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ARTICLE

Principles of prescribing for persistent non-cancer pain

SUMMARY

Chronic pain (persistent and recurrent) is a major cause of distress and disability in the community.

Patients need to be comprehensively assessed to determine the biomedical, psychological, social and cultural contributions to their pain.

Although drug therapy is only part of a multimodal approach to management, its role in modifying distress is important.

Paracetamol, opioids and some antidepressants and anticonvulsants are used to treat chronic pain. A combination of these drugs is often needed for adequate pain relief.

Parenteral and short-acting oral opioids should be avoided for long-term persistent pain.

Drug treatment should be seen as a trial of therapy. Monitoring its effectiveness and safety and the patient's quality of life should guide treatment.

Introduction

Chronic non-cancer pain is a major source of distress and disability in the community. It can become a problem in its own right, even when underlying predisposing conditions are being managed optimally.

Although pain is appreciated conceptually in a 'biopsychosocial' framework that identifies somatic, psychological, societal and cultural contributions, the person in pain is still commonly managed through a narrow biomedical model, where the emphasis is on finding – and treating – an underlying pathological condition. However, this model may not work in some instances of musculoskeletal pain, as pathologies such as osteoarthrosis or spondylosis do not reliably predict distress or disability and the underlying 'disease' is essentially untreatable.

Most patients with chronic non-cancer pain are likely to experience some pain for the rest of their lives. Pain itself is the problem – not as a symptom of something else, not as a broken part to be fixed, not as a disease, but as a persistent or recurrent distressing experience.

The aims of medical management should be:

- to reduce distress to a bearable level
- to help the person function as well as possible
- to minimise the adverse effects of treatments.

Comprehensive patient assessment

The fundamental clinical approach of identifying a treatable somatic cause applies as much to persistent pain as to any other symptom. However, chronic pain is commonly due to altered central nervous system function, including central sensitisation of nociception. Recognising clinical features of altered nociception, such as allodynia, hyperalgesia and hyperpathia, and not 'chasing' structural pathology in the absence of clinical indicators is important (Box).

Identifying 'non-somatic' contributions to the pain is just as relevant. These include what is happening to the person such as mood, impact on activities of daily living, work, recreational activity, sleep and nutrition. It is also worth asking about their family, relationships and events in their life that could cause distress.

Non-drug therapies

Managing a patient's beliefs and expectations about their diagnosis and prognosis and the treatment can be difficult, but is important. The most powerful therapy is adequate explanation, emphasising the complex interaction between the somatic, psychological and social components that contribute to the pain. Advice regarding the use of the painful part of the body, the role of exercise programs and sleep hygiene can be helpful. Support from a physical therapist, occupational therapist, psychologist, social worker or rehabilitation counsellor may be appropriate.

Box **Features of neuropathic pain**

Allodynia	pain in response to normally innocuous stimulus such as touch, pressure or movement
Hyperalgesia	an increased response to a stimulus that normally evokes pain
Hyperpathia	a painful syndrome, characterised by increased reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. Faulty identification and localisation of the stimulus, delay, radiating sensation, and after-sensation may occur.

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Pharmacotherapy as part of an overall strategy

Pharmacotherapy should only ever be part of a multimodal plan. Drugs are used here mainly to control symptoms and reduce distress as an adjunct to non-drug therapy. In some situations where the mechanism of pain can be confidently determined, such as inflammatory or 'neuropathic' conditions, anti-inflammatory or anti-neuropathic drugs may be helpful.

