

NSAIDs — select patients carefully

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Case study 44:  
Selecting analgesics

## Analgesic options for pain relief

Almost 1 in 5 patients seen in general practice has some form of chronic pain, with symptomatic osteoarthritis and back complaints the most common conditions.<sup>1,2</sup> Controversy over the risks of nonsteroidal anti-inflammatory drugs (NSAIDs) has created uncertainty about the use of this class, while recent changes to PBS availability have improved access to paracetamol and opioid analgesics. This issue of *NPS News* provides an update on the use of analgesics in chronic musculoskeletal pain.

### Paracetamol still first choice

Paracetamol remains the analgesic of choice for mild-to-moderate persistent pain. Although NSAIDs may produce greater reductions in pain intensity, any efficacy advantage in milder pain is small.<sup>3,4</sup> Paracetamol has a more favourable adverse-effect profile, making it a suitable first choice for many.

#### Use adequate doses

People who seek a health professional's advice on pain control may report that they have already tried paracetamol unsuccessfully; however, they may have used inadequate doses. A US survey of older women living in the community with musculoskeletal pain found that 41% used paracetamol at an average of one quarter of the maximum dose.<sup>5</sup>

Ask people who report insufficient pain control with paracetamol about the dose and frequency they have used to date. Increasing the dose and/or taking doses regularly may be sufficient to manage pain more effectively — dosing in persistent pain should be time contingent, rather than pain contingent. The addition of increased quantities of paracetamol to the *Schedule of Pharmaceutical Benefits* in April 2005 makes it simpler to prescribe 6 months' supply at the recommended dose.

Reassure patients that paracetamol can be used safely in the long term on medical advice and if the maximum dose is not exceeded. Paracetamol-induced hepatotoxicity is very rare at therapeutic doses.<sup>6,7</sup> The risk may be increased by poor nutrition or chronic alcohol abuse, although conclusive evidence for this is lacking. Inadvertent overdose, often from taking two paracetamol-containing preparations concurrently, is the more common cause of liver injury

caused by paracetamol.<sup>8</sup> Advise patients not to exceed the maximum daily dose and to avoid other paracetamol-containing preparations (such as cold and flu tablets).

#### Sustained-release paracetamol: greater convenience?

For some people, the need to take 4 daily doses to maintain around-the-clock pain relief is a barrier to using paracetamol. The extended-release formulation of paracetamol may help by reducing the number of doses to 3 per day.

Two bioequivalent brands of extended-release paracetamol, Panadol Osteo and Duatrol, are listed on the PBS for osteoarthritis. Each prescription provides sufficient for 6 months at the recommended dose (Box 1). The Panadol Osteo brand has a \$4.88 premium, which doubles its price for people with concession cards. Extended-release paracetamol is also available over the counter in quantities of 18 or 36 tablets, under the brand name Panadol Extend, but will be more expensive for patients who require regular doses.

#### Box 1: Recommended paracetamol doses in adults<sup>9</sup>

##### Immediate-release tablets

1–2 × 500 mg tablets every 4–6 hours  
Maximum 8 tablets (4 g) per day

##### Sustained-release tablets

2 × 665 mg tablets every 6–8 hours  
Maximum 6 tablets (3990 mg) per day

NPS is an independent, non-profit organisation for Quality Use of Medicines, funded by the Australian Government Department of Health and Ageing.

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## NSAIDs: carefully select patients to maximise the benefits

NSAIDs are valuable analgesics with a low risk of serious adverse effects when used appropriately in carefully selected patients.

Lately, safety concerns have centred on the risk of thrombotic events associated with COX-2 selective and conventional NSAIDs, and the need to assess overall cardiovascular risk when considering an NSAID. However, it remains important to consider risk factors for gastrointestinal and renal adverse effects. For information about risk factors for NSAID-induced adverse effects, see the *NPS RADAR* review 'Elevated cardiovascular risk with NSAIDs?', available at [www.npsradar.org.au](http://www.npsradar.org.au).

Combining an NSAID with paracetamol allows lower NSAID doses to be used. Intermittent use (for example, before activity or during a flare in pain) has a lower risk of adverse effects than continuous use.

