Chronic pain management options in general practice

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Keywords: chronic pain, management, general practice

Abstract

Chronic pain affects almost one in five patients, making it one of the most common conditions that any practitioner has to manage on a daily basis. Poorly managed chronic pain has a significant impact on work, social and psychological functioning. This guideline aims to review the most common medications and treatments available in general practice, and how to follow a safe, stepwise approach to managing chronic pain.

S Afr Fam Pract 2012;54(2):94-99

Introduction

Almost one in five patients who are seen in general practice has some form of chronic pain. Symptomatic osteoarthritis and back complaints are the most common complaints.[1,2] Musculoskeletal pain affects as many as one in four adults, and is the most common source of serious long-term pain and physical disability.[3] Chronic musculoskeletal conditions are primary health problems that limit work in industrialised nations. Up to 60% of people on early retirement, or long-term sick leave, have chronic musculoskeletal ailments.[4]

Managing patients with chronic musculoskeletal pain can be difficult, as the experience of chronic pain is individual and multifactorial, as well as being influenced by culture, previous pain experiences, beliefs, moods, and the ability to cope. Although pain may indicate tissue damage, it can be experienced in the absence of an identifiable cause. Significant variability occurs in the degree of disability experienced in relation to pain, and there is individual variation in response to pain treatments.[3]

What is chronic musculoskeletal pain?

Chronic pain is pain that has been present for longer than three to six months.[5] The development of chronic pain is likely to be the result of small, cumulative changes in lifestyle, that have been made to cope with acute musculoskeletal pain.[6] A combination of behaviours, beliefs, and emotions, is likely to be involved in the development of chronic pain.[6]

The mechanisms of chronic pain are complex, and continue to be unravelled. On a molecular level, chronic pain is caused by changes in the central and peripheral nervous system, activation of inflammatory chemical pathways and nerve receptive pathways, peripheral sensitisation, and the altering of central neuroplasticity in the perpetuation of pain, and links between inflammation, pain and psychological status.[7,8]

Treating chronic pain

Pharmacological options in the management of chronic pain include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids and adjunctive treatments, such as steroids, anti-inflammatories and antidepressants, all of which play an important role in the management of pain.

Analgesics, NSAIDs and opioids

The World Health Organization (WHO) analgesic ladder provides a rational basis for the progressive therapeutic management of cancer pain, and provides good pain control in over 90% of cases. It has been adopted as the recognised stepwise approach to acute and chronic non-cancer pain.[9]

Fundamentally, the WHO analgesic ladder allows the practitioner to increase the strength and intensity of treatment, dependent on the specific pain experienced by the individual, as illustrated in Table I.

Table I: The World Health Organization analgesic ladder[9]

Step 1	Non-opioid
	± Adjuvant therapy
Step 2	Weak opioid
	+ Non-opioid
	± Adjuvant therapy
Step 3	Strong opioid
	+ Non-opioid
	± Adjuvant therapy

Paracetamol

Minor analgesics have been shown to provide definite benefits in chronic pain.[10] Paracetamol remains the first choice in the management of mild-to-moderate persistent pain (see Table II).[11]

Table II: Summary of paracetamol for the treatment of chronic pain

Active agent	Brand name	Dosage	Max dose
Paracetamol[12]	Adco-Paracetamol®, Antalgic®, Fevamol®, Go-Pain P®, Pacimol®, Painomol Be Tabs®, Panado®, Prolief®, Tylenol®, Tylenol Extended Release®, and Perfalgan®	Oral: 1-2 500 mg q 4-6 hourly Intravenously: (> 50 kg) 1 g q 6 hourly	4 g/day

Although NSAIDs may produce greater reductions in pain intensity, any efficacy advantage in milder pain is small.[13,14] Paracetamol has a more favourable adverse-effect profile than NSAIDs, and according to the National Institute for Health and Clinical Excellence (NICE) guidelines, should always be considered as the first choice ahead of oral NSAIDs, cyclo-oxygenase 2 (COX-2) inhibitors or opioids.

