Pharmacology in the management of chronic pain

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Abstract

Management of chronic pain should be achieved with a bio-psychosocial approach and often requires multidisciplinary input. Pharmacological treatment can play an important role in the successful management of chronic pain. When planning a pharmacological strategy for chronic pain it is important to consider the nature and likely source of the pain. This review article will summarize common pharmacological options in current clinical use for the management of chronic pain.

Keywords Chronic pain; pharmacological treatment

Royal College of Anaesthetists CPD Matrix: 2E03

Learning objectives

After reading this article, you should be able to:

- discuss the general principles of use of pharmacological treatment in chronic pain
- describe the mechanisms of action of most commonly used pharmacological agents
- outline the evidence base for these drugs

Outline

Pain management strategies show considerable overlap between those categorized as acute and chronic pain; chronic pain being that which is present for greater than 12 weeks.[1] Additionally, there may be causative overlap i.e. acute pain following surgery or trauma has been shown to progress to chronic pain in as many as 50% of cases while other cases of chronic pain may not have an obvious precipitant.

When deciding upon a pharmacological strategy for chronic pain it is important to consider the nature and likely afferent source of the pain e.g. deep viscus versus superficial wound pain, nociceptive versus neuropathic. We can then target and rationalize the agents appropriately. We will often employ a 'multi-modal' approach to treatment, meaning the use of a number of different agents perhaps acting at differing pain receptor sites. There is evidence that this approach can be beneficial in acute post-operative pain but there may be increased likelihood of poor medicine compliance in chronic pain. The aim of a multi-modal strategy is to gain a degree of synergism between agents or to perhaps gain the most benefit from each drug while reducing its dosage and subsequent side effects.

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Specific medications

Paracetamol

Paracetamol was first introduced into medical practice in the late 19th century but its popularity did not really increase until the middle of the 20th century. The use of paracetamol is almost universal as a routine analgesic for acute and chronic pain due to its perceived low side effect profile, low cost and availability in oral, intravenous and rectal preparations. Despite its widespread use, its mechanism of action is still not fully understood. While urinary prostaglandin metabolites are reduced following administration of paracetamol, synthesis of prostaglandins is unchanged. It is thought that the mechanism of action may be via cyclo-oxygenase (COX)-3 inhibition as paracetamol is known to be a weak inhibitor of both COX-1 and COX-2. Because of this it has traditionally been regarded as an NSAID, although it differs from other commonly used NSAIDs particularly in its side effect profile. While it's potential COX inhibition explains the antipyretic and weak anti-inflammatory properties it doesn't fully explain its analgesic action. Studies have demonstrated peripheral as well as central activity through prostaglandin, 5-HT2 and 5-HT3 receptors.[2] The mechanism of action of paracetamol is an ongoing area of research and may yet yield a better understanding of this drug.

The evidence for efficacy in chronic pain, particularly with chronic back pain is particularly limited with only small and inconclusive trial data available.[3] It has little effect in neuropathic pain although some benefit has been seen when combined with a weak opioid such as codeine or tramadol.[4] It has been shown that the combination of paracetamol and ibuprofen is superior to paracetamol alone for chronic knee pain. However, one must be cautious of the side effects of regular and long term use of NSAIDs (see below).

NSAIDs

The primary mechanism of action of the NSAIDs is mainly due to inhibition of cyclo-oxygenases which are usually involved in the formation of prostaglandins. Prostaglandins are involved in pain pathways at a number of sites both centrally and peripherally in the pain pathway. Inhibition of prostaglandin formation will therefore reduce the inflammatory effect of prostaglandins and subsequently modulate pain thresholds. The two most clinically important forms of COX isoenzyme (1 and 2) have different biological functions with the majority of the analgesic action seemingly being mediated by COX-2 inhibition. It was an attempt to avoid the gastrointestinal side effects of COX-1 inhibition that led to the development of selective COX-2 inhibitors — the

'coxibs'. Their use has since been curtailed following evidence of increased risk of myocardial infarction and other thrombotic events.

The risks of GI disturbance, renal and cardiovascular disease must be considered and therefore their use should be subject to very careful consideration of dose and duration of treatment. NSAIDs may be contraindicated in those with vascular diseases of the heart, brain and renal system. Caution is advised in patients with cardiac risk factors (smoking, diabetes, raised cholesterol or hypertension.)

Recent work has suggested NSAIDs may also work by a COX-independent mechanism. The NSAIDs may be able to penetrate cellular membranes and affect a variety of intra-cellular processes. One such process involves interfering with L-selectin within neutrophils.[5] L-Selectin is a chemical that is involved in the inflammatory response of the neutrophil and therefore the subsequent sensitization to pain in inflammatory conditions.

