# *PAIN MATTERS*

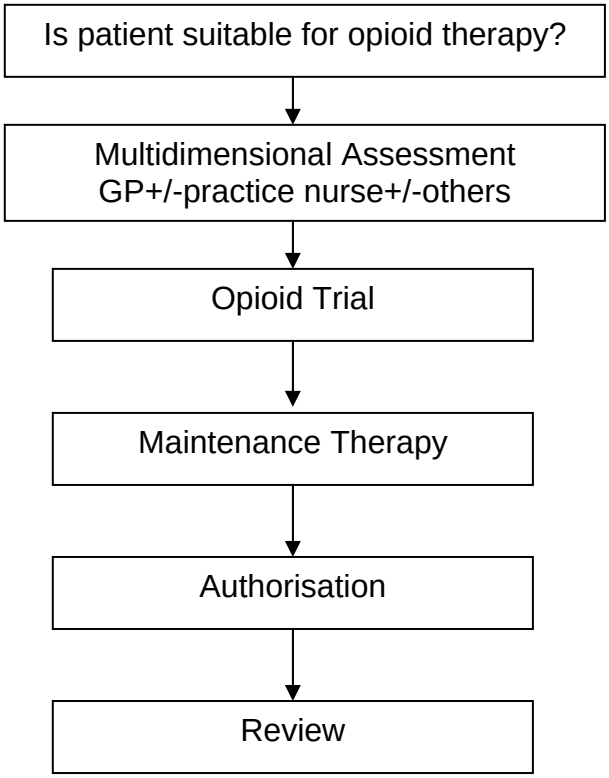
**Medical Practice Guidelines**
**Hunter Integrated Pain Service**
**Updated May 2007**

## Opioid Use in Persistent Pain

**Summary**

1. Opioids are widely prescribed for persistent pain. However, the evidence on which this is based is equivocal.
2. Randomised controlled trials have demonstrated that opioids reduce severity of persistent pain. However the reductions in pain were modest, tolerance was a problem and length of follow-up was relatively short.
3. Multidimensional assessment and a positive response to an opioid trial are needed before initiation of maintenance therapy.
4. Opioids are best used as part of a structured, multi-modal approach rather than unimodal therapy.
5. Adverse effects, including tolerance, are relatively common.
6. Opioid substitution may improve analgesic efficacy and reduce adverse effects.

### Opioid Pathway




Exit from Pathway

i. Goals of therapy not achieved in trial or maintenance phase
ii. Predominance of psychosocial issues
iii. Evidence of aberrant drug related behaviour

**Other Australian Guidelines**

1. NSW Therapeutic Assessment Group (TAG). General Principles. Rational use of opioids in chronic or recurrent non-malignant pain. 2002. www.nswtag.org.au
2. NSW TAG. Guidelines for General Practitioners. Low Back Pain: Evidence based prescribing and rational use of opioids. 1998. www.nswtag.org.au
3. Management Consensus of Directors of the Australian Pain Society. Graziotti PJ, Goucke CR. The use of oral opioids in patients with chronic non-cancer pain. MJA 1997;167:30-34.
4. NSW Health Department: Pharmaceutical Services Branch. Guidelines for the management of patients with chronic non-cancer pain.
5. SPHERE Positive Management of Persistent Pain www.spheregp.com.au

## What is the current evidence?

1. There is a body of expert opinion that "a subgroup of patients with persistent non-cancer pain may function better and have less pain if treated with opioids, without requiring rapidly escalating doses or showing addictive behaviour".[1]
2. In Australia increasing numbers of patients are receiving oral opioids for persistent non-cancer pain[2]. This is despite a lack of trials assessing long-term benefit.
3. There is evidence from randomised controlled trials of analgesic benefit from oral opioids in both persistent musculoskeletal [3,4,5] and persistent neuropathic [6,7,8,9] pain. However duration of benefit is a key issue. Most of the trials have used a 4 week treatment period. The best designed trial [4] used 9 weeks treatment and found that substantial tolerance developed over that time frame. This study also found a lack of improvement in physical and psychological function despite improved analgesia. More comprehensive studies incorporating multidimensional management and longer-term follow up are required.
4. The use of opioid substitution to treat tolerance has demonstrated effectiveness in prospective case series in the palliative care setting.[10]
5. Physical deactivation, emotional distress and social problems are commonly associated with persistent non-cancer pain. These issues may cloud assessment of opioid responsiveness. Opioid use may be harmful in some cases due to increasing patient passivity, development of drug related adverse effects and the potential for addiction.
6. Whilst the evidence for use of opioids in persistent pain is equivocal there is support from systematic review of benefit from "self-management" approaches [11,12]. Therefore, opioid therapy should not be used as stand-alone treatment, but as part of a structured, multi-modal approach that includes educational, physical and psychological inputs.

