

Symptom Control in Palliative Care

5th Edition (2013)



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For the Illawarra Shoalhaven Local Health District

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Introduction

This booklet has been prepared for and on behalf of the Illawarra Shoalhaven Local Health District to provide medical practitioners with practical therapeutic approaches to common symptoms encountered in the palliative care setting. It does not set out to be comprehensive, aims to be pragmatic, may be oversimplified, and does at times reflect personal and local practices.

This booklet aims to give practitioners quick, user-friendly recipes to manage the vast majority of symptom-control problems we encounter in the care of terminally ill patients. For more detailed information of drugs prescribed for symptom management in palliative care I recommend the web-site **www.palliativedrugs.com**. Register and access the 'formulary' and 'document library' with the option to purchase the PCF (palliative care formulary) for personal use. There is also an excellent Bulletin Board where a practitioner can discuss challenging individual cases with international palliative care colleagues.

This edition has been updated on the last publication in 2006 to include a number of new drugs: Jurnista, a long-acting form of hydromorphone; Targin, which combines Oxycontin with naloxone to combat the constipating effect of oxycodone; Methylnaltrexone, a subcutaneous medication for opiate-induced constipation; and Norspan transdermal patches for pain relief. The sections on pain management have been extensively rewritten to reflect current approaches to the introduction of a wide range of opiates including methadone, and the section on neuropathic pain has been extensively reviewed with regard to current practices.

Palliative drug administration and dosing in renal failure has developed over the last few years and reference is made to dose adjustments and best drug selections for many of the prescribed medications outlined in this edition. An appendix with a table showing renal failure dose adjustments for commonly prescribed drugs is included in this edition.

The scope of this booklet is to outline guidelines that need individual consideration at a clinical level, with careful review and consultation with MIMS for appropriate dose adjustments in moderate to severe renal failure.

This booklet has been widely circulated to medical and nursing practitioners, hospitals and aged care facilities in our region to encourage common approaches to symptom management. This enhances the existing high level of interdisciplinary co-operation taking place in the home and institutional care of people affected by various symptoms in palliative care.

Medical practitioners are encouraged to consider the home as the preferred setting for death if this is the wish of patients and families. A good approach to therapeutics and the use of available palliative care services (including access to syringe-drivers for the terminal phase) is a recipe to successful management of someone dying at home.

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Pain Control

Introduction

Relieving pain in advanced incurable illness is essential to alleviate the suffering experienced by both patients and their extended family. Understanding the principles of pain management and the application of clinical therapeutics using appropriate drugs for different pain situations is of vital importance in achieving consistent success in this field. The aim, for the patient to be continually pain free most of the time, is achievable in around 90% of cases.

Principles of Pain Management

The following steps are recommended:

- Establish the cause of pain through a thorough history, examination and selected investigations. Especially consider the possibility of neuropathic pain ([see page 8](#)) which is commonly missed and may not respond well to the usual analgesic management.
- Reduce sensory input by prescribing a peripherally active drug (paracetamol [Panadol, Panamax] 500–1000mg every 4 hours and/or a nonsteroidal anti-inflammatory drug [NSAID]). Modified release Panadol Osteo 665mg, 2 caps every 8 hours is recommended. Studies have shown an equal clinical effect to paracetamol 1G every 6 hours
- If pain persists, add the following medicines (depending on the intensity of the pain):
 - a weak opioid: codeine phosphate 30–60mg [compounded with paracetamol in Panadeine Forte or Codalgin Forte] orally every 4 hours; dextropropoxyphene 32.5–65mg [compounded with paracetamol in Digesic, Capadex or Paradex] orally every 4 hours; tramadol [Tramal] 50–100mg orally every four hours, or slow-release tramadol [Tramal SR] 100–200mg orally every twelve hours.
 - a strong opioid (details below): morphine [Ordine, MS Contin, MS Mono and Kapanol]; fentanyl [Durogesic, Denpax or Fenpatch patches and Actiq lozenges]; oxycodone [Endone, Oxycontin, OxyNorm and Targin]; hydromorphone [Jurnista and Dilaudid]

The intensity of pain may be assessed by determining which analgesics the patient has already tried, without success. Note that 60mg codeine and 65mg dextropropoxyphene is equivalent to roughly 5–10mg of morphine or oxycodone.

- **Never** depend on ‘as required’ prescribing alone. The aim is to control pain and prevent its recurrence through regular prescribing. Use the oral route whenever possible.
- Consider interventions that raise the ‘pain threshold’, including discussion of the disease, its treatment and prognosis, counselling, relaxation techniques and anxiolytic therapy.
- **Always prescribe an aperient** when starting narcotics. For example, docusate sodium with senna (Coloxyl with senna) – initial therapy, 1–2 tablets at night ([see page 14](#)).
- Be prepared to prescribe treatment for nausea in half to two-thirds of patients on narcotics. For example, haloperidol (Serenace) 1.5–3mg immediately then 1.5–5mg at night. Consider adding metoclopramide (Maxolon, Pramin) 10–20mg every 4–8 hours if resistant to this ([see page 13](#)). Anti-emetics may not be required after the first week in these patients.

Use of Strong Opioids

Initiating treatment with strong opioids has changed in recent years as a result of gaining experience in the clinical application of newer products. These include fentanyl patches [Durogesic, Denpax or Fenpatch patches], buprenorphine patches (Norspan), controlled-release oxycodone [OxyContin, Targin], modified release hydromorphone (Jurnista), a wider dose range and flexibility of immediate-release formulations of oxycodone [Endone, OxyNorm capsules and liquid], hydromorphone [Dilaudid tablets, liquid and injection], Fentanyl Lozenges (Actiq), and a growing place for the use of methadone [Biodone forte, Methadone syrup and Physeptone] in opioid rotation for resistant pain situations.

Traditionally we used to titrate liquid morphine to effect, then continue the effective dose four-hourly with a double dose at bed-time. This approach (of initiating treatment with a liquid or tablet form of an immediate-release preparation) should still be undertaken for patients with severe or unstable pain where the opiate requirement is difficult to predict and titration is needed. It is a common and reasonable practice these days for experienced practitioners to initiate treatment with a long acting opiate (Targin or OxyContin, Durogesic or Norspan patches, Jurnista, MS Contin, Kapanol or MS Mono) but it is necessary to co-prescribe a number of tablet, capsule or patch sizes to allow titration of

the opiate. It is also important to prescribe a suitable immediate-release preparation for 'breakthrough pain', usually in one-sixth of the total daily opiate requirement (calculated against 'morphine equivalence' for the patches [see P6 on opiate conversions]). The amount of opiate used for breakthrough pain gives an indication about how much to increase the long acting opiate formulation.

This range of opiates has increased flexibility and choice with regard to appropriate prescribing. Patients who have severe side effects, eg nausea and vomiting, on one may tolerate another easily. A fentanyl patch is less constipating and is preferred by patients as it doesn't have to be taken orally. However it doesn't have a readily accessible breakthrough product (Actiq lozenges are expensive but are now on the PBS scheme for patients who can't tolerate morphine for breakthrough pain) so immediate-release morphine, oxycodone or hydromorphone are generally used for this. The fentanyl patch is also cumbersome in unstable or progressive pain situations. Norspan patches are useful in situations where a low initial opiate dose is indicated (Norspan 5 \equiv morphine 2mg every 4-hours orally) and can be supplemented by immediate release preparations as for fentanyl. In renal failure morphine accumulates active metabolites that complicate its use, and hydromorphone or fentanyl (also in 50-75% the usual dose for EGFR < 20mls/min) are preferred.

Use of Morphine

Morphine is available in immediate release liquid (Ordine) and tablet (Sevredol 10 and 20mg; Anamorph 30mg) forms; as well long-acting preparations including sustained-release capsules (Kapanol), and controlled-release tablets (MS Contin, MS Mono, Momex, Apotex) and suspension (MS Contin).

Initiating Morphine

- In most patients commence a long-acting preparation in combination with liquid morphine for breakthrough pain. The usual starting dose (especially in patients transferring from Digesic or Panadeine Forte) should be 30-60mg daily given as 12-hourly MS Contin or once daily in the case of MS Mono or Kapanol. Most patients should also be started on Panadol Osteo 2 tablets every 8-hours. The breakthrough dose of liquid morphine should be 1/6th of the total daily dose for most patients (eg 10mg 4-hourly PRN for a patient prescribed 60mg morphine a day). It will have a clinical analgesic effect lasting 4-6 hours. Half the breakthrough dose if it causes drowsiness. Ask the patient to record the number of breakthrough doses required per day over the first few days, then increase the long-acting preparation to account for this. The

breakthrough dose will also have to be increased to reflect this too. Repeat this process to titrate the morphine to effective pain relief or drowsiness. If the patient becomes drowsy without good relief they may have neuropathic pain (see p..) and require specialist review if available. Once on a stable dose it is acceptable to need occasional 'breakthroughs' without further escalating the long-acting preparation.

- Opiate-naïve and elderly patients who are not severely distressed can be started on lower doses (eg MS Contin 5-10mg every 12 hours). In older patients it may be better to start regular liquid morphine in a dose of 1-2mg every 4-6 hours to establish its effect and tolerance before introducing the long-acting forms. This dose can be titrated up to effect then appropriately replaced by the long-acting form. It would be pointless, however to start such a low dose in a patient who has been taking regular codeine, dextropropoxyphene or tramadol without good effect.

In renal failure choose another opiate (fentanyl or hydromorphone are recommended) as active morphine metabolites can accumulate unpleasantly or dangerously. If you have to use morphine then give 25% of the dose as liquid morphine every 6-8 hours (EGFR 20-50mls/min) or introduce a smaller starting dose of 1-2mg every 6-8 hours (EGFR <20mls/min).

Use of Oxycodone

Oxycodone is available in immediate-release liquid [OxyNorm 1mg/ml], capsules [OxyNorm 5, 10 and 20mg] and tablets [Endone 5mg], as well as long-acting, controlled-release formulations [OxyContin 5, 10, 20, 40 and 80mg, and Targin] of various strengths. This gives it as much flexibility as morphine for initiating strong opioid analgesia. Like morphine, its short acting formulations have a duration of 4-6 hours of analgesia, while its long-acting formulations are given 12-hourly. The outline above for initiating treatment with liquid or long-acting morphine also applies to these oxycodone preparations, bearing in mind that oxycodone is considered more potent in a ratio 1:1.5 (eg 20mg of oxycodone is equivalent to 30mg of morphine orally). It is safer than morphine in renal failure and can be prescribed in normal dose for EGFR>10mls/min.

- **Targin** is a recently introduced combination of long-acting Oxycontin and naloxone. The naloxone is an opiate antagonist with little oral bioavailability (< 3%) and is used for its local effect on the bowel to reduce the side effect of constipation. Naloxone does have a significant systemic effect in higher doses however. While there is little data to guide dosing, it is recommended here that Oxycontin alone is added to Targin for doses above Targin 40/20mg twice daily.

Use of Fentanyl

Fentanyl is a potent strong opioid available as long-acting transdermal patches [Durogesic, Denpax, Fenpatch], immediate-acting lozenges [Actiq] and as fentanyl injections. As with the other opioids it is usually prescribed with regular paracetamol, NSAIDs and/or other 'co-analgesic' medications for optimal analgesia (see P...). Patients generally prefer transdermal fentanyl and it works well alongside breakthrough morphine, oxycodone or hydromorphone. It is less constipating than the other opioids and is excellent for continuing the management of stable pain. It is not such a good option for controlling unstable or progressive pain problems due to its delayed onset of action after dose adjustments.

- The transdermal patches release fentanyl in a controlled manner over 72 hours, with an onset of analgesic action about twelve hours after its application. It works by forming a sub-dermal drug reservoir, which then drives the serum levels. This accounts for the delayed onset of action and a 'wash-out' period of up to 22 hours after removing the patch. Patches are changed every 3 days (some patients report a wearing off of good analgesia after two days and need to change the patch every 48 hours). Patients are advised that the first dose and any subsequent dose increase will not be effective for 12 hours, and that they will need to rely on breakthrough ('as required') doses of morphine, oxycodone or hydromorphone in the meantime.
 - Transdermal patches are available in five strengths: Durogesic 12, 25, 50, 75 and 100, which deliver 12, 25, 50, 75 and 100 mcg per hour of fentanyl respectively. These would be roughly equivalent to a four-hourly, oral morphine dose of 7.5, 15, 30, 45 and 60mg respectively (equivalent oral oxycodone would be 2/3rd of each of these morphine doses, while equivalent hydromorphone would be 1/5th of the morphine doses). These figures can be used to calculate appropriate doses for breakthrough pain (usually the 4-hour equivalent dose, eg 30mg morphine and for transferring patients between patches and the different opioids.
 - Being aware of the morphine equivalence of each patch size, gives the prescriber a sense of patch potency and also predict the correct breakthrough dose of morphine and other opiates. For each increase of 25mcg/hr the roughly equivalent oral morphine dose increases in 15mg Q 4-hourly steps. Thus a 25mcg/hr patch is equivalent to 15mg oral morphine every 4 hours, a 50mcg/hr patch is equivalent to 30mg every 4-hours, and so on. The equivalent 4-hourly dose is also the oral breakthrough dose. For oxycodone this dose would be 10mg orally every four
- hours (2/3rd morphine dose) for each 25mcg/hr patch, while hydromorphone would be 3mg orally every 4-hours (1/5th morphine dose). If these breakthrough medications are given parenterally (usually SC) then half the oral dose applies.
- When commencing patients on fentanyl patches, be aware of the opiates that have been inadequate for good pain control. Most still symptomatic patients transferring from regular tramadol (400mg daily) Panadeine Forte (8-10 daily), Digesic (8-10 daily) or oxycodone (30-60 mg daily) will need a 25 mcg/hr patch with liberal PRN breakthrough medication over the first 24-48 hrs. These patients are likely to need a 50 mcg/hr (or higher) maintenance dose. Careful telephone review and prescribing more than one patch strength plus the breakthrough medications will enable the practitioner to titrate the dose effectively.
 - For opioid-naïve patients or those without major distress on lower doses of the above medications, the starting dose should be 12 mcg/hr and breakthrough requirements over the first 24-48 hrs will guide maintenance prescribing. Practitioners should be aware that this fentanyl dose is still equivalent to 45mg oral morphine a day, which might be too much for opioid naïve patients, especially the elderly. An alternative approach would be wiser in some of these patients (eg Norspan-5 which is equivalent to 12 mg oral morphine daily).
 - For patients with progressive pain on fentanyl patches, the situation can often be managed by using regular breakthrough medication while increasing the patches. An alternative is to continue the current dose of fentanyl and titrate regular liquid or subcutaneous morphine (or the equivalent oxycodone or hydromorphone) until analgesia is achieved, and then adjust to the appropriate patch dose.
 - Fentanyl lozenges [Actiq] are now available on the PBS (for palliative cancer patients who don't tolerate morphine as a breakthrough medication) in 200, 400, 600 and 800, 1200 and 1600mcg strengths for breakthrough pain. They are sucked and moved around the oral cavity using the applicator (hence the term 'fentanyl lollypop') to maximize mucosal contact. Fentanyl is rapidly absorbed during this process and the lozenge is removed from the mouth when pain is controlled or excessive opioid effects appear (drowsiness). The right strength of fentanyl lozenge is not easy to predict with wide individual variability but it generally recommended to start on the 400 mcg size with most patients.
 - Fentanyl injections come in a concentration of 100mcg/2ml or 500mcg/10ml. The other fentanyl preparation are equivalent to parenteral administration