If administered regularly, paracetamol has 95% of the efficacy of compound preparations.[15] Many patients who complain that they have tried, and failed, to control pain with paracetamol, have been provided with inadequate doses to provide pain relief. A USA survey of older women living with musculoskeletal pain, found that on average, 41% used paracetamol at a quarter of the maximum dose.[16]

When prescribing paracetamol, it is important to find out what dosage and frequency of use has been implemented to date.[11] Increasing the dose, or taking doses regularly, may be sufficient to manage the pain more effectively. It is important to emphasise that paracetamol should be taken timeously and regularly;and should not be based on the presence of pain.[11]

Paracetamol can be used safely on medical advice in the long term, and if the maximum dose is not exceeded, paracetamol-induced hepatotoxicity is very rare.[17,18] Poor nutrition, alcohol abuse, and inadvertent overdose (usually by patients who are taking other combination medications containing paracetamol) are the most common causes of paracetamol-induced liver injury.[19]

NSAIDs

The primary mechanism of NSAID action is inhibition of the enzyme cyclo-oxygenase (COX), resulting in the blockade of prostaglandin synthesis.[20,21] Controversy over the risks of NSAIDs has created uncertainty about the use of this class. NSAIDs are valuable analgesics, with a low risk of serious adverse effects, when used appropriately in carefully selected patients.[11] All NSAID active ingredients and brand names that are available in South Africa have been listed in Table III.

Non-specific NSAIDs vs. COX-2 inhibitors

COX-2 selective NSAIDs have equivalent efficacy, and a similar range of adverse effects, to those of conventional NSAIDs. Therefore, they are not preferred routinely to conventional NSAIDs. When choosing an agent, individual patient risk factors, including age, should be taken into account. Monitoring is of key importance for long-term prescription of NSAIDs.[22]

Safety concerns focus primarily on an increased risk of gastrointestinal bleeding and ulcers, renal impairment, as well as cardiovascular events in more recent years.[23-26]An increased risk of myocardial infarction, stroke, and death, has been linked to selective COX-2 inhibitors, and this increased risk of cardiovascular side-effects appears to be a class effect of NSAIDs, including nonselective agents.[27]

Gastrointestinal side-effects

The most clinically significant difference between COX-2 selective and conventional NSAIDs is likely to be in their propensity to cause serious gastrointestinal adverse events. However, evidence of a safety advantage for celecoxib or meloxicam, over conventional NSAIDs, is limited, particularly in the long term.[28]

Risk factors that may indicate that a patient is at high risk of adverse gastrointestinal effects include:[29]

- Age ≥ 65 years
- History of ulcer
- Concomitant use of anticoagulants or corticosteroids
- Presence of serious co-morbidity
- Use of NSAIDs with higher gastrointestinal risk
- Prolonged use of high NSAID doses (including the combination of aspirin and another NSAID, or of two non-aspirin NSAIDs).

In these patients, using a COX-2 selective NSAID is justified, provided the cardiovascular risk is low. In the general NSAID-using population, the incidence of serious ulcer complications is low, so the absolute reduction in the risk of complications when using a COX-2 selective NSAID, rather than a conventional NSAID, is small for most people.

NICE suggest routinely co-prescribing a proton-pump inhibitor for people over 45 who have been taking a NSAID for more than three months.[30]

Table III: Nonsteroidal anti-inflammatory medications that are available in South Africa

