Background
Migraine occurs in up to 10-20% of the population. It is a source of major distress, disability and absenteeism from both paid and household work. The management of migraine usually involves the administration of specific anti-migraine drugs rather than analgesics alone and certainly the use of major analgesics such as opioids should be avoided.

A review of authorities issued for opioid use for chronic non-malignant pain found that more than 40% of pethidine authorities were for migraine, even though this is an inappropriate choice of analgesic for most patients and should have an extremely limited role. Opioids are often prescribed for patients with social problems, high levels of emotional distress and unclear medical diagnoses. Rather than treating the complaint of migraine effectively, doctors appear to be responding to patients' frustration and distress. The use of short acting injectable opioids is a particular problem, as escalation of opioid use (and accompanying increase in pain and dysfunction) is common in people treated with these agents.

Escalation of opioid use is common in people taking short-acting opioids, as they reinforce drug seeking behaviours. This presents the general practitioner with the dual problem of inadequate management of migraine and the potential for drug dependence.

Several guidelines have been produced to assist clinicians to manage pain associated with migraine. The purpose of this document is to integrate the key points from these guidelines with practice based experience from general practitioners.

The recommendations are based on the best available evidence, although it is recognised that knowledge and understanding of migraine and its treatment is still evolving. Where possible the level of evidence is noted against each treatment to assist in the interpretation and implementation of the guidelines in your individual practice (see table).

Approach
A comprehensive approach to migraine management is required. Non-pharmacological approaches may be important, but this document deals principally with the pharmacological considerations that are an integral part of migraine management. It assumes that a diagnosis of migraine has been established. In some patients, however, headache that was initially migraine may transform into predominantly non-migraine headache. The diagnosis of migraine therefore needs to be reassessed over time and if not the current predominant diagnosis, this needs to be addressed with the patient.

These guidelines have been designed to reflect the ways in which patients present in general practice and should assist with acute management of patients who suffer frequent episodes of migraine.

These guidelines do not deal with the prophylactic therapy that such patients may require. For further information about prophylaxis, refer to Therapeutic Guidelines: Neurology (Version 2, 2002).

Usually migraine episodes commence with mild headache and evolve in severity over time. If the headache evolves during sleep, then headache may be intense on waking. The aim of management of an acute attack of migraine is to terminate the attack as soon as possible after its onset, preferably before it has reached a disabling severity.

Choice of medication is not necessarily stepwise. It should be based on the patient's previous experience, severity and duration of the headache and any associated symptoms. Over the course of multiple attacks, many patients with migraine will identify from their own experience the agent of greatest efficacy for managing their acute attacks. In subsequent attacks, that agent should be employed at the very first hint of migraine, ie when the attack is mild. Failure to use an effective treatment promptly may increase pain, disability and the impact of the headache.

In addition to prescription of medications, the management of migraine involves patient education. The patient's active participation is required in recording attacks and the outcomes of therapeutic intervention. It is important that the aims and expectations of any therapeutic intervention are explained and discussed with the patient.
General Points

Is there a place for opioids in migraine management?
The Australian Association of Neurologists does not recommend the use of pethidine in treatment of migraine. A number of randomised controlled trials have concluded that pethidine is no more effective than dihydroergotamine, chlorpromazine or a non-steroidal anti-inflammatory drug (NSAID),6

Pethidine is short acting compared with the duration of migraine and is therefore an inappropriate choice of analgesic.

Codeine 25 mg in combination with paracetamol has been shown to be similar in efficacy to aspirin alone for relief of pain in migraine.11 The addition of codeine (30-60mg) to paracetamol has been demonstrated to be better than paracetamol alone in relieving non-migraine pain, but the magnitude of this difference is small (approximately 5%).12

The profound delaying effect of codeine on gastric emptying generally precludes its use in migraine.

Dextropropoxyphene is available in Di-gesic®, Dolozone®, Capadex® and Paracetamol® preparations. One small non-randomised blinded study in 25 patients found that dextropropoxyphene was as effective as ergotamine in aborting an acute episode and more effective than aspirin 600 mg.13 (Level 3 evidence)

There is no evidence that the addition of doxylamine in compound analgesic preparations such as Mersyndol® or Mersyndol Forte® provides additional benefit over the codeine and paracetamol combination.

