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Pain management – 2

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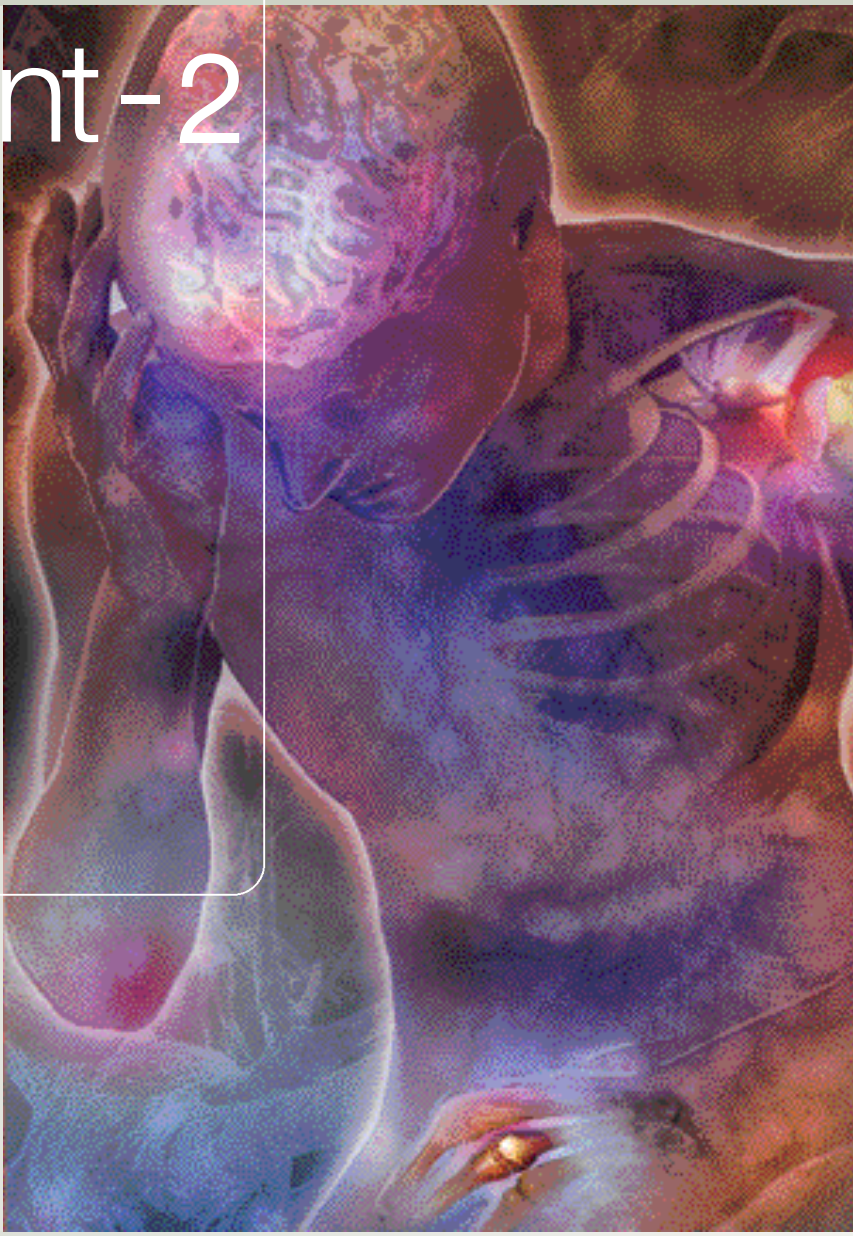

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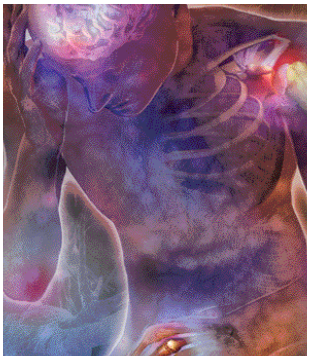

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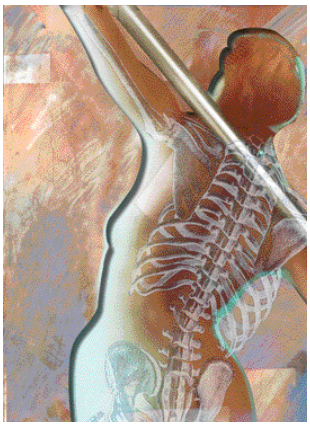

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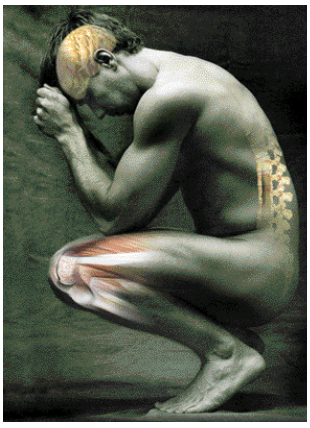

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Managing chronic nonmalignant pain

Treatment of chronic nonmalignant pain requires consideration of the type of pain, commonly nociceptive or neuropathic, experienced by the patient. Also, common management pitfalls, such as resting the painful area, should be avoided.

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Recent estimates indicate that in 2007 there were 3.2 million people in Australia experiencing chronic pain.[1] A large percentage of these people require ongoing medical management, which puts a large burden on Australian health care budgets. Estimates place the total cost of chronic pain to the Australian community at $34 billion per annum.

The limited number of multidisciplinary pain units in Australian hospitals cannot manage even a small percentage of these patients and, therefore, that responsibility appropriately falls largely to the GP. It is unlikely that contemporary GPs have had more than a rudimentary training in pain management because pain is usually poorly represented in undergraduate teaching curricula. Hopefully, this imbalance will be addressed in the future.

Unfortunately, those who like a black and white solution to clinical problems will be disappointed, because pain management is still very much more of an art than a science. There are shades of grey, misconceptions and pitfalls that contribute to making this a fascinating area in which to work.

Acute pain

Acute pain, associated with trauma or surgery, is generally easier to manage than chronic pain. This is because the type of pain is usually related to a form of tissue damage resulting in excitation of nociceptor nerve endings and there is unlikely to be learned pain behaviour. The time of onset is predictable and there is every expectation that pain relief will follow wound healing. Few would deny that the use of potent opioid drugs in these circumstances is worthwhile.

Chronic pain

Chronic pain is defined as pain lasting more than

IN SUMMARY

- **In 2007 there were 3.2 million people in Australia experiencing chronic pain, defined as pain lasting more than three months.**
- **The causes of pain behaviour are nociceptive pain, neuropathic pain or pain disorders.**
- **Chronic pain is very unlikely to resolve spontaneously and in most cases treatment can be assumed to be ongoing.**
- **An opioid trial should be considered in patients with nociceptive pain; anticonvulsants should be the treatment of choice for patients with neuropathic pain; and psychological management should be used for the treatment of patients with pain disorders in the absence of nociceptive and neuropathic pain.**
- **The common chronic pain management pitfalls such as resting when in pain and treating the site of referred pain should be avoided.**

three months, which is the upper limit of normal time for wound healing. This time course implies that factors other than wound-generated nociception may be contributing to the pain.

Pain behaviour

Distinct from acute pain, it is important to think of chronic pain in terms of pain behaviour. Patients experiencing pain do not present with objective signs or symptoms as they would with high blood pressure or a raised blood glucose level. They do, however, present with symptoms and signs that, when taken together, allow practitioners to make subjective assessments of the likely causes of the observed pain behaviours.

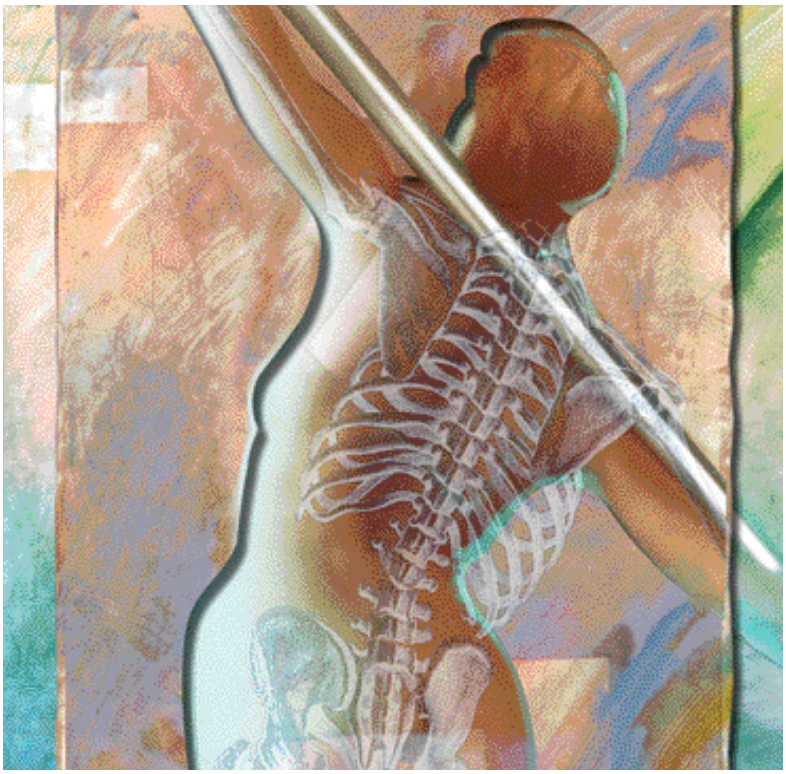
The causes of pain behaviour in decreasing incidence are:

- nociceptive pain due to excitation of mechanical, thermal or chemical nociceptors
- neuropathic pain, defined as pain related to disease or injury of the peripheral or central nervous system (extending to the spinal cord)
- pain disorders that exist when it is not possible to explain the patient's symptoms on a physical basis.

An organic pain disorder exists when a patient has some evidence of physical disease, but it is insufficient to explain the severity of the presenting symptoms. Where there is no evidence of any physical disease, a pain disorder should be considered. Pain disorders can be either subconscious (conversion or hysterical disorders) or, less likely, conscious (malingering).

A patient can present with one or more of these types of pain. As the management of each situation is significantly different, it is important to have a clear understanding of the likely contributors to a patient's pain behaviour before embarking on therapy.

In addition to the three main causes of pain behaviour, the psychological and social consequences of experiencing pain for many months or years and the behavioural consequences of different cultures should be considered. Hence, the assessment of a patient's pain behaviour can often be a complicated and time-consuming matter. In some cases referral of patients to a pain medicine specialist will be required. Chronic pain is very unlikely to resolve spontaneously and, therefore, in most cases treatment can be assumed to be ongoing.



Management options

A summary of management options for chronic pain is given in the box on page 6.

Nociceptive pain

Opioids (such as fentanyl, morphine and oxycodone) remain the drugs of choice to treat patients with nociceptive pain. Specialist pain units have tests available that can determine a patient's opioid responsiveness. These cannot be realistically performed in general practice, especially rural practice, and therefore an opioid trial should be considered. The patient is commenced on a low dose of a sustained-release opioid preparation and the benefits and side effects are monitored over the trial period.

The patient should be given a clear diagnosis and have an understanding of what would be considered an acceptable increase in function to offset the known adverse effects of opioids. The patient and GP should be in agreement about the issues of prescribing intervals and compliance.

Incredibly, with the number of patients increasingly moving between different states and territories in Australia, there are differences in opioid-prescribing rules throughout the country. In South Australia, for example, it is possible for patients to have their blood opioid levels measured (specifically for fentanyl, morphine and methadone, with oxycodone measurement a work

Management summary

Patients presenting with pain behaviour indicating either nociceptive or neuropathic pain as the principle contributor should, in the first instance, be managed by their GPs. I encourage rural GPs in particular to phone the closest pain unit for advice on managing these patients, particularly if they are uncomfortable about commencing long-term opioids or gabapentinoid-type drugs. If a pain disorder is suspected then these patients, who form a very small minority, should ideally be referred to a pain unit.

in progress). This provides an objective addition to patient management.

Chronic pain is usually present 24 hours a day, so sustained-release opioids or transdermal preparations, such as buprenorphine or fentanyl patches, should be used. This decreases the possibility of significant opioid troughs and resulting breakthrough pain. Methadone, with a variable and unpredictable half life, is most likely to be too difficult to use in general practice.

Neuropathic pain

Until about 15 years ago, there was little need to differentiate between patients with nociceptive and those with neuropathic pain because the treatment for both groups was much the same. However, with the recent availability of the gabapentinoid membrane stabilising-type drugs – that is, gabapentin and pregabalin – opioids are no longer indicated for neuropathic pain. Other anticonvulsants, such as sodium valproate and carbamazepine, given together with an antidepressant medication, such as amitriptyline, nortriptyline, duloxetine or venlafaxine, had been the mainstay of pharmacological therapy for patients with neuropathic pain (off-label use). However, the side effects and poor overall efficacy of these drugs in the management of patients with neuropathic pain have seen them gradually supplanted by the gabapentinoids.

Unfortunately, it is elderly and immunosuppressed patients who tend to experience neuropathic pain, such as diabetic peripheral neuropathy, postherpetic neuralgia and neuropathies associated with HIV. However, these patients are least able to tolerate the side effects of the anticonvulsants. The gabapentinoid drugs appear to offer better efficacy with a much more acceptable side effect profile. In fact, some of the side effects, such as promoting sleep and anxiolysis, can be positive effects. However, cost is a significant factor, especially as these medications are not listed on the PBS for the treatment of neuropathic pain.

Pain disorders

The management of patients with pain disorders – in the absence of nociceptive or neuropathic pain – does not require the use of opioids or gabapentinoids. Therefore, the prescription of these drugs to patients with pain disorders becomes part of the problem and not the solution. Psychological management is the treatment of choice but, in my experience in managing these patients, outcomes have been poor. However, it is obviously important to identify these patients' pain behaviours, discontinue non-indicated therapy and involve a psychologist, preferably one who has cognitive behavioural therapy (CBT) management skills.

Pain and compensation

The assessment of an injured worker with pain behaviour can be challenging and the presence of secondary gains should be taken into account. While not being malingerophobic, GPs should be aware that pain disorders in injured workers are often at a subconscious level.

If a worker presents with a history of low back pain related to a work injury and there is little clinical or radiological support for a physical diagnosis, the use of opioids may only confirm to the patient the seriousness of the complaint. Withdrawing the opioid from the patient will be a major issue and may damage the important doctor–patient relationship. Pain units with a physiotherapy- or CBT-based program provided as an inpatient or outpatient facility are ideally placed to help manage these patients. If the program is outpatient based then local accommodation should be available for patients from remote areas so as not to disadvantage them.

Management pitfalls

Resting when in pain

If you break an arm as a child, you realise that keeping it immobile is not as painful as when the arm is moved. By keeping it immobile (often in plaster), the fracture heals and the arm can once again be moved painlessly. So pain becomes associated with something harmful occurring, which is improved with rest. This is a useful, if simple, algorithm but when applied to chronic pain it is the antithesis of what should be happening.

Healing has long since finished by the time a patient is diagnosed with chronic pain behaviour. However, many patients accept the acute pain model and want to rest the painful part of the body. The part of the body affected and its support structures then become dysfunctional and wasted, making it even more difficult to return to normal function. This is why physiotherapists have an important role in multidisciplinary pain units. Their role is primarily to re-educate patients about why it is important to build up function and activity of a painful part of the body and its supporting structures.

Lesson – do not rest the injured part of the body.

Referred pain

If a part of the body is painful, it would not be unreasonable to assume that the painful area is responsible for the

generation of whatever pain signals are present. Unfortunately for those of us who follow the KISS (keep it simple – stupid) approach, this can be misleading because the phenomenon of convergence, otherwise known as referred pain, exists. Pain signals from visceral structures often share the same neurones as somatic structures in the spinothalamic tract. The area of the cerebral cortex responsible for localising pain assumes, incorrectly, that any signals arriving from the spinothalamic tract originated somatically.

Referred pain is probably a defence mechanism to protect our exposed soma. Therefore, patients with conditions such as renal colic, diaphragmatic pain or angina, as well as many other examples, present with diffuse pain in an area of the body remote from the source of the nociception. Caution should be adopted when making conclusions about the likely cause of pain.

Lesson – do not make assumptions about the likely cause of pain.

The concomitant use of serotonin reuptake inhibitors

The introduction of the sustained selective serotonin reuptake inhibitors (SSRI) was a major breakthrough, particularly in the management of depressive disorders. However, the concomitant use of another medication, that unknowingly contains a similar constituent, can cause serotonin syndromes, which can be extremely unpleasant for the patient. A common example is the use of tramadol with an SSRI such as fluoxetine. Tramadol is a mixture of two enantiomers – one a very weak opioid drug, the other with serotonin reuptake inhibiting properties among others.

Lesson – when using tramadol be aware of other SSRIs that the patient may be concomitantly prescribed.

The concomitant use of opioids

In the management of chronic nonmalignant pain, various opioid cocktails are sometimes prescribed to patients. Most of the available strong opioids act on mu opioid receptors. If one strong opioid is ineffective then one of two conditions exists:

- the blood level of the opioid (that is, the dose of the opioid) is below the minimum effective concentration
- the pain behaviour is no longer opioid-responsive.

A measurement of the patient's blood opioid level will rapidly identify the reason for ineffective opioid use.