Active agent	Brand name	Dosage	Maximum dose
Non-specific NSAIDs			
Ibuprofen[12]	Adco-ibuprofen®, Betagesic®, Betaprofen®, Brufen®, Iboflam®, Ibucine®, Ibumed®, Nurofen®, Pedea®, Ranfen®, and Sandoz ibuprofen®	200-400 mg q 4-6 hourly	1200 mg/day
Indomethacin	Adco-indogel®, Adco-indomethacin®, Arthrexin®, Betacin®, Elmetacin®, Flamecid®, Methocaps®, and Sandoz-indomethacin®	25-50 mg q 6-8 hourly	200 mg/day
Ketoprofen	Fastum®, Ketoflam®, and Oruvail®	200 mg daily with food	300 mg/day
Mefenamic acid	Fenamin®, Ponac®, Ponstan®, and Ponstel®	500 mg q 8 hourly	1500 mg/day
Naproxen	Adco-naproxen®	500 mg q 12 hourly	1000 mg/day
Lornoxicam	Xefo®	8-16 mg/day, in 2-3 divided doses	16 mg/day
Piroxicam	Adco-Piroxicam®, Brexecam®, Piricam®, Pyrocaps®, Rheugesic®, Rolab-Piroxicam®, and Xycam®	20-40 mg daily	40 mg/day
Diclofenac	Diclohexal-K®, Dynak 50®, K-Fenac®, Voltaren Acti-Go®, A-Lennon Diclofenac®, Adco-Diclofenac®, Catafast-D®, Cataflam D®, Dicloflam®, DicloHexal®, Fortfen SR®, Mylan Diclofenac®, Panamor®, Sandoz Diclofenac®, Veltex®, and Voltaren®	Oral: 25-50 mg q 8 hourly, to a maximum of 150 mg/day Drops: (only Voltaren®) 15 mg = ml, 1 drop = 0.5 mg, 1 ml = 30 drops 100 mg in 2-3 divided doses Daily maximum = 150 mg Intramuscular: 75 mg q 12 hourly, maximum of 150 mg/day for 2 days only Suppositories: 100 mg daily	150 mg/day
Sulindac	Adco-Sulindac®	100-200 mg q 12 hourly	400 mg/day
Phenylbutazone	Inflazone®	200-400 mg q 12 hourly	400 mg/day
COX-2 inhibitors			
Meloxicam	Adco-Meloxicam®, Arrow Meloxicam®, Arthoxox®, Coxflam®, Flexocam®, Loxiflam®, M-Cam®, Meflam®, Mobic®, and Zydus Meloxicam®	7.5 mg q 12 hourly or 15 mg daily	15 mg/day
Etoricoxib	Arcoxia®	60-90 mg q 12 hourly	120 mg/day
Celecoxib	Celebrex®	100-200 mg q 12 hourly	400 mg/day
Parecoxib	Rayzon®	40 mg q 6-12 hourly h IV/IM	80 mg/day

Cardiovascular risk

Safety concerns about the risk of thrombotic events associated with COX-2 selective and conventional NSAIDs, mean that it is particularly important to consider cardiovascular risk factors when contemplating NSAID use for chronic pain.[11]

The American Heart Association recommends COX-2 inhibitors as a "last resort" in the management of chronic musculoskeletal pain in patients with increased cardiovascular risk. This recommendation was made after multiple studies indicated an increased risk of cardiovascular disease complications resulting from COX-2 selective NSAIDS.[31]

Risk factors that may indicate that the patient is at high risk of adverse cardiovascular events, include a history of: [32]

- Ischaemic heart disease
- Cerebrovascular disease
- Peripheral artery disease
- Moderate-to-severe congestive heart failure [New York Heart Association (NHYA) II-IV]
- Hypertension
- Hyperlipidaemia
- Diabetes
- Smoking.

The European Medicines Agency has recommended that all COX-2 inhibitors should be avoided in patients with established ischaemic heart disease, cerebrovascular disease, moderate-to-severe congestive heart failure (NYHA II-IV), or peripheral arterial disease. COX-2-specific NSAIDs should also be avoided in patients with hypertension, whose blood pressure (BP) is persistently above 140/90 mmHg, and has not been adequately controlled.[32]

COX-2 inhibitors can lead to impaired renal perfusion, sodium retention, and increases in BP, which may contribute to their adverse cardiovascular effects. Therefore, renal function and BP should be monitored in subjects taking COX-2 inhibitors, and extra caution should be practised when these drugs are given to subjects with pre-existing hypertension, renal disease, and heart failure.[31]