(transdermal and transmucosal absorption) so subcutaneous fentanyl infusions can replace the patches at exactly the same rate per 24 hours. If used for breakthrough pain a dose equivalent of 2-4 hours of the fentanyl delivered by the patch is recommended (eg 50-100mcg subcutaneously, 2-4-hourly PRN in a patient on Durogesic 25). This is not very practical in patients on higher strength patches as the volume for injection becomes too high.

Use of Hydromorphone

Hydromorphone is a synthetic derivative of morphine and is available in a long-acting modified-release tablet (Jurnista 4, 8, 16, 32 and 64mg), as instant-release tablets [Dilaudid 2, 4, and 8mg], as an oral liquid [Dilaudid oral liquid 1mg/ml] and in an injectable form (with 2mg/ml, 10mg/ml and 50mg/5ml concentrations). Its efficacy and side-effects are similar to morphine, although it has a higher potency (1mg hydromorphone \equiv 5mg of morphine). Hydromorphone has less active metabolites than morphine and is a better choice of analgesic in patients with renal failure (EGFR < 50ml/min).

- Hydromorphone may be introduced as the convenient once daily modified-release tablet Jurnista in a dose of 4-8 mg in still symptomatic patients transferring from regular tramadol (400mg daily) Panadeine Forte (8-10 daily), Digesic (8-10 daily), oxycodone (10- 20 mg daily) or morphine (15-30mg daily). Use additional breakthrough doses of an immediate release preparation in 1/6th of the Jurnista dose given orally every four-hours PRN. The Jurnista dose can then be titrated according to the breakthrough requirements, noting however that Jurnista accumulates to a 'steady state' by its fourth dose.
- In opioid-naïve and elderly patients, the starting dose of 4mg may be too high (unless there is severely distressing pain). In such cases it would be wise to initiate a low dose of Dilaudid oral liquid (0.25–0.5mg every four hours) and titrate to response before considering substituting Jurnista. It might be a better alternative to use another opiate such as MS Contin or Oxycontin in such cases, as these are available in lower initial dose-equivalence.
- To convert oral to the equivalent subcutaneous dose of hydromorphone give half the oral dose.

Use of Methadone

Methadone is a synthetic strong opioid with some unique characteristics, available on the PBS as 10mg tablets (Physeptone), a 5mg/ml solution (methadone syrup) or as a 10mg/ml injection (Physeptone). As well as being an opioid-receptor agonist, it inhibits

serotonin reuptake and is an NMDA-receptor-channel blocker. These properties probably contribute to often impressive benefits in opiate-resistant pain, especially in neuropathic pain ([see page 8](#)). Patients are generally transferred from another opiate (eg morphine) when it has been determined that this is not working despite optimal or high doses, combined with appropriate 'co-analgesics' such as amitriptyline, an anticonvulsant and dexamethasone. Unfortunately it has very complex pharmacokinetics with a long and unpredictable half-life (8-75 hours) so the drug accumulates on repeated doses. As 'steady-state' may be reached over a week or more on the same dose, patients initially relieved of pain may later develop coma and respiratory depression. For these reasons methadone should only be prescribed under the supervision of someone experienced in its application and requires daily telephone-monitoring at least while stabilizing the patient's dose over the first week. The dosing approach recommended by MIMS is potentially dangerous and not recommended here.

Important note: Methadone can prolong the QT interval on ECG and its introduction has been associated (very rarely and usually in higher doses than we generally use in palliative care) with sudden death due to complex ventricular tachycardia (torsades de pointes). Caution is advised in patients at risk of prolonged QT interval including cardiac hypertrophy, hypokalaemia, hypomagnesaemia, diuretic use with electrolyte abnormalities, calcium channel blockers, tricyclic antidepressants, neuroleptic drugs and a history of arrhythmias (see MIMS for more detailed list). If there is concern an ECG should be obtained before considering methadone.

The following international guidelines are accepted ways of initiating treatment with, and transferring over to methadone from morphine. It is acknowledged here that these approaches to transferring from high doses of other opiates are complex and often confusing, even in a palliative care unit with developed guidelines. As a consequence of this I have included a section of a personal and regional approach (Method 3 below) that can be managed effectively in a community setting for most patients.

For opiates other than morphine, first convert to their morphine-equivalence and proceed from there ([see page 11](#)).

Initiating Treatment with Methadone

When prescribing oral methadone as a first-choice strong opioid: start on methadone 5mg q12-hourly and 5mg q3-hourly PRN. (use half these doses in the elderly). If pain relief remains minimal, consider increasing to 10mg q12-hourly after 1–2 days (and 5mg q3-hourly PRN), but

generally do not increase the regular dose for one week. If necessary, continue to titrate the regular dose upwards by about 1/4–1/3 once a week, guided by PRN use with higher regular doses, increase the PRN dose to 1/4 of the q12-hourly dose.

Transferring from Morphine

There is no single potency ratio for methadone and other opioids. When switching from morphine, the eventual 24h dose of methadone is typically 5–10 times smaller than the previous dose of morphine, sometimes 20–30 times smaller, and occasionally even smaller. Inevitable accumulation is the reason for the week-long intervals between adjustments in the regular dose. Switching to methadone must be closely supervised, often as an inpatient. The following two methods are the most frequently referenced amongst palliative care services. The third method is a simplified version that we have developed regionally that is more practical particularly for community patients.

Method 1

(Morley and Makin, 1998 [slightly modified])

1. Stop regular short-acting morphine abruptly when starting the methadone. If switching from a slow-release morphine formulation give the first dose of methadone 6 hours after the last dose of the 12-hourly preparation, or 12 hours after the last dose of a 24-hour preparation.
2. Give a single loading dose of oral methadone equal to 1/10th of the previous total 24-hour oral morphine dose, up to a maximum of 30mg. If very elderly or cachectic, omit the loading dose.
3. Give 1/3rd of the loading dose of methadone q3-hourly PRN, up to a maximum of 10mg per dose.
4. For patients in severe pain and who are unable to wait 3 hours before giving the next methadone dose, prescribe 50-100% of the breakthrough dose of morphine (or other opioid) that was used before the switch on a 2-4 hourly PRN basis.
5. On Day 6, the amount of methadone taken over the previous 2 days is noted and divided by 4 to give a regular q12-hourly dose, and 1/4 of this regular q12-hourly dose is given q3-hourly PRN.
6. If 2 or more doses/day of PRN methadone continue to be needed, the dose of regular methadone should be increased once a week, guided by PRN use.
7. If the patient becomes persistently drowsy, that drowsiness is unlikely to wear off in less than 24-hours. Stop methadone for 24 hours and recommence in half to two-thirds the dose and continue to titrate according to pain response and drowsiness. Continue

PRN breakthroughs of alternative opiate during this time unless patient is too drowsy.

Method 2

(Blackburn et al, 2002 [slightly modified])

1. Stop regular short-acting morphine (or other opiate) abruptly when starting the methadone. If switching from a slow-release morphine formulation give the first dose of methadone 6 hours after the last dose of the 12-hourly preparation, or 12 hours after the last dose of a 24-hour preparation. This should be timed with the loading dose below.
2. Give a loading dose of 1/10th of the previous total 24-hour oral morphine dose, up to a maximum of 30mg of methadone at bedtime. If very elderly or cachectic, omit the loading dose.
3. Prescribe 1/2 of the loading dose as a regular q12-hourly dose (starting on the same day at bedtime), and give 1/4 of the regular q12-hourly dose q3-hourly PRN.
4. In the event of severe uncontrolled pain, despite repeated PRN doses, a second loading dose can be given. This is most likely in the first 48 hours after the switch.
5. If the patient is very drowsy, omit one dose and then continue with a reduced regular dose.
6. On Day 6, the amount of methadone taken over the previous 2 days is noted and divided by 4 to give a regular q12-hourly dose, and 1/4 of this regular q12-hourly dose is given q3-hourly PRN.
7. If 2 or more doses/day of PRN methadone continue to be needed, the dose of regular methadone should be increased by about 1/4–1/3 once a week, guided by PRN use.
8. If the patient becomes persistently drowsy that drowsiness is unlikely to wear off in less than 24-hours. Stop methadone for 24 hours and recommence in half to two-thirds the dose and continue to titrate according to pain response and drowsiness. Continue PRN breakthroughs of alternative opiate during this time unless patient is too drowsy.

Method 3

(personal approach)

1. Stop regular short-acting morphine abruptly (or other opiate) when starting the methadone. If switching from a slow-release morphine formulation give the first dose of methadone 6 hours after the last dose of the 12-hourly preparation, or 12 hours after the last dose of a 24-hour preparation. This should be timed with the loading dose below.
2. Give a loading dose of 1/10th of the previous total 24-hour oral morphine dose, up to a maximum of 30mg

of methadone at bedtime. If very elderly or cachectic, omit the loading dose.

3. Give 1/3rd of the loading dose q6-hourly regularly.
4. Use the previous breakthrough medication every 2-4 hours PRN in full dose (ie morphine, oxycodone, etc).
5. Make a daily phone call initially to assess progress.
6. Continue current management if the patient is still in pain without excessive drowsiness over the first 24-48 hours. Using the same dose, reduce dose interval to q8-hourly after 24-48 hours in patients who become pain-free, and be prepared to reduce further by halving this dose and giving it q6-hourly regularly over the next 24-48 hours. This progressive dose reduction and use of the previous opiate for breakthrough pain anticipates methadone accumulation and attempts to avoid excessive drowsiness. In patients who become pain free in the first 24-48 hours the maintenance dose is often a quarter to one-half of the initial dose (progressively titrated in 24-48 hour intervals by dropping to same dose q8-hourly followed by half this dose q6-hourly) and I aim for the same but titrate upwards again if pain begins to return without drowsiness. The correct dose can usually be achieved by daily or 2nd-daily review in one week in most uncomplicated cases.
7. If the patient is still in pain without drowsiness after 48 hours increase the dose by approximately 50% (possibly by 100% if severely distressed, although such patients should probably be admitted at this point) and continue the alternative opiate for breakthrough pain. If they become pain free over the next 24-48 hours then this probably represents the maintenance dose but it should be reduced if the patient becomes too drowsy.
8. After establishing the total daily dose give half of this every 12 hours. Use ¼ of the 12-hourly dose for breakthrough pain q3-hourly PRN. Increase the 12-hourly dose of methadone by ¼ to 1/3rd once a week if 2 or more breakthrough doses continue to be required.
9. If the patient becomes persistently drowsy that drowsiness is unlikely to wear off in less than 24-hours. Stop methadone for 24 hours and recommence in half to two-thirds the dose and continue to titrate according to pain response and drowsiness. Continue PRN breakthroughs of alternative opiate during this time unless patient is too drowsy.

Use of Buprenorphine

Despite being an opioid agonist-antagonist analgesic buprenorphine has not been shown to have a 'ceiling' to its analgesic effect in clinical trials (ie the dose can be

increased exponentially until benefit or side-effects limit its use). In Australia it is available in three transdermal (TD) patch sizes, Norspan 5, 10 and 20, releasing 5, 10 and 20mcg/hr of buprenorphine. These are changed once-weekly. It is also available as sublingual tablets (Temgesic 0.2mg; Subutex 0.4mg, 2mg and 8mg; Suboxone preparations combined with naloxone for drug dependency programmes) and as an injection (Temgesic 300mcg/ml). None of these are PBS-listed for pain management although Temgesic sublingual tablets come in packs of 50.