Tramadol is a centrally active analgesic with opioid-like effects. It appears to act by modifying transmission of pain impulses via inhibition of noradrenaline and serotonin reuptake, and also by binding weakly to mu opioid receptors. Tramadol is widely available and is included in Doctors’ Bag stocks. Although its efficacy in acute and chronic pain is established, its efficacy in migraine is unproven. Tramadol must be used with caution in patients on monoamine oxidase inhibitors (MAOIs) or selective serotonin re-uptake inhibitors (SSRIs), because such combinations may precipitate a serotonin syndrome.9

If all else fails... In very rare episodes the general practitioner may determine that other treatments have been unsuccessful and that a parenteral opioid such as morphine is required in that specific attack. This should only be contemplated for patients known personally to the doctor. In such cases the patient should be advised of the relatively short duration of action of the medication and potential for dependence. An escalation of opioid dose or administration frequency should be cause for reassessment in regard to psychosocial factors, drug dependence and doctor shopping. Contact should be made with an appropriate specialist for early advice. The patient should be referred to a specialist in drug dependence or a specialist pain clinic as soon as a problem is suspected. If early referral is not practical, advice can usually be obtained by telephone.

For clinical advice on the management of a patient with problems related to opioid dependence, call the NSW Drug and Alcohol Specialist Advisory Service on 1800 203 687 or (02) 9557 2305. Doctors can call the Commonwealth Health Insurance Commission (HIC) on 1800 631 181 or NSW-HIC on 02 9885 3333 to check whether there is any information on a patient seeking benzodiazepines or opioids who may be seeing other doctors or obtaining multiple PBS prescriptions. However there are limitations to the value of such information (eg it may not be current or comprehensive).

When to use a triptan Three 5-HT1B receptor agonists (‘triptans’) are available in Australia for the treatment of migraine (naratriptan, sumatriptan, zolmitriptan). All have similar efficacy and side effects.

Sumatriptan has the advantage of multiple dosage forms (oral, nasal spray and injection). Triptans may not be as effective if taken during the aura phase before the headache commences. Triptans must not be combined with ergotamine containing preparations.

To prevent progression of an acute migraine episode, a single oral dose of sumatriptan (50-100 mg), naratriptan (2.5 mg) or zolmitriptan (2.5-5 mg) should be given and the patient assessed for response. Alternatively, sumatriptan may be given initially by subcutaneous injection (6 mg) or nasal spray (10-20mg) and the patient reassessed after additional doses are given. If headache does not respond, no further doses should be given (neither should ergotamine preparations be used for at least 6 hours). If the headache responds but recurs, further doses may be given - up to a total daily dose of sumatriptan 300 mg orally, 40mg intranasally, or 12 mg subcutaneously (or equivalent doses of other triptans).

Pharmacodynamic differences between the triptans are minor and head to head trials are limited. What seems to matter most are differences between patients rather than differences between triptans, although naratriptan may be less effective than other triptans at standard doses19. If patients do not respond to one triptan, they may respond to one of the others, or to an alternative route of administration. A critical appraisal of the triptans is provided in a recent review by Goosby et al.20

In a randomised controlled trial it was found that the combination of aspirin (900 mg) and metoclopramide (10 mg) was as effective as sumatriptan in the treatment of migraine and was better tolerated.20 It is also significantly less expensive. A recent systematic review20 concluded that subcutaneous sumatriptan was more effective than aspirin (900mg) and metoclopramide (10mg) at 2 hours, but that intranasal sumatriptan was not (adverse effects were not reviewed).

When not to use triptans or ergotamine

Ergotamine, dihydroergotamine and triptans should not be given to patients known or suspected to have ischaemic heart disease, other severe physical or psychological illness or uncontrolled hypertension. Triptans should be used with caution in patients on lithium, monoamine oxidase inhibitors or SSRIs, because of the possibility of serotonin syndrome.

Is there a place for NSAIDs in migraine management?