### Avoid NSAIDs in people with heart failure ...

A recent study of the risk of hospital admission for heart failure in NSAID users was a timely reminder that certain patient groups are at particularly high risk of NSAID-induced adverse effects.<sup>10</sup> In this cohort of people aged > 60 years, using an NSAID\* was associated with a 30% increase in the risk of hospital admission for heart failure (relative risk [RR] 1.3, 95% confidence interval [CI] 1.1 to 1.6). The relative risk was much greater in people with established heart failure (RR 8.6, 95% CI 5.34 to 13.84) or who were taking antihypertensives (RR 3.76, 95% CI 2.70 to 5.24). A history of diabetes or renal failure also increased the risk of hospital admission for heart failure in people taking NSAIDs. These findings are consistent with those of previous studies<sup>11,12</sup> and highlight the importance of assessing a patient's risk of heart failure, particularly those with osteoarthritis who tend to be older and have comorbidities.

### ... or aspirin-induced asthma

Most people with asthma can take NSAIDs safely. However, those with diagnosed or suspected aspirin-induced asthma — symptoms of asthma usually accompanied by facial flushing and rhinitis within 3 hours of exposure to an NSAID — should avoid all NSAIDs.<sup>13</sup> Prevalence estimates range from 5% to 20% of adults with asthma.<sup>14–16</sup> An Australian survey found a prevalence of about 10%.<sup>17</sup>

Aspirin-induced asthma is thought to be caused by inhibition of cyclo-oxygenase-1 (COX-1). Although there have been reports of successful use of COX-2 selective NSAIDs in people with aspirin-induced asthma, cases of asthma have been reported in association with celecoxib and rofecoxib.<sup>18,19</sup> In the absence of comprehensive safety data, the same precautions apply to COX-2 selective NSAIDs as to other NSAIDs in people with known or suspected aspirin-induced asthma.

Paracetamol should be used first line: there is very little cross-sensitivity to paracetamol in aspirin-induced asthma.<sup>15,20</sup> If paracetamol alone does not provide adequate pain relief for people with aspirin-induced asthma, consider adding a weak opioid such as codeine or tramadol.

Advise people with aspirin-induced asthma to check the labels of medicines bought in the supermarket or over the counter to ensure that they do not contain aspirin or other NSAIDs.

Advise others with asthma to seek medical advice if their symptoms worsen after taking an NSAID, because previous exposure to NSAIDs is not required for aspirin-induced asthma to develop. Some patients may also not recognise that NSAIDs exacerbate their asthma because of the time delay between exposure and symptoms.



\* Patient data for this study were from 1997 to 2000. Consequently, COX-2 selective NSAIDs were not included in the analysis. In the absence of good evidence that COX-2 selective NSAIDs are associated with a lower risk of heart failure, the same precautions apply as to conventional NSAIDs.

## Opioids: when are they appropriate for musculoskeletal pain?

In recent years there has been an increase in the number of prescriptions written for opioids in chronic non-cancer pain<sup>21</sup>, indicating a growing acceptance of this class outside the palliative care context. Last year's PBS restriction changes mean that there is now greater access to opioid analgesics for chronic non-cancer pain in general practice (Box 2).

### Where do weak opioids fit?

A weak opioid may be considered an alternative to an NSAID when paracetamol alone is inadequate, particularly for people at high risk of NSAID-induced adverse effects. Guidelines also suggest that a weak opioid be added if a patient's pain does not respond adequately to an NSAID (with or without paracetamol).<sup>22,23</sup> However, the use of weak opioids in long-term management of persistent pain should be carefully considered because they produce the same range of adverse effects as strong opioids but with lower efficacy. Evidence in persistent pain is scarce; studies in acute pain suggest only modest additional analgesic efficacy when a weak opioid is added to paracetamol, but a higher rate of adverse effects after repeated doses.<sup>24,25</sup>

Codeine is the weak opioid of choice. Avoid dextropropoxyphene: its combination with paracetamol is no more effective than paracetamol alone and regular use leads to accumulation of the parent drug (causing dizziness and confusion) and the major metabolite, which is cardiotoxic. Tramadol may be useful in selected patients, but consider the possibility of drug interactions and adverse effects (see back page).

Add a weak opioid as a separate tablet so that a full dose of paracetamol can be given and the opioid dose titrated to effect and tolerability. After reaching a stable effective dose it may be possible to switch to an equivalent combination tablet.