- Buprenorphine TD patches are much more frequently prescribed overseas in the management of chronic, severe cancer pain. This has been facilitated by the availability of 35-70mcg/hr patches that are changed every 4-days. Experience suggests that doses well in excess of the manufacturers recommended upper limit of 140mcg/hr can be applied with breakthrough doses of morphine or morphine equivalent opiates being completely effective despite the theoretical opiate antagonistic action of buprenorphine (this does not affect the μ -receptor however). Buprenorphine is considered potentially better in neuropathic pain, to cause less hyperalgesia and to be less constipating than morphine.
- The oral morphine equivalent for Norspan patches is 2mg every 4 hours for each 5mcg/hr of Norspan (ie Norspan 5 \equiv 2mg q4-hourly; Norspan 10 \equiv 4mg q4-hourly and so on). Another way of determining the oral morphine equivalent is to multiply the patch dose in mcg/hr by a factor of 2.4 to get the total daily oral dose of morphine in mgs (eg Norspan 10 \equiv 24mg oral morphine daily).
- Sublingual tablets are probably not the ideal breakthrough medications for patients on Norspan patches. They have a 50% bioavailability and are only slowly systemically absorbed after an initial rapid mucosal absorption. It can take an hour or more for analgesic effect and the effect can then last for 6-7hrs (compared to ~ 4 hrs for morphine) which is too long. They are also approximately 80 times as potent as morphine so 0.2mg \equiv 16mg oral morphine which is unsuitable until the Norspan dose is 40mcg/hr. The recommendation here is to prescribe oral morphine, oxycodone or hydromorphone in roughly equivalent q 4-hourly doses as the breakthrough medication (eg for Norspan 10 use morphine 4mg, oxycodone 2.5mg or hydromorphone 1mg q4-hourly PRN).
- TD Norspan patches will initially require 24 hours to take effect and up to 3 days to reach maximal effect. This is true of initiating treatment and changing the dose. This makes Norspan unsuitable for the management of pain where rapid dose escalation is required. It is however an excellent option for initiating

low-dose opiates including the elderly in residential settings where there are limited registered nurses available for drug administration, such as nursing homes.

- When a Norspan patch is removed its effect reduces by approximately 50% in the first 24hrs and it then takes 2-3 days to wear off completely.
- Inflammation and urticaria at the patch site are relatively common. This can be prevented in some cases by waving the patch in the air before application to enable alcohol to evaporate. Avoid re-using inflamed sites and cease altogether if the reactions are severe or upsetting to the patient.
- Buprenorphine is a relatively safe opiate analgesic in renal failure. The parent drug doesn't accumulate and isn't removed by dialysis, while its principal metabolite norbuprenorphine has no central action of clinical significance.

Use of Tramadol

Tramadol [Tramal] has a dual action, acting as an opioid, and by presynaptic, serotonin reuptake blockade (cf tricyclic antidepressants). These analgesic actions are synergistic, without antidepressant or anticholinergic effects. Its potency is roughly equivalent to codeine, with lower adverse opioid effects including constipation. As it lowers the seizure threshold it should be used with caution in epileptics, and can interact with other drugs, including antidepressants and psychotics, that also have this effect. Tramadol is available in short-acting (Tramal 50mg capsules), sustained-release (Tramal SR 100, 150 and 200mg tablets; Durotram XR Once-daily SR 100, 200 and 300mg tablets), oral drop (100mg/ml) and injectable (100mg/2ml) forms.

- Dose: 50-100mg capsules orally four times a day or Tramal SR 100-200mg every twelve hours, or Durotram XR 100-400mg once daily. Breakthrough doses of the 50mg capsules can be given to supplement Tramal SR or Durotram XR up to a maximum of 400mg of tramadol per day. Alternatively give morphine or alternative strong opiate for breakthrough pain using the equation tramadol 100mg \equiv 10 mg morphine to estimate a reasonable breakthrough dose.
- Changing to morphine: Commence morphine 10mg orally every four hours in patients needing stronger analgesia (from tramadol 400mg orally a day), then titrate the morphine to effect as described above in the section on morphine (P...).
- Serotonin toxicity (serotonin syndrome) has been occasionally reported in patients receiving another serotonergic drug (eg SSRI antidepressants).

Neuropathic Pain

Neuropathic pain may not respond fully to the general analgesic approaches described above. It is due to compression or infiltration of nerves by tumour, or to painful peripheral neuropathy. It may be associated with clinical evidence of deafferentation (abnormal or absent sensation in the painful area). The following approaches are recommended in addition to the use of opiates and peripherally active analgesics. Steroids are recommended for a rapid response, while the addition of either amitriptyline, gabapentin or pregabalin has been shown to be equally effective in clinical trials. Furthermore the prescribing of amitriptyline with gabapentin or pregabalin has been shown to be better than one drug alone in difficult cases. Using two anticonvulsants together has not been shown to have extra benefit. It may be better to favour amitriptyline where there is numbness, burning or painful paraesthesia, although the evidence-base for this is limited. Consultation with a palliative care or pain specialist is also recommended.

For nerve root compression/infiltration:

- Dexamethasone (Dexamethasone): Give 8mg immediately then 8mg in the morning daily for 72 hours, reducing to 4mg each morning for 48 hours. If pain control remains good, maintain with 2-4mg each morning in patients who are in the terminal phase. Otherwise attempt to withdraw completely over three weeks while introducing an anticonvulsant and/or amitriptyline etc (see below) for long-term management
- Anticonvulsants: If there is nil or only a partial response to dexamethasone in terminal phase patients, add one of the following anticonvulsants or an antidepressant (see below).
 - Pregabalin (Lyrica) is now PBS-listed and so the drug of choice for most patients. Start with 75mg every 12 hours, and increase to 150mg every 12 hours after 3 days if necessary (initiate treatment in a lower dose of 25-50mg every 12 hours for the frail and elderly). If the symptoms persist after another 7 days, increase to 300mg every 12 hours. See appendix for dosing patients with renal failure.
 - Gabapentin (Neurontin) is the best option where pregabalin is either toxic or ineffective. However it is not listed on the PBS scheme in Australia for neuropathic pain (it is on the RPBS [repatriation] scheme), and can be used in patients with mesothelioma covered by the dust-diseases board. With gabapentin, start on 100mg every 8 hours increasing by 100mg every 8 hours daily, up to 300mg every 8hours unless pain is controlled on a lower dose (introduce more gradually in the frail

and elderly). Then increase the dose weekly from 300-600-900-1200mg every 8 hours or until there is a response. See appendix for dosing patients with renal failure.

- Sodium valproate (Epilim) is accessible and easy to prescribe, starting with 500mg at night, increasing to 1G if no benefit after 3 days (start with 200mg in the elderly, quickly increasing to twice daily if well tolerated).
- Carbamazepine (Tegretol) 100-400mg every 12 hours (but high frequency of side effects) may also be considered.
- Antidepressants: Amitriptyline (Endep) is a reasonable first choice with plenty of evidence based research to support its use here. However nortriptyline (Allegron) and imipramine (Tofranil, Toleride) are also considered effective if it is not well tolerated. Of the other classes of antidepressants the SNRI drugs venlafaxine (Efexor-XR) and duloxetine (Cymbalta) have the most evidence to support their use at this time, although a number of SSRI drugs may be effective. Of these sertraline (Zoloft) or citalopram (Cipramil) are recommended for their lower incidence of side-effects.
- Amitriptyline: commence 10mg nocte, increasing by 10mg daily to 2nd-daily up to a maximum dose of 50mg nocte (the max dose of amitriptyline is 150mg nocte but there is little evidence for benefit on neuropathic pain above 50mg nocte). Add an anticonvulsant if there is residual pain a week after reaching 50mg nocte.
- Nortriptyline: as for amitriptyline above.
- Imipramine: as for amitriptyline above
- Venlafaxine: commence 37.5mg nocte, increasing to 75mg nocte in 1 week if necessary. A further increase to 150mg nocte could be considered for residual pain 2 weeks later in patients with normal renal function.
- Duloxetine: commence 30mg daily increasing to 60mg daily in patients without severe renal failure (EGFR < 30mls/min). Further increase to a maximum of 120mg/day can be considered if symptoms persist.
- Local Anaesthetic Cogener: Most palliative care physicians would occasionally consider the introduction of a local anaesthetic cogener (lignocaine infusion, flecainide [Tambocor, Fleccatab]) when severe residual neuropathic symptoms persist despite the above measures, as well as the failure to control symptoms with ketamine (see next section) and opiate rotation to methadone. It is noted here that the place of ketamine is now controversial. In the most severe cases a subcutaneous infusion of lignocaine can be

tried with maintenance on oral flecainide. Otherwise commence oral flecainide alone. Each patient should be considered on an individual basis and practitioners are requested to consult with MIMS with regard to risk factors. It may be advisable to obtain an ECG prior to this intervention.

- Lignocaine infusion (regional approach): Give 100mg SC statim (5mls 2% lignocaine), followed by 600mg by continual SC infusion over 24hrs. Increase the dose to 1200mg if necessary after this time. If pain is well-controlled, commence flecainide 50-100mg twice daily, increasing to 150mg twice daily after 4 days if symptoms return. If pain not well-controlled, abandon the trial of local anaesthetic cogener.
- Flecainide: Commence 50mg twice daily, increasing by 50mg twice daily up to a maximum of 150mg twice daily.
- Other options include opiate rotation to methadone, ketamine infusion (see p..) and clonidine (Catapres) 25-100 mcg every 8-hours.

Important Note: Narcotic analgesic drugs are usually prescribed up to the point of drowsiness to establish the degree of effectiveness in these situations. Further increases are a recipe for restlessness, agitation or oversedation of the patient. Some patients resist all these therapeutic interventions and may be considered for interventional approaches, including nerve blocks, and epidural or intrathecal analgesic approaches. Patients who are in the end-stages might be better managed with sedation if symptoms are severe. Many patients are able to accept the limitations of treatment and use frequent (eg half-hourly) doses of breakthrough opioid medications for particularly painful exacerbations.

Intractable Pain and Ketamine

Ketamine, an anaesthetic induction agent, had an established role in control of intractable pain including reported efficacy with neuropathic pain, incident pain (ie caused by movement) and cytotoxic-induced mucositis. However an Australian study has shown it to be not superior to placebo across this range of complex pain. This has led to controversy about its use but 'the jury' is out on certain aspects of study-design, and many practitioners continue to use burst or oral ketamine as a trial in difficult cases. A personal preference is to introduce oral ketamine, limiting side effects and making it relatively easy to withdraw if there is toxicity.

Ketamine has a propensity to cause tachycardia, a sense of disassociation and hallucinations. The latter may be dose-limiting, though co-prescribing diazepam, midazolam or haloperidol can settle hallucinations or 'strange feelings'. In our unit we usually mix midazolam

5mg with the ketamine dose, given as a subcutaneous infusion over 24 hours.

A common approach is referred to as 'burst ketamine' in which a short burst of ketamine is given over a number of days then stopped. This is thought to reset pain transmission and inhibitory pathways in the central nervous system such that pain may respond dramatically and then continue to be controlled on the previously ineffective analgesic regimen. Care must be taken as opiate toxicity can result due to a rapid reduction in analgesic requirements (see below).

- **Burst Ketamine:** Begin with 1-2.5mg/kg/24 hours by continual subcutaneous infusion, and titrate to effect. In practical terms start with 100mg/24 hours on day 1. If effective, continue this dose for three days then cease. If not, then increase to 300mg/24 hours on day 2. If this dose is effective continue for three days, then cease. If not, then increase to 500mg/24 hours on day 3 and continue for 3 days if effective. This upper limit of 500mg/24 hours is arbitrary and higher doses are safe if the patient tolerates the treatment (3.6G/24 hours have been reported). I would go higher than 500mg in the same 200mg steps if a partial response was observed at 500mg, although I have never used more than 700mg/24 hours.
- **Responses:** In the best-case scenario the pain remains controlled after stopping the infusion. It may return again after an interval of weeks or months and can then respond to another 'burst'. If pain returns after stopping the infusion then the patient will need to be maintained on continual subcutaneous or oral ketamine (see below).
- **Oral ketamine:** When used for maintenance, oral ketamine is given (from the ampoules) in 1/3rd of the total daily dose that was effective by subcutaneous infusion. This allows for 'first pass' enhancement of its effect through active metabolites. It doesn't taste too good but can be flavoured in cordial (50mg/5ml). The oral dose needs to be divided into four or more administrations daily as it can give a 'hit' effect with unpleasant side effects compared to the steady state levels of a continual infusion. If treatment is to be initiated orally start with 10mg q6-hourly. Increase the dose in 10mg steps up to a maximum of 50mg q6-hourly (again this is arbitrary and doses up to 200mg q6-hourly have been reported). Continue the effective dose for three days then cease, and follow the steps given for infusions above thereafter.
- **Concurrent Treatment:** Ketamine, if effective, may lead to a substantial reduction in the concurrent opiate dose through improved analgesia. Bear in mind that your patient may become excessively drowsy or develop hallucinations due to opiate toxicity.

This is relatively easy to manage by dose reduction of short-acting morphine but it could be more of a problem with slow-release preparations, methadone or transdermal fentanyl. It is wise to recommend transfer to a short-acting product before starting the infusion.

- **Severe Pain:** in a patient with severe pain it may be necessary to use morphine and midazolam in doses that semi-sedate, whilst introducing ketamine. This might require parenteral hydration until such treatment can be reduced.
- **Site reactions:** Some patients develop inflammatory reactions, including sterile abscesses at the infusion sites. These can be stopped by adding 0.5-1mg of dexamethasone to the infusion.
- **Drug compatibility:** Ketamine is compatible with morphine sulphate, metoclopramide, haloperidol, midazolam and low-dose dexamethasone in the syringe-driver.