## Patient Selection

1. Selection criteria are not clearly defined in the literature.
2. Multidimensional assessment is recommended. This can be done by the GP alone but may include input from a practice nurse or other health care professionals (psychologist, physiotherapist, social worker, occupational therapist). The Hunter Integrated Pain Service (HIPS) Patient Screening Questionnaire is one available multidimensional assessment tool.
3. It is desirable if a clear source of pain can be defined although it is recognised that the significance of pathology is not always easy to interpret[1].
4. It has been recommended that patients should be psychologically stable, recognising that this is difficult to define[1]. The use of opioids to treat emotional distress should be avoided.
5. In practice a useful indicator is whether the patient is able to consider the use opioids as part of a multi-modal approach. If the focus is simply on opioid use as a "magic fix" then the outcome of therapy is likely to be poor.

## Trial versus Maintenance Therapy

1. An opioid trial needs to be undertaken prior to a decision regarding maintenance therapy.
2. The goals of therapy need to be agreed between patient and doctor prior to commencement of the trial (see Appendix 1 consent form). Goals may address pain reduction, activities of daily living, exercise and psychological issues.
3. Duration of the trial is typically 2-4 weeks.
4. Opioid dose may be adjusted frequently during the trial period.
5. The decision about whether to proceed to maintenance therapy will depend on whether or not pre-set goals have been achieved and the balance of beneficial and adverse drug effects.
6. Patients on maintenance therapy are generally reviewed monthly. Ongoing emphasis on a broad based management approach and discussion of goals of therapy is recommended.
7. The Brief Pain Inventory (BPI) can be used before and at completion of an opioid trial to assess response. It can also be used to monitor maintenance therapy. The BPI is available on this website Health Professionals/Assessment tools.

## Consent

Informed consent is an essential part of opioid prescribing. Obtaining consent in writing may help to reinforce key issues (see Appendix 1 consent form).

## Prescribing and Authorisation

1. One nominated doctor (generally the GP) should prescribe opioids and assess response.
2. If necessary, a deputy prescriber can be organised to cover periods of medical absence.
3. Medicare/Pharmaceutical Benefits Scheme (PBS) Authority:
    a. For extended prescription of one months supply of medication at a time (ie. more than the standard prescription of 20 tablets/capsules) authorisation from PBS is required.

b. If maintenance opioid therapy will continue for longer than 12 months then review of the case by a second medical practitioner is required in the 9-12 month time period after commencement of opioid therapy.
c. Input from a Specialist Pain Management Centre can be used for the second medical opinion and this may be clinically desirable in some cases. However it is not required for the purpose of the authority.
d. Pharmaceutical Benefits Scheme contact details:
Phone 1800 888333
GPO Box 9826 in your capital city
http://www.medicareaustralia.gov.au

4. Pharmaceutical Services Branch (PSB) Authority:
a. This authority is distinct from the Medicare/Pharmaceutical Benefits Scheme Authority and relates to Section 28 of the Poisons and Therapeutic Goods Act.
b. PSB Authority is always required when prescribing opioids to a person with drug addiction as defined by an overwhelming desire for continued administration of the drug.
c. PSB Authority is also required when prescribing the following opioids for pain management for a period of longer than 2 months:
- Any injectable opioid
- Hydromorphone
- Methadone (including Physeptone tablet)

d. PSB may require case review by a Specialist Pain Management Centre as part of the authorisation process.
e. PSB contact details Fax 98595175
Phone 98795239.
PO Box 103, Gladesville, NSW 1675
http://www.health.nsw.gov.au/public-health/psb/pubs.html

5. Hunter Integrated Pain Service support for opioid authorisation (Medicare/PBS or PSB) can be requested by sending a medical referral letter along with the Patient Screening Questionnaire that your patient has completed. Often these cases are handled via a telephone based case discussion.

