complex pathophysiology of persistent or chronic pain conditions.[22,23] As such, NSAIDs represent a sensible strategy for treating patients with acute and chronic musculoskeletal pain.

NSAIDs have an established analgesic efficacy in the treatment of patients with acute postoperative pain.[16] They are also similarly effective in the treatment of those with chronic low back pain and acute ankle sprain.[24] In patients with OA, NSAIDs provide clinically meaningful analgesia superior to paracetamol and comparable with opioids.[15,25] There seems to be no difference in efficacy between appropriate doses of nonselective NSAIDs (nsNSAIDs) and the selective NSAIDs, cyclo-oxygenase (COX)-2 inhibitors.

The main concerns with short- and long-term use of nsNSAIDs are upper and lower gastrointestinal (GI) events (i.e. ulceration, bleeding, perforation or NSAID enteropathy), risks of cardiovascular (CV) events and renal impairment.[26] Adverse renal effects increase in patients with preexisting renal impairment, hypotension, hypovolaemia, concurrent use of nephrotoxic drugs and multiple NSAID use. Risks of upper GI problems follow long-term and short-term use of nsNSAIDs.[24]

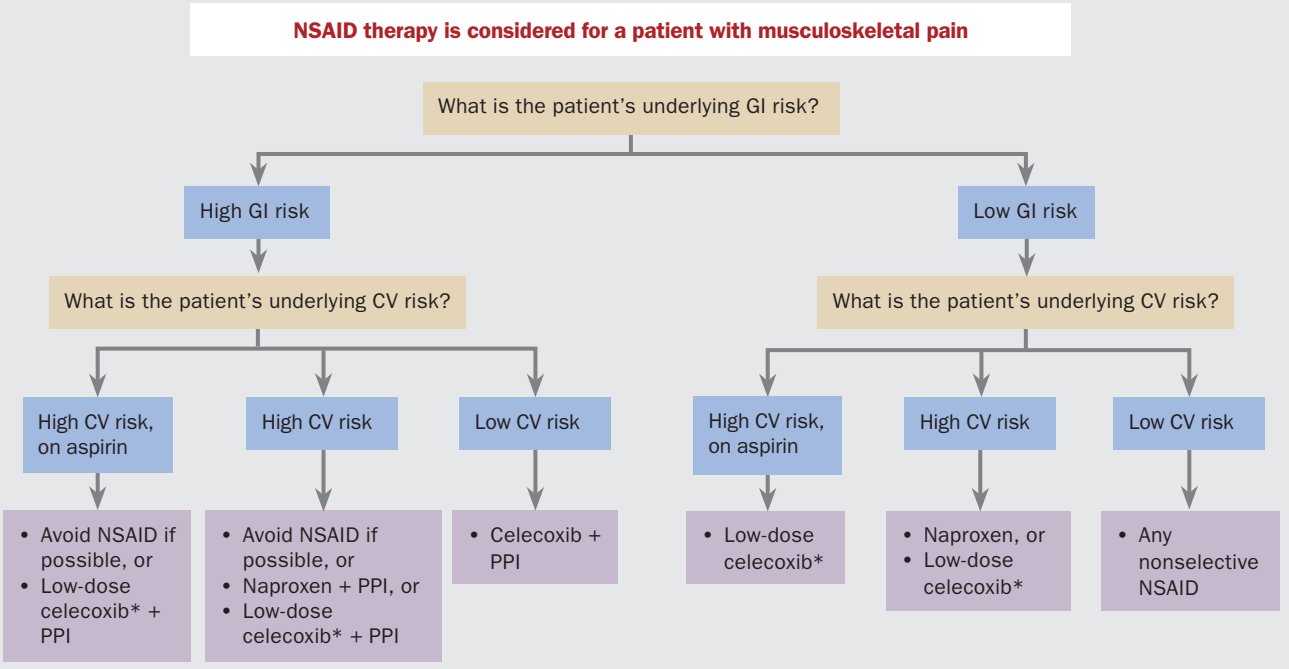
COX-2 inhibitors selectively inhibit the inducible isoenzyme COX-2, preserving function of the constitutional isoenzyme COX-1, which determines protective functions of prostaglandins, in particular in the GI tract. Therefore, COX-2 inhibitors show reduced GI adverse effects compared with nsNSAIDs.[27] Upper GI events due to nsNSAIDs are relatively reduced when combined with proton pump inhibitors (PPI) in susceptible patients, but PPIs are not protective for NSAID enteropathy.[22] Compared with the COX-2 inhibitor celecoxib, the nsNSAID diclofenac plus a PPI caused more clinically significant upper and lower GI events.[28] The best gastroprotective combination in high-risk patients who had previous GI bleeding is a COX-2 inhibitor plus a PPI.[29]

