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The judicious use of opioids in managing chronic noncancer pain

Chronic pain is a common consequence of chronic disease and increasingly of lifestyle factors such as eating too much and exercising too little. Pain itself can become a problem in its own right, especially if any underlying predisposing condition is already being managed optimally. The use of opioids in these patients should be considered carefully before a trial is started.

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The complexity of pain – for patients, healthcare professionals and indeed society – was eloquently presented in a past issue of *Medicine Today*.[1] Contributing significantly to the complexity are the multifactorial nature of pain and the difficulties in language faced by both the sufferer in presenting his or her predicament and the clinician in attempting to understand, diagnose and explain that predicament.

Although pain is appreciated conceptually in a 'biopsychosocial' framework that identifies somatic, psychological, societal and cultural contributions, the person in pain is still commonly processed through a narrow biomedical model, where the emphasis is on finding – and treating – an underlying pathological condition that 'causes' the pain. However, when considering the most common type of chronic pain, so-called musculoskeletal pain, the biomedical model usually breaks down. This is because the presence of demonstrable anatomical pathology, such as osteoarthrosis or spondylosis, does not reliably predict distress or disability, or the underlying 'disease' is essentially untreatable.

Applying a broader biopsychosocial framework requires not only skill but also time, which is

IN SUMMARY

- **Symptom control in the patient with chronic pain is an important aim of treatment, as part of a multimodal approach and as a passport to improved quality of life.**
- **Consider the use of opioids for managing chronic pain when non-opioid drugs have been found to be ineffective or not tolerated.**
- **Before prescribing opioids, assess psychological status, history of substance abuse and social context.**
- **Opioid treatment is an ongoing trial of therapy: response to opioids and problems with opioids are difficult to predict.**
- **Regularly assess the six As: analgesia, activity, adverse effects, affect, aberrant behaviours and accurate records.**
- **Seek advice if an apparent increase in opioid requirement is occurring.**

in short supply in general practice. It is, therefore, not surprising that the management of patients with chronic pain so often relies on the use of analgesics, frequently opioids. This presents a new set of dilemmas: the tension between adequate symptom management and the fear of adverse consequences (the 'opiophilia' *v*. 'opiophobia' debate); the unpredictability of who may respond well or adversely to opioids; and the challenge of managing pain in someone with previous or current drug dependence.

This article will address the rational, compassionate and safe use of opioids in the treatment of people with chronic noncancer pain. It will review the principles of appropriate opioid prescription (including identification of patient and choice of drug), the recognition of 'risk' potential and what to do if a trial of opioid pharmacotherapy is inappropriate or unsuccessful.

Most patients with chronic noncancer pain are likely to experience some pain for the rest of their lives. The aims of medical management for these patients should be to:

- reduce the pain to a bearable level
- help the patient achieve the functional state they desire
- minimise adverse effects of medication.

Pharmacotherapy as part of an overall strategy

The aim of drug therapy in patients with chronic pain is mainly symptom control. In situations where the mechanism of pain can be confidently determined, such as patients with inflammatory or neuropathic conditions, treatment aimed at the mechanism (anti-inflammatory or antineuropathic agents, respectively) may be helpful in modifying pathogenesis. However, in most cases, symptom control itself is important as an adjunct to non-drug therapy for the reduction of a patient's distress and therefore as a passport to an improved quality of life.