## Choice of Opioid Agent

1. Long acting agents are generally preferred in the management of persistent pain. Options include sustained release morphine, oxycodone and tramadol. Methadone is long acting due to its prolonged elimination half-life. Transdermal fentanyl and buprenorphine are alternatives.
2. Short acting oral or sublingual opioids can be used for dose finding (this is usually unnecessary), breakthrough pain or where the daily pattern of pain is one of intermittent fluctuations.
3. Paracetamol-codeine phosphate is a short acting combination therapy with high risk of constipation. Fixed doses of long acting agents are generally preferred for persistent pain. Panadeine Forte 8 tablets daily (codeine 240mg) is equivalent to MS Contin or Kapanol 20mg twice daily.
4. Intramuscular pethidine is short acting and has high addiction potential. Norpethidine accumulation from repeated dosing can cause seizures. Ongoing use for persistent pain is not recommended.
5. Methadone has a variable and long elimination half-life (15-60 hours). It may take up to 2 weeks to reach steady state levels. Drug accumulation may cause excessive sedation if the dose is increased rapidly. The dose can generally be increased on a weekly basis.
6. Tramadol may interact with other drugs effecting serotonin levels (including SSRI's) to cause central nervous system excitation (serotonin toxicity).
7. Buprenorphine is a partial agonist at $\mu$ opioid receptors and an antagonist at $\delta$ and $\kappa$ receptors. It binds strongly to the $\mu$ receptor site but does not fully activate it. Drug interactions can occur when buprenorphine is combined with pure $\mu$ agonists (eg. morphine, oxycodone, fentanyl or methadone). If buprenorphine is administered to a person on maintenance pure $\mu$ agonist then a withdrawal reaction can be precipitated. Conversely, if pure $\mu$ agonists are administered to a person on maintenance buprenorphine then the pure agonist may be less effective due to reduced access to the receptor site. However these interactions are dose related with animal[13] and human[14] models showing effectiveness of breakthrough pure $\mu$ agonists in those on maintenance buprenorphine analgesia. Antagonism of response to pure $\mu$ agonists has been demonstrated in animal models[13] but only at buprenorphine doses exceeding the analgesic therapeutic range. In practice these drug interactions are unlikely in the buprenorphine dose range used to manage pain. The management of acute pain in those on maintenance buprenorphine is outlined in Appendix 2.
8. For neuropathic pain oxycodone ($\mu$, $\delta$ and $\kappa$ receptor agonist), methadone ($\mu$ and NMDA receptor activity) and tramadol ($\mu$ receptor agonist and reuptake inhibitor of 5-HT and noradrenaline) may be more effective than morphine ($\mu$ receptor agonist). Buprenorphine (partial $\mu$ agonist and $\delta$ and $\kappa$ antagonist) may also have advantages in this situation.
9. In renal impairment accumulation of metabolites may cause problems
a. Morphine to M3G (neuroexcitation) and M6G (analgesia and sedation)

b. Hydromorphone to H3G (neuroexcitation)
c. Pethidine to norpethidine (neuroexcitation)
d. Oxycodone and buprenorphine – metabolites only weakly active
e. Methadone and fentanyl have no active metabolites

| Generic name | Long acting agents | Short acting agents |
|---|---|---|
| Morphine | MS Contin tabs 5,10,15,30,60, 100,200 mg<br>MS Mono caps 30,60,90,120 mg<br>Kapanol caps 10,20,50,100 mg | Ordine liquid 1,2,5,10 mg/ml<br>Sevredol tabs 10,20 mg<br>Anamorph tabs 30 mg |
| Oxycodone | Oxycontin tabs 5,10,20,40,80 mg | Endone tabs 5 mg<br>Oxynorm caps 5,10,20 mg and liquid 1,10 mg/ml<br>Proladone suppositories 30 mg |
| Methadone | Physeptone tabs 10 mg | |
| Hydromorphone | | Dilaudid tabs 2,4,8 mg and liquid 1 mg/ml |
| Fentanyl | Durogesic patches 12, 25,50,75,100 mcg/hr | |
| Buprenorphine | Norspan patches 5,10,20 mcg/hr | Temgesic sublingual tabs 200 mcg |
| Tramadol | Tramal SR tabs 100,150,200 mg | Tramal caps 50 mg |
| Codeine | | Multiple codeine combinations |

## Dose Recommendations

1. The recommendation of Hunter Integrated Pain Service to general practitioners is not to exceed the following doses without discussion with a Specialist Pain Management Centre:
    a. Morphine 120mg daily (MS Contin or Kapanol 60mg bd)
    b. Oxycodone 80mg daily (OxyContin 40mg bd)
    c. Methadone 40mg daily (Physeptone 20mg bd)
    d. Fentanyl transdermal patch 25 mcg/hr applied 3rd daily
    e. Buprenorphine transdermal patches 40 mcg/hr applied weekly
2. Elderly patients are sensitive to opioids. Lower doses and slower titration are required.

