Pharmacology in the management of chronic pain

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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

Abstract

Pharmacological treatment can play an important role in the successful management of chronic pain and should be prescribed as part of a biopsychosocial approach. When planning a pharmacological strategy for chronic pain it is important to consider the nature and likely source of the pain. This article will summarize common pharmacological options in current clinical use for the management of chronic pain.

Keywords Analgesia; chronic pain; neuralgia; nociceptive pain; pharmacological treatment

Royal College of Anaesthetists CPD Matrix: 2E03

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.

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 viscous versus superficial wound pain, nociceptive versus neuropathic) in order to target medication appropriately. A 'multi-modal' approach can be used, combining medication that act synergistically at different pain receptors. This minimizes the dosage of any particular drug and thus reduces the potential side effect profiles.

Specific medication

Paracetamol

Paracetamol was first introduced into medical practice in the late 19th Century but its popularity didn't 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. One suggested mechanism of action is by peripheral cyclo-oxygenase inhibition, which explains the anti-pyretic and weak anti-inflammatory properties; however it does not fully explain its analgesic action. Studies have demonstrated peripheral as well as central activity through prostaglandin, 5-HT2 and 5-HT3 receptors. The variability of paracetamol's analgesic effect may come from genetic polymorphisms in two of the enzymes and a receptor (TRPV1) involved in its metabolism[1] with only one-third of patients being strong responders and experiencing good pain relief with paracetamol.

The evidence for efficacy in chronic pain however, including in chronic back pain, is particularly limited with only small and inconclusive trial data available.

There is also considerable evidence that the side effects of paracetamol are not insignificant. Paracetamol, especially in higher doses, is associated with an increased mortality, an increase in gastrointestinal and cardiovascular side effects, and a reduction in GFR of 30 ml/min/1.73m^2. Patients taking paracetamol are also four times more likely to have abnormal liver function tests.[2]

NSAIDs

The primary mechanism of action of the non-steroidal anti-inflammatories (NSAIDs) is through the inhibition of cyclo-oxygenases. This inhibits the formation of prostaglandins, which are integral in both central and peripheral pain pathways. Clinically, the two most important forms of COX isoenzyme (1 and 2) have different biological functions with the majority of the analgesic action being mediated through COX-2 inhibition. In an attempt to avoid the gastrointestinal side effects of COX-1 inhibition, the selective COX-2 inhibitors (the 'coxibs') were developed. Their use has since been curtailed following evidence of an increased risk of myocardial infarction and other thrombotic events.

NSAIDs may also work by a COX-independent mechanism. 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.[3] 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.

Cochrane reviews looking at the use of NSAIDs in neuropathic and chronic low back pain report that the data supporting use of NSAIDs are of low quality. The review failed to conclude whether NSAIDs are of use in neuropathic pain conditions, and suggested that although there is evidence that NSAIDs are associated with

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analgesia compared to placebo in chronic low back pain, the strength of the association is small and not clinically relevant.[4]

Careful consideration of dose and duration of treatment should occur during NSAID use due to the risk of GI disturbance and renal and cardiovascular adverse events. 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).

One potential way of increasing the effectiveness and reducing the adverse events of NSAIDs is by alternative drug delivery systems. Topical NSAIDs avoid many of the systemic side effects seen with oral formulation (plasma concentration when topically administered is <5% of that when given orally) and give equivalent amounts of pain relief. This makes them an attractive choice for older patients in whom NSAIDs may otherwise be contraindicated.[5] Another recent suggestion is to introduce ibuprofen via niosomes, non-ionic surfactant vesicles that act as therapeutic nanocarriers. These can theoretically be targeted to areas of inflammation through the lower pH found in those areas, thus concentrating the drug at that area[6] and potentially allowing a reduced dose to be given and thus reducing the side effects seen.

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.

Although initially designed as anticonvulsants, the gabapentinoids (which include pregabalin and gabapentin) have significant analgesic properties, and gabapentin is licensed in the UK for the treatment of peripheral and central neuropathic pain. In neuropathic pain, α2δ-1 subunit forms a complex with NMDA-type glutamate receptors to increase their expression in the synapses of the spinal dorsal horn. Gabapentin selectively binds α2δ-1 and by doing so, inhibits the synaptic expression of the α2δ-1 NMDA receptor thus reducing neuropathic pain.