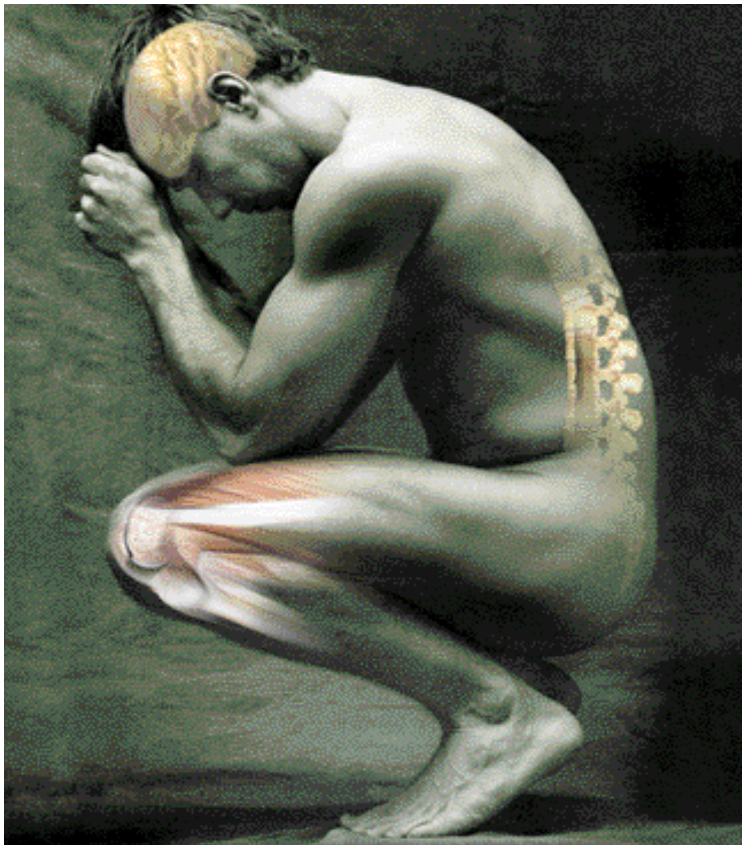
Evidence for the effectiveness of opioids in managing chronic noncancer pain

After a 'honeymoon' period of about a decade following their introduction, the appropriate use of sustained-release oral opioids is a vexed and controversial issue. A recent comprehensive review of the literature concluded that there is strong evidence from randomised controlled trials that opioids can provide short-term initial relief for patients with persistent pain.[2] These trials tended to be conducted over periods of 16 weeks or less and used doses of up to a morphine equivalent of 180 mg daily.

These randomised controlled trials are, however, limited by several major methodological factors:

- too great a diversity of subjects (almost inevitable when the 'diagnosis' is pain)
- inability to take into account the complexities of nonsomatic influences on the experience of pain

The judicious use of opioids



Patients with chronic noncancer pain should be treated by applying a broad biopsychosocial framework that identifies somatic, psychological, societal and cultural contributions. The use of opioids should be considered for symptom control as part of a multimodal approach to treating patients with pain.

- marked variability with respect to patients with substance abuse problems – varying from being excluded from studies to no data regarding that aspect
- lack of agreement regarding primary outcomes including pain relief, patient satisfaction, functional improvement and improved quality of life
- general poor quality – low participant numbers, not blinded, short duration, variable dosing protocols.

Interestingly, in those studies with an open-label phase following the randomised controlled trial, up to 55% of patients discontinued treatment while those who chose to continue using opioids reported satisfactory pain control. This could be interpreted as opioids somewhat non-specifically decreasing distress but not in all patients with pain.

Due to their constraints, randomised controlled trials may not be the best way to determine the efficacy, especially in the long term, of opioid treatment of patients with chronic pain. However, the effectiveness of such treatment in the individual patient is another matter. Clinicians experienced in the management of patients with chronic pain, whether in primary care, community specialist practice or tertiary settings, testify to the usefulness of long-term opioids in some patients. They report an association of long-term opioids with improvement in overall quality of life, although pain itself is not always reported as reduced. However, it is not possible to predict the opioid responsiveness of the individual patient, so the use of opioid analgesic therapy should always be considered to be a trial. Furthermore, the risks and benefits of opioid pharmacotherapy may vary over time, arising out of changes in biomedical, psychological and sociocultural factors influencing a patient, underlining the need to monitor outcomes frequently.