NSAIDs are a reasonable first line treatment choice for mild to moderate acute attacks or for severe attacks which have been responsive in the past to NSAIDs, and are comparable with oral sumatriptan in terms of efficacy, onset of analgesic effect and tolerability.9 However, NSAIDs (including COX-2 inhibitors) must be used with caution in the elderly, in patients who are volume depleted and in patients with renal dysfunction or a history of peptic ulcer.

Ketorolac is an effective NSAID analgesic which can be administered by injection and may be used for patients who cannot tolerate oral agents. Intramuscular ketorolac has been shown to be as effective as intravenous chlorpromazine 25 mg21 and as effective as a combination of pethidine 75 mg and promethazine 25 mg given by intramuscular injection.21

Although COX-2 inhibitors (eg celecoxib, rofecoxib) may reduce the risk of serious gastrointestinal adverse events,22,23 they are no more effective than traditional NSAIDs. They should be reserved for patients at high risk for upper GI bleeding.
Changing from a triptan to ergotamine or vice versa

A triptan should not be used if ergotamine has been used in the previous 24 hours. Ergotamine should not be used if a triptan has been used in the previous 6 hours.

Over the counter (OTC) preparations and complementary medicines

Many patients buy preparations from their pharmacy or supermarket in order to treat migraine. It is important to ask the patient about any non-prescribed drug use to ensure that confusion with brand names does not lead to inappropriate combinations or to overdosage. Note should be taken of herbal or other alternative medicines being consumed.

Although feverfew (Tanacetum parthenium L.) has been used with some success in prophylaxis of migraine, there have been no published trials in treatment of acute episodes. Similarly, white acupuncture has been demonstrated to be effective for prophylaxis, to value for analgesia during an acute episode is unclear.

Although there is no clear evidence, it is possible that an interaction may occur between triptans and the herbal remedy St John’s wort (Hypericum perforatum), which may result in an increase in side effects.

Dealing with refractory cases or status migrainosus

Status migrainosus should be managed in the hospital setting. Rehydration with intravenous fluids is usually required and parenteral therapy is appropriate.

Intravenous lignocaine

Intravenous infusion of lignocaine (with electrocardiogram monitoring) has been advocated for severe persistent migraine. Although there is reasonable evidence for its use in the more chronic pain setting, evidence supporting efficacy in migraine is lacking. A randomised double-blind trial comparing lignocaine 1mg/kg with placebo failed to demonstrate a difference in relief of migraine headache. In comparative studies lignocaine has been less effective than chlorpromazine and dihydroergotamine.

Chlorpromazine

The mechanism of action of chlorpromazine in migraine is uncertain, but may involve a combination of its anti-serotonergic effect, anti-dopaminergic effect in the chemoreceptor trigger zone and vascular effects through its alpha-blocking action. Because of its propensity to cause hypotension and occasionally dystonia, parenteral chlorpromazine should only be administered in a monitored environment where patients can be regularly observed and assessed. Blood pressure and vital signs should be measured before and monitored closely after injection. Note that intramuscular injection has been associated with development of sterile abscesses.

Analgesic rebound headache and medication overuse headache

Medication overuse headache (drug-induced chronic daily headache) and analgesic rebound headache may result from prolonged, frequent use of analgesics or caffeine, especially when patients use acute medication on more than 2-3 days per week. It may also occur with antihistamines, opioids, anti-migraine nasal sprays and vasoactive medications (ergotamines and triptans). The character of the headache may be indistinguishable from the original headache. Patients exhibit escalating medication use with increasing frequency and intensity of headaches, which allows diagnosis to be made before medication is withdrawn. Cessation will lead to withdrawal headaches with increased frequency. This requires careful management and sustained support, sometimes in an inpatient setting.

Prochlorperazine or metoclopramide for nausea and vomiting

The Tfelt-Hansen study provides the basis for the aspirin-metoclopramide combination recommendation (Level 2 evidence).

Relative cost of medicines

(The following cost structures are provided for the information of doctors and patients.)