A 2017 Cochrane review looking at **gabapentin** suggests that it gives good pain relief for postherpetic neuralgia and diabetic neuropathy at doses of 1800–3600 mg daily (NNT 6.9 for postherpetic neuralgia and 5.9 for painful diabetic neuropathy). However, this analgesic action only occurs in 30–40% people, with the non-responders still at risk of adverse events. Evidence for gabapentin in other neuropathic pain types such as radicular leg pain, spinal cord injury, nerve injury pain, phantom limb pain and chronic back pain remains limited. The evidence for adverse events in people taking gabapentin is high, with NNH (number needed to treat for an additional harmful outcome) of 7.5. Side effects include somnolence, dizziness, peripheral oedema and gait disturbance.[7,8]

In chronic neuropathic conditions **pregabalin** is generally reserved for those patients in whom 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.[9,10]

Anticonvulsants

Gabapentin	Painful diabetic neuropathy –NNT 5.9 Post herpetic neuralgia –NNT 6.9 Evidence for other types of neuropathic pain is limited
Pregabalin	Post-herpetic neuralgia and diabetic neuropathy –NNT 5
Carbamazepine	Trigeminal neuralgia –NNT 1.7

Table 1

From 1 April 2019, gabapentin and pregabalin were reclassified as Schedule 3 controlled drugs under the Misuse of Drugs Regulations 2001, and Class C of the Misuse of Drugs Act 1971. No more than 30 days supply can be issued at one time.

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. Study data demonstrating its effectiveness have not been of the highest quality. Around two-thirds of patients using carbamazepine report good pain relief in the short term although the same number also experience at least one side effect.[9] Potential side effects include thrombocytopenia, leukopenia, hyponatraemia, somnolence, dizziness, headache, ataxia, nystagmus, diplopia, blurred vision and hepatotoxicity (Table 1).

Anti-depressants

Drugs which up-regulate the noradrenergic and serotonergic systems such as tricyclic antidepressants (TCAs), selective serotonin uptake inhibitors (SSRIs) and serotonin noradrenergic reuptake inhibitors (SNRIs) can be of benefit in chronic pain. The evidence is that TCAs and SNRIs (such as venlafaxine and duloxetine) have greater efficacy than SSRIs for neuropathic pain. SNRIs have been shown to be efficacious in fibromyalgia, painful diabetic neuropathy and painful osteoarthritis of the knee.

The COMBO-DN study compared high-dose monotherapy with duloxetine or pregabalin with a combination of these two agents in patients with diabetic peripheral neuropathic pain. It found that combination therapy was safe and effective but demonstrated no significant advantages over standard dose mono-therapy[11] (see Table 2).

Antidepressants

Tricyclics	Neuropathic pain –NNT 2–3. Potential efficacy in fibromyalgia Reduced incidence of post-herpetic neuralgia when used in acute phase
Serotonin-norepinephine reuptake inhibitors (SNRI)	Neuropathic pain –NNT 5–6
Serotonin selective reuptake inhibitors (SSRI)	Neuropathic pain –NNT 6.8. May offer sleep and mood benefits for fibromyalgia but little effect on pain

Table 2

Topical agents	
Topical lidocaine	Better than placebo for post-herpetic neuralgia
Topical NSAIDs	NNT 5–9.8 Better than placebo for osteoarthritis of hand or knee
Topical capsaicin (8%)	Post herpetic neuralgia –NNT 11

Table 3

Tricyclic antidepressants such as **amitriptyline** or **nortriptyline** have common usage in postherpetic neuralgia, painful diabetic neuropathy and fibromyalgia. There is little good quality evidence to support their use in chronic low back pain. There is evidence that amitriptyline used in the acute pain episode of herpes zoster infection can reduce the likelihood of developing postherpetic neuralgia.

One must be cautious in initiating TCA therapy in elderly patients as this group of medicines may have enhanced anticholinergic activity that could result in cognitive dysfunction.

Topical agents

Intravenous and topical **lidocaine** has been shown to be effective in acute and chronic pain and its benefits may be related to modulation of the neuroinflammatory response to pain. Lidocaine and capsaicin patches are recommended as second-line agents in neuropathic pain. Lidocaine 5% plaster can be of benefit in localized neuropathic pain such as postherpetic neuralgia[9] (see Table 3).