Visceral Pain

Like neuropathic pain, visceral pain is relatively insensitive to narcotics. The following treatments are recommended:

- **Hepatic pain** which is secondary to capsular distension: dexamethasone 4mg daily in addition to other analgesic measures
- **Genito-urinary pain** (dysuria, bladder spasms, renal colic): [See page 22.](#)
- **Gastrointestinal colic:** [See page 16.](#)

Epidural and Intrathecal Pain Control

Patients with intractable pain (especially neuropathic) may only respond to epidural or intrathecal infusions of opiates, local anaesthetics, clonidine or ketamine. While it is not within the scope of this book to detail such approaches it is useful to know the basic recipes for success and safety, though consultation with a pain consultant (usually an anaesthetist) experienced in these techniques is essential. I have outlined basic recipes for lumbar epidural and intrathecal infusions of morphine plus bupivacaine below, suitable for pain beneath the umbilicus. For thoracic and cervical infusions the doses are more conservative.

- **Typical Epidural Recipe (Morphine plus Bupivacaine):**
 - **Morphine** – Begin with 1/30th of the daily oral morphine dose (or 1/15th parenteral dose) up to a maximum initial infusion of 10mg per 24 hours. For opioid naive patients begin with 1-3mg per 24 hours. With severe pain the dose of morphine may need to be progressively increased up to 50mg or more per 24 hours.

- Bupivacaine – Begin with 0.125% bupivacaine (125mg in 100mls). Give 10ml statim as a bolus dose, then run at 1-20mls per hour, starting the infusion at 10mls per hour. With severe pain the patient may require increased concentrations of bupivacaine (up to 0.5% = 500mg in 100mls) run at the same rates.
- Typical Intrathecal Recipe:
 - Morphine – Begin with 1/200th of the daily oral dose (1/100th parenteral dose) up to a maximum initial infusion of 5mg per 24 hours. For opioid naive patients, begin with 0.5-1mg per 24 hours. With severe pain the morphine dose may need to be progressively increased to 15mg per 24 hours, above which there is a high risk of convulsions.
 - Bupivacaine – Begin with 0.125% bupivacaine. Give a 3ml bolus, then start the infusion at 2mls per hour and run at 1-5mls per hour. A rising level of dermatomal block indicates that the rate of infusion is too high (easily tested by running a block of ice over the abdomen and chest wall).
- A fall in blood pressure indicates that the infusion is producing an effect. Most people tolerate a systolic of 85-90mm Hg.
- Be aware that pain relief may dramatically improve requiring a sharp reduction in systemic opiates to prevent toxicity.

Renal Failure

- Morphine: In patients with abnormal renal function (including some elderly or cachectic people with a normal creatinine) highly active metabolites of morphine accumulate. Patients typically develop good analgesia initially, but this may be followed by coma and respiratory depression over the next 48 hours. With so many alternate opiate options available today morphine is best avoided in patients with an EGFR < 60mls/min. If it must be used then careful supervision aiming initially to relieve pain, then reducing the morphine dose by 75% (EGFR 20-60ml/min) over the next 1–2 days to a lower maintenance level is recommended. Extreme caution is recommended for EGFR <20ml/min. These patients should not be commenced on sustained-release preparations until the steady-state morphine dose has been established with liquid morphine.
- Hydromorphone also accumulates the parent drug and metabolites, but these are relatively inactive compared with morphine. It can be introduced in about half its normal dose in patients with severe renal failure (EGFR < 30ml/min).
- Oxycodone has no significant active metabolites but the parent drug accumulates. It is a safer choice but

should be used in about half the usual dosage after an initial 'loading dose' for 24hours in patients with EGFR < 30ml/min. It is recommended not to use in patients with EGFR < 10ml/min due to high risk of excess sedation.

- Fentanyl has no active metabolites and about 75% is eliminated through the kidneys. It is a safe option, though the elimination time may be increased in severe renal failure and a lower dose may be effective. Some authorities recommend using about 75% of the usual dose for EGFR 10-20ml/min and half-doses for less than this.
- Methadone has few active metabolites and is considered by some authorities to be the drug of choice in renal failure. However it already has complex, unpredictable pharmacokinetics and the parent drug can accumulate in renal failure. It is not recommended here except under the supervision of a pain specialist experienced in its use.
- Buprenorphine (Norspan) has no significant active metabolites and is considered safe in renal failure patients, although it is dialysed, which may make its use complex in these patients.

Hepatic Failure

All the opioids are metabolized through the liver, so may have increased bioavailability in liver failure. This doesn't usually present clinical problems in patients already stabilized on opiate analgesics, although it might be a cause of increasing drowsiness or other toxicity in patients with deteriorating liver function. If opiates are introduced for patients with marked liver dysfunction, careful introduction of lower-than-usual initial doses are recommended (e.g. commencing 5mg of morphine orally every 4 hours).

Intravenous Drug Users

Reluctance to prescribe adequate analgesic doses of narcotic drugs to this group of patients is a significant cause of morbidity. Concern about addiction should be secondary to good symptom management, and 'limit setting' used only in patients clearly misusing prescribed regular medications.

Common Opiate Conversions

In the past, opiate conversions were mainly limited to transferring from a weak opioid to morphine. It is much more common these days to transfer patients from one opioid to another. This may be for convenience, or to avoid the side-effects of one preparation, or an attempt to improve pain by opioid rotation. Commonly used conversions as applied in our service are given here. It

is emphasized that while these guidelines have reliable clinical application they are, at best, good estimates and there is individual variability.

Conversions are given here from different opioids to the oral equivalence of immediate-release morphine every four hours. The equivalent doses of long-acting preparations could be used in place of these. To convert between other opioids you can work back from their morphine equivalence (eg from oxycodone to hydromorphone, multiply by 1.5 to get the morphine equivalence of oxycodone then divide this by 5 to get the right dose of hydromorphone). Conversions from oral to parenteral routes of administration are also given for the drugs where relevant.

Converting oral to parenteral morphine

- SC, IM or IV morphine has equivalent effect in one-half of the oral dose. This is due to first-pass hepatic metabolism of one-half to two-thirds of the orally administered morphine dose. Like most services around the world we use one-half the oral dose when changing patients over to subcutaneous administration.

Converting codeine to morphine

- Two codeine tablets (60mg) are equivalent to morphine 5–10mg (about 1/8th of the dose of codeine) every 4 hours.

Converting tramadol to morphine

- 100mg of tramadol is roughly equivalent to morphine 10mg orally.

Converting oral to parenteral oxycodone

- Parenteral oxycodone is now available although it is expensive and not yet listed on the PBS. Use half the total daily oral dose, divided into six, four-hourly SC injections.

Converting oxycodone to morphine

- Use a conversion factor of 1:1.5 (Oxycodone 10mg is equivalent to 15mg of morphine).

Converting hydromorphone to morphine

- Use a conversion factor of 1:5 (Hydromorphone 1mg is equivalent to 5mg of morphine).

Converting oral to parenteral hydromorphone

- Give one-half of the oral dose.

Converting transdermal (TD) fentanyl to morphine

- Every 25mcg/hr represents 15mg q4-hourly of oral morphine.
- Durogesic 12 \equiv 7.5mg oral morphine every 4 hours (range: up to 45mg oral morphine per 24 hours)

- Durogesic 25 \equiv 15mg oral morphine every 4 hours (range: 45-135mg oral morphine per 24 hours)
- Durogesic 50 \equiv 30mg oral morphine every 4 hours (range: 135-220mg oral morphine per 24 hours)
- Durogesic 75 \equiv 45mg oral morphine every 4 hours (range: 220-310mg oral morphine per 24 hours)
- Durogesic 100 \equiv 60mg oral morphine every 4 hours (range: 310-400mg oral morphine per 24 hours)
- Every subsequent increase in durogesic of 25mcg/hour \equiv an additional 15mg of morphine every 4 hours orally. The full range equivalences are given in MIMS for reference.

Converting transdermal to parenteral fentanyl

- The same dose should be given by infusion (eg for Durogesic 25, change to parenteral fentanyl in a dose of 25mcg/hour), starting the infusion 6-12 hours after removing the patch. If the patient becomes drowsy half the dose of the fentanyl infusion for 6 hours or until pain breaks through.

Converting transdermal (TD) Buprenorphine (Norspan) to Morphine

- Every 5mcg/hr represents 2mg q4-hourly of oral morphine
- Norspan 5 \equiv 2mg oral morphine every 4 hours
- Norspan 10 \equiv 4mg oral morphine every 4 hours
- Norspan 15 \equiv 6mg oral morphine every 4 hours
- Norspan 20 \equiv 8mg oral morphine every 4 hours
- Alternatively multiply the Norspan patch dose by a factor of 2.4 to calculate the total daily dose of oral morphine in mgs.

Converting methadone to morphine

- No direct conversion between methadone and other opioids can be used. The use of methadone is covered in more detail in the earlier section ([page 5](#)).

Gastrointestinal Symptoms

Nausea and Vomiting

The common causes of nausea and vomiting are:

- Metabolic problems
- Drug-induced
- Upper gastrointestinal inflammation
- Raised intracranial pressure
- Constipation
- Bowel obstruction

The most common is opiate-induced nausea and vomiting. The choice of anti-emetic depends on the cause as there are three levels where drug therapy may be effective: 1. Chemoreceptor trigger zone (CTZ; D2 and 5HT3 receptors): haloperidol, prochlorperazine (Stemetil), metoclopramide, ondansetron (Zofran), tropisetron (Navoban); 2. Gastric emptying: domperidone (Motilium), metoclopramide, erythromycin; 3. Vomiting centre (H1 and cholinergic receptors): promethazine (Phenergan), cyclizine, hyoscine hydrobromide (Hyoscine injection, Kwells).

Chemoreceptor Trigger Zone Blockade

For metabolic, opiate and other drug-induced nausea:

- Haloperidol: 3mg immediately orally or SC, then 3mg orally at night. Advantage is long half-life enabling successful control with once-daily administration. Depending on response, reduce to 1.5mg or increase to 5mg nightly for maintenance
- Prochlorperazine: 10mg every 4–8 hours orally or 25mg every 12 hours by suppository
- Metoclopramide: 10-20mg orally or SC, then every 4–8 hours orally
- Ondansetron: 4-8mg orally or SC, then every 8–12 hours orally
- Tropisetron: 5mg once daily orally.

If unsuccessful, or only partially successful, add a different class of drug to combine the effects with increased gastric emptying or vomiting centre blockade. Ondansetron and tropisetron may have an additive effect when used with other drugs that act on the CTZ.

Increasing Gastric Emptying

For gastric stasis (the aetiology in 5–10% of opiate-induced vomiting) and for combination with CTZ-blocking drugs, if needed:

- Metoclopramide: 10-20mg orally or SC, then every 4–8 hours orally or SC
- Domperidone: 10-20mg every 4–8 hours orally
- Cisapride: 5 to 10mg every 8 hours orally (only available through the special access scheme in Australia). Also stimulates small and large bowel. Reportedly synergistic when combined with metoclopramide.
- Erythromycin: 75mg oral elixir every 8 hours (this has developed popularity for patients with denervated stomachs, eg following oesophagectomy with thoracic stomachs and gastric stasis). Combination with cisapride is contra-indicated.

These drugs may increase colic in patients with constipation or bowel obstruction. With upper gut obstruction vomiting may be increased due to reverse peristalsis, in which case this class of drug should be withdrawn.

Vomiting Centre Blockade

The following drugs may be used in combination with other classes of drugs in resistant cases and may be considered first-line treatment in vomiting due to gastrointestinal obstruction and steroid-resistant raised intracranial pressure:

- Promethazine: 10–25mg orally or SC, then every 12 hours orally or SC
- Cyclizine: 25-50mg orally or SC, then 25-50mg every 8-12 hours orally or SC (the tablets are only available on the special access scheme in Australia)
- Hyoscine hydrobromide: 0.3–0.6mg every 8 hours orally or 0.2-0.4mg SC every 8–12 hours.

Broad-Spectrum Anti-Emetic

Recommended for mechanical bowel obstruction (see P..) where other measures have failed:

- Levomepromazine 6-12.5mg PO or SC stat, then every 6-12 hours or by continuous SC infusion (levomepromazine is only available on the special access scheme in Australia).

Important Points

For intractable symptoms consider:

1. Colonic faecal loading or impaction (P.R. examination, x-ray). [See page 15.](#)

- Hypercalcaemia. Consider treatment with oral sodium clodronate (Bonafos), disodium pamidronate (Aredia) 30-90mg IV, or Zoledronic acid (Zometa) 4-8mg IV.
 - Upper GI inflammation. Omeprazole (Losec) 20-40mg orally in the morning, or Esomeprazole (Nexium) 20-40mg orally in the morning (may be used twice-daily). Ranitidine (Zantac) injections can be given SC.
 - Bowel obstruction. [See page 16](#). Avoid bowel stimulants such as metoclopramide, cisapride, docusate sodium with senna, senna (Senokot).
 - Raised intracranial pressure. Use steroids and consider further investigation if appropriate.
2. Parenteral therapy in patients unable to tolerate oral medications:
- Initiate treatment through the SC route using medication options already discussed. Continue with regular SC injections in place of the oral regimens, or consider a syringe driver for at least 48 hours. A combination of promethazine 25-100mg per 24 hours and metoclopramide 40-60mg per 24 hours by syringe driver is often effective for most causes of nausea and vomiting. A small dose of dexamethasone (0.5mg) can be added to the infusion if local inflammation at the injection site is a problem.
 - Consider rehydration with SC fluids, using 1-2 litres of normal saline or 4% dextrose and 1/5th normal saline, if desirable.

Constipation and Faecal Impaction

There is a considerable range of options for the management of these symptoms even in our local service. The following guidelines reflect a personal approach, which is not necessarily better than others. The most important recipe for success however is to have a systematized approach that includes regular review and sensible medication changes if required, using faecal softeners, bowel stimulants, contact evacuants or 'flushing' agents, with or without rectal measures. One important introduction in recent years has been macrogol 3350 (Movicol, Osmolax), which has considerably reduced the need for rectal measures in our service.