Judicious use of opioids

The judicious use of opioids involves a set of five principles.[3]

1. Comprehensive assessment

Pharmacotherapy for the patient in pain should only ever be part of a multimodal plan. However, such a plan does not imply that many healthcare personnel need to be involved, especially when resources are limited. Rather it refers to the importance of recognising and, if possible, addressing nonsomatic contributions to the patient's predicament, especially the social environment (including work). This may include:

- eliciting beliefs regarding diagnosis and prognosis (a task made more difficult by imprecision of concepts and nomenclature in this area)

- assessing the impact of pain on activities of daily living ('how does the pain interfere with your life?')
- enquiring about changes in sleep, recreational activity and nutrition.

Psychological assessment includes exploring beliefs, expectations and mood. Social assessment draws on the family doctor's knowledge of the patient and the patient's family, relationships, work situation, leisure pursuits and, if possible, events in his or her life that could influence distress (such as a change in financial circumstances).

If possible, a somatic diagnosis should be made, although our diagnostic language can make that difficult. Once so-called 'red flag' conditions have been identified on clinical grounds, the probable mechanism of many cases of chronic musculoskeletal pain will be biomechanical dysfunction, justifying a diagnostic label of 'biomechanical impairment', 'symptomatic spondylosis' or 'symptomatic osteoarthrosis'. In other cases of chronic pain, musculoskeletal or visceral, central sensitisation of nociception may be a mechanism of pain, allowing an inference of neuropathic pain.

For example, in a patient complaining of spinal pain, one would expect to see painful limited movements of that spinal segment. The complaint of spinal pain in the presence of normal spinal movement and with no clues to an underlying disease state or to central sensitisation (such as tenderness) should alert the clinician to the fact that nonsomatic factors may be playing a major role in the presentation. That in itself would not exclude consideration of a trial of opioid therapy but would be factored into the risk assessment. Regrettably, a succinct clinical language has not yet evolved to capture the nonsomatic contributions to pain that should form part of a diagnostic label.

Risk assessment for problematic opioid usage at initiation

Psychiatric comorbidity is common in patients with chronic pain, although it is usually hard to distinguish cause from effect. Depression or anxiety disorders are common also in drug-dependent patients. Patients with chronic pain are at increased risk of developing a dependence on opioids. However, this area is controversial and research is difficult. There are no satisfactory ways at present of distinguishing true addiction from other problematic behaviours.[4]

Broadly speaking, the potential for problematic opioid usage, including addiction, is higher in:[5]

- younger patients (85% of substance abuse problems start by age 35 years)

Table. Sustained-release or long-acting opioids for chronic noncancer pain

Generic name	Suggested ceiling dose*
Oral opioid agonists	
Hydromorphone†	16 mg daily
Methadone	40 mg daily
Morphine†	120 mg daily
Oxycodone†	80 mg daily
Oral opioid-like analgesic	
Tramadol†	400 mg daily
Transdermal opioids	
Buprenorphine	40 µg/hr weekly
Fentanyl	25 µg/hr every three days

* Dose above which advice should be sought from a pain specialist.
† Sustained-release formulas should be chosen.

- patients without a confident somatic diagnosis
- patients in contact with users of nonprescribed medication (either family or in geographical region)
- patients with active substance abuse problems
- patients with active psychiatric disorders.

A recent comprehensive review of the literature found there was only limited evidence for the utility of tools to predict aberrant drug-related behaviours in patients with chronic noncancer pain who are being considered for an opioid trial or who are receiving ongoing opioid therapy.[6]

2. Poor response to adequate trial of other therapies

The second principle for the judicious use of opioids raises the question of what might be an 'adequate' trial and indeed what other modalities may be available in the primary care setting. Nondrug therapies include explanation about the nature of pain and that 'hurt' does not equate with 'harm', realistic information regarding prognosis, and advice about sleep hygiene and use of the painful part of the body, including structured exercise programs. Where possible, input should be included from a physical therapist, occupational therapist, psychologist, social worker or rehabilitation counsellor.