There is moderate evidence for the use of high concentration (8% rather than 0.075%) capsaicin in postherpetic neuralgia (NNT 11). Capsaicin works by activating and desensitizing the TRPV1 receptor. The use of low concentration capsaicin is associated with a higher risk of adverse events than topical NSAIDS (NNH 2.5 for capsaicin versus NNH 16 for NSAIDs), although this is often just a local skin irritation, with systemic adverse effects being rare.[5]

As a result of the low side-effect profile of topical analgesics, more drugs are being formulated to be given in this way. There may be a role for topical gabapentin in the future, with animal experiments looking promising – good analgesia with few side effects.[12]

Ketamine

Ketamine is an NMDA receptor antagonist with significant analgesic and opiate sparing properties. As the NMDA system is important in the development of central sensitization, down-regulation of these pathways by ketamine may reduce the incidence and severity of chronic pain conditions such opioid-induced hyperalgesia.

NICE guidance from 2014 concluded that there was no good quality evidence to support the use of oral ketamine to treat chronic pain.[13] This is possibly because oral ketamine has extensive first pass metabolism, with only 17–24% ketamine reaching the systemic circulation. This poor bioavailability and the high risk of adverse effects limits its clinical use. Adverse effects of ketamine include cognitive disturbances, psychological addiction, severe and persistent urinary disease, hepatic dysfunction and hypersalivation.

Opioids

A small proportion of individuals with chronic pain may benefit from the use of opioids. There is little evidence for their efficacy in longer-term pain relief. Oral preparations include codeine, tramadol, morphine, oxycodone and tapentadol; transdermal patches include buprenorphine and fentanyl. However there is a significant risk of adverse events with chronic opioid use, particularly constipation, dizziness, drowsiness, puritus, nausea, vomiting and increased sweating. The 'Opioids Aware' website of the Faculty of Pain Medicine is a resource for patients and healthcare professionals to support prescribing opioids for pain.

The SPACE trial looked at opioid versus non-opioid medication for chronic back pain and hip and knee osteoarthritis. It found that opioids were not superior to non-opioids for improving pain related function at 12 months and suggested that opioid treatment should not be initiated in these cases.[14]

Opioid prescriptions for chronic pain in the USA increased 300% during 2000–2010, resulting in a serious public health problem with over 15,000 fatalities from prescription opioid overdoses during 1999–2015.[15] MOP (Mu) receptors are expressed in the pleasure and reward areas (ventral tegmental area, nucleus accumbens), and stimulation of these centres increases the addiction potential, particularly when an opioid is rapidly delivered to the brain by snorting or injecting. A 2017 Cochrane review looked at possible interventions to help reduce the prescribed opioid use in chronic pain, finding that simple unsupervised reduction of opioid use is challenging. It is not clear how best to help patients reduce their opioid use, but two studies delivering 'Mindfulness-Orientated Recovery Enhancement' and 'Therapeutic Interactive Voice Response' showed a significant reduction in opioid use post treatment.[16]

Cannabis

Medical use of cannabis was legalized in the UK on 1 November 2018. Cannabis contains two major active ingredients, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). These act on the cannabinoid (CB) receptors; CB1 receptors being mostly found in the central nervous system and CB2 receptors found in immune cells.

A 2018 Cochrane review found that not only was there a lack of good evidence for the use of cannabis-based medicine in chronic pain, but that the potential benefits of cannabis-based medicine might be outweighed by their potential harmful effects. Side effects include psychiatric disorders such as mania, psychosis and suicidal behaviour, poor cognition and cannabinoid hyperemesis syndrome.[17]

Based on the lack of good evidence that cannabis is an effective treatment for chronic pain, the Faculty of Pain Medicine have stated that 'any use of cannabinoids for pain management should only occur after conventional interventions have failed and then only within the confines of a limited number of secondary care multidisciplinary specialist pain services, with all cases being nationally audited'.[18] They also warn about the potential parallels with the widespread use of opioids over the past few decades despite no good evidence for their use in chronic pain, and the current opioid abuse/misuse crisis. A similar position is also taken by the European Pain Federation (Table 4).

Novel Agents[19]	
Tropomyosin receptor kinase A (TrkA) inhibitors	Activation of TrkA, expressed on c-fibres and A-δ fibres, leads to chronic sensitization and pain. Can be inhibited by monoclonal antibodies (acting against nerve growth factor, which binds TrkA) or small inhibitors
TRP receptor antagonists	Largest family of nociceptive pain receptors which include TRPV1 and 4 and TRPA1 Involved with inflammatory, neuropathic and visceral pain
AAAK1 kinase inhibitors	Inhibiting AAAK1 reduces neuropathic pain, probably linked to the noradrenergic pathway
Sodium channel blockers	New drugs being developed to join the carbamazepine family which do not act in the brain, thus reducing the side effect profile