<table>
<thead>
<tr>
<th>Medicines</th>
<th>Cost per dose</th>
</tr>
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<tbody>
<tr>
<td>Simple analgesics</td>
<td>approximately $0.20-$1.20</td>
</tr>
<tr>
<td>COX-2 selective NSAIDs</td>
<td>approximately $0.75</td>
</tr>
<tr>
<td>Anti-emetics</td>
<td>approximately $0.25</td>
</tr>
<tr>
<td>Prochlorperazine or metoclopramide</td>
<td>approximately $1.00-$2.00</td>
</tr>
</tbody>
</table>

Two studies have compared prochlorperazine and metoclopramide as single agents for treatment of acute migraine. Prochlorperazine provided better pain and nausea relief than metoclopramide but rescue analgesic therapy was often necessary. Neither drug can therefore be recommended as a single agent therapy for migraine. The comparative effectiveness of the two drugs in combination with an analgesic or ergotamine is unclear.

Intranasal therapy for migraine

Intranasal preparations of sumatriptan, lignocaine and dihydroergotamine have been evaluated in clinical trials, although only sumatriptan is marketed as an intranasal preparation in Australia. Intranasal sumatriptan was found to be more effective than placebo in two studies. Partial headache relief was achieved in 40-60% of patients treated with sumatriptan versus 29-35% of patients treated with placebo. Intranasal sumatriptan appears to have the same efficacy as oral sumatriptan, but a quicker onset of action.

Migraine in pregnancy

Two-thirds of women with a history of migraine do not experience migraine during pregnancy and should not require treatment after the first trimester. However should migraine occur it is important to ensure adequate hydration (as it is with non pregnant patients) and intravenous rehydration should be considered if necessary. Should medication with prochlorperazine and paracetamol be ineffective, the patient may require referral to hospital for consideration of parenteral therapy including sedation under observation.

Triptans and ergotamine should not be used in pregnancy.
**Acute Migraine Treatment**

- Treat attacks promptly with effective agents that terminate the attack as early as possible.
- Although stronger medications tend to be necessary for treating severe migraine attacks, many attacks can be controlled with simple analgesics, especially if taken promptly.
- Arrange follow up visit for evaluation of response to therapy and further education.

<table>
<thead>
<tr>
<th>Stage of migraine</th>
<th>Recommendation</th>
<th>Level of evidence</th>
<th>Other options</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early/mild migraine</td>
<td>Aspirin 600-900mg initially followed by 600 mg every 4 hours OR Paracetamol 1000mg orally then Paracetamol 1000mg every 4 hours (max 4g paracetamol/day) and Metoclopramide 10 mg orally or Prochlorperazine 5 mg orally</td>
<td>Level 2</td>
<td>Naproxen 750-1250mg OR Ibuprofen 400-1200mg OR Diclofenac 50-100 mg</td>
<td>Level 2</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide will improve gastric emptying which may be desirable for some patients</td>
<td>Level 2</td>
<td>Use one to two doses only. Avoid NSAIDs, including COX-2 inhibitors, in patients who are volume depleted, elderly or have renal dysfunction. Avoid conventional NSAIDs in patients with a history of peptic ulcer disease.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prochlorperazine will cause greater sedation (which may be desirable for some patients)</td>
<td>Level 2</td>
<td>Diclofenac 50-100 mg</td>
<td>Level 2</td>
</tr>
<tr>
<td>Persistent/moderate to severe migraine</td>
<td>Aspirin 900 mg followed by aspirin 600 mg every 4 hours OR Ergotamine 1-2 mg orally as an initial dose (not exceeding 10 mg per week) OR Sumatriptan 50-100mg orally</td>
<td>Level 2</td>
<td>Naratriptan 2.5mg orally OR Zolmitriptan 2.5-5mg orally</td>
<td>Level 2</td>
</tr>
<tr>
<td>Able to tolerate oral medication</td>
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<tr>
<td>Persistent / Moderate to severe migraine</td>
<td>Dihydroergotamine 0.5-1mg SC, IM or IV and Metoclopramide 10 mg IM or IV or prochlorperazine 12.5mg IM OR Sumatriptan 6 mg SC. A second dose may be given after one hour but only if there is a response to the first dose and Metoclopramide 10 mg IM or IV or prochlorperazine 12.5mg IM OR, if in a monitored environment, Chlorpromazine 12.5-25mg IV or IM* (Note sedative and hypotensive effects. IM injection can cause sterile abscesses.)</td>
<td>Level 2</td>
<td>Ketorolac 30-60mg IM* OR Intranasal sumatriptan 20 mg</td>
<td>Level 2</td>
</tr>
<tr>
<td>Unable to tolerate oral medication</td>
<td></td>
<td></td>
<td>Prochlorperazine suppositories may be useful when oral medication is not tolerated</td>
<td>Level 2</td>
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<td></td>
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<tr>
<td>Severe migraine and patient has taken ergotamine or triptans without effect</td>
<td>If in a monitored environment Chlorpromazine 12.5-25mg IV or IM* (Note sedative and hypotensive effects. IM injection can cause sterile abscesses.) Chlorpromazine has been shown in small RCTs to be at least as effective as dihydroergotamine, sumatriptan (unblinded study), ketorolac and pethidine plus promethazine</td>
<td>Level 2</td>
<td>Ensure adequate hydration OR Paracetamol or NSAID</td>
<td>Level 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If ergotamine trial ineffective, wait 6 hours and try sumatriptan. If triptan trial ineffective, wait 24 hours and try ergotamine</td>
<td>Level 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>If necessary consider opioids</td>
<td>Level 4</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Migraine during pregnancy</td>
<td>Paracetamol 1000mg orally or rectally every 4 hours OR Chlorpromazine 12.5-25mg IV or IM* (up to week 32)</td>
<td>Level 4</td>
<td>Ensure adequate hydration OR Add prochlorperazine (to week 32) OR Metoclopramide (after week 32)</td>
<td>Level 4</td>
</tr>
</tbody>
</table>