Drug treatment in chronic pain should be seen as an ongoing trial of therapy, addressing the question of effectiveness – is this patient's predicament responsive to this medication? The goals are beyond pain relief alone and should also relate to improvements in physical, emotional and interpersonal function. A treatment plan can be helpful. The following criteria can be used to monitor response:[1]

- analgesia (reduction – not elimination – of pain)
- activity (as negotiated with the patient)
- adverse effects
- affect (the patient's feelings or emotions)
- behaviours indicative of unsanctioned use (for patients prescribed opioids).[2]

Inappropriate use of opioids does not necessarily equate to addiction, but may reflect a chaotic lifestyle, psychological or physical dependence or inadequate treatment of pain. Other possibilities include a search to relieve comorbid depression or anxiety, preoccupation with being unwell or a search for sympathy, meaning or a social context. Appropriate responses include comprehensive re-assessment, a program to stabilise opioid intake (possibly including urine drug testing or restricted dispensing) and referral to a pain clinic or addiction medicine service.[2,3]

How effective are drugs for chronic pain?

Finding good evidence for drug efficacy in chronic pain is difficult because of the heterogeneity of clinical trial populations, lack of consideration of psychosocial influences on the pain experience, variable primary outcomes and generally poor quality studies.

Most literature concerns 'neuropathic' pain and is difficult to extrapolate to the clinic, as most trials have been performed in clearly defined states such as diabetic neuropathy or postherpetic neuralgia. However, the liberal definition of neuropathic pain has led to drugs being used 'off-label' in a variety of painful conditions.

In chronic pain trials, the efficacy of drugs is often expressed as the number needed to treat. Calculating this is typically based on a minimum of a 50% reduction in pain intensity, which may exclude patients with a smaller but clinically meaningful reduction. In trials over 8–16 weeks, drugs with different mechanisms (tramadol, opioids, antidepressants, gabapentin and pregabalin) have been found to be similarly effective for chronic pain. The numbers needed to treat for 50% pain reduction ranged from 2.6 to 6.4 with large 95% confidence intervals for different drugs in different conditions.[4,5]

Paracetamol

Paracetamol remains the baseline analgesic for persistent pain. It can be taken around the clock or in anticipation of activity that may worsen pain or before going to bed.[6] The extended-release form may improve adherence.

Tramadol

Tramadol has been shown to have consistent efficacy in various chronic pain states. However, adverse drug reactions with tramadol are common.[7]

Opioids

Injectable and short-acting oral opioids are not appropriate for long-term management of persistent pain. Oral controlled-release or transdermal opioids are recommended.[8]

The effectiveness and misuse of strong opioid agonists in chronic pain is the subject of current controversy.[9,10] A practical approach has recently been proposed.[2,3,11] Numbers needed to treat of 2.6 (95% confidence interval 1.7–6.0) have been quoted.[5]

Non-steroidal anti-inflammatory drugs

In most instances of chronic pain, inflammation is not the relevant mechanism. Given their potential for interaction with other drugs for common comorbidities and their adverse effect profile, non-steroidal anti-inflammatory drugs might be limited to short-term use only, for incident pain in patients who respond. They should be avoided in older patients if possible.[6]

Antidepressants

Low doses of tricylic antidepressants (amitriptyline, nortriptyline, dothiepin, imipramine) have been used for many years to treat chronic pain. The number needed to treat is 2–4,[5] but anticholinergic adverse effects are often limiting.

The serotonin and noradrenaline reuptake inhibitors duloxetine and venlafaxine have documented efficacy in painful polyneuropathy.[4] Duloxetine is reported to be effective in chronic musculoskeletal pain (fibromyalgia).[12] Selective serotonin reuptake inhibitors have been studied in a few trials and have demonstrated a weak analgesic effect.[5]

Chronic pain is often associated with changes in

mood. Comorbid depression or anxiety needs to be managed appropriately, including using full doses of an antidepressant if necessary. Low-dose tricylics are not effective for treating depression.

Anticonvulsants

The use of antiepileptic drugs in true neuropathic pain (where there is neural pathology) is rational, but evidence is available only for gabapentin and pregabalin in diabetic neuropathy or postherpetic neuralgia.[5] These drugs bind the alpha-2 delta subunit of voltage-gated calcium channels of primary afferents channels, interfering with the release of neurotransmitters such as substance P, noradrenaline and glutamate. Pregabalin in relatively large doses has been effective in chronic musculoskeletal pain.[12]

Evidence for other antiepileptic drugs such as lamotrigine, topiramate and valproate in chronic pain is very limited. Carbamazepine has been used in trigeminal neuralgia.