Table 4

Summary

- It is important to consider the likely afferent source of the pain.
- Discuss drug treatment limitations and manage expectations of pain relief as part of the overall management plan.
- Regular review and reassessment is important with awareness of variation of efficacy and possible side effects. Stop or change medication that is not working effectively.
- Due to different mechanisms of pain transmission and mechanism of action of drugs, individuals with chronic pain, particularly neuropathic pain, often require a combination of analgesics.
- Multi-modal therapy may help reduce the side effects from high doses of individual drugs.
- It is recommended that patients with neuropathic pain conditions excluding trigeminal neuralgia are offered a choice of amitriptyline, duloxetine, gabapentin or pregabalin as the initial pharmacological treatment. In situations where the first line agent is not successful then the medication should be switched between these four drugs.
- Carbamazepine is the recommended first line agent in trigeminal neuralgia.[9,10]
- There is no robust evidence for the use of cannabis-based products for medicinal use in chronic pain and their use is not recommended.

Pharmacological treatment can play an important role in the management of patients with chronic pain and should be used after careful consideration of potential benefits and risks for the individual patient. ◆

REFERENCES

1 Pickering G, Creveaux I, Macian N, Pereira B. Paracetamol and pain modulation by TRPV1, UGT2B15, SULT1A1 genotypes: a randomized clinical trial in healthy volunteers. *Pain Med*, 2019; https://doi.org/10.1093/pm/pnz037 [Epub ahead of print].

2 Moore RA, Moore N. Paracetamol and pain: the kiloton problem. *Eur J Hosp Pharm* 2016; **23:** 187–8.

3 Díaz-González F, Sánchez-Madrid F. NSAIDs: learning new tricks from old drugs. *Eur J Immunol* 2015 Mar 1; **45:** 679–86.

4 Enthoven WT, Roelofs PD, Koes BW. NSAIDs for chronic low back pain. *Jama* 2017 Jun 13; **317:** 2327–8.

5 Derry S, Wiffen PJ, Kalso EA, et al. Topical analgesics for acute and chronic pain in adults-an overview of Cochrane Reviews. *Cochrane Database Syst Rev*, 2017.

6 Marzoli F, Marianecci C, Rinaldi F, et al. Long-lasting, antinociceptive effects of pH-sensitive niosomes loaded with ibuprofen in acute and chronic models of pain. *Pharmaceutics* 2019 Feb; **11:** 62.

7 Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*, 2017.

8 Moore A, Derry S, Wiffen P. Gabapentin for chronic neuropathic pain. *Jama* 2018 Feb 27; **319:** 818–9.

9 Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015 Feb 28; **14:** 162–73.

10 NICE Guideline [CG173]. Neuropathic pain in adults: pharmacological management in non-specialist settings. November 2013. Available at: http://www.nice.org.uk/guidance/CG173/chapter/1-Recommendations#list-of-all-recommendations [Accessed May 2019].

11 Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"–a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain* 2013 Dec 31; **154:** 2616–25.

12 Shahid M, Subhan F, Ahmad N, et al. Topical gabapentin gel alleviates allodynia and hyperalgesia in the chronic sciatic nerve constriction injury neuropathic pain model. *Eur J Pain* 2017 Apr; **21:** 668–80.

13 NICE Guideline [ESUOM27]. Chronic pain: oral ketamine. February 2014. Available at: http://www.nice.org.uk/advice/esuom27/chapter/Key-points-from-the-evidence [Accessed May 2019].

14 Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. *Jama* 2018 Mar 6; **319:** 872–82.

15 Volkow N, Benveniste H, McLellan AT. Use and misuse of opioids in chronic pain. *Annu Rev Med* 2018 Jan 29; **69:** 451–65.

16 Eccleston C, Fisher E, Thomas KH, et al. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. *Cochrane Database Syst Rev*, 2017.

17 Mücke M, Phillips T, Radbruch L, Petzke F, Haeuser W. Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*, 2018.

18 Faculty of Pain Medicine of the Royal College of Anaesthetists. Faculty position statement on the medicinal use of cannabinoids in pain medicine. 2018. Available at: https://www.rcoa.ac.uk/sites/default/files/FPM%20Cannabis%20Position%20Statement%20Oct18.pdf (accessed May 2019).

19 Kaye AD, Cornett EM, Hart B, et al. Novel pharmacological non-opioid therapies in chronic pain. *Curr Pain Headache Rep* 2018 Apr 1; **22:** 31.

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