A further development recently has been the introduction of methylaltrexone injections (Relistor) given subcutaneously for opiate-induced constipation.

Prophylaxis When Commencing Regular Opiates

It is recommended that all patients on opiate treatment receive prophylaxis, even when reporting 'normal' bowel habit.

The following stepwise approach is recommended:

1. Docusate sodium with senna (Coloxyl with Senna) or bisacodyl (Duloxyl): 2 tablets at night (Bisacodyl is available through the PBS in Australia). If effective, continue with this and consider reducing the dose if it causes abdominal pain or diarrhoea. If ineffective by 3rd day, go to the next step.
2. Glycerine, bisacodyl (Duloxyl) or docusate plus bisacodyl (Coloxyl) suppository immediately. Increase docusate sodium with senna or bisacodyl to 2-3 tablets twice-daily. If ineffective by 2nd day, go to the next step.
3. Substitute oral macrogol 3350 (Movicol 2-4 sachets; or Osmolax 3-6 level scoops) in the morning or at night. As a bowel flushing agent it would seem rational to use macrogol 3350 once daily rather than in divided doses. Some patients who dislike the taste or feel nauseated on Movicol appear to tolerate Osmolax better, although treatment may need to be discontinued. Movicol can be given in a dose of 8 sachets daily (or Osmolax 12 scoops daily) for up to 3 days to treat faecal loading or impaction (see below). If ineffective after the 2nd day, increase the dose or go to the next step.
4. Repeat suppository and/or phosphate enema if required. Try liquid paraffin (Agarol) or lactulose (Duphalac, Actilax) 20-30mL plus senna granules 1-2 teaspoons twice to three times daily. Alternatively try a different bowel flusher – Epsom salts 1-3 teaspoons in the morning.
5. Some patients are resistant to all these measures and require the combined use of oral aperients and rectal measures, using suppositories every 2-3 days and/or enemas once or twice a week.

Evaluation of the Constipated Patient

The following steps are recommended:

- Take a history of duration, extent and nature of constipation including whether stool is hard, soft or spurious (diarrhoea)
- Abdominal examination to detect colonic loading. Rectal examination to determine whether stool is hard or soft, impacted or not impacted. Dilated rectum suggests high colonic loading or impaction. A lax anal tone suggests a neurological problem, such as disease affecting the cauda equina.
- Obtain x-ray when extensive faecal loading is suspected
- Proceed to digital disimpaction of the rectum if indicated following adequate analgesia and sedation (e.g. midazolam [Hypnovel] 2-5mg plus an opioid, both by SC or IM injection).

Management of Severe Constipation with High Colonic Loading

For high **colonic loading with 'hard' faeces** in rectum, the following stepwise approach may be followed:

1. Softening regimen avoiding bowel stimulants: e.g. daily Microlax enemas plus oral liquid paraffin 30mL 3 times daily; or docusate sodium (Coloxyl 120mg tablets) 240mg 3 times daily; soap and water enemas 100-200mL daily for 2 days.
2. Try macrogol 3350 as a bowel flusher. The recommended dose for patients with colonic loading is Movicol 8 sachets a day (Osmolax 12 level scoops a day) for up to three days. This may sometimes result in distressing faecal incontinence so it is recommended here to initially trial a dose of Movicol 4 sachets (Osmolax 6 scoops) in the morning. Subsequent dosing will depend on the response. It is not uncommon to give 8 sachets a day without response for the first day or two, then have the passage of normally formed stools on subsequent doses. If no response or patient unable to tolerate the Movicol (some of these patients tolerate Osmolax well) go on to the next step.
3. As an alternative second or third step for patients with opiate-induced constipation trial methylalnaltrexone (Relistor) by SC injections (see MIMS for doseage and precautions in hepatic and renal failure). This could be administered daily to 2nd –daily according to response, and can be combined with the other approaches if desired (eg 2nd-daily PRN).
4. Evacuant washouts: continue paraffin or docusate sodium orally. Soap and water enemas 200-500mL daily for 2 days (give up to 1 litre if volume easily passed). Hyoscine butylbromide (Buscopan) 20mg IM injection may be given to prevent colic. Midazolam 2–5mg IM injection may be required for sedation. Repeat x-ray following this to check radiological clearing (ideally).
5. After success, commence an aperients regimen, which must be more aggressive than previous (failed) aperient regimen ([see page 14 on prophylaxis](#)). If the macrogol 3350 flushing approach succeeded then it is often easy to maintain on 1-2 sachets Movicol (or 2-3 scoops Osmolax) every morning or night plus or minus coloxyl with senna.

For high **colonic loading with 'soft' faeces** in rectum, the following steps are recommended:

1. Evacuation: Try Movicol or Osmolax as described above. Failing this use liquid paraffin 30mL 3 times daily or docusate sodium tablets 240mg 3 times daily, and soap and water 200-500mL plus bisacodyl enema (Bisalax) 10mL (mixed) daily for 3 days. Give

up to 1litre of enema solution if well tolerated. Repeat x-ray following this to check for radiological clearing (ideally).

2. As an alternative for patients with opiate-induced constipation, trial methylalnaltrexone (Relistor) by SC injections (see MIMS for doseage and precautions in hepatic and renal failure). This could be administered daily to 2nd –daily according to response, and can be combined with the other approaches if desired (eg 2nd-daily PRN with daily Movicol).
3. After success, commence aperients following review of previous (failed) aperient regimen ([see page 14 on prophylaxis](#)). Use maintenance Movicol 1-2 sachets or Osmolax 2-3 level scoops in the morning if this was effective and well tolerated.

For high **colonic loading with an 'empty' rectum** on P.R.:

1. Evacuant washouts: Movicol/Osmolax as described above. Alternatively Epsom salts 1-3 teaspoons in the morning. Failing this try oral liquid paraffin 30mL 3 times daily or docusate sodium tablets 240mg 3 times daily **plus** soap and water enema 500mL–1 litre daily for 3 days. Repeat x-ray to check radiological clearing (ideally).
2. As an alternative for patients with opiate-induced constipation trial methylalnaltrexone (Relistor) by SC injections (see MIMS for doseage and precautions in hepatic and renal failure). This could be administered daily to 2nd –daily according to response, and can be combined with the other approaches if desired (eg 2nd-daily PRN).
3. After success, commence aperients following review of previous (failed) aperient regimen ([see page 14 on prophylaxis](#)). Use maintenance Movicol 1-2 sachets or Osmolax 2-3 level scoops in the morning if this was effective and well tolerated.

Notes

- High volume soap and water washouts: slow administration over 20 minutes via rectal tube may be needed in patients who have recto-sigmoid spasm and 'flush-back' effect. This administration can be managed by setting up an infusion with IV stand. Spasm may be prevented by prior administration of hyoscine butylbromide 20mg by IM injection.
- Perseverance is the key to success in difficult cases. For example, soap and water enemas 500ml-1 litre daily for 7 days is sometimes needed (patient is invited to call 'rest days').
- These approaches may be inappropriate in the last days of life when bowel management should be dictated by symptoms and common sense.

Medical Palliation of Bowel Obstruction

Surgical Palliation

This should be considered first. Generally surgical palliation is the best form of management of bowel obstruction under the following conditions:

- A fit and willing patient
- A single site of obstruction or a potentially reversible cause.

Modern stenting techniques should be considered for patients with proximal obstruction of the duodenum or gastric outlet where appropriate and not in the terminal phase. Otherwise medical palliation should be the approach.

Principles of Medical Palliation

- Avoid 'drip and suck' (unless considering surgery)
- Eliminate nausea and vomiting using antiemetics. Some patients may continue to experience vomiting once or twice a day in the absence of nausea
- With high volume secretions reduce volume with octreotide (consult with your local palliative care services)
- Eliminate colic using antiperistaltic drugs
- Use enemas to reduce low obstruction if possible (especially with subacute bowel obstruction)
- Reduce peri-tumour oedema with corticosteroids.
- Encourage ambulation, eating and drinking.
- Continue current oral opiates in half dose subcutaneously

Management of Nausea and Vomiting

My preference is to use promethazine and metoclopramide in combination despite the possibility of increasing the vomiting of high small bowel obstruction with metoclopramide due to reverse peristalsis. This is rare in practice, especially where steroids are used concurrently, and the stimulant effect of metoclopramide can overcome functional or partial obstructions, and eliminate gastric stasis. These orders

- Give promethazine 25mg SC statim, then 50mg SC infusion over 24 hours plus metoclopramide 10mg SC statim, and 40mg by SC infusion over 24 hours (or promethazine 25mg SC, twice daily plus metoclopramide 10mg SC every 6 hours). These drugs can be mixed in a syringe driver with hyoscine butylbromide (Buscopan [colic]) and morphine or hydromorphone (pain).

- Add 0.5mg of dexamethasone (as the last) to the infusion if there are problems with SC-site inflammation due to promethazine.
- Commence octreotide (Sandostatin) 0.1-0.5mg SC every 8 hours, which can be added to the syringe-driver as a 24-hour infusion, plus dexamethasone 8mg SC daily in patients with persistent high volume vomiting or where you suspect vomiting will be difficult to manage.
- Add levomepromazine 6.25mg SC statim, followed by 25-50mg SC infusion over 24-hours in resistant cases. This drug can be used in higher doses if terminal sedation is desirable for people who are dying. The author has combined this drug with the other drugs mentioned above in the same syringe-driver. Levomepromazine is only available through the special access scheme in Australia.
- Alternative anti-emetics include:
 - Cyclizine 25mg SC statim, then 50-150mg by SC infusion over 24 hours. Only accessible by the special access scheme in Australia and less compatible with Buscopan in a syringe-driver than promethazine. Considered the drug of choice in many centres.
 - Hyoscine hydrobromide 0.3mg sublingually every 8 hours
 - Hyoscine hydrobromide 0.2-0.4mg by SC injection every 8-12 hours
 - Prochlorperazine suppositories 25mg every 8-12 hours
 - Haloperidol 1-3mg subcutaneously every 8 hours (or combined in the syringe-driver)

Patients should remain free of nausea but may still vomit once or twice a day. This is worth explaining to the patient and family. Some patients require continual parenteral treatment, while others may be subsequently managed using the same drugs orally. Some patients have repeated episodes of acute obstruction that can be well-managed at home with a few days of treatment, avoiding repeated episodes of hospitalization. Good planning with available drugs in the household and written orders for nurses to follow are required for this. The availability of subcutaneous fluids, eg 1L normal saline given over 4-6 hours every 24 hours, may also be needed.

Management of Colic

- Discontinue all stimulant aperients: i.e. docusate sodium with senna; senna; bisacodyl
- Consider docusate sodium tablets 240mg or liquid paraffin 30mls every 8 hours as a faecal softener after

controlling vomiting. Commence in all patients with subacute (incomplete) bowel obstruction

- Determine the level of obstruction: gastroduodenal, proximal or distal small bowel, large bowel. There is often no colic with high bowel obstructions.
- For faecal colonic loading or impaction follow the evaluation steps on [page 15](#). This is a common cause of presentations with large bowel obstruction, even when a significant organic component is present
- Initial parenteral treatment: hyoscine butylbromide 20mg IM and parenteral morphine 5–10mg IM or SC (in patients already on morphine give 1/12th the daily oral dose parenterally) followed by hyoscine butylbromide 20mg every 4-8 hours SC (the daily dose may be given as continual SC infusion by syringe driver, combined with other drugs as described above). Long term parenteral maintenance may be required in some patients.
- Once vomiting is controlled, any of the following oral antispasmodics may be employed long-term if continuing treatment is required:
 - Lomotil 2.5–5mg every 8–12 hours (a personal favourite with little anticholinergic effect)
 - Mebeverine (Colofac) 135–270mg every 8 hours (no anticholinergic side-effects)
 - Hyoscine hydrobromide 0.3mg sublingually every 8-12 hours
 - Hyoscine butylbromide 10-20mg every 6 hours (may not work due to low bio-availability when given orally)
 - Donnatal 1-2 tablets every 6-8 hours.
 - Propantheline (Pro-Banthine) 15-30mg every 6 hours.

Maintenance Therapy in Patients with Subacute Bowel Obstruction

These patients have partial organic obstruction and require colic prevention whilst maintaining a regular soft stool. Existing faecal loading or impaction should be managed in accordance with the steps given on [page 15](#). Care must be taken where the degree and level of organic obstruction is uncertain. Endoscopy or radiocontrast studies may be indicated. For management after treating the initial presentation, the following is recommended:

- Lomotil 2.5–5mg plus docusate sodium 240mg every 6–12 hours. From personal experience this surprising combination frequently results in a colic-free patient passing normal stools. Movicol 1-2 sachets daily can be added. Glycerine, coloxyl or bisacodyl suppositories to be used if required every 2–3 days. Soap and water enemas 100–500mL may be needed once or twice a

week. Some patients require high volume soap and water enemas (up to 1L) once or twice a week.

- Continue appropriate antiemetic regimen as described above.
- Consider reducing obstruction by using dexamethasone. If desirable, commence 8mg daily for 5 days and, if of benefit, continue on 2-4mg daily. I have often found this to be essential and symptoms can respond well but return as the steroid dose is reduced necessitating continuing high-dose steroids.