Adding another opioid would, in my opinion, only confuse matters. The use of an immediate-release opioid for breakthrough pain is indicated when stabilising a patient with pain related to cancer but will cause more problems than it cures in nonmalignant pain.

Lesson – stick to one potent opioid and become familiar with it.

Conclusion

It is clearly the domain of the GP to manage most patients presenting with chronic pain behaviour. Following these basic guides to diagnosis and management should significantly decrease the number of patients who need assessment in pain management units and speed up individual patient management. MT

Reference

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Cancer pain management

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Pain is one of the most feared and debilitating symptoms of cancer. Cancer pain can be controlled in most patients with strategies that are available in the community. By correcting misconceptions about opioids and providing comprehensive assessment and pain management, a patient's quality of life can be improved.

More than half of people with cancer at any stage of the disease experience pain, and one-third of those describe it as severe.[1] The presence of pain has a significant impact on every aspect of a person's life – from the quality of sleep obtained to the ability to work, from appetite to relationships, and from mood to the ability to think. The experience of cancer pain for a patient is complex and is influenced by psychological and social issues, as well as past experiences and beliefs. It is important that all doctors involved in the care of patients with cancer are able to perform a thorough assessment of pain and provide excellent pain management. The US National Comprehensive Cancer Network has published guidelines for the management of patients with cancer pain.[2]

This article explores the assessment and management of patients with cancer pain, barriers to the management of patients with cancer pain and patient education.

Assessing patients with cancer pain

All patients with cancer should be assessed at each visit for the presence of pain because cancer pain is so common. The causes of cancer pain are shown in Table 1.

A comprehensive pain assessment of a patient with cancer should investigate the presence of persistent and breakthrough pain, the type and severity of the pain, and the impact the pain is having on the patient (Table 2). Valid pain assessment tools should be employed to assess the severity of pain and the patient's response to treatment (Table 3).[3]

IN SUMMARY

- **Cancer pain can be controlled in the majority of patients.**
- **Cancer pain is common and screening for pain should be performed at each patient visit.**
- **Strong opioids with paracetamol are first-line management in all patients with moderate to severe cancer pain.**
- **When opioids are used to treat patients with cancer pain, addiction and clinically significant tolerance are rare.**
- **Misconceptions regarding opioids are common, so all patients benefit from education when commencing opioids.**
- **Adverse effects of opioids can be prevented or effectively managed.**
- **Anticancer treatment, adjuvant therapy, nonpharmacological treatments and addressing psychosocial issues are all important elements of pain management.**

Table 1. Causes of cancer pain

- Direct pressure of the cancer on the organs, bone or nerves
- Poor circulation due to the cancer obstructing blood vessels
- Obstruction of the bowel or urinary tract
- A side effect of treatment
- Pathological fractures
- Musculoskeletal pain because of inactivity

Oncological emergencies presenting with pain

- Bowel obstruction
- Impending or actual bone fracture
- Spinal cord compression
- Brain metastases

Table 2. Comprehensive assessment of patients with cancer pain

- Location of pain, including radiation
- Temporal factors, including onset, duration and frequency of pain
- Character of pain – i.e. sharp, dull, aching, burning, stabbing etc
- Severity of pain measured on a pain assessment scale
- Interference by pain with daily living – e.g. sleep, mood, ability to walk, ability to work and relationships
- Factors that aggravate and relieve the pain
- Current and past analgesia and response to analgesia
- Patient's impressions on the meaning of pain and beliefs related to pain, which may act as barriers to pain relief
- Associated psychological symptoms, distress or depression
- Current cancer status and intercurrent medical problems
- Physical examination
- Radiological examination and laboratory tests, if appropriate

Each type of pain that the patient experiences should be addressed separately and assessment repeated when the patient experiences a new type of pain. The multidimensional nature of pain should be assessed, including the psychosocial and spiritual dimensions.

The patient is the key factor in the assessment, because pain is a subjective experience. Patient populations at high risk of poor pain control include the elderly, children, those from a different cultural or linguistic background, and those with a past history of substance abuse.[4]

The aim of pain assessment is to determine the type of pain the patient is experiencing and the likely cause (e.g. pain shooting down the leg may be neuropathic pain from cancer pressing on a nerve root in the back; see the box on page 11 for description of the types of pain experienced) and any complicating factors that may be exacerbating the pain.

Table 3. Pain assessment tools

- Pain numerical rating scale – The patient is asked 'what is your pain level on a scale of 0 to 10 where 0 is no pain and 10 is the worst pain imaginable?'
- Categorical pain scale – The patient is asked 'would you rate your pain as none, mild, moderate or severe?'
- Visual analogue scale such as the Johns Hopkins pain rating instrument (Figure)
- Use of a pain diary
- Pain FACES scale[3]

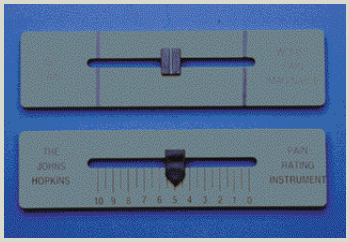

Figure. Johns Hopkins pain rating instrument.

From Hockenberry MJ, Wilson D, Winkelstein ML: Wong's Essentials of Pediatric Nursing, ed 7, St. Louis, 2005, p. 1259. Used with permission. Copyright, Mosby.

Patient-related barriers to cancer pain management

Many barriers have been identified that may prevent a patient from reporting pain or using adequate analgesia.[5] The most common barriers and ways to effectively address them are given below.

- **Fear of addiction:** patients can be reassured that using opioids such as hydromorphone, morphine or oxycodone for pain rarely causes addiction.
- **Fear that using strong pain relief now means that nothing will be available later if the pain gets worse:** adjustments to medication and dose can be made that will allow pain control to be achieved.
- **Fear that once using strong pain relievers, they can never be stopped:** if anticancer treatment removes the source of pain

then pain relief can be weaned.

- **Fear of side effects:** it is true that morphine does cause side effects, but often a patient will become tolerant to the side effects after three to five days and will no longer experience them. Constipation is always a side effect and must be prevented with the regular use of laxatives.
- **Fear of injections:** most pain relievers are now given as tablets.
- **Not wanting to trouble or distract the doctor:** all doctors are busy but pain control for patients is a high priority.
- **Stoicism:** there is no benefit from being in pain and pain causes significant interference with many aspects of daily life.
- **Fatalism:** pain can be controlled.

Principles of managing patients with cancer pain

Managing patients with cancer pain involves a team approach with the GP and the patient at the centre. Other members of the team include the medical and radiation oncologists, nurse, pharmacist, occupational therapist, physiotherapist, pastoral carer, social worker, diversional therapist, palliative care specialist, pain specialist and psychologist. Treatment for patients with pain should be aggressive and given early; however, pain is rarely the only symptom in patients with cancer. Other symptoms and the presence of distress must be addressed concurrently to achieve optimal pain relief.

Patient and caregiver education is an essential part of the pain management plan in order to address potential misconceptions about pain and opioid use (see patient handout on pages 15 and 16).

Anticancer therapy is most important and where possible should be given to reduce the cancer, which is the cause of the pain. Palliative radiotherapy is equally effective in single and multiple fractions for relief of pain from bone metastases. Bisphosphonates have been shown to reduce pain and skeletal complications of bone metastases in patients with myeloma, breast cancer or prostate cancer.[6,7]

Evidence-based pain management guidelines are available online.[2]

Pharmacological treatment

Paracetamol or an NSAID such as ibuprofen or naproxen should be considered to treat patients with mild pain. The paracetamol dose should be reduced by 25 to 50% in patients with hepatic impairment. NSAIDs are particularly useful if inflammation is present but careful consideration should be given to their use in cancer pain because of potential toxicity, especially gastrointestinal and renal toxicity. COX-2 inhibitors such as celecoxib or meloxicam can also be used to treat patients with cancer pain.

In patients with moderate or severe pain, opioids can be used in combination with paracetamol (Table 4).[8]

Opioids

All pain management guidelines recommend a trial of a short-acting opioid for pain levels scored between five and 10 on a scale of 0 to 10, where 0 is no pain and 10 is the worst pain imaginable. The short-acting opioid should be given regularly and not on an as-needed basis, and should be titrated according to the pain levels and side effects to achieve the correct dose for each individual.

All patients commencing an opioid should also start a bowel regimen with a laxative to prevent constipation – for example, docusate sodium with senna two tablets twice a day or macrogol 3350 one sachet once a day dissolved in 125 mL of water and an antiemetic such as metoclopramide 10 mg three times a day for use as needed.

Types of pain experienced by patients with cancer

- Nociceptive pain is due to the involvement of soft tissues or bone and is aching, throbbing or sharp in nature.
- Neuropathic pain is due to the involvement of nerves and may be burning, tingling or shooting in nature. It may be associated with sensory changes over the affected area or muscle weakness.
- Visceral pain is due to the involvement of organs and may be cramping or gnawing in nature.

Table 4. Starting dosages of analgesics for average pain severities

Severity of pain (scale)*	Analgesic and dosage†
Mild pain (1 to 4)	Paracetamol two 500 mg tablets every four hours (up to eight tablets per day) Or an NSAID
Moderate pain (5 to 6)	Paracetamol two 500 mg tablets every four hours (up to eight tablets per day) And/or oral morphine 5 to 10 mg or oxycodone 5 mg every four hours
Severe pain (7 to 10)	Paracetamol two 500 mg tablets every four hours (up to eight tablets per day) And/or oral morphine 10 mg or oxycodone 5 to 10 mg every four hours

* Pain severity is scored on a scale of 0 to 10, where 0 is no pain and 10 is the worst pain imaginable.
† Halve the dose for elderly patients.

Table 5. Dose equivalence for strong opioids for patients with cancer pain

Type of opioid*	Equivalent dosages
Immediate-release opioids	
Morphine	15 mg orally every four hours
Oxycodone	10 mg orally every four hours
Hydromorphone	3 mg orally every four hours
Methadone	Only commence with advice from a pain specialist or palliative care specialist
Sustained-release opioids	
Morphine	45 mg orally twice a day
Oxycodone	30 mg orally twice a day
Hydromorphone	16 mg orally once a day
Fentanyl	25 µg/hour patch replaced every 72 hours

* Pethidine is not recommended for the treatment of patients with cancer pain. Buprenorphine patches are not recommended for cancer pain because they are partial agonists; also, they are seven-day patches and therefore cannot be rapidly titrated in patients with moderate to severe pain.

Patients with severe pain (rated seven to 10) should be reassessed within 24 hours of starting an opioid, and patients with moderate pain (rated five to six) should be reassessed within 48 hours. Once the pain is stabilised, a long-acting opioid can be commenced with a short-acting opioid available for breakthrough pain at a dose equivalent to one-sixth of the total daily dose (Table 5). The starting dose of morphine for oral titration is 5 to 10 mg (although the National Comprehensive Cancer Network guidelines suggest 5 to 15 mg)[2] every four hours (Table 4). If pain is unchanged after an hour, the dose should be doubled. If the pain is reduced but not relieved, the dose should be repeated.

Table 6. Common adverse effects of opioids

Adverse effect	Management
Constipation	Occurs almost universally and requires prophylaxis with use of a laxative
Nausea and vomiting	Often resolves after three days. All patients should be provided with metoclopramide (10 mg three times a day) or haloperidol (1.5 mg at night or twice a day) to take if nausea occurs
Sedation	Common at the beginning of treatment and often resolves after two to three days
Dry mouth	May be managed with frequent sips of water

Uncontrolled pain requires reassessment of the patient and a new dosing regimen.

Ongoing management of pain involves reassessment of the patient at each consultation, titrating analgesics if the pain level changes, and providing the patient with written instructions and ongoing education as needed.

Opioids may be given by alternative routes. For example, morphine may be given by subcutaneous injection for those unable to take opioids orally. The relative potency of subcutaneous morphine is double that of oral morphine so the dose should be halved when calculating the equivalent analgesic dose of subcutaneous morphine. Opioids can also be given intrathecally or epidurally, which may reduce central adverse effects.[9]

Adverse effects of strong opioids

Strong opioids have a number of adverse effects (Table 6). The presence of myoclonus, confusion or hallucinations suggests toxicity, which should be managed by reducing the opioid dose, ensuring adequate hydration is given and administering haloperidol 1.5 to 3 mg twice a day.[10] Switching to another opioid may also help to manage toxicity.[11]

Choosing a strong opioid

There is no significant evidence for the benefit of one opioid over another. Morphine has the advantage of being inexpensive and available in a number of formulations. Morphine metabolites accumulate in patients with renal impairment so another opioid should be trialled or the dose frequency of immediate-release morphine should be reduced to two or three times daily depending on the severity of renal impairment.

Transdermal fentanyl should only be commenced in patients with stable pain. The advantages of transdermal fentanyl are a reduced incidence of constipation, the convenience of only needing to change the patch every three days and the dose not

needing to be reduced in patients with renal impairment. Other opioids that can be used in patients with renal impairment include oxycodone and hydromorphone, with dose reduction and careful titration when needed.

Sustained-release oxycodone has biphasic distribution and so analgesic plasma concentrations are achieved sooner than with other controlled-release preparations. It is now available as a combination with naloxone, an opioid antagonist to minimise constipation. However, the fixed dose does not allow flexibility with titration, which is often needed in patients with cancer pain, and there is limited local experience in the cancer pain setting.

Methadone has some N-methyl-d-aspartate (NMDA) receptor antagonist activity and is suitable for patients with complex pain issues. Its use is limited to specialists familiar with it because it has variable pharmacokinetics depending on a patient's previous opioid use.

Buprenorphine, available as a slow-release seven-day patch, is not recommended for patients with cancer pain, because it does not allow for rapid titration of dose.

Dependence, tolerance and addiction

Tolerance to the analgesic effects of opioids is rarely seen in patients with cancer pain and increasing requirements for analgesia are more often attributable to progressive disease.[12] Physical dependence is a physiological adaptation to chronic opioid dosing and does occur. Opioids should not be withdrawn abruptly because withdrawal syndrome, including sweating, tachycardia, agitation and flu-like symptoms, can occur. Addiction rarely occurs in this setting.[13-15]

Coanalgesics

Coanalgesics, also known as adjuvants, are medications used primarily for an indication other than pain but which have an analgesic action for pain that is partially responsive to opioids such as neuropathic pain. These adjuvants include antidepressants, anticonvulsants, corticosteroids, antiarrhythmics and local anaesthetics.

Antidepressants effective in the treatment of patients with pain include: tricyclic antidepressants such as amitriptyline and nortriptyline; selective serotonin reuptake inhibitors such as fluoxetine and sertraline; and serotonin noradrenaline reuptake inhibitors such as duloxetine and venlafaxine. However, the use of antidepressants to treat patients with pain is off-label. Anticonvulsants effective in the treatment of patients with pain include gabapentin, pregabalin (both indicated for the treatment of patients with neuropathic pain), carbamazepine and sodium valproate (both used off label). A trial of an antidepressant or anticonvulsant should be given for patients with neuropathic pain that is not fully responsive to opioid analgesia.

Corticosteroids such as dexamethasone are useful for pain associated with raised intracranial pressure, nerve compression or bone pain.

Mexiletine is an antiarrhythmic agent that may be beneficial in patients with neuropathic pain (off-label use). A topical local anaesthetic such as lignocaine applied to the painful area is useful and results in little systemic absorption. Ketamine, an NMDA antagonist, may be used in specialist palliative care units to treat patients with resistant neuropathic pain (off-label use).

Interventional techniques

Some pain is not adequately controlled using oral, transdermal or subcutaneous routes and may need intrathecal analgesia or a nerve block. Examples of such pain are sacral plexopathy and pancreatic cancer pain, for which a coeliac plexus block may improve pain levels and indeed survival. Referral to a pain clinic is necessary for these treatments and many clinics will see urgent referrals promptly.

Table 7. Nonpharmacological treatments for cancer pain

Psychological strategies
- Hypnosis
- Relaxation
- Imagery
- Psychotherapy and structured support
- Distraction
- Cognitive restructuring
- Support in communicating with health professionals

Physical strategies
- Transcutaneous electrical nerve stimulation
- Massage
- Acupuncture
- Positioning (e.g. sitting position)
- Walking aids
- Immobilisation
- Use of heat or cold
- Exercise

Spiritual strategies
- Prayer

Nonpharmacological treatments

Evidence exists for the use of psychological, physical and spiritual strategies in patients with cancer pain (Table 7).

Quality of life and psychological issues

Pain is often related to depression either as an exacerbating factor or as a consequence of the pain. Concomitant depression should be treated in patients with cancer pain. Anxiety, insomnia and fear can all exacerbate pain and should be addressed to optimise analgesia.

Palliative care – what it is and when patients should be referred

Palliative care is defined by the World Health Organization as 'the active total care of patients whose disease is not responsive

to curative treatment'.[16] Control of pain, other physical symptoms and psychological, social and spiritual problems is paramount. The goal of palliative care is to achieve the best quality of life for patients and their families.

Palliative care aims to:

- affirm life and regard dying as a normal process
- neither hasten nor postpone death
- provide relief from pain and other distressing symptoms
- integrate the psychological and spiritual aspects of care
- offer a support system to help patients live as actively as possible until death
- offer a support system to help the family cope during the patient's illness and in their own bereavement.