There is evidence supporting NSAID use in chronic low back pain. However, there is seemingly no added benefit from using COX-2 selective NSAIDs over non-selective NSAIDs.[6] There does seem to be a place for topical NSAIDs in chronic joint pain conditions with a NNT of 11 for topical Diclofenac gel and none of the potential adverse gastrointestinal risks when compared with enteral therapy.[7] A Cochrane review recently examined the use of NSAIDs in neuropathic pain conditions as the use of NSAIDs in this area has been reported to be nearly 50%.[8] The review reported that the trial data supporting the use of NSAIDs for neuropathic pain was of poor quality and failed to conclude either way whether NSAIDs are of use in neuropathic pain conditions. This remains an area of future research interest and the findings of the Cochrane review are unlikely to alter the NSAID use for many patients with chronic neuropathic pain.

Anticonvulsants

The anticonvulsant drugs in use for treating chronic pain act via calcium channel blockade, sodium channel blockade, interference in glutamatergic transmission or a combination of these mechanisms.

The use of **gabapentin** in the perioperative period has become increasingly common as many of the agents used in chronic pain management are finding a place in the acute post-surgical arena. Although initially designed as anticonvulsants, the gabapentinoids (which include pregabalin and gabapentin) have significant analgesic properties. Their analgesic activity is likely to come via selective inhibition of a voltage gated calcium channel containing the $\alpha 2\delta$-1 subunit.

A single preoperative dose of gabapentin has been shown to reduce opioid use by up to 60% for the first 24 hours after surgery but there is a need for further work to pinpoint specific surgical procedures that may benefit most. Additionally, it is uncertain as to the optimal dose and whether they need to be continued post-operatively. It has particular possibility in reducing the development of chronic post-surgical pain (CPSP). A recent systematic review found that the gabapentinoids showed greatest promise with breast surgery but the trials included in the study found them to be ineffective for amputations or cardiac surgery which are two of the other high-risk procedures for developing CPSP.[9]

Gabapentin is recommended in the treatment of chronic neuropathic pain where it is has proven effectiveness particularly in post-herpetic neuralgia and painful diabetic neuropathy. The evidence supporting its use in fibromyalgia is less convincing. At daily doses of 1200 mg or more it demonstrates a NNT of between 5 and 8.3 for neuropathic pain conditions. Its use can, however, be associated with drowsiness, oedema, dizziness, weight gain and gait disturbance causing around one in 10 people to stop taking the medication.

In chronic neuropathic conditions **pregabalin** is generally reserved for those patients in who first-line therapy has not been tolerated. Doses of 300–600 mg daily have been shown to be effective in various types of neuropathic pain. It has a similar side effect profile to gabapentin. A recent meta-analysis as well as the current NICE guidance both strongly recommended gabapentinoids as first line treatment in neuropathic pain.[10,11] Pregabalin can cause side effects similar to gabapentin.

In the treatment of chronic neuropathic pain **carbamazepine**, which primarily acts via inhibition of sodium channels leading to neuronal suppression, has proven very effective with a NNT of 1.7. It is commonly used in patients with trigeminal neuralgia at doses up to 1600 mg daily. The study data demonstrating its effectiveness has not been of the highest quality. Around two-thirds of patients using carbamazepine reported good pain relief in the short term although the same number also experienced at least one side effect.[10] The potential side effects include thrombocytopenia, leukopenia, hyponatraemia, somnolence, dizziness, headache, ataxia, nystagmus, diplopia, blurred vision, hepatotoxicity (Table 1).

Antidepressants

There is potential that drugs that up-regulate the noradrenergic and serotonergic systems such as tricyclic antidepressants (TCAs), selective serotonin uptake inhibitors (SSRIs) and serotonin noradrenergic reuptake inhibitors (SNRIs) could be of benefit in chronic pain. The evidence is that the TCAs and SNRIs have greater efficacy than SSRIs for neuropathic pain. The SNRIs in common clinical practice include **venlafaxine** and **duloxetine**. They have been shown to be efficacious in fibromyalgia,[12] painful diabetic neuropathy[10] and painful osteoarthritis of the knee.[13] With regards to osteoarthritis of the knee, duloxetine has been shown to be as effective as NSAIDs for analgesia and is now a recommended treatment for this patient group. In terms of the

Anticonvulsants

Gabapentin	NNT of between five and 8.3 for neuropathic pain Moderate benefit in preventing development of chronic post-surgical pain
Pregabalin	NNT of around five for post-herpetic neuralgia and diabetic neuropathy Moderate benefit in preventing development of chronic post-surgical pain
Carbamazepine	NNT of 1.7 in trigeminal neuralgia

Table 1