Gastroduodenal and High Small Bowel Obstruction

This condition may not respond effectively to measures outlined above, particularly in relieving vomiting. The following treatments are recommended:

- Remove metoclopramide from the treatment above in patients not responding in case it is causing reverse peristalsis against an organic obstruction.
- Dexamethasone 8mg SC daily may relieve obstruction by reducing tumour-induced inflammation. Give a 3-5 day clinical trial
- Octreotide (Sandostatin) 0.1-0.5mg every 8 hours SC will reduce the volume of intestinal secretions and improve vomiting in most patients. Consider a 3–5-day trial in distressed patients who wish to avoid a nasogastric tube or ‘venting’ gastrostomy.
- Consider a nasogastric tube or gastrostomy to relieve vomiting in patients who do not respond to the measures outlined above, assuming that they are fit and willing.
- Dehydration is desirable in terminally ill patients due to reduction in volume of intestinal secretions. IV fluids are particularly contraindicated in this group as they will increase vomiting and lead to a more unpleasant death.
- Consider SC fluids to maintain hydration in other patients, usually around 1-2 litres a day but lean towards ‘the dry side’.

Squashed Stomach Syndrome

This condition is characterised by dyspeptic symptoms associated with compression of the stomach from hepatomegaly or an upper abdominal tumour. Symptoms are:

- Fullness
- Early satiety
- Epigastric pain
- Flatulence
- Nausea
- Vomiting

- Heartburn
- Hiccups.

Treatment is as follows:

- Antiflatulent: Mylanta 10mL every 4–6 hours; simethicone (Degas, Gasbusters) 100-200mg with meals or every 6 hours.
- Acid reduction: Omeprazole 20-40mg in the morning; esomeprazole 20-40mg in the morning.
- Increase gastric emptying: Metoclopramide 10–20mg every 4–8 hours; domperidone 10-20mg every 6 hours.
- Dietary advice regarding small meals.

Anorexia

This is a common and sometimes distressing symptom in people with advanced cancer or in other terminal care situations often associated with weakness, decreased energy and low well-being. Therapeutic options include:

- Dexamethasone 4mg daily, discontinue after 5 days if no effect. Reduce the dose to a minimal effective level where there is a good response. Dexamethasone may also enhance well-being, strength and energy. Dexamethasone may not be appropriate in patients with a life expectancy beyond 2 or 3 months due to progressive side effects including the potential to cause proximal myopathy.
- Megestrol acetate (Megostat) 160mg –800mg daily (may require the largest dose to be effective [5 tablets])
- Amitriptyline 10–50mg at night
- Cyproheptadine (Periactin) 4mg every 8 hours.

Hiccups

Hiccups are likely to be caused by one of the following:

- Gastric distension
- Diaphragmatic irritation
- Phrenic nerve irritation
- Brain tumour
- Infection.

Stopping the Attack

- Baclofen (Clofen, Lioresal) is a personal preference, although it can be sedating or cause postural hypotension even in small doses. Start with 10mg orally then 5mg three times a day.
- Reduce gastric distension: metoclopramide (20mg orally or SC) plus antiflatulent (e.g. Mylanta 20mL or simethicone 200mg)
- Pharyngeal stimulation: swallow 2 heaped teaspoons of granulated sugar or 2 glasses of a liqueur; drink from 'wrong' side of a cup

- Central suppression of hiccup reflex: chlorpromazine (25–50mg then 25mg every 8 hours orally). Chlorpromazine 25mg IV may be used in a distressed patient
- Other: nifedipine (Adalat) 10mg orally or sublingually then 10-20 mg every 12 hours; there have been reports of using benzotropine, which has the advantage of SC administration, although I have no local experience with this.

Options for Maintenance Treatment

- Baclofen (Clofen, Lioresal) 5mg three times a day increasing to 10-20mg three times a day if required.
- Correction of gastric distension: metoclopramide (10–20mg every 4–8 hours) plus antiflatulent (e.g. Mylanta 10mL every 4–8 hours or simethicone 100-200mg every 6 hours)
- Central suppression of hiccup reflex: chlorpromazine 10–25mg every 8 hours orally
- Suppression of central irritation from intracranial tumour: dexamethasone 16mg daily reducing to 4–8mg maintenance, sodium valproate 500–1000mg at night and phenytoin (Dilantin) 200–300mg daily
- Other: nifedipine 5-20mg every 12 hours orally or sublingually.

Respiratory Symptoms

Breathlessness

In patients where death is not imminent, with recently developed or increasing dyspnoea, appropriate investigation and treatment of an underlying cause may be worthwhile. Underlying causes of breathlessness include:

- Bronchospasm
- Cardiac failure
- Pulmonary infection
- Pleural effusion
- Superior vena cava obstruction (SVCO)
- Pericardial effusion
- Lymphangitis carcinomatosa
- Anaemia.
- Chronic airways limitation (CAL)

Use of Morphine

- Low dose regular oral morphine is usually effective in relieving dyspnoea. With careful titration of the dose, there is little or no risk of shortening life through respiratory depression, assuming the patient does not have renal failure or CO₂-retention. In patients with renal failure, select hydromorphone (Dilaudid oral liquid) in 1/5th the recommended morphine doses below.
- In patients without pain, commence 2mg (1mg in elderly patients or those at risk including COPD patients with CO₂-retention) every 4 hours, increasing the 4-hourly dose by 2mg daily until relief or drowsiness is achieved. It is unusual to require more than 5–10mg every 4 hours.
- In patients with pain, morphine will have little benefit on dyspnoea until adequate analgesia has been achieved. This usually requires appropriate combination of morphine and other analgesic medications as described in the section on Pain Control ([page 2](#)). Following this, an incremental 25–50% increase in the morphine dose above its analgesic dose is recommended for control of dyspnoea.

Use of other Opioids

- The availability of multiple opioids (morphine, fentanyl, hydromorphone, oxycodone, buprenorphine and methadone) has led to some discussion as to the relative value of these in comparison to morphine. There is no convincing evidence that they are different from one another in the management of dyspnoea. The

recommendation here is to use morphine if it is well tolerated and to reserve other agents for patients who have undue side effects or allergy.

Use of Anxiolytics

Many patients with dyspnoea have related anxiety and a feeling of panic, particularly when intermittent acute attacks occur. Fear of a suffocating death is often present. The following approaches can be usefully combined with morphine at the outset of treatment:

- Chlorpromazine 10–50mg at night or promethazine 12.5–25mg twice daily. The literature reports that these agents may have a significant effect of reducing the symptom of dyspnoea whereas benzodiazepines do not. In clinical experience though benzodiazepines are useful adjuncts, relieving anxiety or panic when given with an opiate.
- Diazepam (Valium) 2–10mg at night.
- Lorazepam (Ativan) 0.5-1mg sublingually during an attack of dyspnoea and panic can be very effective. Its availability with written instructions to administer this with a breakthrough dose of opiate will give the family confidence in managing this situation. The dose can be carefully titrated up to 2.5mg sublingually PRN if a 1mg dose is ineffective. Regular lorazepam 0.5-1mg every 8-hours can be prescribed for patients with anxiety in this setting.
- Alprazolam (Xanax) 0.25-1mg sublingually during an attack of dyspnoea and panic can be very effective (as for lorazepam above). Regular alprazolam 0.25-1mg every 8-hours can be prescribed for patients with anxiety in this setting.
- Clonazepam (Rivotril) oral liquid 0.25-1mg sublingually during an attack. This has a long half-life and may accumulate with drowsiness if used regularly. However it has the advantage of coming in liquid form as many patients with dyspnea have dry mouths.

Counseling and reassurance of the patient that breathlessness can be relieved and that they will not be allowed to 'suffocate' in the terminal phase can give great relief to many patients who have experienced acute attacks of dyspnoea in the past.

Use of Oxygen

Most patients should not require continuous oxygen where there has been optimal management with morphine and anxiolytics. A recent study has shown that a high-pressure electrical, hand-held fan is equally

effective in the management of dyspnoea for patients without low oxygen saturations. While emphasis is on proper symptomatic management oxygen should be available at home in the following settings:

- Where acute attacks are likely – e.g. in end-stage COPD, cardiac failure or thromboembolism
- Where the patient remains extremely anxious despite efforts to counsel and control symptoms
- When there is geographical isolation from after-hours medical and nursing services.

Parenteral Approaches in Terminal, Breathless Patients

For acute or distressing dyspnoea in the dying patient:

- Give morphine SC, IM or IV with clonazepam (Rivotril) 2mg sublingual, or midazolam 5–10mg SC, IM or IV. The dose of morphine depends on the patient's usual oral or SC dose but is often 30mg or more
- Establish a continual SC infusion of morphine + midazolam 30–60mg every 24 hours, or morphine + clonazepam oral liquid 2mg sublingually every 4–6 hours, with the aim of keeping the patient asleep and asymptomatic. ([Other medications should be continued by alternative routes to oral administration, see page 27](#)). The recommended initial morphine dose is 30mg over 24 hours; or 2 times the total 24-hour dose that was being administered parenterally (or the same dose that they were receiving orally) prior to deterioration. The morphine equivalence of other opioids is covered on [page 11](#)
- If adequate sedation (i.e. sleep) is not achieved, [see page 24](#).
- For subacute or progressive dyspnoea in the terminal patient, in association with agitation, delirium or distress, the above approaches are recommended. The addition of haloperidol 2.5mg SC statim then 2–10 mg in the infusion is also recommended for delirium. It is appropriate to provide heavy sedation if the patient requests it in this setting.

Dyspnoea Associated with End-stage Non-Malignant Pulmonary Diseases (including COPD) or End-stage Cardiac Failure

- When symptoms are limiting despite optimal therapy, management with morphine and anxiolytics as described above is both safe and appropriate in most patients with normal renal and hepatic function. Care should be taken with patients at high risk of developing or increasing CO₂ retention including those with COPD and neuromuscular conditions affecting respiration. It would be judicious to commence treatment at the lowest dose ranges and titrate until the desired effect is produced, e.g. starting with morphine 0.5–1mg

orally every 4 hours. In patients with neuromuscular conditions who have hypoventilation and CO₂-retention consideration of positive flow ventilation in the context of opiate use might be appropriately considered in consultation with respiratory services.

- If the patient experiences acute breathlessness, the prognosis of these conditions may be better than with terminal cancer but decision-making is more complex. Options include:
 - Intensify medical management with full investigation of the reasons for deterioration
 - Management as for a dying patient as outlined above
 - An approach that is intermediate between the first two options which involves intensification of medical investigation and treatment, while concurrently increasing the doses of morphine and anxiolytics. This gives a 'window' for recovery while ensuring a patient considered to be 'probably dying' can do so comfortably, avoiding a very distressing respiratory death.
 - Patient and family involvement with these options and decision-making is important, particularly in anticipating and respecting the patient's wishes should deterioration take place.

Cough

In the fittest of patients, consider treatable options rather than solely depending on suppressive therapy. Such options may include:

- Mucolytics for inspissated sputum
- Treatment of gastro-oesophageal reflux
- Antihistamines or steroid nasal sprays for post-nasal drip
- Antibiotics for chest infection
- Bronchodilators for bronchospasm
- Stopping (or substituting for) ACE inhibitors
- Treatment of cardiac failure
- Radiotherapy, chemotherapy or corticosteroids to modify pathological processes.

Cough suppression is indicated in all patients with persistent symptoms.

Suppressing Cough

The following options are available to suppress cough:

- Reduce pharyngeal stimulation using e.g. Simple Linctus 10mL every 2–4 hours
- Central suppression of the cough reflex using narcotic medications such as codeine phosphate 30–60mg every 4 hours (or as Codeine Linctus), Linctus

- Pholcodine (Durotuss forte) 5-10mls every 4-6-hours or morphine 2–20mg every 4 hours. If already taking morphine, try a 25–50% increase in dose and titrate against drowsiness. The same applies to using alternative opiates to morphine with oxycodone and hydromorphone being the most accessible options in appropriate dosage (see morphine equivalent doses on p...). Select hydromorphone in patients with renal failure and EGFR<60mls/min. As a personal approach I often mix linctus pholcodine with the stronger opioid to keep the benefit of the syrup-effect of the linctus.
- Paroxetine (Aropax) 5-20mg has been reported to be very effective though its site of action is unknown.
 - Methadone: some authorities advocate methadone as a better opiate for cough-suppression. Evidence for this is limited but it's worth a trial in difficult cases. Commence 2.5-5mg every 6-hours for 24 hours then reduce dose to 12-hourly (this can be added to the patients other opiate regimen, although drowsiness and a long sleep has been reported with the first dose). The dose can be escalated according to effect but should only be changed at weekly intervals in 25-50% steps. Excessive drowsiness on methadone will take 24-hours to settle and doses should be omitted for this time then recommenced in half the dose.
 - Local anaesthetic blockade of cough receptors may be used in patients whose symptoms persist despite central suppression. Options include: lignocaine 2%, 5mL by nebuliser every 4-12 hours or bupivacaine 0.25%, 10mL by nebuliser every 4-12 hours. Only one or two doses a day may be required when effective. Mechanical cough receptors at the level of the carina will be blocked with standard nebuliser. If symptom control is not achieved, an ultrasonic nebuliser (e.g. Bird nebulizer) can produce a smaller particle size that will additionally block chemical cough receptors in bronchioles. Patients should be advised not to eat or drink for an hour following the treatment as they may be at risk of aspiration.
 - Dry secretions, if indicated, with amitriptyline 10–50mg at night, hyoscine hydrobromide 0.2-0.4mg every 4 hours SC, hyoscine butylbromide 20mg SC initially, then 40mg SC per 24 hours (this avoids the sedative effects of hyoscine hydrobromide), or glycopyrrolate (Robinul) 0.2-0.4mg initially, then 1.2-2.4mg by SC infusion per 24 hours (also avoids sedative effect of hyoscine hydrobromide).
 - Dexamethasone 8mg orally daily for 5 days, reducing to 4mg daily as maintenance, may be a useful adjunct in patients with lymphangitis carcinomatosa or upper airways compression.