## Reduced Opioid Responsiveness

1. In some cases the effectiveness of opioid analgesia declines over time. This may relate to:
    a. Underlying disease progression
    b. Opioid tolerance
    c. Opioid induced hyperalgesia
2. Tolerance is defined as the need for increasing doses of a drug to maintain the original effect. It is a major clinical problem in the use of opioids for persistent pain.
3. Opioid induced hyperalgesia is a drug induced amplification of pain responses in the central nervous system (central sensitisation). The counterproductive hyperalgesia is superimposed on any opioid analgesic benefit. The clinical significance of opioid induced analgesia has not yet been clearly defined. Morphine is more likely to produce hyperalgesia than buprenorphine[15,16]. It has been proposed that the $\kappa$ antagonism of buprenorphine contributes to an anti-hyperalgesia effect[16].
4. Activation of the N-methyl-D-aspartate receptor in the dorsal horn of the spinal cord, contributes to the mechanism of opioid tolerance and opioid induced hyperalgesia[17,18,19]. Ongoing research seeks to clarify associated complex cellular mechanisms.

## Opioid Substitution

1. Opioid substitution can be used to treat opioid tolerance and opioid induced hyperalgesia. It can also be used to reduce other opioid related adverse effects.
2. Individual opioid agents have different structures and act via different receptor mechanisms. Therefore cross-tolerance is incomplete and adverse effects including hyperalgesia vary.
3. A simple strategy is to rotate between 2 opioids approximately every 12 months.
4. Although dose conversion ratios have been published there is considerable variation in what provides an “equi-analgesic” dose.
5. Generally when making an opioid switch a lower dose equivalent of the new agent is used in the first instance with the option to titrate upwards in dose if necessary. Often improved analgesia and fewer adverse effects can be achieved with a lower dose equivalent of the new agent.
6. A crossover period of approximately 1 week can be used to smooth the opioid substitution. The original opioid is tapered and ceased while simultaneously the new agent is commenced at low dose and built up to the target dose.
7. Typically the target dose of a new agent is calculated by finding the equivalent dose and then reducing it by approximately 30%. Depending on response the target dose can then be titrated up to the full equivalent dose.

8. The following ratios (oral administration unless otherwise specified) are considered dose equivalent for the purpose of this guideline:
    a. Morphine : Oxycodone 1.5 : 1 (eg morphine 60mg = oxycodone 40mg)
    b. Morphine : Methadone 3 : 1 (eg morphine 60mg = methadone 20mg)
    c. OxyContin : Methadone 2 : 1 (eg oxycodone 40mg = methadone 20mg)
    d. Morphine : Hydromorphone 7.5 : 1 (eg morphine 90mg =hydromorphone 12mg)
    e. Morphine : Tramadol 1 : 5 (eg morphine 10mg = tramadol 50mg)
    f. Morphine : Codeine 1 : 6 (eg morphine 10mg = codeine 60mg)
    g. Fentanyl transdermal 25 mcg/hr = Morphine 120mg daily
    h. Morphine : Buprenorphine transdermal 75:1

    Buprenorphine 5 mcg/hr = Morphine 9mg daily (simple approximation MS Contin 5mg bd)
    10mcg/hr = Morphine 18mg daily (simple approximation MS Contin 10mg bd)
    20mcg/hr = Morphine 36mg daily (simple approximation MS Contin 20mg bd)

## Endocrine Effects

Opioid therapy can cause hypopituitarism. Studies of intrathecal opioid administration[20,21] have shown that hypogonadotrophic hypogonadism is common in men (85% prevalence). Secondary amenorrhoea is similarly common in pre-menopausal women. Hypoadrenalism (ACTH deficiency) and growth hormone deficiency are less common (15% prevalence of both). TSH deficiency and increased prolactin levels are rare. All patients on intrathecal opioid therapy should be assessed for hypopituitarism.

Prevalence of endocrine abnormalities in those on oral opioids is not known although cases have been reported[22,23]. Men should be questioned about libido and erectile dysfunction prior to initiation of opioids and while on maintenance therapy. Endocrine screening tests include morning levels (8-9am) of testosterone, cortisol, TSH and prolactin. Pre-menopausal women who stop menstruating while on opioid therapy should have morning measurement of LH, FSH, oestrogen, progesterone, cortisol, TSH and prolactin. Replacement therapy with testosterone or oestrogen/progesterone can be considered in a general practice setting if a deficiency develops on opioid therapy. Referral to an endocrinologist is recommended for hypoadrenalism, secondary hypothyroidism, hyperprolactinaemia or multiple endocrine deficiencies.