Unfortunately, several observational studies suggest that some increased cardiovascular risk may apply to all NSAID users, irrespective of their baseline cardiovascular risk. The greatest concern relates to chronic use of high doses of NSAIDs. Even patients with a low Framingham risk score showed increased risk of cardiovascular events after long-term NSAID use.[33]

It is fair to say that research has also shown that not all NSAIDs pose a similar cardiovascular risk. The risk of thrombotic events is relatively lower with naproxen and low-dose ibuprofen, compared to other NSAIDs (see Table IV).[34]

Table IV: Risk of cardiovascular events using nonsteroidal anti-inflammatory drugs[34]

Drug	Pooled relative risks (95% CI)
Naproxen	1.09 (1.02-1.16)
Ibuprofen	1.18 (1.11-1.25)
Celecoxib	1.17 (1.08-1.27)
Rofecoxib	1.45 (1.33-1.59)
Diclofenac	1.40 (1.27-1.55)
Indomethacin	1.30 (1.19-1.41)
Piroxicam	1.08 (0.91-1.30)
Meloxicam	1.20 (1.07-1.33)
Etodolac	1.55 (1.28-1.87)
Etoricoxib	2.05 (1.45-2.88)
Valdecoxib	1.05 (0.81-1.36)

With NSAIDS, the guiding principle is to select patients carefully, use the minimum dose of the "safest" NSAID, and monitor the patients regularly for side-effects.

Renal events

Renal adverse effects are no less likely with COX-2 inhibitors, than with nonselective NSAIDs.

Risk factors that may indicate that the patient is at high risk of adverse renal effects include a history of:[28]

- Congestive heart failure
- Cirrhosis
- Glomerular filtration rate of $\leq$ 60 ml/minute
- Age > 60 years
- Use of diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, cyclosporin or aspirin
- Salt-restricted diet.

Always monitor patients carefully if there is a clinical need for NSAIDs, but a higher risk of renal impairment.

Opioids

As the WHO analgesic ladder indicates, if pain cannot be controlled by paracetamol and NSAIDs, or if NSAIDs are contraindicated, the addition of an opioid is recommended to manage chronic pain.[35]

A weak opioid may be considered an alternative to an NSAID when paracetamol alone is inadequate, or if a patient's pain does not respond adequately to an NSAID (with or without paracetamol).[36]

A weak opioid should be added as a separate tablet so that a full dose of paracetamol can be given, and the opioid dose can be titrated to effect and tolerability. After reaching a stable effective dose, it may be possible to switch to an equivalent combination tablet. Usually, a dosage of around 60 mg per day of codeine is required, but the lowest dose that is able to control the patient's pain should be used.[15,37] The commonest opioids used in general practice are listed in Table V.

Strong opioids can be used when other analgesics do not provide sufficient pain relief, or if they are unsuitable because of adverse effects. Generally, morphine is considered to be the first-choice strong opioid because of familiarity, cost, and the available range of formulations. Oxycodone and hydromorphone are alternatives for people who cannot tolerate morphine.[11]

Safety

It's important to consider side-effects when prescribing opioids. Typically, weak opioids produce the same range of adverse effects as stronger opioids, but are less effective analgesics. However, when combined with paracetamol,[15,37] they offer moderate pain relief.

The incidence of addiction is very low, if strong analgesics are used appropriately.[38,39] An overcautious attitude to the use of strong opioids will deny optimal pain relief to patients who have severe pain. "Pseudo-addiction" has been described as the result of routine under-prescription of analgesics, when the patient's demand for more medication appears to be similar to demands made by opiate abusers.[40]

Ideally, patients should be referred to a multidisciplinary pain clinic or a pain specialist before a strong opioid is prescribed. However, it can be difficult to get an appointment in a timely manner. Consider whether it is appropriate to initiate opioid therapy before a visit to the pain clinic, or seek advice from a specialist by telephone.[11]