Patients should be referred early in the process of metastatic disease so they are aware of the service and their needs can be addressed as they arise. MT

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Further reading

Overcoming cancer pain. A guide for people with cancer, their families and friends. NSW Cancer Council booklet and DVD. Available online at: http://www.nswcc.org.au/html/patientsfamiliesfriends/livingwithcancer/cancerpain/downloads/overcoming_cancer_pain.pdf (accessed August 2010).

Caresearch website. www.caresearch.com.au

COMPETING INTERESTS: None

Cancer pain management

This handout provides information for patients about dealing with the pain associated with cancer.

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Talk to your doctor

- It is always important to tell your doctor or nurse if you are experiencing pain. Treating it early can prevent problems down the track.

Keep a note of your pain levels

- It is helpful to keep track of how much pain you are experiencing. You can use a pain diary (see below), which shows the day and time, your pain score (0 to 10, where 0 is no pain and 10 is the worst pain imaginable), the pain relief medication and dose you used and the response achieved after one hour.

Example of a pain diary

Day	Time	Pain level (0 to 10)	Drug and dose taken for pain relief	Pain level one hour after taking drug (0 to 10)	Comments
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Don't suffer in silence

- Relief of pain is important and there is no benefit to suffering with pain.
- Pain can usually be well controlled with medications taken by mouth.
- If oral medications do not work, many other options are available.

COPY FOR YOUR PATIENTS

- Using a script may help you communicate with your doctor about your pain, such as:

'Hello, Dr___, this is____. I'm calling to talk with you about the pain I'm having. Over the past week, my pain has been____on a 0 to 10 rating scale. The pain has been so severe that I have not been able to sleep, do my usual activities, or visit with my friends. I've been taking my pain medicine as you prescribed it. I've also been taking ___ additional doses of medicine every day. The medicine isn't working. Can we change the pain medicine so I can get better pain control?'[1]

Don't be afraid to try an opioid

- Opioids such as morphine are often used to relieve pain.
- When opioids are used to treat cancer pain, addiction is rarely a problem.
- They are controlled substances that need to be properly safe guarded in the home.
- They must be used with caution and should not be mixed with alcohol or illicit substances.
- If you take opioids now, they will still work later.
- You need to take laxatives to prevent constipation when using these medications.

Keep the lines of communication open

- Communication with doctors and nurses is critical.
- Doctors and nurses cannot tell how much pain you have unless you let them know.
- Doctors and nurses want to know about any problems that you think the pain medications may be causing, because there are probably ways to make these better.
- Tell your doctor or nurse if you have any difficulties getting the medications or concerns about taking them. They have dealt with such issues before and will help you.
- Expect optimal treatment of pain and side effects.

Ask your doctor for all the necessary information

Make sure you get the following from your doctor:[2]

- a list of each medication prescribed, a description of what each medication is for and instructions of how and when to take each one
- a list of potential side effects of each medication and what to do if these occur
- a list of all medications to be discontinued
- a list of telephone numbers of various healthcare professionals and specific instructions of who to call if the following occur:
  - any problems in getting the prescription or taking the medication
  - new pain, change in pain or pain not relieved by the medication
  - nausea and vomiting that prevents eating for one day
  - no bowel movements for three days
  - difficulty awaking from sleep easily during the daytime
  - confusion
- a plan for follow-up visits and/or telephone calls.

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COPY FOR YOUR PATIENTS

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The challenges of postoperative pain

Inadequate postoperative pain control is a frequent reason for patients to contact their GP after discharge from hospital. Postoperative pain impairs recovery and rehabilitation, and should be treated with judiciously prescribed analgesics and, when necessary, referral to pain medicine specialists.

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The possibility of experiencing pain is usually the worst fear of patients facing surgery. Postoperative pain causes deleterious physiological and psychological effects leading to prolonged recovery and hospitalisation.[1] Furthermore, acute pain limits functional rehabilitation and may develop into chronic pain.[2]

Although pain-free surgery is not a reality, with the evolution of medicine postoperative pain is now better understood and managed. Advances in pain medicine have led to major developments in postoperative analgesia, including:

- the formation of acute pain services
- the development of the concept of multimodal analgesia
- the utilisation of patient-controlled and regional analgesia techniques.

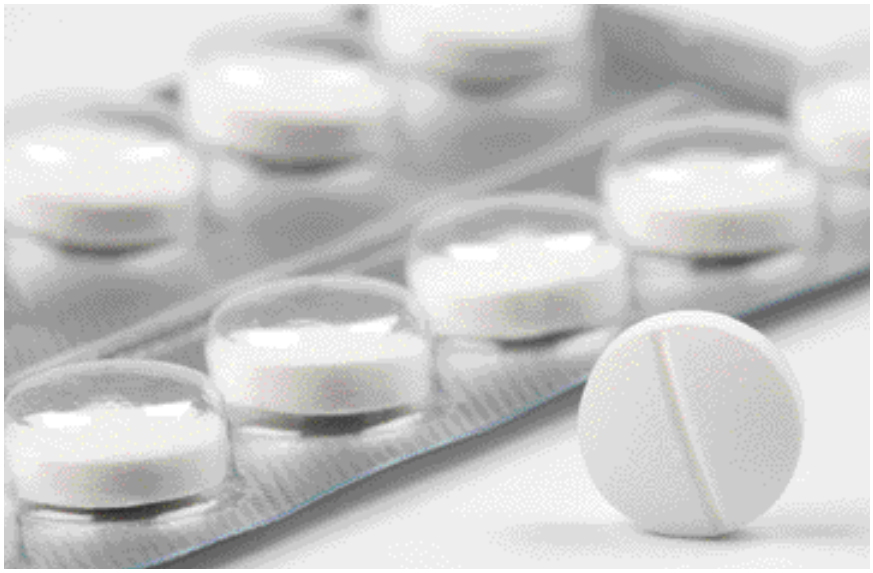
What is postoperative pain?

Pain is defined by the International Association for the Study of Pain as an 'unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'.[3] It is therefore not only the trauma of surgery but also the physiological and psychological make-up of the patient that determines how pain is felt.

A surgical incision is a tissue injury that activates specific nociceptors.[4] It is associated with a release of inflammatory mediators resulting in peripheral sensitisation, which is manifested by hyperalgesia and allodynia (increased sensitivity to painful and nonpainful stimuli). Intense and ongoing peripheral nociceptive input will then increase the excitability of neurons in the spinal cord and

IN SUMMARY

- **Patients with postoperative pain most often present to their GPs rather than returning to the hospital, particularly after ambulatory surgery and with current trends for early discharge.**
- **Appropriate analgesics should be provided to such patients and any treatable causes of postoperative pain should be identified.**
- **Acute pain can progress to chronic pain, so should be adequately managed to prevent this occurring.**
- **Psychological, behavioural, environmental and social factors influence pain and may contribute to the progression from acute to chronic pain.**
- **Patients exhibiting hyperalgesia, opioid tolerance and/or addictive behaviour (including aberrant medication taking) should be identified and, if necessary, referred to pain specialists.**



lead to central sensitisation.[4]

Neuropathic pain is associated with injury or disease of the peripheral or central nervous systems – for example, nerve injury during surgery. This can result in changes such as hyperexcitability of damaged peripheral nerves, central sensitisation and reorganisation of synaptic connections in the spinal cord.[5]

Pain management in the hospital setting

Increasingly, hospitals are providing acute pain services comprised of nursing and medical staff (usually anaesthetists or pain medicine specialists) dedicated to pain management and supplying patients with information and staff with education. These services supervise advanced 'multimodal' analgesic techniques and set the goals for effective and appropriate pain management. This approach aims to facilitate rapid recovery and return of the patient to full function, thereby reducing morbidity and allowing early discharge from hospital.[6]

The current concept of multimodal (or balanced) analgesia suggests the use of multiple medications with different mechanisms of action to improve analgesia and reduce medication doses, and therefore their adverse effects.[6] This is particularly useful if these techniques are opioid sparing.

Modalities used include:

- background medication with non-opioids, such as paracetamol and/or NSAIDs (including COX-2 inhibitors)
- opioids administered by patient-controlled analgesia for titration to effect
- adjuvants, such as ketamine and pregabalin
- local anaesthetic infiltration
- regional catheter techniques (in the epidural space or near peripheral nerves).

To facilitate rehabilitation and early discharge from hospital, patients are switched early to oral analgesics, including oral opioids titrated to effect and to reduce adverse effects (in particular sedation).

Postoperative pain assessment after hospital discharge

Patients are most often discharged from hospital on oral analgesics, usually with detailed instructions and a limited (five day) supply of medication. Importantly, the exact analgesic medications and doses prescribed on discharge should be specified, with clear instructions to the patient on their use. This will provide useful information when assessing and managing a patient's pain issues. A guide to postoperative pain management in general practice is given in the box on page 19.

When seeing a patient after discharge, treatable causes of pain should be identified and therapy directed to the cause of pain. The presence of surgical complications, such as haematoma, dehiscence or infection needing further immediate investigation, should be excluded. Regional anaesthesia techniques provide good anaesthesia and analgesia but carry inherent risks. Extremely rare but serious complications, such as meningitis or epidural abscess, can occur after hospital discharge in patients with epidural catheters. New symptoms of severe back pain, weakness, increasing numbness or loss of sensation in the legs, or loss of bladder or bowel control in a patient after epidural analgesia warrant immediate hospital referral for further investigation.[7]

Headaches following a dural puncture for spinal anaesthesia occur with an incidence of about 1%. They are classically postural in nature and more common in patients under the age of 50 years and in the parturient. Non-opioid and opioid analgesics may provide temporary relief. About 90% of cases improve spontaneously within 10 days.[8]

Persistence of postoperative pain

Acute pain (such as postoperative pain) is pain of recent onset and limited duration caused by tissue injury, while chronic pain commonly persists beyond the time of healing. Studies have shown that acute postoperative pain can persist as chronic pain, thus showing the need to prevent the progression from acute to chronic.[2,9]

To prevent acute pain becoming chronic, the cause of and reason for the occurrence of the pain should be understood. Although the reason why some people develop chronic pain after

surgery while others do not is still a mystery, risk factors for progression of pain have been identified and this has helped the development of strategies to reduce its incidence.

Factors that determine if a patient is at risk of developing chronic pain include genotype, medical history, past experiences of and beliefs about pain and its meaning, and psychosocial circumstances. Medical factors, such as the types of surgery and anaesthesia received, perioperative analgesia and treatments given, also have an effect.[2,9]

Pain that persists beyond the time of recovery frequently has a neuropathic element. Certain operations carry an increased risk of nerve injury, putting patients at risk of developing chronic pain. With an incidence of chronic pain of up to 60%, such operations include, but are not limited to, amputations (with up to an 80% risk of phantom limb pain), thoracotomies, mastectomies, cholecystectomies and hernia repairs.[2,9]

Analgesic options for the management of postoperative pain

A summary of the analgesic drugs used in general practice to treat patients with acute pain is given in the Table.

Paracetamol

Paracetamol is the most widely used analgesic drug worldwide for all pain. It is exclusively an analgesic and antipyretic. Unlike NSAIDs, it does not inhibit peripheral cyclo-oxygenase activity and does not cause gastrointestinal ulceration or bleeding.[10]

Hypersensitivity to paracetamol is very uncommon and at the suggested therapeutic dosage of 4 g a day, it has minimal adverse effects. However, if taken in excessive doses, paracetamol can cause fatal liver damage. There is a debate about whether precautions are necessary in those patients with pre-existing liver disease or malnourishment.

Postoperative pain management in general practice

Patient presents with pain after surgery

- Exclude any treatable cause or surgical or anaesthetic complication
- Assess for a neuropathic component of the pain.

If obvious nociceptive pain, i.e. ongoing postoperative pain, is present

- Use paracetamol 1 g four times a day in all patients
- If pain is not relieved by paracetamol and there are no contraindications, use an NSAID to its maximum daily dose. Contraindications include the presence or history of gastrointestinal ulcers, renal impairment, other nephrotoxic medications, bleeding risk or aspirin-sensitive asthma
- Use celecoxib 200 to 400 mg a day if any risk factors for NSAID use are present but consider that renal risk factors are similar to those for NSAIDs; if there is an increased risk or past history of gastrointestinal ulcer, co-medicate with a proton pump inhibitor
- If pain is not relieved by non-opioids, offer immediate-release opioids at doses titrated against pain, but limited by sedation; allow two to six doses a day to be taken only as needed. Doses should be at the lower end of the range in older patients:
  - tramadol 50 to 100 mg
  - oxycodone 5 to 20 mg
  - morphine 5 to 20 mg
- If there are ongoing opioid requirements for obvious pain and no aberrant medication-related behaviour, convert about 50% of daily opioid requirements to sustained-release preparations
- Reduce dose of opioid gradually as pain improves; watch for aberrant behaviour and maintain firm boundaries with regard to dose increase. Organise review by pain medicine specialist if opioid requirements continue.

If neuropathic pain or mixed nociceptive and neuropathic pain are present, consider using adjuvants

- Tricyclic antidepressants or serotonin noradrenaline reuptake inhibitors (off-label uses):
  - amitriptyline 5 to 10 mg at night, then increase dose as tolerated
  - nortriptyline 5 to 10 mg at night, then increase dose as tolerated
  - duloxetine 30 to 60 mg a day
  - venlafaxine (modified release) 25 to 37.5 mg a day
- Anticonvulsants:
  - gabapentin initially 300 mg three times a day, then increase dose as tolerated to a maximum of 1200 mg three times a day
  - pregabalin initially 75 mg twice a day, then increase dose as tolerated to a maximum of 300 mg twice a day
  - other anticonvulsants such as carbamazepine, phenytoin, sodium valproate or clonazepam (off-label use) may also be used, but there is no good supportive evidence for their use in peripheral neuropathic pain and they have increased adverse effects.

Consider referral

- Consider urgent referral to a pain medicine specialist if the patient has any of the following:
  - persistent, in particular neuropathic, pain
  - pain poorly responsive to opioids with dose escalation
  - features of aberrant medication-related behaviour.

continued

Table. Analgesic drugs used in general practice

Drug	Route	Standard dosage
Paracetamol	Orally	Two 500 mg tablets every four hours
NSAIDs		
Ibuprofen	Orally	Two 200 mg tablets three or four times a day
Diclofenac	Orally	25 to 50 mg two to three times a day
	Rectally	25 to 50 mg two to three times a day
Naproxen	Orally	Initially 500 mg, then 250 mg every six to eight hours
Celecoxib*	Orally	200 mg a day, twice a day in acute pain
Immediate-release opioids (titrate dose for acute pain relief and against adverse effects, primarily sedation)		
Tramadol	Orally	50 to 100 mg two to four times a day to a maximum of 400 mg a day
Oxycodone	Orally	5 mg every four to six hours to a maximum of 400 mg a day
Morphine		
– tablets	Orally	10 to 30 mg every four to six hours
– solution	Orally	5 to 20 mg every four hours
Hydromorphone	Orally	2 to 4 mg every four hours
Adjuvants for neuropathic pain		
Gabapentin	Orally	Initially 300 mg three times a day; may increase to a maximum of 3600 mg a day
Pregabalin	Orally	Initially 75 mg twice a day; may increase to 150 mg twice a day after three to seven days; may increase to a maximum of 300 mg twice a day after another seven days
Amitriptyline†	Orally	5 to 25 mg at night
Nortriptyline†	Orally	25 mg three to four times a day
Duloxetine†	Orally	60 mg a day
Venlafaxine,† modified release	Orally	25 to 37.5 mg a day

* Used off label for acute pain; † Used off label for all pain.

Nonsteroidal anti-inflammatory drugs

NSAIDs are the second-line treatment for mild to moderate acute pain. Their analgesic and anti-inflammatory actions are explained by their mechanism of action, that is the inhibition of cyclo-oxygenase. Thereby, their effects are inherently linked to their adverse effects, namely gastric and duodenal ulceration, renal impairment, cardiovascular complications and induction of asthma in sensitive patients.[10] In addition, the use of NSAIDs may lead to prolonged bleeding time, increasing perioperative blood loss.

The selective COX-2 inhibitors such as celecoxib and parecoxib have advantages with regard to their lower risk of adverse effects. However, the possibility of renal impairment in the perioperative period remains and is a major contraindication for the use of COX-2 inhibitors in such situations.[11]

Tramadol

Tramadol as an atypical centrally acting analgesic is another good option for the management of postoperative pain. The analgesic effect of tramadol is partially mediated via opioid receptor effects and partially via reuptake inhibition of noradrenaline and serotonin at nerve terminals. As a result, it carries a lower risk of adverse effects such as respiratory depression, constipation and the potential for abuse than other opioids.[12]

Tramadol should not be used in patients taking the monoamine oxidase inhibitor (MAOI) class of antidepressants and should be used with caution in those at increased risk of seizures or taking tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). The mechanism of action of tramadol on noradrenaline and serotonin, which is similar to that of TCAs, may explain its efficacy in treating neuropathic pain.[13]

Opioids

Opioids such as hydromorphone, morphine and oxycodone remain the mainstay analgesics for use in moderate to severe acute pain. Interindividual opioid requirements vary greatly; therefore, opioid dose is best titrated in the acute setting with immediate-release opioids given at doses as needed to suit each patient.

Slow-release and transdermal (buprenorphine and fentanyl) opioid preparations have a slow onset of effect and should not be used in acute pain situations; transdermal fentanyl is contraindicated in acute pain. However, slow-release and transdermal preparations may be useful in providing background analgesia in carefully selected cases of persistent pain or in patients with high opioid requirements. Often patients requiring these preparations need advice from a pain medicine specialist.