Practical pharmacotherapy

Different classes of drugs are often used in combination. All of them act on the central nervous system and, with the exception of paracetamol, share adverse effect profiles, especially drowsiness, cognitive impairment and nausea. This is why conservative dose regimens, targeting certain drugs to times of the day when sedation is desired, and awareness of drug interactions are so important.

Although it is not possible to be prescriptive regarding any order in which these drugs should be used, regimens should be rational, safe and as simple as possible. A guiding principle is to assess their ongoing effectiveness in terms of the patient's overall quality of life.

In general, chronic pain should not be treated with short-acting drugs. For patients whose pain is opioid-responsive, sustained-release oral or transdermal preparations are preferred, starting with low doses. Titration need not be rapid but the prescriber should be alert to under-dosing, especially in a patient who is demonstrating improved function and increased activity. Improved overall well-being may in fact incur incident (not breakthrough) pain. This can be addressed by modifying activity and increasing or redistributing the background drug dose rather than adding a short-acting drug.

From comparative trials in painful polyneuropathy and postherpetic neuralgia, there is little difference in efficacy between opioids, tricyclic antidepressants, gabapentin and pregabalin.[5] Extrapolation to other clinical situations is empirical.

There is probably a limit to drug-responsiveness and it is unlikely that chronic pain can be eliminated. The aim is to establish the lowest dose of drug that is associated with overall improvement in quality of life. Any reduction in dose should be made slowly. The rule of thumb is a 10% reduction of the daily dose each week.[8]

Conclusion

Drug treatment is only ever part of a multimodal plan for the patient experiencing chronic pain. The aim is to reduce distress by controlling symptoms, as an adjunct to non-drug therapy, and thereby to improve function and quality of life. The main drugs available are paracetamol, tramadol, strong opioid agonists, tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors and alpha-2 delta binding drugs. Drug treatment is an ongoing trial of therapy and requires regular review. ≺

Dr Cohen sits on an advisory board for Mundipharma. He has received fees from Mundipharma for preparation and presentation of educational material, and fees for presentation at seminars sponsored by Pfizer and Janssen-Cilag.

Q:

SELF-TEST QUESTIONS

True or false?

1. In comparative trials, opioids appear to be no better than gabapentin for postherpetic neuralgia.
2. Low-dose tricyclic antidepressants are effective for comorbid depression in patients with chronic pain.

Answers on page 143

REFERENCES

1. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med 2005;6:107-12.
2. Wodak AD, Cohen ML. Judicious use of opioids in chronic non-malignant pain. Med Today 2010;11:10-8.
3. Cohen ML, Wodak AD. Opioid prescribing in general practice: a proposed approach. Med Today 2012;13:24-32.
4. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005;118:289-305.
5. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain 2010;150:573-81.
6. NPS Prescribing Practice Review 35. Analgesic choices in persistent pain. NPS MedicineWise; 2006.
7. Kaye K. Trouble with tramadol. Aust Prescr 2004;27:26-7.
8. McDonough M. Safe prescribing of opioids for persistent non-cancer pain. Aust Prescr 2012;35:20-4.
9. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. Clin J Pain 2008;24:469-78.
10. The Royal Australasian College of Physicians. Prescription Opioid Policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use. Sydney: RACP; 2009.
11. Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists. Principles regarding the use of opioid analgesics in patients with chronic non-cancer pain. Professional Document PM1. ANZCA; 2010.
12. Mease PJ, Choy EH. Pharmacotherapy of fibromyalgia. Rheum Dis Clin North Am 2009;35:359-72.

FURTHER READING

NPS Prescribing Practice Review 51. Opioids in chronic non-cancer pain: use a planned approach. NPS MedicineWise; 2010.