In terms of CV risk, naproxen seems to be associated with less harm from CV events compared with other nsNSAIDs.[30] However, celecoxib may have a similar rate of CV effects[27] and may be an alternative to naproxen with reduced GI adverse effects.[22] The Flowchart shows a risk-based algorithm for the selection of the most appropriate NSAID in various risk situations.[22]

Even in patients with acute renal failure, COX-2 inhibitors may be advantageous over nsNSAIDs. In a large case-control study, the risk of renal impairment was shown to increase with a decrease in cyclooxygenase selectivity, favouring the use of COX-2 inhibitors.[31]

Elderly populations are at increased risk of adverse events from NSAIDs. However, in a large retrospective study of an elderly cohort in the USA, risks of falls, fractures and hospital admissions were lower with nsNSAID and COX-2 inhibitor use than

AN APPROACH TO LONG-TERM NSAID THERAPY FOR MUSCULOSKELETAL PAIN



Abbreviations: CV = cardiovascular; GI = gastrointestinal; PPI = proton pump inhibitor.
* Low-dose celecoxib is 200 mg/day.
Adapted from BMC Med 2015; 13: 55.[22]

with opioid use.[32] Overall, all NSAIDs showed a reduced relative risk of safety events including mortality, challenging the notion that opioids are safer in this age group.

Topical NSAIDs

Topical NSAIDs are effective for the treatment of patients with short-term exacerbation or acute attacks of localised pain, such as strains, sprains or sports injuries, which often occur in the setting of chronic musculoskeletal pain. Application of a topical gel of ketoprofen, ibuprofen, diclofenac and piroxicam, but not indomethacin, two to three times daily provides effective pain relief with systemic adverse effects comparable with placebo.[33] Similarly, topical diclofenac and ketoprofen can provide pain relief in individuals with chronic pain due to OA with adverse effects comparable with placebo.[34] Topical rubefacients containing salicylates seem not to be effective in people with acute and chronic conditions.[35]

Opioids

There is a worldwide ongoing debate on the use of opioids for the treatment of people with chronic pain of nonmalignant origin.[36] Issues are the limited efficacy in this setting as well as problems with aberrant use, abuse and diversion. The resulting epidemic of prescription opioid overdoses with an unacceptably high mortality in the USA[37] and also in Australia[38] suggest that a more cautious approach to opioid use is required. In addition, chronic opioid use seems to relegate self-efficacy and promote an externalised locus of control, leading to further dependence on the healthcare system thereby contradicting the functional goals of pain management.[39] Therefore, evidence-based guidelines, for example in elderly patients with chronic musculoskeletal pain, recommend chronic opioid therapy only with great caution and when all other safer alternatives have not been effective or not suitable.[40] Use of opioid risk assessment tools to identify patients at risk of aberrant drug-related behaviours should be considered.[41]

Specifically, in patients with chronic pain due to OA, strong opioids have not been found to be more effective than NSAIDs[25] or, in some studies, than placebo.[42] At the same time, use of opioids resulted, as outlined above, in more falls, fractures, hospital admissions and mortality than NSAID use in this high-risk elderly population.[32] Other adverse effects, which need to be considered when using opioids in the long term include opioid-induced androgen deficiency (leading to decreased testosterone levels and subsequent osteoporosis), immune suppression and opioid-induced hyperalgesia, paradoxically increasing pain levels.[36]