Adjuvant analgesics (co-analgesics) for the management of postoperative pain

The Latin word *adjuvans* means to help, particularly to reach a goal. Adjuvant

analgesics enhance the effects of classic analgesics, particularly in complex settings such as in patients with neuropathic pain, pre-existing chronic pain, long-term opioid usage with tolerance or poor responsiveness to opioids. They are commonly initiated by pain medicine specialists; some are not suitable or not available in the GP setting.

N-methyl-D-aspartic acid receptor antagonists

N-methyl-D-aspartic acid (NMDA) receptor antagonists may not only prevent the development of wind-up or central sensitisation, but may also downregulate hyperexcitability after sensitisation has taken place.[14] The neurotransmitter glutamate binds to this receptor. There is evidence for NMDA receptor involvement in many types of pain, including inflammatory, postoperative, neuropathic and ischaemic.

Ketamine is the most common NMDA receptor antagonist in clinical use. It was initially developed as a dissociative anaesthetic agent. Low-dose ketamine is often added to opioid analgesic regimens to reduce the requirement for use of opioids, to manage opioid-tolerant patients and to manage patients with neuropathic and ischaemic pain. Such low doses of ketamine are rarely associated with psychomimetic side effects (such as nightmares and hallucinations), which, if they do occur, may be reduced with the use of benzodiazepines.

Antidepressants

TCAs inhibit the reuptake of the monoamine neurotransmitters noradrenaline and serotonin into nerve terminals and modulate pain sensation via descending inhibitory pathways in the spinal cord. Of those TCAs used for chronic pain, amitriptyline has been most widely studied; however, nortriptyline can be used as an alternative.[15] Side effects result from their anticholinergic actions and sedation is reasonably common.

Table. Analgesic drugs used in general practice continued

Drug	Route	Standard dosage
Slow-release opioids (not used in acute pain; only used in highly selected patients with increased opioid requirements and only for a limited duration if improving function and rehabilitation)		
Tramadol, sustained release	Orally	100 to 200 mg twice a day to a maximum of 400 mg a day
Oxycodone	Orally	
– controlled release tablets		Usual starting dose 10 mg twice a day; may titrate to more than 80 mg a day only in highly selected patients
– controlled release combination with naloxone		Same dosage and efficacy as oxycodone; reduced incidence and severity of constipation; reduced risk of diversion due to effectiveness when crushed and injected parenterally
Morphine		
– controlled release tablets	Orally	Initially 10 to 20 mg every 12 hours; may administer every
– controlled release solution	Orally	eight hours; may increase dose at 48-hour intervals Initially 20 mg sachet (reconstituted in 10 mL of water)
– sustained release capsules	Orally	every 12 hours; may increase dose at 48-hour intervals 20 mg every 12 hours or 40 mg every 24 hours
– modified release capsules	Orally	Initially 30 mg a day; may increase dose in 30 to 50% increments
Hydromorphone, modified release	Orally	8 mg a day
Buprenorphine patches	Trans-dermal	Initially 5 µg an hour; titrate at three-day intervals or longer as needed by replacing or adding patches (maximum two concurrent patches); replace patch every seven days
Fentanyl patches	Trans-dermal	Initially 12 to 25 µg an hour; may titrate up or down by 12 or 25 µg an hour every three days; replace patch every 72 hours

The serotonin noradrenaline reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, are increasingly used to manage patients with postoperative pain. They are most suited to use in patients with neuropathic pain and chronic pain states, although patients may need to be assessed by pain medicine specialists.

The use of both TCAs and SNRIs to treat patients with pain is off label.

Anticonvulsants

Gabapentin and pregabalin are two anticonvulsants that are becoming more frequently used as first-line treatment for neuropathic pain because of their good efficacy, but even more so because of their low incidence of adverse effects.[16] These drugs have been shown to successfully treat patients with a wide range of neuropathic pain conditions and may offer some protection from progression to chronic pain.

However, these drugs are costly and are not listed on the PBS for the treatment of neuropathic pain. This limits

their use in the general practice setting, but treatment with gabapentin or pregabalin is increasingly initiated by pain medicine specialists who will regularly titrate the dose accordingly.

Anticonvulsants such as carbamazepine (evidence of efficacy based mainly in trigeminal neuralgia), phenytoin, sodium valproate and clonazepam are also used to manage postoperative pain (used off label), although they have more severe side effects and the data on their efficacy are not as good as for gabapentin and pregabalin.

Problems with opioid use

Tolerance

Tolerance to a drug results in a lesser effect from the same dose of medication, or the need for progressively larger doses to maintain the same effect. In patients with pain, true tolerance rarely limits the effectiveness of opioids.[17]

Dependence

Physical dependence is a physiological adaptation to a drug characterised by the emergence of a withdrawal syndrome if the drug is abruptly stopped, reduced in dose or antagonised. Dependence is common with opioid use beyond 10 days' duration, but can be easily overcome by tapering opioid doses. This approach of gradual, not abrupt, discontinuation of opioid treatment should be used to withdraw postoperative patients from opioid use.

Opioid-induced hyperalgesia

Opioids can actually worsen pain by causing opioid-induced hyperalgesia. This is one of the reasons why patients taking long-term high-dose opioids increase their dose and yet pain continues to worsen over time. In such a situation, gradual reduction of opioid dose may surprisingly lead to better pain relief or at least no worsening of pain but fewer side effects such as constipation, drowsiness or nausea.[17]

Abuse and aberrant medication-related behaviour

Addiction is a pattern of drug use characterised by aberrant drug-taking behaviours and the compulsive use of a substance in order to experience its psychic effects or to avoid the effects of its absence. Users continue to take the drug despite the risk of physical, psychological or social harm to themselves.

Aberrant medication-related behaviour is commonly linked to abuse of opioids or is at least a clue to predict an emerging problem during opioid therapy.[18] It is often a big problem in the management of patients after surgery and trauma. Major behavioural patterns of this condition are concurrent abuse of alcohol or illicit drugs, non-sanctioned dose escalations, medication and/or prescription loss, injecting of oral formulations, selling or stealing drugs, forging prescriptions and deteriorating function.

If such aberrant behaviour is detected, it should be addressed in a conversation with the patient to establish clear ground rules about the use of opioids. It might be useful to use a written treatment agreement with the patient, even at the start of any long-term opioid exposure. Ongoing problems should lead to consideration of a referral to a pain medicine and/or addiction medicine service, depending on the specific aberrant behaviour demonstrated.

Establishment of long-term treatment with opioids, which can easily develop out of short-term use for acute pain, requires careful regular reviews and for the patient to adhere to well-established rules.[19,20] Involvement of a pain medicine specialist is also recommended.

Conclusion

Often patients will present to their GPs with ongoing pain after surgery. This may still be acute pain and surgical causes should be excluded and analgesics given for ongoing management of the pain.

Pain is an individual and subjective experience, and is not only influenced by physiological factors but also by psychological, behavioural, environmental and social factors. These factors influence pain perception and therapy, and can contribute to the transition from acute to chronic pain. Therefore, persistent postoperative pain needs to be considered as a complication of surgery and should be investigated and diagnosed. Often such pain is neuropathic in origin, and if treatment is unsuccessful then patients should be referred to a pain medicine specialist. MT

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Management of migraine

Migraine is a common problem in patients presenting to their GP. There are a number of pitfalls to be aware of in the assessment, acute treatment and prophylaxis of migraine.

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Migraine is an extremely common and disabling condition, which is often poorly managed. The incidence of migraine is about 18% in women and 6% in men. A large portion of these patients do not seek medical attention and self-medicate. Patient awareness of specific treatments is insufficient and potentially harmful codeine-based analgesics can be over relied on. This article outlines some of the issues in the management of migraine.

Diagnosis

Migraine is a syndrome of recurrent headaches with specific criteria (see the box on page 25).[1] If the criteria for migraine are met and the presentation is typical, there is no need to perform cerebral imaging or pathology tests. However, it is important to remember that headache can also be the presenting feature of several serious conditions that require further investigation.

There are some red flags that the clinician should be aware of that indicate further investigation is needed. These include:

- new pattern of headache, especially abrupt onset or relentless progression
- the presence of any focal symptoms or signs (except for typical migraine aura)
- the presence of fever, confusion, an altered mental state or neck stiffness/meningism.

Also, the possibility of temporal arteritis should be considered if the patient is older than 55 years of age.

Treatment

The management of migraine requires an individualised approach for every patient. The three main factors in migraine management are the avoidance of trigger factors, the management of acute attacks and, if appropriate, prophylaxis.

Trigger factors

The trigger factors for migraine vary greatly from individual to individual. Often the patient will be aware of precipitants from previous experiences. Common triggers include various foods, in particular cheese, chocolate, red wine and oranges. The potential for common daily foods such as bread

IN SUMMARY

- **Migraine is a common condition that is often managed suboptimally.**
- **Acute treatment is best initiated early in the course of a migraine attack, partly because gastric stasis may affect treatment efficacy.**
- **Prophylaxis is effective and underused.**
- **Beware of medication overuse, which can increase headache frequency and decrease the effectiveness of prophylactic agents.**
- **If the diagnosis is unclear or management is ineffective, consider referring the patient to a neurologist.**

International Headache Society 2 criteria for the diagnosis of migraine[1]

Migraine without aura

At least five attacks fulfilling the following three criteria:

- Headache attacks lasting from 4 to 72 hours
- Headache with at least two of the following:
  - unilateral location
  - pulsating quality
  - moderate or severe intensity
  - aggravation by simple exertion
- Headache with presence of at least one of:
  - nausea and/or vomiting
  - photophobia and phonophobia

Plus secondary causes should have been clinically excluded.

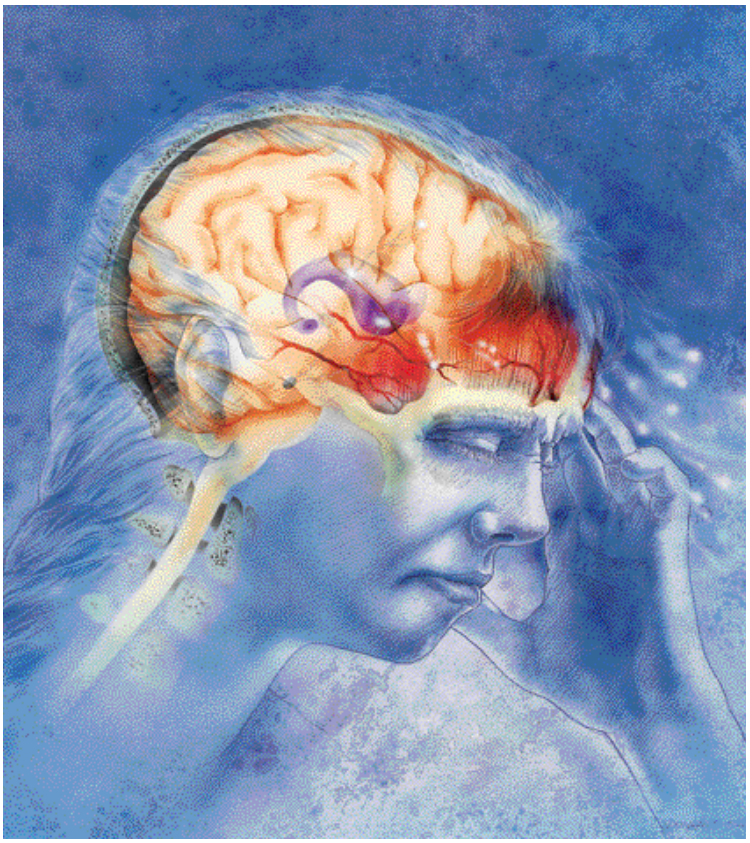
Migraine with typical aura

At least two attacks fulfilling the following three criteria:

- Aura consisting of at least one of the following, but with no motor weakness:
  - fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) and/or negative features (e.g. loss of vision)
  - fully reversible sensory symptoms including positive features (e.g. pins and needles) and/or negative features (e.g. numbness)
  - fully reversible dysphasic speech disturbance
- Presence of at least two of the following:
  - homonymous visual symptoms and/or unilateral sensory symptoms
  - at least one aura symptom developing gradually over five minutes or longer and/or other aura symptoms occurring in succession over five minutes or longer
  - each symptom lasting between 5 and 60 minutes
- Headache beginning during the aura or following aura within 60 minutes

Plus symptoms cannot be attributed to another disorder.

Management of migraine

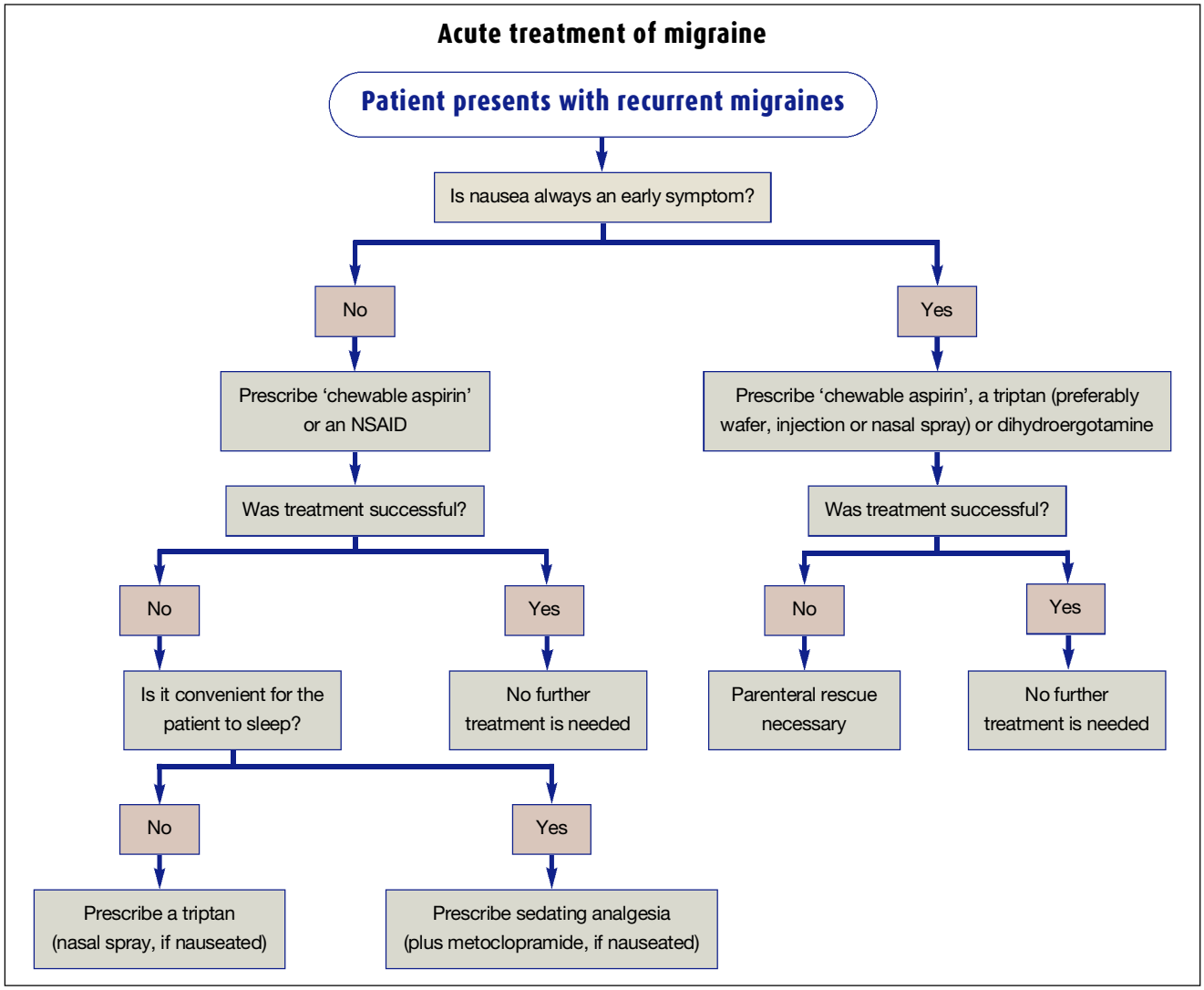


Migraine is a common condition affecting 18% of women and 6% of men. The condition is often poorly managed, and a large portion of patients do not seek medical attention and self-medicate. However, modern treatments mean that most patients with migraine can be treated effectively.

and milk to be trigger factors in some patients is more controversial.

Hormonal factors are important triggers, and frequent links are seen between migraines and a patient's menstrual cycle. Elements of a patient's lifestyle such as stress, irregular sleep patterns or irregular meals can be major factors, and physical trauma to the head or neck (e.g. from heading the ball at soccer or whiplash injuries) can precipitate migraine events.

A headache diary detailing the factors present at and around the time of the headache can be a useful tool to help the patient and clinician identify possible precipitants.



Management of acute attacks

The treatment of an acute attack can either address specific symptoms or be migraine specific (see the flowchart on this page). The types of symptomatic treatments that can be used include analgesics, sedatives, antiemetics and anti-inflammatories. There are a number of factors to be considered in the choice of acute therapy (Table 1). These include:

- the usual severity and frequency of attacks
- the duration and reliability of warning signs
- the presence and timing of any nausea and vomiting.