Ensure that an adequate dose of codeine is used — trials have demonstrated the efficacy of codeine 60 mg added to paracetamol.<sup>24,25</sup> The lowest effective dose is not established but it is generally accepted that doses below 30 mg are unlikely to be effective. About 10% of Caucasian people and 1–2% of Asian people cannot metabolise codeine to morphine and so do not receive any analgesia.<sup>23</sup>

### Strong opioids for severe pain

Strong opioids can be used when other analgesics do not provide sufficient pain relief or are unsuitable because of adverse effects. Morphine is usually considered the strong opioid of first choice because

of familiarity, cost and the range of formulations available.<sup>9</sup> If the patient has an inadequate response or intolerable side effects on morphine, switching to another opioid may be helpful; although the evidence for this is poor.<sup>9</sup> Oxycodone and hydromorphone are alternatives for people who cannot tolerate morphine.

Ideally, patients should be referred to a multidisciplinary pain clinic or a pain specialist before a strong opioid is prescribed. However, it can be difficult to get an appointment in a timely manner. Consider whether it is appropriate to initiate opioid therapy before a visit to the pain clinic, or seek telephone advice from a specialist.

### Dose by the clock

Regular rather than as-needed doses should be prescribed for around-the-clock pain control. Some guidelines recommend initial dose titration using short-acting formulations<sup>23,26</sup>; however, expert opinion appears to increasingly accept initiation with controlled-release opioids.<sup>9,27</sup> If treatment is started with a short-acting opioid, switch to a controlled-release opioid when the optimal dose is established, to allow fewer daily doses.

Transdermal patches have a limited role in chronic non-cancer pain. Fentanyl patches should be reserved for opioid-tolerant patients who cannot take other opioids because of adverse effects. Buprenorphine patches are unsuitable for people who are physically dependent on other opioids, because they may precipitate withdrawal and antagonise analgesia.

### Box 2: PBS requirements for opioid prescribing

Changes to the PBS prescribing requirements mean that subsidised opioid analgesics for persistent non-cancer pain can now be started in the community.

To obtain an authority to continue the opioid for more than 12 months, the prescriber needs to seek a second doctor's review of the patient's pain management within the past 3 months to confirm the clinical need for ongoing opioid analgesics. See the *Schedule of Pharmaceutical Benefits* for full details of the authority requirements.

The review need not be conducted by a specialist or a pain management unit. However, for patients who are likely to need ongoing opioid treatment and who are unable to get an appointment at a pain clinic or with a pain specialist when an opioid is started, it may be practical to schedule such an appointment so that this review can be used to fulfil the PBS criteria for ongoing opioid supply.

## Alternatives to pethidine

Injectable opioids should not be used for exacerbations of chronic pain, except in very exceptional circumstances.<sup>23</sup> If an injectable opioid is required — for example, when oral intake is prohibited — morphine is preferred. Tramadol injection has a more limited role; it may be a useful alternative for people who cannot tolerate conventional opioids or who are at particular risk of opioid-induced respiratory depression.

Pethidine has recently been removed from the 'doctor's bag' emergency supply list because it has a number of significant disadvantages compared with other injectable opioids, including that it:

- has a short duration of action and is no more effective than other opioids

- has similar adverse effects to those of morphine, including increased biliary tract pressure
- is metabolised to norpethidine, which may cause serious adverse effects such as seizures, particularly in patients with renal impairment
- can cause serotonin syndrome when combined with other serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs)
- is more likely than other opioids to be abused by patients and health professionals.<sup>23</sup>

The New South Wales Therapeutic Advisory Group has published guidance on management of people who regularly use pethidine (see [www.ciap.health.nsw.gov.au/nswtag/publications/guidelines/GeneralPrinciples41202.pdf](http://www.ciap.health.nsw.gov.au/nswtag/publications/guidelines/GeneralPrinciples41202.pdf)).

## Thinking about tramadol

Tramadol has a range of potential adverse effects and drug interactions that make it unsuitable for some patients. Note that it:

- should not be used within 2 days of moclobemide or 14 days of an irreversible MAOI because of the risk of central nervous system excitation or depression, hypertension or hypotension

- may be used **with caution** in combination with other serotonergic drugs (such as SSRIs, mirtazapine, venlafaxine and St John's wort), although these combinations should be avoided if possible because of the risk of serotonin syndrome
- should be used with caution in people with epilepsy or at risk of seizures, and when combined with other drugs that lower the seizure threshold (such as tricyclic antidepressants), because seizures have been reported in association with tramadol.

The originally published version of *NPS News 47* contained an error. This is the corrected version. Further details are available at [www.nps.org.au](http://www.nps.org.au).

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NPSN0116/a