Controlled-release preparations or long-acting opioids are usually recommended for prolonged treatment in patients with chronic pain; however, recent guidelines issued by the Centers for Disease Control and Prevention (CDC) question this rationale. No evidence was found that

continuous administration of controlled-release opioids is more effective or safer than intermittent use of immediate-release opioids or reduces opioid misuse or addiction.[43] If controlled-release preparations are used, then abuse-deterrent formulations such as a slow-release oxycodone preparation should be chosen.[44]

Specifically, transdermal buprenorphine and, even more so, the atypical centrally acting analgesics tramadol and tapentadol may offer some advantages in the chronic pain setting.

Transdermal buprenorphine

Transdermal buprenorphine is widely used in the setting of chronic musculoskeletal pain, particularly in elderly patients. One advantage with using transdermal buprenorphine is the option of starting at a very low dose of 5 μg/h. Furthermore, buprenorphine shows a ceiling effect for respiratory depression but not analgesia with increasing doses, which might increase its relative safety;[45] other advantages are less constipation, immune and androgen suppression. Last, but not least, it might cause less tolerance and hyperalgesia than other opioids.[46]

Buprenorphine patches at doses of 5 to 20 μg/h were reported as being effective or very effective with high treatment adherence in a recent UK observational study in patients with chronic musculoskeletal pain.[47] The results were comparable with those seen with sustained-release tramadol in patients with musculoskeletal pain who had had no relief with nsNSAIDs.[48] Buprenorphine patches were also successfully trialled in multimorbid patients with significant analgesic efficacy and tolerable adverse effects.[49]

Atypical centrally acting analgesics: tramadol and tapentadol

Tramadol is classified as an atypical centrally acting analgesic. Its opioid effects are from an active metabolite (M1) and its more important analgesic efficacy results from noradrenaline and serotonin reuptake inhibition. This mechanism of action leads to improved analgesia with reduced opioid side effects such as constipation and a lower risk of respiratory depression and abuse.[50] It has been used with benefit in patients with OA.[51,52] However, disadvantages of tramadol include serotonergic adverse effects such as nausea and vomiting, potential interactions with other serotonergic drugs (e.g. antidepressants) and the reliance on the opioid effect of a metabolite. The metabolic pathway to this metabolite is via cytochrome (CYP) 450 2D6 and is thereby dependent on the specific phenotype for this enzyme in an individual patient.[53]

The recently registered tapentadol overcomes most of these disadvantages because the molecule itself is an opioid agonist with 18 times less affinity to human mu-receptors than morphine and strong noradrenaline reuptake inhibition with negligible effects on serotonin.[54,55] Despite the weak opioid agonism, it can match the analgesic efficacy of morphine in a 3:1 (tapentadol to morphine) dose ratio and oxycodone in a 5:1 (tapentadol to oxycodone) dose ratio.[56]

In patients with chronic low back pain or OA, a meta-analysis showed that the analgesic effect of slow-release tapentadol was noninferior to that of slow-release oxycodone.[56] However, improvement of quality of life measures were superior in the tapentadol group, which experienced significantly lower rates of GI adverse effects (i.e. nausea, vomiting, constipation) and fewer treatment discontinuations. These results were confirmed in a network meta-analysis against several other conventional opioids (i.e. fentanyl, hydromorphone, morphine and oxymorphone).[57] Also, data from the USA so far suggest a significantly lower risk of abuse than with conventional opioid use.[58]

Symptomatic slow-acting drugs for osteoarthritis

Guidelines from the European League against Rheumatism (EULAR) for managing patients with pain due to knee OA suggest compounds such as glucosamine and chondroitin sulfate should be used as an initial approach.[59] A recent consensus statement from the European Society for Clinical and Economic Aspects of