*see general discussion, page 4-5
Follow up visits

| Education | • Reassure the patient  
• Discuss self management of acute migraine episodes with emphasis on early treatment and avoiding precipitating factors  
• Encourage patient to return for regular review if episodes of migraine occur frequently  
• In cases of repeated migraine episodes discuss prophylaxis  
• Discuss overlapping pain syndromes such as tension-type headache and associated nuchal myalgia and medication induced headache  
• Review psychosocial factors |
| Assessment of the efficacy of treatment used in previous migraine episode | • Ascertain the effectiveness of the treatment regimen used in the last migraine episode  
• Discuss progression of migraine, timing of therapy and adverse effects  
• If the previously used regimen did not produce acceptable results the alternative options for management of migraine episode should be tried in a stepwise fashion |
| Plan for self medication in subsequent migraine | • Discuss/agree on treatment goals for the drug management of acute episodes  
• Agree on how treatment success will be measured  
• Select a treatment option based on the patient's treatment experience and features of the migraine episode. The options for self-management are identical to those outlined in the table within the limits of the patient's ability to self-administer the medication. |

Levels of evidence

| Level 1 | Evidence obtained from systematic review of relevant randomised controlled trials |
| Level 2 | Evidence obtained from one or more well-designed, randomised controlled trials |
| Level 3 | Evidence obtained from well-designed, non-randomised controlled trials; or from well designed cohort or case control studies |
| Level 4 | Opinions of respected authorities based on clinical experience, descriptive studies, reports of expert committees |

WHY PETHIDINE IS NOT RECOMMENDED

• Pethidine has a shorter duration of action than morphine with no additional analgesic benefit  
• It has similar side-effects to morphine, including increased biliary pressure  
• Pethidine is metabolised to norpethidine, which has potential toxic effects (eg convulsions), especially in patients with renal dysfunction,  
• Pethidine is associated with potentially serious interactions in combination with other drugs.  
Because of its euphoric effects:  
• Pethidine is the drug most commonly requested by patients seeking opioids, and  
• Pethidine is the drug most commonly abused by health professionals.
References

1. Silberstein SD, Resnick L. Multiphasic comorbid diagnoses and treatment of headache. Neurology 2002; 59:1403-

These guidelines were developed by the NSW Therapeutic Assessment Group Inc (NSW TAG). NSW TAG is an association of clinical pharmacologists, directors of pharmacy and other clinicians from the teaching hospitals in New South Wales. NSW TAG aims to investigate and establish therapeutic initiatives that foster high quality, cost-effective drug usage in the public hospitals of NSW and the wider community.

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