Radiotherapy in a small, single fractionated dose may stop cough in lung cancer.

Haemoptysis

Haemoptysis may be controlled with any of the following approaches:

Dexamethasone: 8mg orally or SC daily for 3 days, reducing to a maintenance of 2-4mg daily if desirable.

- Radiotherapy in a single palliative fraction.
- Tranexamic acid (Cyclokapron): Complex dosing - refer to product information. Typical prescribing - 1g orally every eight hours, continuing for 48 hours after bleeding stops. Repeat for further episodes. A maintenance dose might be desirable if bleeding keeps returning, in which case aim for 500mg every eight hours.

Death Rattle

This describes the rattling noise produced during respiration, when secretions are retained in large airways, in patients too weak to expectorate effectively.

Patients are often moribund and unaffected but relatives, other patients and staff may be distressed by it. Counseling relatives is usually advisable to reassure them that the patient is not suffering. The treatment described below is mainly preventive and should be initiated at the first sign of respiratory noises in an unconscious patient.

Treatment

Any of the following treatment options may be considered:

- Hyoscine hydrobromide 0.4mg every 4 hours SC, or 1.2-2.4 mg by continuous SC infusion after an initial dose of 0.4mg.
- Hyoscine butylbromide 20mg SC initially, then 20-40mg SC infusion per 24 hours.
- Glycopyrrolate 0.4mg SC initially, then 1.2-2.4mg SC infusion per 24 hours (same dosing as hyoscine hydrobromide)..
- Midazolam or clonazepam may be added as outlined on [page 24](#) if patient is agitated or restless
- If the symptom is severe, administer midazolam or clonazepam, tilt the foot of the bed and position the patient to achieve postural drainage.
- If associated with purulent sputum consider a statim subcutaneous injection of Ceftriaxone (1g reconstituted in 3.75 mls 1% lignocaine, administering half at two separate sites).

Urinary Symptoms

Frequency and Urgency

Treatable causes should be considered, including:

- Bladder outlet obstruction, irritation or compression by pelvic tumour:
 - TURP for prostatomegaly
 - Dexamethasone 8mg daily for 5 days followed by 4mg maintenance where pelvic tumour is implicated.
 - Chemotherapy or radiotherapy may be options
- Infection
- Diuretic therapy
- Oversedation
- Polyuria which will not respond to the treatment options outlined below (check BSL in patients on steroids).

Treatment

Treatment options include the following:

- Ural sachets (urgency): 1-2 orally, four times a day
- Cranberry juice or tablets for urgency (available in most pharmacies): Adjust dose to response.
- Anticholinergic drugs:
 - Amitriptyline 25–50mg, orally, at night is recommended. It often markedly improves nocturia and has additional hypnotic and anxiolytic benefits. In patients with outflow obstruction, start in a lower dose and increase after 48 hours, then it will generally not lead to urinary retention.
 - Propantheline 15-30mg every 6-8 hours, orally
 - Oxybutynin hydrochloride (Ditropan) 5-10mg orally every 12 hours (2.5mg nocte-q12-hourly in the elderly or debilitated).
- Sympathomimetics:
 - Terbutaline (Bricanyl elixir) 15ml every 8 hours, orally
- NSAID
 - Choice depends on prescriber-preference. May aggravate or cause haematuria in patients with a genito-urinary malignancy. Potentially contraindicated in renal failure.
- Non-drug measures including regular time-contingent voiding (every 1–3 hours), ready availability of bottle, bedpan or commode, proximity to toilet and a rapid nursing response time.

Bladder Spasm

This is usually experienced as painful spasm in the lower abdomen in a catheterized patient. Leaking around an indwelling catheter is a sign of bladder spasm. Treatable causes should be considered. These include:

- Infection requiring antibiotics, with change of indwelling catheter or using intermittent catheterisation every 4–6 hours
- Catheter irritation requiring reduction in balloon volume
- Catheter sludging requiring bladder washouts or continuous irrigation.

Treatment

Treatment options include the following:

- Effective analgesia with NSAID such as naproxen 250–500mg every 12 hours + morphine if required every 4 hours titrated upward until there is effective relief of pain or the occurrence of drowsiness
- Anticholinergic drugs:
 - Amitriptyline 10–50mg at night is recommended
 - Oxybutynin hydrochloride (Ditropan) 5-10mg orally every 12 hours (2.5mg nocte-q12-hourly in the elderly or debilitated).
 - Propantheline 15-30mg every 6-8 hours.
 - Hyoscine hydrobromide (Kwell's) 0.3mg every 8–12 hours sublingually
 - Hyoscine hydrobromide 0.2–0.4mg every 8–12 hours SC
 - Hyoscine butylbromide 10–20mg every 8–12 hours SC (avoids sedative action of hyoscine hydrobromide)
- Nerve blocks
 - Lumbar sympathetic block
 - Inferior hypogastric plexus block
- Catheter change
 - For catheter leakage insert a smaller gauge catheter to reduce bladder spasm

Hesitancy

Consider treatable causes including:

- Withdrawal of drugs with anticholinergic side effects

- Opiate induced hesitancy may respond to changing the opiate, and is often relieved by co-prescribing prazosin (see below).
- Assisted posture where there is difficulty voiding lying down
- Prostatomegaly.
- Loaded rectum

Treatment

Treatment options include the following:

- Prazosin (Minipress) 0.5–1mg once or twice daily. Mode of action is sympathetic antagonism, which promotes voiding
- Terazosin (Hytrin) 1mg daily for 4 days, 2mg daily for 7 days then 5mg daily if increased dose is required. Maintenance of 5-10mg daily. Same mode of action as prazosin but more expensive in Australia unless the patient is a war veteran on the RPBS scheme.
- Tamsulosin (Flomaxtra) 400mcg once daily. Same mode of action as prazosin but also more expensive unless the patient qualifies for the RPBS scheme.
- Bethanechol (Urocarb) 10–30mg every 8-12 hours orally or sublingually. This is a cholinergic drug that may be used synergistically with prazosin
- Pyridostigmine (Mestinon) 60–120mg every 6–8 hours, or the long-acting preparation 180-360mg once daily. This drug exerts an anticholinesterase effect and results in a generalised cholinergic response. It is usually prescribed for myasthenia gravis and I have no personal experience in using it for urinary hesitancy.
- Permanent or intermittent catheterisation.

Haematuria

The following approaches are frequently effective:

- Tranexamic acid: Complex dosing - refer to product information. Typical prescribing - 1g orally every 6-8 hours, continuing for 48 hours after bleeding ceases. Repeat process if bleeding returns. A continual maintenance dose may be required in which case aim for 500mg every 8 hours. Use a smaller dose 500mg every 8-hours in patients with EGFR10-30mls/min; and 500mg every 12-hours for EGFR<10mls/min. This may dramatically improve bleeding though there is a reported risk of clot retention in the ureter with heavy renal bleeding, or of hard clots remaining in the bladder. We have used tranexamic acid frequently in this setting without encountering these problems so far.
- Bladder irrigation for severe bleeding and clots.

Delirium, Agitation, Restlessness, Twitching and Fitting

Assessment

It may be appropriate to exclude or manage reversible organic factors that cause acute brain syndrome and delirium. This is especially important in a patient who had been functioning well before a rapid change. Such factors include:

- Sepsis: especially urinary, respiratory, cellulitis, infected ulcers
- Metabolic factors – hypercalcaemia, hypoglycaemia, hyponatraemia, renal failure with obstructive uropathy, liver failure with biliary obstruction
- Drug reactions and interactions (e.g. recently introduced benzodiazepines)
- Urinary retention
- Inadequate pain control.

The physician needs to determine who is being adversely affected by the restlessness or agitation, which will involve discussion with:

- The patient – if possible
- The family – who are often greatly distressed and will probably support immediate sedation of the patient
- The nursing staff – to assess if the patient's condition is distressing other patients and/or making their proper care impossible.

It is also important to determine the severity of distress and the level of co-operation that may be expected from the patient. Patients may fight if held down and given parenteral medication when they may have taken oral medicine easily.

Severe Agitation or Restlessness in the Terminal Phase

The aim here is to induce and maintain hypnosis. Parenteral treatment by subcutaneous administration of midazolam or sublingual clonazepam (Rivotril oral liquid) are the preferred options for first-line management. Levomepromazine or phenobarbitone sodium may be added by subcutaneous injection if the benzodiazepines have limited benefit. Co-prescribing haloperidol 2-5mg S/C statim, then 2-10 mg S/C daily is recommended where delirium is apparent or suspected.

The approaches outlined here have been developed regionally and are commonly applied. The use of phenobarbitone as a second line of treatment in patients failing to settle on midazolam and clonazepam has been developed locally in the recommended doses and is favoured over levomepromazine in our area.

First-line Treatment Options

- Midazolam: Statim dose 5–10mg SC or IM repeated in 30 mins, if necessary, and followed by 30–90mg every 24 hours given by continued SC infusion via a syringe driver. Midazolam is miscible with morphine, hyoscine, haloperidol or metoclopramide in a syringe driver. It has a short duration of action (2 hours), which leads to unreliable efficacy when given by intermittent 4-hourly injection, unless given in high dose.
- Clonazepam drops (oral liquid): Statim dose 2mg (0.8ml) sublingually, repeated in 30 mins, if necessary, and followed by 2mg every 4-6 hours. It may also be administered subcutaneously (Rivotril injection), giving 2mg SC statim, repeating the dose in half an hour if necessary, then 8mg per day given by continuous SC infusion via syringe driver, or as intermittent injections of 2mg every 6 hours. Clonazepam is miscible with morphine, hyoscine, haloperidol or metoclopramide in a syringe driver. It has a long half-life of 22 hours which may lead to accumulation — this may be an advantage in this setting. Although up to 70% of the dose may be unavailable due to adherence to the plastic of the syringe we have found the above doses usually effective on the rare occasion that we have administered as a continuous SC infusion..
- Combining midazolam and clonazepam. In our experience we have found that some patients who didn't respond to high doses of midazolam or clonazepam were well sedated when switched from one to the other. It is my approach to order midazolam 30mg S/C infusion over 24 hours with a back-up of clonazepam 2mg sublingually every 6 hours PRN.
- Rectal diazepam: Statim dose 10–20mg via small tube (e.g. 'butterfly' with needle removed, 'drawing up' tubes or paediatric nasogastric tube), repeated if necessary in 30–60 minutes, and followed by 20mg every 8 hours. Although this is an option it is rarely used these days with the availability of the other drugs. SC or IM administration of diazepam are not

recommended because of poor absorption and local toxicity.

Second-line Treatment Options

- Phenobarbitone sodium. In our experience, when patients are not adequately sedated by 8mg of clonazepam plus 30mg midazolam per day, then increasing these doses is unreliable and patients may or may not respond. Valuable time can be lost trying to get an effect. Since we introduced phenobarbitone sodium to our service we have virtually eliminated the restless deaths we used to see. The recommended dose is 400mg subcutaneously every four hours (it may occasionally need to be given hourly to begin with as there can be a delay in the drug concentrating in the brain, and an occasional patient requires 400mg every 2 hours for maintenance). It can be administered in a separate syringe-driver giving 400mg SC stat, then 2G over 24-hours as a continuous SC infusion. These doses are higher than usually recommended in the literature. We believe that these patients are relatively resistant to sedation and have found lower doses to be as unreliable as increasing the benzodiazepines. It is our practice to continue the benzodiazepine when we commence phenobarbitone. Patients will generally become settled and calm for the last 24-48 hours of life much like we would expect if they had settled well with benzodiazepines.
- Levomepromazine 12.5-25mg S/C statim, then 50-200mg S/C via a syringe-driver over 24 hours. The stat dose may need repeating hourly until settled with rapid dose escalation to 200mg/24hrs. While this drug is effective in most cases combined with midazolam or clonazepam as above we have experienced several instances of inadequate sedation that didn't respond to dose increasing above 200mg/24hours. All these patients were well sedated when changed to phenobarbitone. Levomepromazine is available for use in Australia through the special access scheme (SAS).

Managing Agitation or Restlessness without Maintaining Hypnosis until Death

Such an intermediate approach may be desirable in the following instances:

- Where meaningful communication is still taking place
- When it is requested or demanded by the patient or family
- Where the symptoms are low grade, not overly distressing to the patient-family unit and, in the hospital setting, not interfering with the proper care of other patients

- Where there is uncertainty as to a reversible aetiology or prognosis.

Initial treatment by rectal, sublingual or parenteral administration may be given in the doses (excluding phenobarbitone which is not indicated) already outlined, if initial hypnosis is required, followed by maintenance therapy in one-third to one-half of the recommended doses. The dose of drugs may then be titrated until the desired effect is achieved. These approaches might be used in a patient with reversible causes of delirium, in the context of rehydrating with subcutaneous fluids (1-2 litres a day is adequate in cachectic patients) and/or administering antibiotics, treating hypercalcaemia etc.

Recommended Treatment Options

- Clonazepam 0.5–2mg every 12 hours or at night
- Midazolam 2.5-5mg SC statim, then 10-15mg SC infusion per 24 hours
- Haloperidol 2-5mg SC statim, then 2-10mg SC per 24 hours as intermittent injections or by continuous infusion. Haloperidol is recommended in all patients who are confused and hallucinating in this setting, usually in combination with a benzodiazepine.
- Diazepam 5–10mg every 12 hours or at night
- Chlorpromazine 25–100mg every 8–12 hours
- Tip: We have found 10-15mg midazolam plus 2-5mg haloperidol in a syringe driver over 24 hours to be effective in many patients.