Osteoporosis and Osteoarthritis (ESCEO) reiterated a similar endorsement. It placed a particular emphasis on the use of a patented prescription formulation of a crystalline glucosamine and chondroitin sulfate combination, for which high-quality evidence of its efficacy compared with other formulations was provided.[60,61]

Adjuvants

With the recognition that central sensitisation and elements of neuropathic pain contribute significantly to chronic musculoskeletal and joint pain comes the development of a new role for antidepressants and anticonvulsants in the management of patients with these pain conditions.[6] For example, pregabalin is now indicated for neuropathic pain and duloxetine for diabetic polyneuropathy. The beneficial effects of tramadol and tapentadol due to their noradrenergic effects, described above, apply also to antidepressants, thereby strengthening descending pathways of pain inhibition.[62]

Antidepressants

Duloxetine is a serotonin and noradrenaline reuptake inhibitor (SNRI) antidepressant, which has been extensively studied for use in patients with neuropathic pain regardless of its disease origin; it is here recommended as a first-line treatment, although it is only indicated for diabetic peripheral neuropathic pain and chronic musculoskeletal pain.[63] In patients with chronic knee OA and chronic low back pain, duloxetine is effective compared with placebo, with significant improvement seen in physical outcomes.[64,65] With the accumulating evidence for its efficacy, duloxetine has been included in the recently updated Osteoarthritis Research Society International (OARSI) guidelines for the nonsurgical management of patients with chronic OA.[66] Commonly observed adverse effects of duloxetine are nausea, fatigue and constipation.[67,68]

Other SNRIs such as venlafaxine and tricyclic antidepressants (TCAs) such as amitriptyline may be useful in managing patients with neuropathic pain (off-label uses); but there are no studies to support their use in patients with musculoskeletal pain. Furthermore, TCAs are best avoided in the elderly because their anticholinergic activity increases the cumulative risk of cognitive impairment and mortality in this age group.[69]

Anticonvulsants

The anticonvulsants recommended as first-line treatment for patients with neuropathic pain are gabapentin and pregabalin.[63] As modulators of the alpha-2 delta subunits of voltage-gated calcium channels in the central nervous system, they diminish neuronal calcium influx and reduce release of excitatory neurotransmitters, primarily glutamate, and thereby reduce central sensitisation.[70] They are, therefore, effective in treating patients with fibromyalgia (off-label uses).[71]

In one randomised controlled trial in patients with knee OA, pregabalin was found to be as effective as meloxicam and the combination of both was superior to each individual component with regard to pain and improvements in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.[72]

Overall principles of pharmacological management of musculoskeletal pain

The aim of medication use for pain control is always to facilitate initiation of daily activities and break the cycle of persistent pain, which leads to fear-avoidance and subsequent musculoskeletal deconditioning. Therefore, when managing musculoskeletal pain in particular, the emphasis should be on the ultimate goal of improved function. Pharmacological therapy should never be used alone, but integrated into multimodal and multidisciplinary management of the sociopsychobiomedical features of chronic pain and is only one component of such management.[73] This approach requires a stepwise integration of broad modalities of nonpharmacological and pharmacological treatments, based on prioritisation of intervention.[61,74]

Conclusion

A therapeutic approach to musculoskeletal pain requires an understanding of the underlying pathophysiology, but also a detailed exploration of the impact on the individual patient's life and therapeutic goals. Nonpharmacological approaches, in particular physical therapies and psychological management, are an important component of such an approach. Pharmacological treatments can and need to complement these approaches with the ultimate goal of improving a patient's daily function and quality of life.

In chronic pain states, long-term continuation of pharmacological treatments has to be balanced against their potential adverse effects and complications. The recent recognition of elements of neuropathic pain and central sensitisation contributing to musculoskeletal pain states has opened new therapeutic avenues. MT

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A list of references is included in the website version of this article (www.medicinetoday.com.au).

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