The patient's social context is also important because it determines whether he or she is able to rest (so that drugs with sedative effects may be appropriate, because sleep is often therapeutic) or needs to keep functioning. By the time a patient receives medical attention, he or she has often tried one or more symptomatic treatments, so it is important to take into account the efficacy and side effects of previously used drugs. Finally, there is a cost differential between some of the medications, which may be important for some patients.

Finding the optimal acute treatment for a patient may be by trial and error, and it is important that the patient is aware of this at the outset. The clinician should have a low threshold for a trial of a triptan. In some patients, triptans are dramatically effective and, even if used infrequently, can give a patient a feeling of control.

Gastric stasis is an intrinsic part of a migraine attack and must be considered in the setting of acute treatment. One strategy to circumvent this problem is to treat the patient with an effective drug early in the attack. Many patients delay taking their medications until the headache is

Table 1. Approaches to acute therapy based on migraine headache frequency

Infrequent migraines	Frequent migraines
Strategic aim	
• Rapid and highly effective treatment	• Effective treatment but minimising the risk of medication-overuse headache
Practical options	
• Early use of a drug or a combination of drugs that has previously proved to be most reliably effective	• Two-stage approach • First stage: early use of rapidly absorbed NSAIDs particularly aspirin
• Early use of triptans should be considered	• Second stage: if first-stage treatments fail, use triptans, but limit use to a maximum of one to two days per week
• Use of strong analgesics or opioids may be a reasonable option	• Opioids are to be avoided

Table 2. Factors to consider when choosing a triptan to use

Clinical issue	First-choice triptan	Problems
Early vomiting	Rizatriptan wafers Sumatriptan nasal spray	Recently introduced and thus less familiar to doctors Can be awkward to use; bad taste
Patient concerned about side effects	Naratriptan tablets	Can be slow to work
Patient keen for speedy treatment with maximal efficacy	Zolmitriptan tablets	More frequent side effects than with naratriptan use
Parenteral treatment required	Sumatriptan subcutaneous injection	Expensive

established, by which time the efficacy of enteral medications is much reduced. Another strategy is to utilise medications that bypass the stomach. Intravenous, intramuscular and subcutaneous medications are all available, as well as suppositories. A 'chewable' aspirin formulation that is absorbed via the oral mucosa and a sumatriptan nasal spray absorbed via the nasal mucosa are available.

The classes of drugs that have been shown to be effective as treatment for acute migraine are NSAIDs (such as aspirin, diclofenac, naproxen), selective serotonin 5-$HT_{1B/1D}$ agonists (such as triptans – ergotamines probably also work in this way) and dopamine antagonists (such as chlorpromazine and prochlorperazine), which appear to have a migraine-lytic effect as well as an antiemetic effect. Pure analgesics should be used as a last resort.

Triptans

There are a number of different triptans on the market in Australia (Table 2); the best agent for an individual will vary.

- Oral sumatriptan was the first triptan available and is thus familiar to many GPs. It works well for many patients but absorption can be variable, so some neurologists would usually choose naratriptan or zolmitriptan ahead of it. Sumatriptan also comes as a nasal spray and subcutaneous injection, which are useful options for patients with early vomiting.
- Oral naratriptan is a gentle agent with a long half-life, making it a good choice for patients who are anxious about possible side effects.
- Oral zolmitriptan works faster and is more potent than other triptans. It is therefore appropriate for patients who have maximal efficacy as their first concern.
- Rizatriptan wafers for sublingual use are now available in Australia. They have the advantages of rapid absorption and are useful for patients with rapidly evolving attacks or early vomiting.

Patients and doctors need to be aware of certain financial issues when considering the use of triptans. A PBS authority prescription will be the cheapest way for healthcare card holders such as pensioners to obtain their medication, but for others the cost of a PBS prescription (for

Table 3. Evidence levels for the efficacy of migraine prophylaxis drugs

Drug	Dosage	Problems
Level 1 evidence		
Propranolol	40 to 120 mg twice daily	Contraindicated in patients with asthma, Raynaud's syndrome, hypotension and peripheral vascular disease
Topiramate	25 to 100 mg twice daily	May cause dysphasia, paraesthesiae, renal calculi or weight loss
Sodium valproate*	400 to 600 mg twice daily	May cause weight gain and is teratogenic
Amitriptyline*	10 to 75 mg at night	May cause dry mouth or drowsiness
Level 2 evidence		
Pizotifen	0.5 to 2 mg daily	May cause weight gain or drowsiness
Methysergide	1 to 2 mg two to three times daily	May cause retroperitoneal fibrosis, drowsiness or cramps
Clonidine	50 mg twice daily	May cause drowsiness or dry mouth, and has a variable efficacy
Cyproheptadine	4 to 12 mg daily	May cause weight gain, drowsiness or dry mouth
Verapamil*	160 to 320 mg daily	May cause constipation, ankle swelling or cardiac conduction abnormalities
Botulinum toxin A*	Three-monthly intramuscular injections	Is expensive and has a variable efficacy
Candesartan*	16 mg daily	May cause hypotension and hyperkalaemia

* Used off label for migraine prophylaxis.

four tablets of any triptan or two sumatriptan nasal sprays) may be greater than the cost of these drugs on private prescription, especially when a larger supply is provided.

Prophylaxis

The current practice recommended by the Australian Therapeutic Guidelines is to commence a patient on regular preventive treatment if they have more than two or three acute attacks of migraine per month.[2] The decision is made in conjunction with the patient on the basis of the frequency, severity and duration of the attacks and the degree of disability caused. Patients with unusually disabling attacks, such as those that are always prolonged and resistant to acute treatments or that arise out of sleep and are already associated with severe nausea and vomiting, may opt for prophylaxis even when attacks are less frequent than twice a month.

There is a wide array of agents used for migraine prophylaxis.[3] These drugs generally have appeared on the market for migraine after establishing themselves for other indications such as hypertension or epilepsy. Despite this, there is excellent evidence available for the use of many of these agents (Table 3).

There seems to be a strong bias in Australia for the use of propranolol or pizotifen,[4] but these are not always the most appropriate choice. As is often the case in conditions with many effective drugs of similar efficacy, the usual first choice of prophylactic agent tends to vary between practitioners, but the general approach to decision-making should be similar. The initial choice of agent is often based on the side effect profile.

A prophylactic drug should be given for long enough for its effect to be established, which can take up to three months. Drugs that are ineffective after this time should be discontinued and others considered. It is worth remembering that prophylactic agents can work for a while and then become ineffective so the clinician should be prepared to rotate through several options.

Chronic daily headache

A history of episodic migraine in a patient can sometimes transform into a pattern of chronic daily headache. Chronic daily headache is defined as daily or near-daily headache lasting more than four hours a day for more than 15 days a month. It is common, being present in 4% of the population.

Half of all cases and the majority of disabling cases of chronic daily headache are due to transformed migraine. Other causes of chronic daily headache include chronic tension-type headache (usually less severe) and the uncommon conditions new daily persistent headache and

hemicrania continua. Any of these headache types can be, but are not always, related to medication overuse.

Medication overuse can be defined as the use of ergotamine, a triptan or codeine for more than 10 days a month, or use of simple analgesics or caffeine for more than 15 days a month.[1] Overuse of codeine is frequent in Australia and is widely recognised as being particularly difficult to manage.

When managing a patient with chronic daily headache, eradicating medication overuse is the first step. Treatment for the underlying condition (i.e. migraine prophylaxis) is often ineffective when the rebound cycle is established, but can become effective later. For successful withdrawal of medication, it is critical that the patient understands the reasoning behind this withdrawal and is motivated to modify their behaviour. A psychiatric assessment is often useful in these patients. Abrupt withdrawal of the offending agent is best, but this inevitably results in a medication-withdrawal headache. Management options for this short-term problem include regular NSAIDs or prednisolone. If the patient has been using large amounts of analgesia, inpatient management may be required. Intravenous dihydroergotamine or lignocaine are then available options. Inpatient observation alone is used in some centres.

There have been limited data on the efficacy of prophylaxis in transformed or chronic migraine, but recent publications support the use of topiramate or botulinum toxin in this context.[5,6]

When to refer to a neurologist

Many patients with migraine can be managed appropriately by their GP. However, in some circumstances a referral to a neurologist is necessary. If there is an element of diagnostic uncertainty because of atypical features or 'red flags', it is best to obtain a neurological opinion. Another indication for referral would be worsening severity or frequency of symptoms despite appropriate prophylaxis and acute treatment.

Conclusion

Given the incidence of migraine in the community and the substantial levels of disability it can produce, all doctors, and particularly GPs, should have a sound understanding of the condition and at least a moderately sophisticated approach to its management.

Modern treatments mean that most patients with migraine can be treated effectively and success in relieving the suffering of these patients is one of the most rewarding experiences in medicine. MT

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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

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.**

is 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

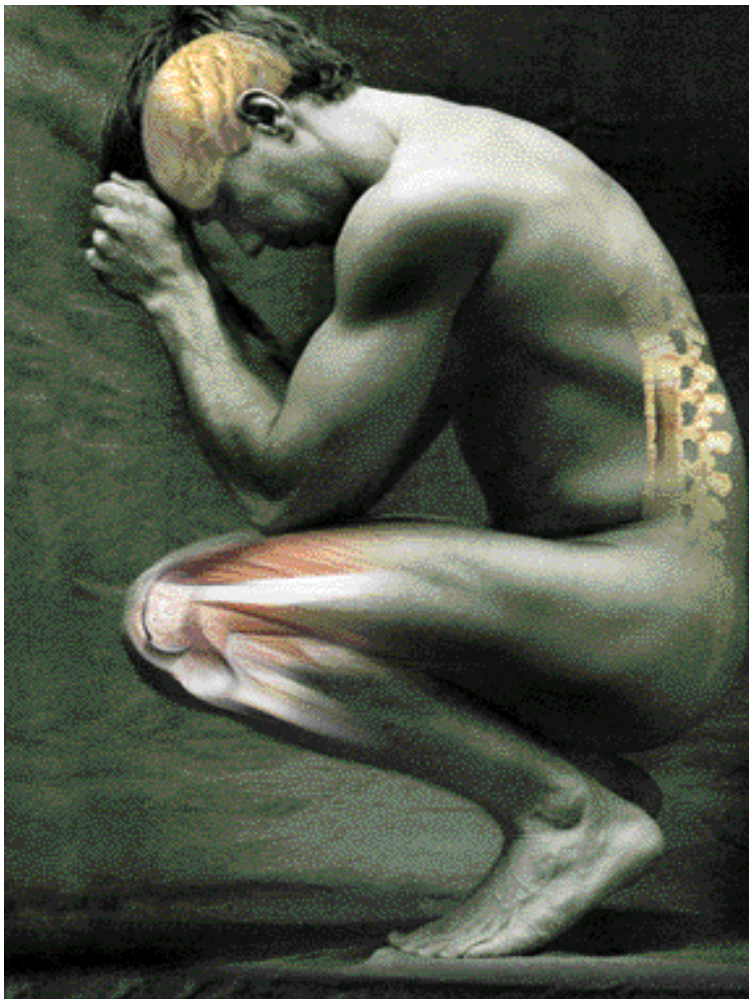
The aim of drug therapy in patients with chronic pain is mainly symptom control. In situations where the mechanism of pain can be confidently determined, such as patients with inflammatory or neuropathic conditions, treatment aimed at the mechanism (anti-inflammatory or antineuropathic agents, respectively) may be helpful in modifying pathogenesis. However, in most cases, symptom control itself is important as an adjunct to nondrug 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:

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.

- 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
- 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 nonspecifically 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 difficult 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)
- 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

Table. Long-acting opioid preparations for patients with 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
Oxycodone plus naloxone†	80/40 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.
† Controlled or sustained-release preparations only.

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 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.

Figure. Spectrum of aberrant drug-related behaviours.

- **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

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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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 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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The significance of chronic back pain

Chronic back pain can be a sign of a serious disorder but more often it is due to an unspecified mechanical dysfunction. It can usually be managed effectively with exercise and use of analgesics.

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Back pain is a near universal human experience with more than 70% of people reporting significant episodes of back pain at some point in their lives. For most individuals, back pain is short lived and not disabling. The significance of back pain lies in the possibility that it is indicative of a serious underlying disorder. People with chronic disabling pain endure significant personal suffering while incurring significant expense to themselves and society as a whole. These patients are the focus of this article.

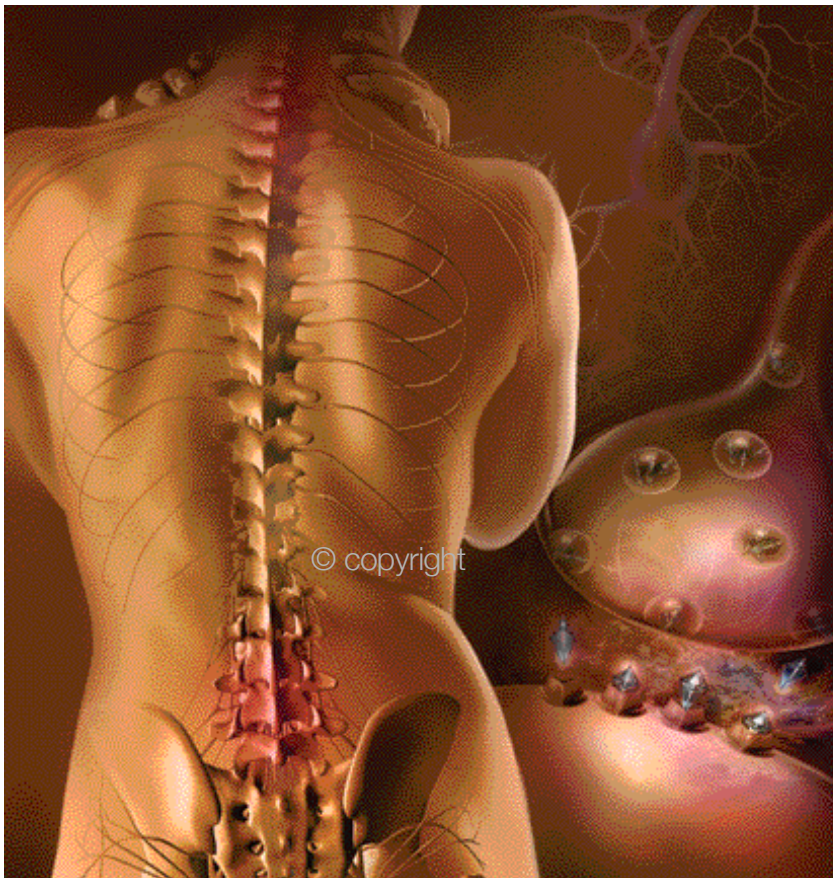
Most cases of back pain are due to unspecified mechanical dysfunction and not to serious underlying medical disorders such as infection or malignancy. It is usually not possible to determine the specific structure or pathology responsible for back pain in a given individual. This pertains to the situation in patients with acute or chronic back pain. Of the putative sources of back pain, including discogenic disease, zygapophyseal joint arthritis and muscle injury, there are no established clinical features that allow one entity to be distinguished from the others.

To date, there have been no population-based estimates of the relative contribution of different types of pathology to the burden of back pain. In a selected, referred population of US patients undergoing investigations for chronic back pain, pain arising from the intervertebral discs, diagnosed by provocation discography, was the most common identifiable cause of chronic low back pain, accounting for about 30% of cases. Pain from the sacroiliac joints or zygapophyseal joints was far less common, accounting for between 10 and 15% of cases of chronic low back pain. However, a substantial number of patients referred for assessment of back pain did not have an anatomical source identified.

IN SUMMARY

- **More than 70% of people report significant episodes of back pain at some point in their lives.**
- **A patient with uncomplicated back pain, no history suggestive of a serious underlying disorder and no history or examination findings suggestive of neurological involvement does not warrant further investigation.**
- **Imaging of patients with chronic back pain should not be performed in a nontargeted fashion.**
- **There is good evidence that a range of exercise interventions are effective for decreasing the frequency of recurrences of back pain.**
- **Short-term use of analgesics and NSAIDs in patients with acute exacerbations of low back pain can facilitate maintenance of activity.**

The significance of chronic back pain



Back pain affects more than 70% of people at some point in their lives. It is usually self-limiting and not disabling. Back pain becomes a significant condition when it is indicative of a serious underlying disorder.

Without the ability to clinically identify a specific painful structure, the role of the clinician in the assessment of a patient with back pain is to determine if back pain is a presenting feature of a serious underlying disorder and to exclude any neurological involvement. The assessment of the patient with back pain is accomplished through clinical assessment. If the patient does not have evidence of an underlying disorder or neurological involvement then the further responsibility of the clinician is to investigate and institute appropriate interventions to help manage the patient's pain.

Eliminating serious underlying causes

Fortunately, serious underlying causes of back pain are rare. The types of conditions that may cause patients to present with back pain include:

- infection (bacterial or fungal)
- inflammatory disease such as ankylosing spondylitis
- malignancy
- metabolic bone disease such as Paget's disease
- vertebral fractures.

Correctly identifying these conditions allows specific targeted therapy to be instituted.

In the primary care setting, tumours have been shown to account for less than 0.7% of cases of low back pain. Infection is even less likely, with a prevalence of 0.01%.[1] A past history of cancer or the presence of marked anaemia are the strongest single risk factors for malignancy being present as a source of low back pain. A history of elevated temperature or fever is strongly suggestive of infection.