Symptom control of pain with medication is an important part of reducing patient distress. The first-line treatment remains paracetamol, ideally in regular doses of the extended-release form. NSAIDs offer little advantage over paracetamol, especially when inflammation is not the relevant pain mechanism. The use of NSAIDs brings its own set of adverse events and interactions, especially in the older patient.

Use of adjuvant analgesics could be considered before opioids. These adjuvants include tricyclic antidepressants such as amitriptyline and nortriptyline (both used off label), serotonin noradrenaline reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine (both used off label), and anticonvulsants such as gabapentin, pregabalin (both indicated for the treatment of neuropathic pain) and sodium valproate (used off label). Low-dose tricyclic antidepressants are often used at night to exploit their sedative as well as analgesic effect. However, numbers needed to treat are of the order of three to six, which is no better than for opioids.[7]

3. Contractual approach to opioid usage

The use of opioids in the management of a patient with recurrent or chronic pain should be considered a clinical trial, requiring informed consent. The aim is to discover if the patient's pain is responsive to opioids. This requires frank articulation of the goals of this therapy, including an agreement that if the goals are not met then the trial will be discontinued. The goals are beyond pain relief alone and emphasise improvement in physical, emotional and mental functioning, including an increase in activity. Thus, a therapeutic contract is established, which can be made explicit verbally, through entries in notes or in a formal written agreement.

Such a 'contract' is not enforceable in a legal sense, but reflects the seriousness of the undertaking between prescriber and patient. There should be only one prescriber of a patient's opioids, with adequate back-up provision available should that prescriber be unavailable.

At present, the mechanisms are not available for real-time online tracking of prescription patterns. However, as part of risk assessment, useful information can be obtained from the Prescription Shopping Information Service (more information is available at http://www.medicareaustralia.gov.au/provider/pbs/prescription-shopping/index.jsp).

An opioid trial can be tailored to the individual patient, such as use on a short-term basis to improve function during the day or administration only at night to help with sleep. The usual duration of an opioid trial, to allow adequate titration of dose and to help distinguish attributable from contextual (placebo) effects, is four to six weeks, with regular review during that period.

4. Practical considerations

The fourth principle for the judicious use of opioids is to consider which drugs should be used. The Table lists the opioids currently available in longer-acting formulations. It should be emphasised that chronic pain should not be treated with short-acting formulations. Thus, long-acting/sustained-release oral or transdermal preparations of opioids are preferred, starting with low doses, irrespective of what the previous dose of over-the-counter codeine may have been.

Skill in titration is required. Although titration need not occur rapidly, the

Figure. Spectrum of aberrant drug-related behaviours.

prescriber should be alert to under-dosing, especially in the patient who is demonstrating improved function and increased activity. Such an improvement in overall wellbeing may in fact incur 'incident' (not 'breakthrough') pain, which again can be addressed by a modification of the long-acting opioid dose rather than by adding a short-acting agent.

A useful approach to evaluating the trial is summarised by the six As:[8]

- analgesia
- activity
- adverse effects
- affect
- aberrant behaviours
- accurate treatment records.

Adverse effects of opioids include constipation, nausea, dry mouth and sedation. Less common side effects include loss of libido, sexual dysfunction and cognitive impairment.

Once opioid responsiveness has been established and the side effect profile addressed, the therapeutic contract can be extended, with caveats such as no early repeats, no replacements of lost prescriptions or medications and an option for random urine monitoring (where appropriate) until a stable dose regimen is established.