## Immune System Effects

The interaction between opioids and the immune system is complex. Trauma and pain in themselves cause immunosuppression. Pain relief in part alleviates this. Opioids however have additional direct effects on many aspects of immune function. These effects depend on multiple factors including structure of the individual opioid agent, dose range used and species studied.

Both acute and chronic opioid use has inhibitory effects on humoral and cellular immune response including antibody production, lymphocyte activity, and cytokine expression[24,25]. Potential mechanisms include:

1. Modulation of the hypothalamic pituitary axis
2. Stimulation of the sympathetic nervous system
3. Direct action via $\mu$ receptors on immune cells

Opioids can be grouped according to degree of immunosuppression as shown below. Although there are theoretical advantages in the avoidance of immunosuppressant opioids in patients with immunocompromise, major surgery, trauma and cancer, this is yet to be confirmed in clinical outcome studies.

| Marked Immunosuppression | Moderate Immunosuppression | Minimal Immunosuppression |
|---|---|---|
| Morphine | Codeine Diacetyl morphine<br>Dihydrocodone Fentanyl<br>Methadone Pethidine | Buprenorphine Hydromorphone<br>Oxycodone Tramadol |

## Addiction Disorder

The presence of behaviour suggestive of addiction disorder may require referral to a Drug and Alcohol team and possible cessation of opioid therapy. Aberrant drug-related behaviours predictive of developing addiction have been defined by Portenoy[26]:

**Major aberrant behaviours (more predictive)**

1. Selling prescription drugs
2. Prescription forgery
3. Stealing or borrowing drugs from others
4. Injecting oral formulations
5. Obtaining prescription drugs from non-medical sources

6. Concurrent abuse of alcohol or illicit drugs
7. Multiple non-sanctioned dose escalations
8. Multiple episodes of prescription loss
9. Repeatedly seeking prescriptions from other sources
10. Deterioration in function at work, in family or socially
11. Repeated resistance to change in therapy despite evidence of adverse drug effects

**Minor aberrant behaviours (less predictive)**

1. Aggressive complaining about the need for more drug
2. Drug hoarding during periods of reduced symptoms
3. Requesting specific drugs
4. Openly acquiring similar drugs from other medical sources
5. Unsanctioned dose escalation
6. Unapproved use of the drug to treat other symptoms

## REFERENCES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## APPENDIX 1: CONSENT FOR USE OF OPIOIDS IN PERSISTENT PAIN

This form provides information about opioid therapy and seeks your agreement about approach to opioid use.

**Potential Benefits**
Opioids (morphine-like pain killers) are used as part of a broad treatment approach rather than as stand-alone therapy. There are a number of potential benefits. These are assessed over a trial period before deciding about maintenance therapy. Specific goals for the opioid trial are:

a. Reduction in my average pain score:
   i. At rest from ___ / 10 to __ / 10
   ii. On exertion from ___ /10 to __ / 10

b. Improvement in the following day to day activities
   i. _____
   ii. _____
   iii. _____

c. Improved performance of the following exercises
   i. _____
   ii. _____

d. Other
   i. _____
   ii. _____

**Potential Problems**

1. Although medical studies show that opioid medication can reduce persistent pain in the short term, there are no high quality studies looking at the longer-term picture. Further studies are needed.
2. It is possible that you may get initial benefit that wears off over time. This is called tolerance. Sometimes switching to an alternative opioid agent may help. Other pain management strategies may also need to be considered.
3. Dependence and addiction may be problems. All patients on long-term opioids become physically dependent meaning that withdrawal symptoms occur if therapy is stopped abruptly. Addictive behaviour occurs in a small proportion of people and may be minimised by appropriate patient selection.
4. Side effects may include mental clouding and sedation, constipation, nausea, itch, sweating, dry mouth and hormonal problems such as weight gain and sexual dysfunction. Sedation may be more troublesome if opioids are combined with other drugs such as alcohol and benzodiazepines.
5. Lack of alertness may affect driving ability especially in the early stages of therapy or after dose escalation. Generally it is safe to drive once the dose is stable.
6. Babies born to women on opioid therapy may require treatment for opioid withdrawal.