There are usually other clinical clues that the person with chronic back pain is unwell or has nonmechanical pain. These features are known as red flags and should prompt assessment for serious underlying conditions (Table). Due to the low frequency of such conditions, the predictive value and accuracy of these features remain uncertain, but they provide a useful means of considering diagnostic possibilities other than unspecified back pain.

Neurological involvement

The presence of neurological symptoms or signs in patients with chronic back pain indicates compression or compromise of nerves either within or as they exit the spinal canal. In the lumbar spine, the most common cause of radiculopathy is intervertebral disc prolapse. However, in older patients, foraminal stenosis caused by a combination of disc and intervertebral endplate disease and osteoarthritic changes of the zygapophyseal or facet joints can lead to compromise of the exiting nerve roots. Patients typically present with back pain and leg pain that is shooting or electrical in quality, and localised to a thin band across the leg. Paraesthesiae and altered sensation over a single dermatome are typical. More severe nerve root compression can lead to weakness or loss of reflexes.

Examination findings

In the absence of red flags or neurological symptoms, physical examination of the patient with nonspecific back pain is of limited usefulness. Findings on examination of the spine are limited to alterations in range of motion and tenderness. There are no established relations between specific physical findings and pain arising from any particular structure. Nevertheless, a careful examination may serve to reassure a patient and aids in establishing a therapeutic rapport.

Assessment should include evaluation of gait, and evaluation of spinal posture and symmetry while the patient is standing. The most important movements to be assessed are flexion, extension and lateral flexion of the lumbar spine. The patient is asked to touch his or her toes, bend backwards and slide his or her hand down the outside of either leg. Palpation of the spine can be performed with the patient either erect or lying prone.

Neurological examination of the lower limbs is essential. A positive nerve tension test involves the reproduction of typical pain down the leg by dorsiflexing the ankle while the leg is raised at an angle less than 60°. Straight leg raising, with the patient in a supine position, involves passively flexing a straight leg at the hip with a fixed pelvis. Pain reproduction in the back is often reported but is not indicative of a positive straight leg raise test in the absence of leg pain. Positive straight leg raising is sensitive but not specific for nerve root compression. A crossed straight leg raise test, where the patient's usual pain in the leg is reproduced by raising the contralateral leg, is specific but not sensitive for nerve root compression.

Further examination should include abdominal examination and hip movements. Peripheral joints should be assessed for inflammation. Other assessments, such as pelvic examination, should be performed if suggested on history.

Investigations

No further investigations are warranted in a patient with uncomplicated back pain, no history suggestive of a serious underlying disorder and no history or examination findings suggestive of neurological involvement. Plain x-rays have not been shown to influence management of the patient.[2] Numerous studies have demonstrated a poor and unreliable relation between back pain and degenerative, osteoarthritic or spondylytic changes in x-rays of the lumbar spine.

Prospective assessment of the findings seen on x-ray shows that the changes seen in the lumbar spine increase in frequency with increasing age. At the same time the very terms used to describe spinal changes, such as 'degenerative', have the potential to alarm and distress patients, particularly those who fail to follow the requests on the stickers sealing the radiologist's report inside the x-ray bag that the envelope should 'only be opened by the referring doctor'. These findings can be explained as being similar to wrinkles or gray hair – they occur more frequently with increasing age and vary in severity from person to person.

In a comprehensive systematic review of observational studies considering the relation between spinal radiographic findings and nonspecific low back pain, spinal degeneration was found to be associated with low back pain in the past 12 months with an odds ratio of 1.2 to 3.3.[3] Stated another way, patients with back pain are twice as likely to have degenerative spinal changes as patients without back pain. At best this is a modest association and in an individual patient it holds little weight. No association was found between low back pain and the presence of spondylolysis, spondylolisthesis, spina bifida, transitional vertebrae, spondylosis or Scheuermann's disease.

Cross-sectional imaging such as magnetic resonance imaging (MRI) or computed tomography (CT) scanning of the lumbar spine is indicated only for the evaluation of neurological symptoms or impairments, specifically radiculopathy or myelopathy. Imaging should not be performed in a nontargeted fashion. Requests for such investigations from patients who believe that imaging will reveal a cause of their back pain should be resisted and careful explanation of the limitations of such an approach discussed with patients. Studies of MRI scans have revealed that they show a high prevalence of abnormalities unrelated to current symptoms. For example, more than half of 40-year-old individuals had reduced disc height and between 25 and 50% had annular tears, disc protrusions, endplate changes or zygapophyseal joint degeneration, among other abnormalities.[4]

Table. Red flags to identify a serious underlying cause in a patient with chronic back pain

Pain characteristics

- Highly localised
- Prominent diurnal variation – especially prolonged early morning stiffness
- Uninfluenced by posture or movement
- Improved rather than worsened by activity

Examination

- No restriction of spinal movement or restriction at one segment
- Localised tenderness

Other features

- Loss of weight
- Fever
- Marked anaemia
- Peripheral arthritis
- Symptoms in other systems (e.g. change in bowel habit, breast mass or cough)
- Past history of malignancy

Preventing chronic back pain

Patients with back pain remain difficult to treat, so there has been considerable interest in the prevention of chronic back pain. Studies have particularly focused on the transition from acute to chronic or persistent pain. Two strategies have emerged as being particularly useful. In one Scandinavian study a multidisciplinary approach incorporating measurements of functional capacity, a work-place visit, back education and an individualised graded exercise program compared with routine care allowed patients in the intervention group to return to work in 10 weeks compared with 15 weeks in the control group.[5] In the year after the study, the intervention group had fewer days off sick from all causes than the control group. However, there was no statistically significant difference in pain intensity between the intervention and control groups, but subjective disability had decreased significantly more in the intervention group.

Perhaps the most impressive results in patients with subacute back pain have been those reported in another Scandinavian study.[6] The study demonstrated that provision of advice and confident reassurance achieved a 50% reduction in work disability at five years' follow up.[7] The advice provided a cogent explanation for the pain, and suggested simple bending and stretching exercises to perform when it occurred.

In a recent systematic review of risk factors for persistent low back pain, known as yellow flags, the authors concluded that the most helpful components for predicting persistent disabling low back pain were maladaptive pain-coping behaviours (such as fear-avoidance behaviour), nonorganic signs (such as pain on simulated spinal rotation, or nonanatomical motor or sensory loss), functional impairment, general health status and psychiatric comorbidities.[8] Conversely, the presence of low levels of fear-avoidance behaviour and low levels of baseline functional impairment were found to be associated with a resolution of symptoms.[8]

Against this background of information, a novel Australian study has tested the effects of a population-based intervention to change back pain beliefs and levels of disability.[9] The study examined a media campaign based on *The Back Book*, which emphasises the generally good prognosis for patients with back pain and the need to move and perform usual activities rather than resting and avoiding physical activities.[10] It was aimed at both GPs and the general public and demonstrated persistent effects on positive attitudes to back pain.

Nonpharmacological treatments

The management of patients with chronic back pain, as with all chronic problems, requires the doctor to establish a soundly based therapeutic relationship with the patient. Mindful of the above mentioned risk factors, reassurance and encouragement to keep moving despite pain are recommended. Explanation of the significance or not of imaging reports should be addressed. Patients should be encouraged to appreciate that 'hurt' does not mean 'harm'. When work issues are pertinent, it has been demonstrated that if the caring doctor appreciates the nature of the individual's work, and where appropriate contacts the patient's employer to explain the situation, then work disability can be reduced.

Specifically exploring the significance and effects of the patient's pain are important in identifying persisting yellow flags. Unrealistic fears and expectations or treatable mood disorders may be identified by asking simple questions such as:

- how does the pain interfere with your life?
- how does the pain affect your mood?
- what are you concerned might be causing the pain?

Formal cognitive behavioural therapy focuses on helping patients develop adaptive-coping behaviours and strategies to self-manage their pain. It has been shown to be effective in patients with chronic low back pain, improving function and disability. Cognitive behavioural therapy should be considered early if adverse psychosocial issues are identified.

Physical treatments

The role of passive physical treatments should be to facilitate restoration of exercises and physical activity. Most physical treatments provide temporary pain relief but should not be the mainstay of therapy. Warm or cold packs may provide some temporary pain relief and allow continuation or resumption of physical activity. Complementary therapies such as massage and acupuncture have been shown to have a beneficial effect in the short term.

Manipulation and mobilisation

Despite their popularity, manipulation and mobilisation techniques have been shown to have a small to modest effect on chronic back pain. However, their effects are at least equivalent to other conservative treatments. There is an extremely low risk of adverse effects from spinal manipulation of the low back. There is no evidence that long-term treatment with programs of passive manual therapy favourably influence outcomes in patients with chronic back pain.

Exercise-based therapy

There is good evidence that a range of exercise interventions are effective for decreasing the frequency of recurrences of back pain. Typical programs include exercises to strengthen low back extensor muscles and abdominal musculature ('core strengthening'), and increase flexibility.[11] Recent systematic reviews have shown benefit from various exercise programs in patients with chronic low back pain, but have not revealed the best type or types of activity.[12]

A reasonable program would initially have two supervised exercise sessions per week until the patient is confident in the performance of the particular activities. This should then progress to a home-based unsupervised program, which should be continued indefinitely.

Other studies have demonstrated that aerobic exercise programs (including activities such as walking, swimming and cycling) benefit people with chronic low back pain, improving pain and function.[13] Exercise also assists with weight control and improves general well-being and should be actively encouraged. Although formal evidence of efficacy is lacking, many patients find water-based exercise programs such as aqua aerobics or swimming easier to comply with than land-based exercise programs.

Combining exercise therapy with manual therapy, with or without massage, results in short-term improvements in pain and may facilitate increased activity.

Pharmacological treatments

Analgesics

There is little evidence to guide the practitioner in the use of analgesics in patients with chronic back pain. Short-term use of analgesics and NSAIDs in patients with acute exacerbations of low back pain can facilitate the maintenance of activity. The principles followed should be to achieve adequate pain relief without causing adverse effects. Paracetamol may be used to reduce the overall daily doses of NSAIDs required, and therefore reduce the risk of adverse effects. Patients should be once again reassured that hurt does not equal harm, and it should be explained that a realistic expectation is that analgesics may relieve but not totally remove the pain.

In patients with persistent back pain, regular dosing is more appropriate than 'as-needed' dosing or the use of alternate analgesia for breakthrough pain. A reasonable starting point is to use regular paracetamol in either standard or modified-release form in divided doses up to a total of 4 g daily. The use of NSAIDs may be useful in some patients, but their benefit should be constantly weighed against their potential for adverse effects, especially with long-term use, including gastrointestinal toxicity, renal toxicity and adverse effects on hypertension control.

Patients who fail to respond to simple analgesia, particularly when other interventions have also been unsuccessful, represent an important therapeutic challenge for the GP. For patients with flares of pain not responding to nonpharmacological interventions or short-term paracetamol or NSAIDs (i.e. less than three weeks), use of opiate-based analgesics such as codeine, tramadol or oxycodone at the lowest effective dose may be justified. The aim of such treatment is to restore function and activity during an exacerbation of pain, and this should be discussed clearly with the patient before initiation.

When patients have ongoing severe pain and are judged to require ongoing analgesia, careful review of the patient's situation, including psychological factors, beliefs and expectations, is important. Nonpharmacological interventions such as physical treatments and physical activity should be optimised. If patients are still in need of ongoing analgesics, despite regular use of an immediate-release opioid, they can be changed to an equivalent dose of a modified-release opioid for up to 12 weeks; there is no evidence supporting the use of opioids beyond this time.

Patients should be monitored and dose adjustments made according to their responses. It is important not to change the dose of modified-release drugs too quickly because they take several days to achieve steady-state levels. Patients with the need for prolonged courses or escalating doses of opiates may benefit from specialist assessment, ideally at a pain clinic.

Coanalgesics

The use of coanalgesics such as tricyclic antidepressants (TCAs) may be of use in patients with back pain (off-label use) if other medications provide insufficient relief from pain persisting beyond two to three weeks. The doses used are much smaller than for depression, and typically start at 10 to 25 mg orally at night, increasing every seven days and titrating against symptoms to a maximum dose of 75 to 100 mg orally at night. Patients should be warned that they may be drowsy and have a dry mouth while taking these coanalgesics. TCAs have the potential to cause many adverse effects and drug interactions and these should be actively considered in the individual patient before use.

The use of other antidepressants, such as serotonin selective reuptake inhibitors (SSRIs), in patients with back pain alone is not supported by the available literature. However, it is important to treat any concurrent depression appropriately.

Some patients with persistent low back pain (more than six months' duration) develop neuropathic pain features. In this setting it may be worth considering a trial of pregabalin but there is no evidence to support its use beyond 12 weeks. Although use of pregabalin is approved for patients with neuropathic pain, it is not currently indicated in Australia to treat patients with chronic back pain.

Injections

There is evidence that intra-articular injections of corticosteroids into painful lumbar zygapophyseal joints are of no benefit to patients when compared with injections of local anaesthetic alone.

A Cochrane review into the effects of radiofrequency denervation for lumbar zygapophyseal joint pain concluded that there was conflicting evidence for its efficacy.[14] However, there has been considerable debate about the techniques used for both diagnosis and treatment in the quoted trials, which may have

lead to some poor results.

At present, radiofrequency denervation of the lumbar zygapophyseal joints is only available in a small number of centres. It is only appropriate for the small percentage of patients with back pain who demonstrate appropriate responses to local anaesthetic blocks of their zygapophyseal joints. These considerations severely limit the technique's general application.

Injections into other structures, such as epidural corticosteroid injections and sacroiliac joint injections, have no proven role in patients with uncomplicated low back pain. Local anaesthetic injections into tender areas, particularly at the muscle attachments to the pelvic brim, may provide temporary relief in some patients and facilitate early return to activity.

Multimodal therapy

Multidisciplinary interventions, either in the form of multidisciplinary pain clinics or rehabilitation programs, aim to combine interventions with an emphasis on restoration of function, physical retraining and cognitive behavioural therapy. A synopsis of systematic reviews concludes that behavioural treatment versus no treatment, placebo or waiting list controls reduces pain in the short term.[15] No significant differences were found between different types of behavioural treatment and there is conflicting evidence for behavioural treatments versus other active treatments. One of the problems in interpreting this data is that it is rare that behavioural therapy is used in isolation. Interestingly, there is moderate evidence that adding a behavioural component to a 'usual treatment' program such as inpatient rehabilitation confers no additional benefit.

There is strong evidence that intensive, inpatient, multidisciplinary biopsychosocial rehabilitation improves levels of pain and function. However, the data on vocational outcomes such as return to work were conflicting and there is no benefit from less intensive, outpatient-based programs.

Surgery

There is no role for surgery in patients with uncomplicated back pain. The principal role of surgery of the spine is to decompress neural structures, such as nerve roots in patients with prolapsed discs and the cauda equina in patients with spinal canal stenosis.

Conclusion

Chronic back pain remains a challenging problem for GPs. Applying a graded approach to treatment, carefully exploring and managing patient's expectations and emphasising safe and potentially effective interventions such as exercise remain the cornerstone of therapy. MT

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Fibromyalgia
Mechanisms and management

The clinical syndrome of fibromyalgia is commonly seen in primary care practice and presents significant challenges in management. A new understanding of the causation of fibromyalgia has led to the development of more effective treatments.

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Fibromyalgia is a common condition. Using the American College of Rheumatology classification criteria, fibromyalgia occurs in about 2 to 5% of individuals in most Western communities. If less rigid clinical diagnostic criteria are used, the prevalence rises to about 5 to 8%.[1] The condition has a high impact on the individual affected and, as a result, on the society in which he or she lives. Consequently, fibromyalgia is extremely costly, not only in terms of the individual's health and loss of personal life choices but also in regard to social costs, including an inability to work, and the need for expensive safety net provision for individuals with the disorder. Due to its high prevalence and high impact, fibromyalgia presents as a significant and relevant clinical disorder requiring renewed interest and focussed management.

Controversies

About 20% of the general population have persisting regional or generalised pain. Fibromyalgia (also known as fibromyalgia syndrome) is the most common of the defined disorders that contribute to this social health burden. There have been more than 60 synonyms for this disorder, including the old term fibrositis, which incorrectly implied there was an inflammatory cause for the disorder.

Fibromyalgia is a chronic pain syndrome that is characterised by changes in biochemical functions within the pain system rather than by a structural musculoskeletal abnormality. There has always been controversy with regard to the recognition, nomenclature and diagnosis of this disorder, usually because there is no 'gold standard' diagnostic clinical test.

Many clinicians are also concerned that 'labelling' an individual with a diagnosis of fibromyalgia might in itself worsen the patient's outcome. However, this has been shown not to be the case[2] and in practice an appropriate diagnosis of fibromyalgia is associated with less health care seeking and improved health outcomes.