5. Response to apparent increase in dosage requirements

The question of whether to impose a 'ceiling dose' of opioids has not been settled. Doses above the morphine equivalent of 120 mg daily require reassessment and probably specialist advice. An apparent increase in dose requirements should prompt the following questions to be asked:

- **Has there been a change in underlying disease state?** This is unlikely in patients with stable noncancer pain but may indicate development of significant damage of a peripheral joint (e.g. osteoarthrosis of a knee), radiculopathy (in the case of limb pain associated with spinal pain) or a comorbidity.
- **Has there been an improvement in function?** Increased activity (a desirable outcome) may incur incident pain. In the absence of other indicators of aberrant drug behaviour, an increased dose of opioid may be justified.
- **Has apparent tolerance developed?** Although tolerance to the euphoric effects of opioids in recreational drug users is common, tolerance to the analgesic effects in patients with pain is less obvious and more controversial. There may be one of two sets of phenomena here:
  - pharmacological tolerance (tested by the development of a characteristic syndrome on withdrawal of the drug) and psychological tolerance (a contextual effect)
  - tolerance that is difficult to distinguish from increased sensitivity to stimuli: the relative contribution from each possibility is not clear.
- **Has there been a change in mood, social (including financial) circumstances or other stressors?**
- **Has aberrant behaviour developed?**

Risk assessment for problematic opioid usage during opioid therapy: recognition of aberrant drug behaviours

The phase of opioid therapy for the recognition of aberrant drug behaviours is relevant to the practitioner-initiated trial of ascertaining opioid responsiveness or dose stability and to the situation where the practitioner is approached to take over the ongoing management of a patient who is already established on opioid therapy. Given the current poor performance of instruments developed to predict or identify problematic opioid use, recognition of aberrant behaviours may require a more practical approach. These are presented in the Figure, on a spectrum from problematic

Consultant's comment

Opioids are useful in a small group of patients with chronic pain and this group should not be denied access to a potentially effective treatment option. However, prescribing of opioids in patients with chronic pain should be conducted with extreme care and following the suggestions for 'judicious use' outlined in this article. Initiating opioid therapy in a patient with chronic pain requires careful consideration because the use of opioids might go against other important principles of chronic pain management aiming at increased self-efficacy: reduced reliance on the healthcare system, reinforcement of pain behaviour and loss of autonomy by externalisation of the locus of control.

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usage to unsanctioned usage.[9]

The presence of behaviours towards the problematic usage end of the spectrum does not necessarily equate to addiction, because they may reflect a chaotic lifestyle, psychological or physical dependence, or inadequate treatment of pain. Other possible reasons for these behaviours include a search to relieve a comorbid condition such as depression or anxiety, preoccupation with being unwell or a search for sympathy, meaning or a social context. The appropriate set of responses includes comprehensive somatic, psychological and social reassessment, a program to stabilise opioid intake (possibly including urine drug testing and/or restricted dispensing) and referral to pain medicine or addiction medicine services.

Behaviours towards the unsanctioned usage end of the spectrum are suggestive of true addiction or may raise suspicion of drug diversion. In such circumstances, the practitioner may choose not to continue prescribing or to make ongoing prescription contingent on thorough reassessment including blood and/or urine testing for nonprescribed substances, restricted dispensing and referral to pain medicine or addiction medicine services.

Conclusion

The management of patients with chronic noncancer pain is an increasing challenge. Opioid analgesics have a place in the treatment of some patients, as a passport to improving quality of life through an approach that appreciates the biopsychosocial framework for evaluating pain and does not rely on pharmacotherapy alone. As the opioid responsiveness of an individual patient is not predictable, all opioid pharmacotherapy should be considered to be a trial. Assessment of risk of potential or actual problematic use is an essential aspect of judicious prescription of opioids, utilising qualitative observation or instruments. Thus, a balance may be maintained between the potential for the sustained analgesic benefit of opioids for patients and the risk of problematic usage. MT

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COMPETING INTERESTS: Associate Professor Cohen is on an advisory board for Mundipharma and has received fees from Mundipharma for preparation and presentation of educational material. Dr Wodak has received fees from Mundipharma for preparation and presentation of educational material.