Table V: Opioids that are available in South Africa

Active agent	Brand name	Dosage	Maximum dose
Low-efficacy agents			
Codeine[12]	Lennon-Codeine Phosphate®	15-60 mg daily per os	60 mg/day
Intermediate-efficacy agents			
Dipipanone	Wellconal®	Oral: 1 tablet q 6 hourly. May increase by ½ tablet increments to a maximum of 3 tablets	150 mg/day
Dihydrocodeine	DF-118®, and Paracodin®	Oral: 30 mg q 4-6 hourly Intramuscular: 25-50 mg q 4-6 hourly	120 mg/day
High-efficacy agents			
Morphine	SRM-RHOTARD MST Continus®, Merck Morphine sulphate®, Micro Morphine Injection®, and Morphine Sulphate- Fresenius® Combination: Morphine and cyclizine = Cyclimorph®	Oral: 10-2 0 mg q 12 hourly Intramuscular: 0.1-0.3 mg/kg q 4 hourly Intravenous bolus: 1-5 mg q 1 hourly Intravenous infusion: Give a loading dose, then titration, depending on pain and sedation scale = 3-5 mg/hour	40 mg/day
Pethidine	Merck-Pethidine HCl®, Micro-Pethidine®, and Pethidine HCl-Fresenius®	Intramuscular: 1-1.5 mg/kg q 3-4 hourly	600 mg/day

Combinations

In South Africa, a wide range of combination medications are available to treat pain. Although compound analgesics produce a greater effect in the case of acute pain, the many additive agents, e.g. caffeine, and antihistamines), can often cause unwanted side-effects in the chronic situation.[11]

However, specifically when using opioids and NSAIDs, the combination of paracetamol with these agents is more effective than either agent alone, and it also reduces the dosage of the opioid, or NSAID, that is required to treat pain.[11,15]

Consider combining paracetamol with other agents to achieve pain control, but do not advise single-combination medications, unless the dosage of the combination is the best clinical recipe for the patient.

Adjunctive medications

Generally, adjunctive or adjuvant medications are defined as medications not containing paracetamol, NSAIDs, or opioids, but which play a role in the management of chronic pain. When treating chronic pain, practitioners should consider these alternative agents.[41]

Adjunctive agents include tricyclic antidepressants, antiepileptic agents, muscle relaxants (baclofen), corti-costeroids, bisphosphonates and calcitonin.[41] Adjunctive agents have often been used with good effect, where chronic pain is neuropathic in origin.[41]

Antiepileptic agents

Antiepileptic drugs, such as phenytoin, carbamazepine and divalproex, have been used for several years to manage neuropathic pain. Other agents, such as gabapentin and lamotragine, have a broader use in the management of chronic pain.[41]

Antidepressants

Tricyclic antidepressants (TCAs) are commonly used in the treatment of chronic pain to alleviate insomnia, enhance endogenous pain suppression, and eliminate other painful disorders, such as headaches. Research supports the use of TCAs to treat both nociceptive and neuropathic pain syndromes, making them particularly useful in the management of chronic musculoskeletal pain.[41]

Newer agents, such as venlafaxine and duloxetine, have also been shown to provide additional pain relief in chronic pain sufferers. Serotonin uptake inhibitors have the added benefit of offering treatment for associated depression, anxiety, fatigue, and reduced coping ability, all of which accompany chronic pain generally.[41]

Controlling chronic musculoskeletal pain

Chronic musculoskeletal pain is one of the most common complaints in primary care. It is important to assess the patient's previous pain control strategies, and to adjust, or step up, treatment, according to his or her clinical needs.

Paracetamol should be the first-line treatment for chronic pain, and it is important to ensure that patients are taking optimal doses, before stepping up treatment. NSAIDs and opioids offer alternatives to those patients who need further pain control, especially when used in combination with paracetamol.

Adjunctive treatments such as antiepileptics and antidepressants can help reduce chronic musculoskeletal pain, and limit the need for analgesics.

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