IN SUMMARY

- **The key clinical elements of fibromyalgia are the presence of widespread chronic pain and widespread abnormal tenderness to gentle pressure.**
- **Fibromyalgia is due to abnormal sensitivity within the pain-related nervous system.**
- **Six or more abnormally tender sites, combined with widespread pain, will allow a diagnosis of fibromyalgia to be made.**
- **Fibromyalgia often co-exists with other conditions and it may have similar presenting symptoms to many other disorders.**
- **The basic management platform of education, exercise and psychological strategies must be initiated in all patients with fibromyalgia.**
- **Analgesics, antidepressants and antiepileptics have been shown to be effective for the treatment of fibromyalgia.**

Table 1. Functional somatic syndromes with similar symptoms to fibromyalgia*

Chronic fatigue syndrome
Irritable bowel syndrome
Irritable bladder syndrome
Regional pain syndromes
Restless leg syndrome
Multiple chemical sensitivities
Cognitive dysfunction
Dysaesthesia
Hypotension
Dizziness, nausea

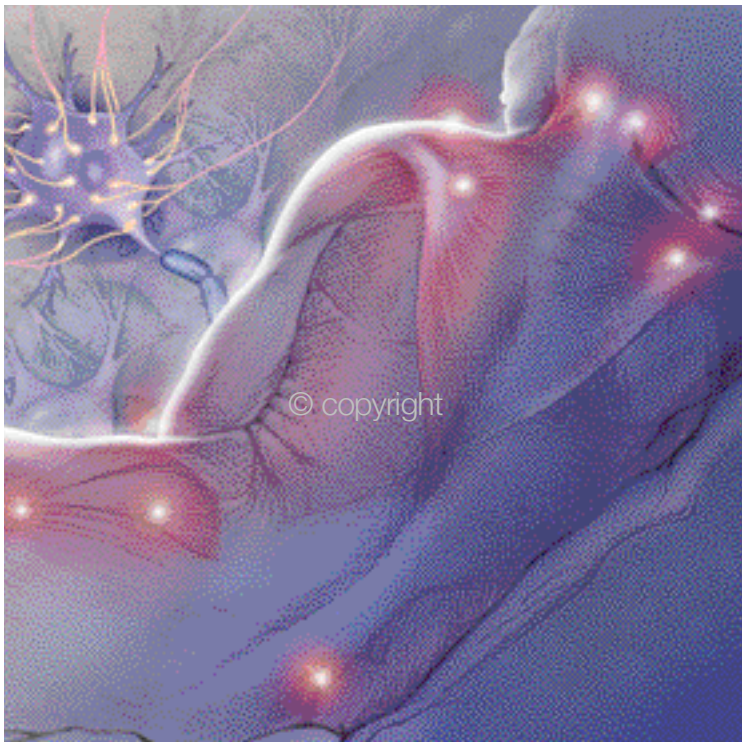
* There is a 20 to 30% overlap between fibromyalgia and other functional somatic syndromes.

A further problem lies in the fact that many patients with fibromyalgia become disabled and are therefore involved in assessment for social safety net provision, such as workers' compensation, disability support pensions or personal litigation. Clinicians who only see patients in this setting are often concerned that the diagnosis labels a functional and potentially reversible problem as being 'organic' and permanent. This results in the individual being locked into long-term disability with the need for significant social support.

Fibromyalgia is caused by abnormal processing of pain mechanisms within the brain and spinal cord. It is influenced by psychological and stress-related factors, so there is often a dichotomy of views about the diagnosis among clinicians. Some consider the problem to be a psychological condition and others as a physical illness. The physical symptoms of the patient with fibromyalgia may be labelled as any number of conditions ranging from 'soft tissue strain' through to 'generalised osteoarthritis', 'age-related changes' or specified 'abnormalities' of regional musculoskeletal structures. Unnecessary and extensive investigation to attempt to identify an 'organic cause' often occurs.

Although the condition remains controversial and much work needs to be performed to bring the different approaches discussed above together, it is argued that the clinical features of fibromyalgia are characteristic and robust. The diagnosis and management are, in fact, quite logical.

Fibromyalgia: mechanisms and management



Fibromyalgia is a common condition caused by abnormal processing of pain mechanisms within the brain and spinal cord. Management of the condition includes education about fibromyalgia, exercise and psychological strategies and appropriate drug therapy to control the pain.

Clinical features

The key clinical elements of fibromyalgia are the presence of widespread chronic pain and widespread abnormal tenderness to gentle pressure. These two features indicate that there is dysfunction of the pain-related nervous system. The pain is generally widespread but at times may be more localised and may alternate between different sites. The clinical features fluctuate with time and may be influenced by external factors such as levels of stress or activity, or changes in weather. Patients with a regional pain syndrome have pain and abnormal tenderness within a specific bodily region only, usually an upper or lower quadrant of the body or the low back or low neck.

Other symptoms of sensory dysfunction may occur in patients with fibromyalgia. These include

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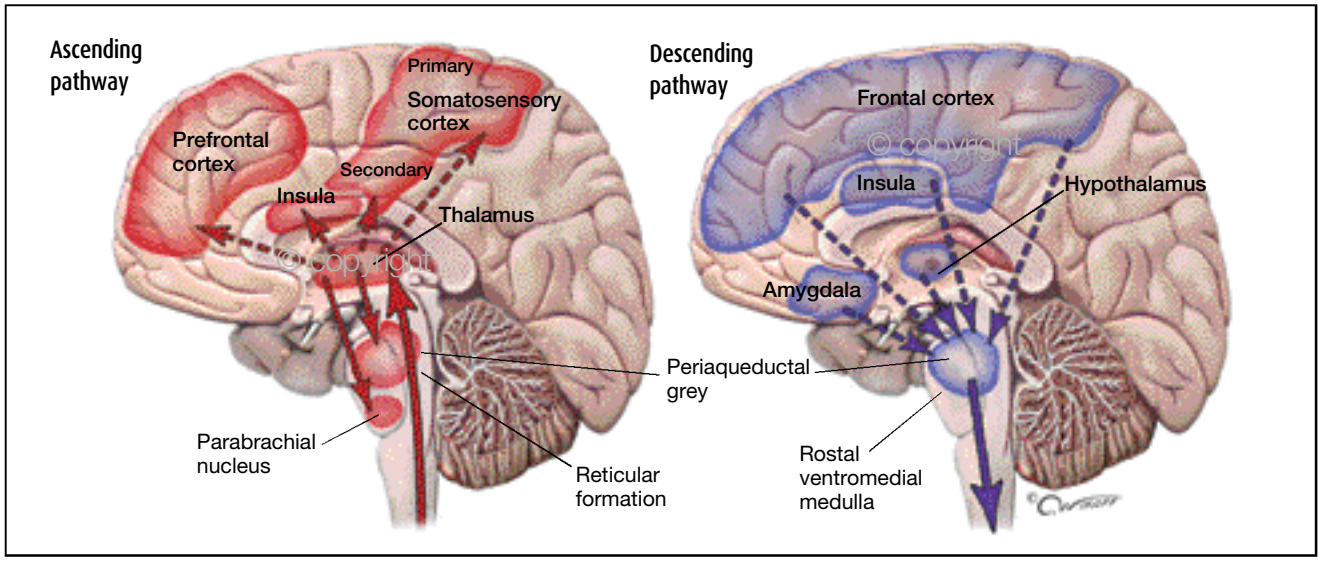


Figure 1. Ascending (left) and descending (right) pathways in normal pain perception. Signals from the dorsal horn of the spinal cord enter the pain neuromatrix (shown in red) to initiate pain processing and response. Descending signals from other centres (shown in blue) send pain modulatory signals to the dorsal horn. Emotional centres are prominent in the descending pathways.

peripheral nonanatomical dysaesthesia, tinnitus, irritability to noise or light, and sensory dysfunction in the bowel or bladder. Hence, many patients with fibromyalgia present with functional somatic disorders involving a range of organ systems to a variety of specialists (Table 1).

Mechanisms

Fibromyalgia is due to abnormal sensitivity within the pain-related nervous system. Studies of patients with fibromyalgia using various neuroimaging techniques have shown marked changes in the pain-control centres of their brains.[3]

The pain-control regions of the brain connect to the dorsal horn of the spinal cord where normal pain modulation occurs. Altered functions at the dorsal horn are involved in the mechanism of pain in patients with fibromyalgia. The cause for this 'top-down' dysfunction remains unclear but it is particularly associated with emotional and stress factors. Defined pathways from the brain that modulate sensory inputs to the spinal cord involve opiate receptors within the brain and serotonin and noradrenaline actions within the dorsal horn.

The resultant abnormal control of sensory input at the spinal cord results in the neurobiological process of sensitisation. Normal subclinical sensory information from mechanoreceptors in muscles and joints 'accesses' the pain pathways, translating otherwise innocuous regional

Table 2. A proposed screening instrument, the Moldofsky Fibromyalgia Score, aimed at identifying patients likely to have fibromyalgia[4]*

Describe how you have been feeling over the past month

	Never	Sometimes	Often	Always	Don't know	Item score
I have pain or stiffness in most parts of my body	0	1	2	3	0	
My body is sensitive to any tightness or pressure	0	1	2	3	0	
I feel energetic	3	2	1	0	0	
My sleep is refreshing	3	2	1	0	0	
I feel sad or nervous	0	1	2	3	0	
I am content with my life	3	2	1	0	0	

* Scores less than five are less likely and those greater than 15 are more likely to predict fibromyalgia. Further clinical assessment is always necessary.

sensory inputs into regional musculoskeletal pain. This effect is particularly prominent where there is a high input of mechanoreceptor information, particularly from the low neck, low back or areas of the spine that might have been compromised by disease or dysfunction. Thus, pain and tenderness in fibromyalgia is invariably located around the neck, shoulder girdle, low back and buttock areas and regions that refer from these sites. It is important to note that in fibromyalgia there is no tissue damage in the area where the pain is perceived (Figures 1 and 2).

Recognition in primary practice

In a patient who has a complaint of persisting pain and on examination has abnormal tenderness to gentle pressure, a possible diagnosis of fibromyalgia should be considered. The characteristic features of the disorder can be summarised by a screening questionnaire that focuses on some key elements of the disorder. Patients with high scores are more likely to have fibromyalgia (Table 2).[4]

The emotional distress that is often in the background of a case of fibromyalgia is usually identified by the clinician. The concept of yellow flags is relevant in regard to these emotional factors and is summarised in Table 3.

Diagnosis

Fibromyalgia is a specific diagnosis. The two key components are the patient's complaint of widespread pain and the clinical finding of widespread tenderness. Tenderness, although subjective, is usually easy to detect by palpation with the thumb or forefinger in areas of the body that are normally more sensitive to touch than other areas. These are known as tender points, and are clustered mainly around the neck, shoulder girdle, chest wall, low back and buttock areas. Palpating the patient's midtrapezius area, the front of the chest wall and the inner scapular region and noting abnormal tenderness can be used as a quick screening examination.

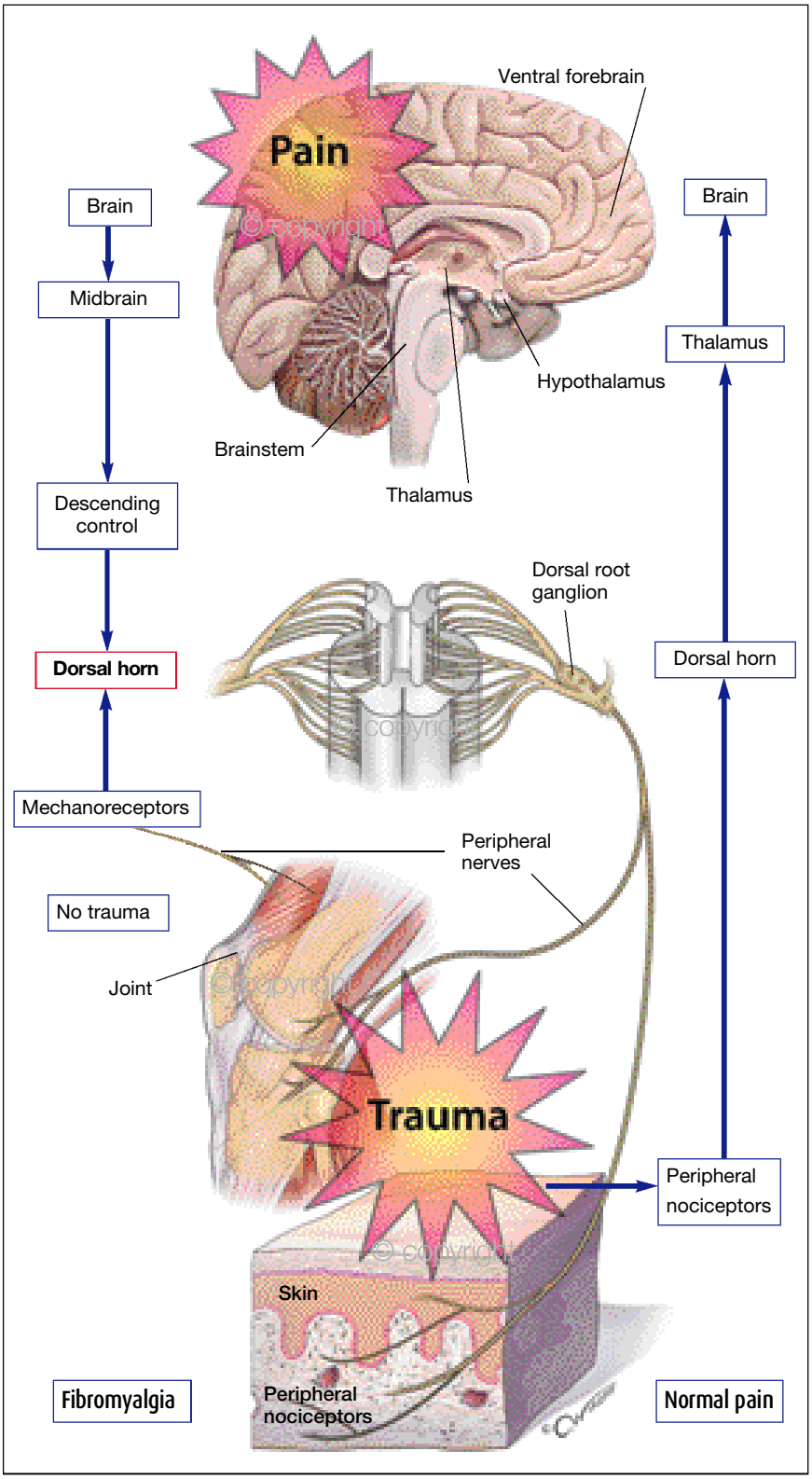


Figure 2. Pathways of pain in fibromyalgia and normal pain. The familiar nociceptive pathway (right) starts at the 'bottom' with stimulation of specific nerves in the periphery leading to pain. Brain-related modulation occurs in the dorsal horn. The fibromyalgia pathway (left) starts at the 'top' allowing for translation of innocuous peripheral mechanoreceptor stimuli to be processed as 'pain' through the overactive sensitised dorsal horn activity (highlighted in red).

continued

Table 3. Yellow flags indicating various psychosocial stressors

Positive family history of fibromyalgia
Previous pain syndrome
Medical condition causing prognostic concern, e.g. systemic lupus erythematosus, rheumatoid arthritis
Family, work or personal stressors
Sleep disturbance
Pain-related work issue
Spinal injury
Events in the past that may link to a stress reaction
Vulnerable personality – poor coping or catastrophising
Presence or past history of a mood disorder
Previous or current substance abuse

Table 4. Medical condition that may mimic fibromyalgia

Cancer
Metabolic disorders
Infection
Connective tissue disease
Inflammatory arthritis
Osteoarthritis
Mechanical back pain/disc disease
Depression

For research purposes, classification criteria exist for the diagnosis of fibromyalgia and specific sites are designated as being necessary to examine for abnormal tenderness. In clinical practice, however, abnormal tenderness can usually be gauged without performing a specific widespread examination (Figure 3). Generally, six or more abnormally tender sites, combined with widespread pain, will allow a diagnosis of fibromyalgia to be made.

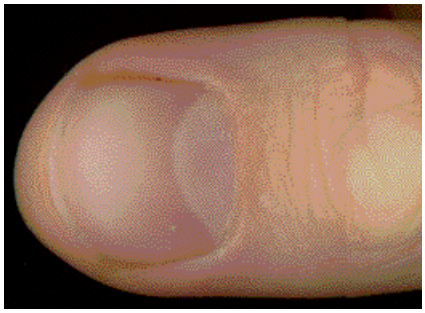


Figure 3. An abnormally low threshold for pain is considered to be present in a patient when pain is elicited at a tender point from pressure that blanches the finger nail.

Other diagnostic signs

Another diagnostic sign present in patients with fibromyalgia is muscle tightness, often noted as muscle co-contraction (whereby there is inappropriate activation of agonist and antagonist muscles) or give-way weakness. Also common are dermatographia (where light stimulation with the finger nail results in a brisk and exaggerated wheal and flare response) and nonanatomical sensory symptoms (where the patient has symptoms of sensory dysaesthesia, such as localised numbness, 'pins and needles' or burning, but no objective evidence of neuroanatomical sensory abnormality).

Mimicking conditions

Although the diagnosis of fibromyalgia is usually straightforward the condition often co-exists with other conditions and presenting symptoms may be similar. Examples of conditions that may mimic fibromyalgia are listed in Table 4.

Thus, a positive diagnosis of fibromyalgia must be accompanied by a considered appraisal of other possible co-existent problems. In particular, indicators of possible serious disease or red flags must always be considered (Table 5) and, if present, require further investigation in their own right.