**Practical Issues**

1. One doctor only is to be responsible for prescribing your opioid medication at any one time. Arrangements can be made for a deputy prescriber to cover medical absences.
2. An initial opioid trial of 2-4 weeks is undertaken to assess your response before a decision is made on whether to begin maintenance therapy. The decision will involve weighing up benefits and side effects. The Brief Pain Inventory can be used before and at completion of the trial to help assess your response.
3. The dose may be adjusted frequently during the trial period. If you progress to maintenance therapy you will need to be reviewed by your doctor on a monthly basis.
4. If you commence maintenance therapy your doctor will need to get authority from Medicare/ Pharmaceutical Benefits Scheme to prescribe up to one month's medication at a time. Authority from Pharmaceutical Services Branch may also be required in some cases.
5. If your behaviour suggests a problem with drug addiction then your doctor will consider tapering and ceasing your opioid medication. Problem behaviours include giving your medication to others, use of your medication in a non-prescribed way, excessive use of other medications (including alcohol), repeated "loss" of medication, doctor shopping, worsening function at home or at work and frequent complaints about the need for a higher dose.

**Agreement**
I have read the information provided and agree to participate in the management plan as outlined.

Patient signature: _____

Witness: _____ Date: _____

## APPENDIX 2: MANAGEMENT OF ACUTE PAIN IN PATIENTS ON MAINTENANCE BUPRENORPHINE

### Background

Buprenorphine is a partial agonist at μ opioid receptors. It binds strongly to the receptor site (high receptor affinity) but does not fully activate it (only moderate intrinsic activity). Drug interactions can potentially occur when buprenorphine is combined with pure μ agonists (eg. morphine, oxycodone, fentanyl or methadone). If buprenorphine is administered to a person on maintenance pure μ agonist then a withdrawal reaction can be precipitated. Conversely, if pure μ agonists are administered to a person on maintenance buprenorphine then the pure agonist may be less effective due to reduced access to the receptor site. However these interactions are dose related. Animal and human models show effectiveness of breakthrough pure μ agonists in those on maintenance buprenorphine analgesia. Antagonism of response to pure μ agonists has been demonstrated in animal models but only at doses of buprenorphine exceeding the analgesic therapeutic range. In practice these drug interactions are unlikely in the buprenorphine dose range used to manage pain. However drug interactions may occur with the high buprenorphine doses used in addiction.

Transdermal buprenorphine (Norspan patch) is used in the management of persistent pain while oral tablets (Subutex) are used for addiction. Generally the buprenorphine doses used in managing pain are much lower.

There are several approaches to consider in managing acute pain in patients on maintenance buprenorphine. These approaches can be used alone or in combination.

### Management Approaches

#### 1. Increasing Buprenorphine Dose

This strategy is appropriate for acute pain of mild to moderate severity. Sub-lingual buprenorphine (Temgesic) can be used to increase buprenorphine levels. Temgesic is a 0.2mg tablet. This is equivalent to 6mg of oral morphine (equianalgesic ratio 30:1). It is held under the tongue until dissolved (5-10 minutes). Sublingual bioavailability is 30-50%. Onset of analgesia takes 15-45 minutes with peak analgesia at 3 hours. Duration of analgesia is 6-8 hours. To increase buprenorphine levels a regime of Temgesic 1 to 2 tablets 6-8$^{th}$ hourly can be used. If this strategy is used in the community there is a cost consideration as Temgesic is not PBS listed.

The maximum recommended dose of transdermal buprenorphine is 40 mcg/hr (approximately equivalent to MS Contin 40 mg bd; equianalgesic ratio 75:1). This is achieved by simultaneously applying 2 of the 20mcg/hr patches. Any increase in transdermal dose takes up to 3 days to have effect. Hence this is inappropriate as a single strategy to manage an acute episode.

#### 2. Use of Pure μ Receptor Agonists

This strategy is appropriate for acute pain of moderate to high severity. A pure μ agonist is simply titrated to effect. The transdermal buprenorphine patch can be either left in place or removed to avoid the confusion of multiple opioid agents. If the patch is removed then buprenorphine levels fall gradually over 3 days.

#### 3. Non-Opioid Analgesics

Adjuvant non-opioid analgesics can be used. Paracetamol and anti-inflammatory agents are effective in acute pain. For hospitalised patients ketamine infusion (either intravenous or subcutaneous) can be used. For acute neuropathic pain antidepressants and anticonvulsants can be added.

#### 4. Neural Blockade

Techniques of neural blockade can be used where appropriate. The use of a femoral nerve block to manage the pain of a fractured femur is an example of this approach.

#### 5. Other Approaches

Psychological approaches such as relaxation techniques and hypnosis can be considered. TENS may have a role in some situations.