Investigations

In the average patient with fibromyalgia, it is usually prudent to perform a baseline set of investigations to ensure that subtle general medical conditions are not mimicking fibromyalgia. Although the requirement for each test needs to be considered in the context of the patient's clinical presentation, many mimicking diseases are initially nonspecific and subtle, and relevant investigations may be critical to reaching an early diagnosis (Table 6).

An 'investigation gradient' exists. The average patient does not require much investigation, whereas someone who has an atypical presentation or red flags present might require more significant and wide-ranging investigations.

Many patients with fibromyalgia undergo multiple investigations while seeking other possible causes for their complaints. In this context it is common for test abnormalities to be found, depending on the sensitivity and specificity of the particular test that has been ordered. For example, about 15% of normal patients will have a 'positive' result on an anti-nuclear antibody test. If this positive result is incorrectly connected to the symptoms of fibromyalgia, a misdiagnosis of a connective tissue disease may occur.

Similarly, a small percentage of patients with regional pain syndromes may have abnormal nerve conduction of the wrist, despite having normal neurological function. These patients may be incorrectly diagnosed with a peripheral nerve disorder, such as carpal tunnel syndrome or peripheral neuropathy, based on misinterpretation of the characteristics of the test and not on correct clinical assessment of the medical problem. In other words, the test that is applied needs to be carefully interpreted in the context of a patient's symptoms.

Comorbidities

Characteristic comorbid conditions often occur in patients with fibromyalgia. These conditions are most likely to be related to the underlying mechanisms of fibromyalgia and will need to be treated in their own right.

It is common to see fibromyalgia

co-existing with other chronic painful or distressing rheumatic conditions such as the inflammatory joint disease of rheumatoid arthritis (20% of patients) and systemic lupus erythematosus (50% of patients). It is also common to see fibromyalgia in patients who have generalised osteoarthritis or regional degenerative spinal diseases. Patients with other medical illnesses, such as inflammatory bowel disease, are also prone to co-existent fibromyalgia.

Many patients with fibromyalgia have co-existent depression. It has been shown that depression does not cause fibromyalgia but may co-exist in about 25% of patients at the time of presentation with fibromyalgia. Anxiety is also a common comorbid disorder in patients with fibromyalgia.

Management

Basic platform

Education, exercise and psychological strategies must be initiated in all patients with fibromyalgia. This basic platform of management cannot be overemphasised even though the thrust of this article is on targeted drug therapies. A checklist is provided to aid assessment of these issues (Table 7). In most patients, adjustment in these areas will be associated with significant improvement.

Education can be facilitated through appropriate website information (e.g. the website sponsored by the US National Fibromyalgia Association and Eli Lilly www.knowfibro.com, or www.pathoutofpain.com.au) or through contact with Arthritis Australia.

Simple analgesia

Pain is the dominant symptom of fibromyalgia. Consideration of analgesia is a common starting point in the medication management of the condition (Table 8).

Paracetamol is often trialled at doses of up to 4 g per day. Compliance issues and a lack of response are common. The use of extended-release paracetamol at 665 mg per tablet improves compliance. However, patients seem to prefer NSAIDs to paracetamol, presumably because of their long-acting analgesic effect and not their anti-inflammatory action. No appropriate trials have been performed on these agents in patients with fibromyalgia and caution regarding their effects on other organ systems is always necessary. Anti-inflammatory agents may reduce inflammation in peripheral pain generators (e.g. joints with osteoarthritis or rheumatoid arthritis), thus reducing the aggravating influence of these painful sensory inputs into the pain amplification state of fibromyalgia.

Table 5. Red flags suggesting serious pathology

Older age at new symptom onset
Weight loss
Night pain
Focal pain
Fevers or sweats
Neurological features
History of malignancy

Table 6. Investigations that may be required in the initial work-up of patients with fibromyalgia

Full blood count
Measurement of erythrocyte sedimentation rate
Measurement of C-reactive protein level
Liver and renal function – including measurements of levels of creatinine, electrolytes, calcium and phosphate
Thyroid function
Measurement of creatine kinase level
Measurement of vitamin D level
Presence or absence of rheumatoid factor
Presence or absence of antinuclear antibody

Opioids

In general, pure opioid medications such as oxycodone or morphine preparations are not clinically useful in the sensitised pain system that characterises fibromyalgia. There are no available trials of pure opioid medication use in fibromyalgia to guide the clinician.

Recent studies suggest that opioid receptors in the brains of patients with fibromyalgia are maximally activated.[5] This indicates that the endogenous opioid system is working well in patients with fibromyalgia and that exogenous opioids may not further improve the central effects of this agent on the fibromyalgia mechanism. Some opioids, such as buprenorphine, may act on the fibromyalgia sensitisation mechanism but clinical trials are lacking.

Tramadol

The unique opioid tramadol combines a mu-opioid agonist with a serotonin noradrenaline reuptake inhibitory action on the dorsal horn. This agent has been shown to be effective in pain control and improves function in patients with fibromyalgia at a dose of 150 to 300 mg per day. Tramadol often causes adverse events such as nausea or constipation and may interact with other agents, particularly psychoactive drugs such as various antidepressants.

Pain system modulators

The use of drugs that target the mechanism involved in the sensitisation process of fibromyalgia is more logical and they are now more frequently used.

Tricyclic antidepressants (TCAs) and serotonin noradrenaline reuptake inhibitors (SNRIs) both increase the levels of noradrenaline and serotonin in the dorsal horn through reuptake inhibition. SNRIs are more selective and have preferential effects on noradrenaline rather than serotonin and have better effects on the fibromyalgia mechanism. However, the TCA amitriptyline, which provides a

continued

Table 7. Treatment targets checklist in patients with fibromyalgia

Factor	Target/Area of assessment
Does the patient have an appropriate understanding of fibromyalgia?	
Diagnosis	Widespread pain and tenderness
Mechanisms	Pain sensitisation, effect of stress
Dimensions	Variable severity, duration or level of disability
Management principles	Education, exercise, psychology and medications
Outcome	Potentially reversible
Is the patient a good self-manager?	
Weight	Ideal
Exercise	Regular aerobic, stretching and strengthening
Simple relaxation	Time-out and breathing techniques
Advanced relaxation	Meditation and yoga
Motivation	Willingness to improve and positive attitude
Other	Coping strategies and good social support
Have social predicaments been addressed?	
Personal	Relationships, goals and level of distress
Economic	Safety-net issues
Domestic	Spouse and family
Work	Relationships, autonomy and injury
Other	Stressors
How does each of the key fibromyalgia domains contribute?	
Pain	Medication review
Stiffness	Fitness level and painful muscle trigger points
Fatigue	Pacing
Sleep	Quality and duration, and whether patients awake refreshed
Mood	Secondary or primary changes
Global effects	Function
Are there emotional issues?	
Mood disorder	Depression
Distress	Anxiety
Other	Catastrophising

relatively balanced reuptake inhibition of these monoamines, has been shown in a number of meta-analysis to be effective in patients with fibromyalgia.[6]

Amitriptyline is currently the most commonly used drug of these classes (off-label use for fibromyalgia). As is the case with most medications used in patients with fibromyalgia, amitriptyline should be given at a low dose and the dose only slowly increased. The medication is used for its pain modulation effect rather than its antidepressant effect, and hence the initial dose is usually about 10 to 20 mg in the mid evening, several hours before bedtime. The dose may be increased over several weeks to 30 to 50 mg in some patients but, in general, lower doses are better tolerated and are as effective. About 40% of patients will respond well to amitriptyline. Side effects can include morning drowsiness and dry mouth and maximal effect might take two to four weeks to be achieved at any one dose.

Drugs in the SNRI class include duloxetine and milnacipran (not available in Australia), which have both been approved by the US Food and Drug Administration for the treatment of fibromyalgia. Their effect on fibromyalgia is independent from any effect on mood. Duloxetine (used off label for fibromyalgia in Australia, but indicated for use in patients with diabetic neuropathic pain) may be effective and better tolerated at a lower dosage of 30 mg per day but many patients require 60 mg per day. Typical side effects include nausea, dry mouth and constipation. Another SNRI, venlafaxine, has benefits in fibromyalgia when used at higher dosages (off-label use), usually more than 150 mg per day.

In contrast, selective serotonin reuptake inhibitors (SSRIs) have much less effect on fibromyalgia (used off label). For example, SSRIs that are highly selective for serotonin, such as citalopram, have little benefit on fibromyalgia symptoms while others, such as fluoxetine, may be beneficial at higher doses where additional noradrenaline effects are seen.

Patients with fibromyalgia who have comorbid depression that has responded well to a SSRI can have low-dose amitriptyline added at a low night-time dose in order to gain extra benefit for the fibromyalgia symptoms. Caution is needed when combining high doses of drugs that act on serotonin because this may increase the risk of serotonin syndrome.

Alpha-2-delta ligands

Drugs that bind to the alpha-2-delta subunit of the voltage-gated calcium channels of neurones reduce calcium influx and inhibit release of neurotransmitters such as substance P and glutamate. This decreases neuronal excitability and as a consequence these drugs are used effectively as antiepileptics. They are also effective in the management of patients with chronic pain such as those with postherpetic neuralgia or diabetic neuropathy.

Pregabalin is a gamma-aminobutyric acid (GABA) analogue although it has no effect on GABA mechanisms. It has been shown in clinical trials to be effective for the pain, sleep disturbance and fatigue of fibromyalgia,[7] although its use is off label. The most common side effects include dizziness, drowsiness, headache, dry mouth and, in a smaller percentage of patients, weight gain. Patients who respond to this medication can maintain sustained benefit over time.

Pregabalin also has benefits for sleep and in patients with fibromyalgia it is best to start with a low dose at night. Common practice is to begin with a low dose of 25 to 75 mg just after the evening meal in order to encourage slow absorption and to limit dizziness and other side effects. The dose can be increased on a weekly basis to a maximum dose of about 450 mg per day or until maximum benefit is achieved. Although clinical trials indicate the most effective dosages may be about 300 to 450 mg per day,[7,8] many patients require a lower dose which is better tolerated. Also, the lower dose is financially better for the patient.

Gabapentin targets the same mechanism as pregabalin and is also effective in fibromyalgia although it is prone to cause more side effects and be less well tolerated. Gabapentin is often required in higher doses, up to 1800 mg per day, and intolerance often limits its application in patients with fibromyalgia. Initial doses should be low dose, about 100 to 300 mg at night, with titration occurring one week at a time.

Table 8. Medications to consider in the treatment of patients with fibromyalgia

Class	Type	Comment
Analgesics	Simple	Paracetamol is often not effective
	NSAIDs	Their analgesic effect may help some patients
	Opioids	No adequate trials to support their use
	Mixed	Tramadol with or without paracetamol is beneficial
Antidepressants	Tricyclic	Low-dose amitriptyline is beneficial (off-label use)
	SSRI	A high dose of fluoxetine may be beneficial (off-label use)
	SNRI	A higher dose of venlafaxine may be beneficial. Duloxetine is also effective (both used off label)
Dopamine agonist	–	Pramipexole may be beneficial (off-label use)
Antiepileptic	Alpha-2-delta ligands	Gabapentin and pregabalin are effective (both used off label)
Central acting	NMDA action	Possible target, no adequate trials (off-label use)

Dopamine agonist

The dopamine agonist pramipexole, which is approved for use in patients with restless leg syndrome and Parkinson's disease, may also be useful in patients with fibromyalgia (off-label use). A dose of 125 mg two to three hours before bedtime, with increasing weekly doses of 125 mg to a dose of 750 mg, as needed, is often used. Nausea and dizziness and, rarely, compulsive gambling among other side effects may occur.

The currently available drugs are summarised in Table 8.

Drug combinations

Many of the above mentioned drugs can be used together, particularly if used at a low dose.

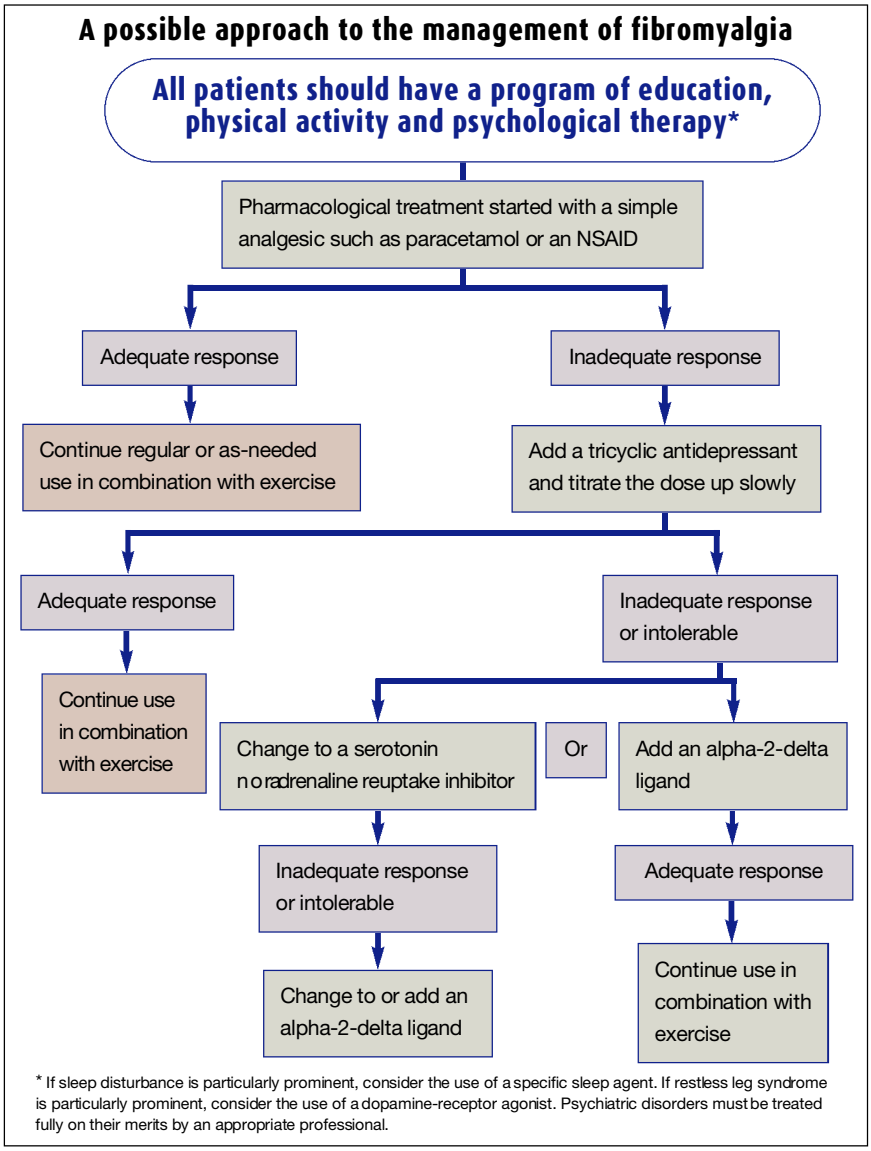
It is usual to commence with a simple analgesic and to then consider tramadol or an anti-inflammatory drug depending on the circumstances. A low-dose TCA is particularly useful in the evening and can be added to the above treatment. If there is depression occurring independently, a SSRI can be combined as a morning dose with the evening dose of amitriptyline. Alternatively, the SNRI duloxetine, which has effects on both depression and fibromyalgia, can be used as monotherapy at a standard dose instead of amitriptyline. Pregabalin can be added to any of these agents because there is no cross reactivity and the drug is well metabolised unless there is severe renal impairment.

A suggested algorithm is shown in the flowchart on page 52.

Treatment response and prognosis

Fibromyalgia is a multicomponent disorder and patients may receive benefits from one of a number of areas. Pain control is a key area and, if achieved, will allow the patient to initiate or further improve on their aerobic fitness and stretching programs. Relief of pain also decreases stress, improves sleep and often reverses some of the other components of the vicious cycle that is frequently associated with fibromyalgia.

Some drugs are more effective for certain components of fibromyalgia such as sleep disturbance, fatigue, muscle stiffness or global function. Even if full control of all symptoms can not be achieved with



medication, the goal of return to normal life activities, such as routine recreational, household and work activities, can often be met despite variable symptoms still being present.

Prognosis is improving with this targeted approach. This is particularly so in the typical community patient with mild to moderate symptoms and when a modifiable trigger is present. Where there are intractable psychosocial stressors the outcome, although better than before, is still guarded.

Future strategies

New drugs

Many drugs are being evaluated for use in treating various components of fibromyalgia. These include drugs effective for the sleep disturbance of fibromyalgia. The drug sodium oxybate has benefits in this regard but is unavailable in Australia due to drug regulation issues. Drugs active on the alpha-receptors, such as propranolol 10 to 40 mg per day, have been used off-label where sympathetic nervous system activation is prominent – for example, where anxiety and related symptoms are prominent.

A number of drugs targeting various aspects of the pain-related nervous system are being developed for use in fibromyalgia. Clinical trials of efficacy and tolerance will dictate their clinical role in fibromyalgia.

Experimental treatments

Treatments that modulate the pain-control centres in the brain may be beneficial in fibromyalgia. These include transcranial magnetic stimulation devices. These approaches are considered experimental at this time.

Conclusion

Fibromyalgia is common and has high impact on individual and social health. Better understanding of symptom mechanisms is associated with a number of more effective therapies. MT

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