Twitching

Assessment

The aetiology is usually organic and associated with central irritation. The following causes should be considered:

- Opiate overdose. Check for miosis, oversedation, excess sweating. Reduce the opiate dose and review current analgesic approaches if pain is still a problem
- Metabolic problems such as hypercalcaemia, hypoxia, renal failure, liver failure. Myoclonic jerks may be exacerbated by opiates in this situation. Consider whether it is appropriate to reverse underlying problem or change to another opiate, avoiding morphine in renal failure if possible.
- Drug interactions. This includes use of opiates with tricyclic antidepressants or major tranquillisers. Drug management should be reviewed to remove potential interactions that may cause myoclonic jerks. Drugs with anticholinergic effects are most likely to be implicated. There have also been specific reports of this side effect when gabapentin is used with oxycodone in occasional patients.

Treatment in the Non-terminal Phase

- Clonazepam 0.25–1mg at night or every 12 hours
- Diazepam 5–10mg at night or every 12 hours.
- Phenobarbitone elixir 30-60 mg every 8-12 hours and titrated upwards for effect. This has the potential to increase the metabolism of other drugs.
- Other anticonvulsants.

Treatment in the Terminal Phase

- Clonazepam as outlined on [page 24](#) if full sedation is desirable.
- Midazolam as outlined on [page 24](#) if full sedation is desirable.
- Diazepam as outlined on [page 24](#)
- Sodium phenobarbitone starting in a dose outlined on page 25 if full sedation is desired, or try 50-100mg S/C every 8 hours and titrate upwards to effect. Barbiturates have been reported as successful in patients where the use of benzodiazepines was ineffective
- Other anticonvulsants.

Fitting

In patients where death is not imminent, initial treatment with clonazepam or midazolam (see page 25), or either rectal or intravenous valium (10mg rectally, 5mg IV) can be followed by appropriate investigation and ongoing anticonvulsant management. In patients who are dying, treatment options include:

- Clonazepam as outlined on [page 24](#)
- Midazolam as outlined on [page 24](#)
- Sodium phenobarbitone as outlined on [page 25](#) where full sedation is desirable. Alternatively give 100-200mg IM stat and repeat in half an hour if convulsions are still occurring. Maintain with 300-600mg daily by continual S/C infusion.

Alternative Routes for Drug Administration

Circumstances Requiring Change from Oral Administration

Oral medications are preferred to parenteral or rectal administration of drugs in palliative care. Common circumstances requiring change to alternative routes include the following:

- Inability to swallow oral medications
- Inability to tolerate oral medications (e.g. nausea and vomiting)
- Decreased level of consciousness (due to disease progression or sedation with drugs)
- Inability to absorb oral medications
- Last 24-48 hours of life: Most patients cannot continue oral medications in this period. Home care in particular requires familiarity with changing to alternative routes of administration while maintaining the existing therapeutic effects of the oral drug regimen.

Principles of Changing from Oral Drug Administration

- Regular oral medications will have been combined and instituted for effective control and prevention of multiple symptoms in palliative care.
- The same control of symptoms must be continued when changing to alternative routes of administration. Pain relief must be maintained even in unconscious patients who might otherwise become agitated and distressed. This may require strict adherence to the appropriate combination of an opiate, an NSAID and other co-analgesics (such as steroids and anticonvulsants) where these previously formed part of the oral regime.
- Nausea and vomiting control can be maintained by parenteral or rectal drug administration.
- Intermittent (4-hourly) or continuous SC administration of drugs via a syringe driver forms the mainstay of management.

Commonly Employed Therapeutic Options

Continuing Effective Pain Control

- Opioid analgesia: Oral morphine, hydromorphone or oxycodone may be given in one-half the total daily oral dose divided into intermittent SC injections (4-hourly), or by a continuous 24-hourly SC infusion via a syringe driver (using an *in situ* SC butterfly). Oxycodone is available parenterally but is expensive and only available in 10 and 20mg ampoules so it is usual to switch to morphine or hydromorphone.
- Transdermal fentanyl or Norspan patches are generally continued with the addition of SC morphine or hydromorphone. It is common practice to maintain a fentanyl patch and to add a SC morphine infusion to titrate the analgesic requirements. Be aware of the morphine equivalence of the patient's patch ([see page 11](#)) and commence an infusion (or intermittent 4-hourly injections) that represents approximately a one-half to one third increase. Parenteral morphine may be more accessible than the other opioid drugs but hydromorphone is preferred in renal failure $EGFR < 50 \text{mls/min}$.
- Peripherally-effective analgesia should generally be available, although it is possible that some patients can manage without these. Our usual practice is to substitute regular paracetamol or anti-inflammatories with ketorolac (Toradol) 10-30mg SC every 8-12 hours in patients with complex pain, or the same dose PRN in patients we feel could manage without. Ketorolac doesn't combine well with drugs in a syringe-driver so we give it intermittently via a 'butterfly'. It can be used with morphine sulphate alone in a syringe driver. Administration once daily is often sufficient in a very terminal phase.
- Paracetamol, and indomethacin (Indocid) can be administered as suppositories. Administering paracetamol suppositories every 6 hours is often impractical, therefore, indomethacin suppositories 100mg every 12-24 hours is recommended.
- If patients have been taking steroids orally, this may be continued SC with dexamethasone 4-8mg daily. This must be given at a separate site from other drugs (i.e. using a second butterfly) as it is incompatible with a

range of other drugs (except morphine sulphate alone), forming a precipitate in the syringe driver.

- In patients taking oral tricyclic antidepressants, amitriptyline can be continued rectally. Although this is not particularly recommended here it might be useful in some patients with complex pain.
- In patients taking oral anticonvulsants, sodium valproate can be continued rectally, clonazepam drops sublingually, while clonazepam, midazolam and phenobarbitone sodium may be given by SC route. It is reasonable to stop current anticonvulsants and substitute midazolam or clonazepam in the dying patient.

Continuing Effective Control of Emesis

- Oral haloperidol or metoclopramide can be continued in the same dosage and interval by intermittent SC injections or by continual SC infusion over 24 hours via a syringe driver. Either medication may be administered with morphine in the same syringe
- Oral prochlorperazine may be continued by rectal route in suppository form, although it is usually better to substitute parenteral alternatives that can be given by intermittent SC injections or loaded in a syringe-driver.
- Promethazine (Phenergan) 25mg SC stat, then 25–50mg by continuous 24-hour SC infusion, or hyoscine hydrobromide 0.2-0.4mg SC every 4–8 hours or by continuous SC infusion may be tried in resistant cases.
- Other parenteral options: 1. Cyclizine 25-50mg SC stat, then 100-150mg/24hrs by continual SC infusion via a syringe-driver (cyclizine is incompatible with many drugs and generally needs to be given in a separate syringe-driver); 2. Ondansetron (Zofran injection, 4mg/2ml or 8mg/4ml) 4-8mg SC every 12 hours. Limited compatibility data are available for ondansetron with other drugs in a syringe-driver but it can be used with morphine sulphate, midazolam and metoclopramide; 3. Levomepromazine 6-12.5mg SC stat, then 12.5-50mg/24hrs by continual SC infusion mixing well with most other syringe-driver drugs.

Continuing Sedation

- The sedative drugs midazolam or clonazepam can usually be combined with those required for controlling pain or emesis in a syringe driver when this is employed for continual infusion. Clonazepam is preferably administered as sublingual drops.
- See also [pages 24-25](#) that outline recommended doses and philosophy.

Patients with Ileostomy or Colostomy

- Rectal route may still be available as above

- Drugs recommended for rectal administration may be inserted into the stoma for therapeutic effect – assuming they are not returned into the bag.

Combining Drugs in the Syringe Driver

Morphine (or hydromorphone; or methadone), hyoscine, haloperidol, metoclopramide, promethazine and midazolam or clonazepam may be combined together without compatibility problems. Crystallisation may occur when a high dose of morphine tartrate (the 120mg-ampule form of morphine) is used in combination with other drugs.

- Compatibility problems are common with dexamethasone, phenobarbitone sodium, cyclizine and ketorolac, which are generally prescribed for separate SC administration.

Itching, Ulcers, Bleeding and Topical Applications

Itch

This potentially distressing symptom has multiple etiologies, including:

Dry skin

- Dry skin is the commonest cause of pruritis in patients with advanced cancer. Itch should also be treated when present in patients with pruritis of other origins.
- Locally applied emollients, antipruritic and protective agents are the mainstay of successful management. There is a wide range of options available including (refer to MIMS/Index/Skin):
 - Alpha-Keri bath oil – add 20mls to bath tub daily
 - Alpha-Keri lotion – apply 3-4 times a day, and as often as required
 - Calamine oily lotion – apply 4 times a day, and as required (calamine creams and ointments will dry the skin further)
 - Paraffin preparations (eg Cream 45) – apply 3-4 times a day, and as required
 - Sorbolene (Sorbolene cream, Hydroderm) – apply 3-4 times a day, and as required
- Try paroxetine (Aropax) 5-20 mg daily in severe and/or resistant cases.

Histamine-mediated

- Histamine-mediated itch is quite common in the first week of starting an opioid analgesic medication. Treatment with an antihistamine for this period is usually successful.
- It may be associated with allergy, contact dermatitis or eczema where the mainstay approaches include the use of anti-histamines, and systemic and local steroid applications.
- Try paroxetine 5-20mg in resistant cases

Bile salt retention (usually in a jaundiced patient)

- Cholestyramine: is generally not recommended as it is unpalatable, can cause diarrhoea and often fails to control pruritis.
- Paroxetine (Aropax): 5-20mg orally daily
- Ondansetron (Zofran): 4-8mg orally or SC daily. This is an expensive option for out-patients as it is not covered on the PBS scheme. In the author's

experience, I have found it possible to stop treatment after a week without pruritis returning.

- Testosterone (Andriol testocaps): 40mg every 12-24 hours.
- Rifampicin (Rimycin, Rifadin): 75mg once daily to 150mg every 12 hours.

Renal failure

- Note that gabapentin and pregabalin have been more recently adopted as effective drugs for this indication
- Emollient creams/lotions as above, with or without night sedation
- Gabapentin: 100mg nocte increasing to 100mg every 8 hours if well tolerated. Further increase according to tolerance and response. Doses above 300mg every 8 hours are not recommended here. For EGFR<15mls/min use a lower dose commencing 100mg nocte daily or on alternate days, increasing to bd if necessary and titrating against response and tolerance to a maximum dose of 300mg daily. For haemodialysis patients give 100-200mg post-dialysis three days a week.
- Pregabalin: 75mg-150mg every 12 hours. EGFR 30-60mls/min commence on 75mg nocte with more gradual dose escalation; EGFR 15-29mls/min commence 25-50mg and titrate up slowly; EGFR <15mls/min commence 25mg daily; give an extra 25mg post-haemodialysis in patients on dialysis.
- Mirtazepine 7.5-15mg at bedtime
- Paroxetine 5-10mg orally daily
- Ondansetron: 4-8mg orally or SC every 12 hours (especially if nausea is present)

Scabies

- Eurax cream or lotion
- Lyclear cream
- **Additional note:** Paroxetine has particularly developed in this role and can be trailed in a dose of 5-20mg daily in most situations where itch is a persistent symptom.

Malignant and infected ulcers

It is not in the scope of this booklet to cover decubitus ulcers or specific approaches to dressings and debridement. The main point I wish to put across is the

importance of managing and preventing odours when ulcers have a necrotic base and are infected by anaerobic bacteria.

- **Metronidazole** (Metronidazole gel, Rosex gel) dressings: Apply twice daily or with each dressing. This can be very expensive and an alternative option is to make up a gel by prescribing metronidazole suspension (Flagyl S 200mg/5ml) and mixing 2.5mls (100mg) of this with approximately 10G of IntraSite gel or hydrogel (Solosite – the cheaper option) and applying to the wound surface. This could also be combined with morphine (10mg/10g gel) for local pain relief and/or sucralfate (Carafate, Ulcyte), 1G tablet crushed and mixed in the gel for haemostasis. Care should be taken by the nurse not to have topical contact with metronidazole preparations. IntraSite and SoloSite gel preparations are also expensive. Although most reports of using topical morphine use these gels, there is probably no reason why other cheaper water-soluble gels (L-gel, KY gel) can't be utilized if cost is a problem. Metronidazole tablets can be crushed and sprinkled, or a suspension of metronidazole for injection can be sprayed on the wound surface using an atomizer prior to dressings without mixing in a gel. Note that complete sterility is not a primary concern where we are aiming to palliate symptoms rather than heal wounds.
- **Antibiotics:** Oral or rectal metronidazole can be given in addition, or as an alternative to local wound applications. To clean up an infected ulcer combination with a suitable broad-spectrum antibiotic can be successful. This is best guided by a wound swab and culture for sensitivities, and a long-term plan that might include continuing low-dose antibiotics or antibiotic rotations. Serious infections complicated by large areas of ulceration or systemic symptoms are best managed by initial intra-venous antibiotics if this is considered appropriate.

Painful Ulcers

- Morphine gel applications as outlined in the metronidazole section above.

Haemorrhagic Areas

In addition to the use of commercial non-adherent haemostatic dressings:

- Topical sucralfate: 1g crushed and mixed in 10g of gel as outlined above in the metronidazole section. Apply 3 times a day.
- Topical tranexamic acid (Cyklokapron): 500mg tablet crushed and mixed in KY-gel, applied locally 3 times a day. This has even been reported as effective in

some instances of vaginal bleeding, using a gel and applicator.

- Systemic tranexamic acid: 1g every 6-8hours orally, reducing to 500mg every 8 hours.
- Topical adrenaline: 1:10,000 adrenaline-soaked non-adherent gauze dressings applied to wound surface. For large areas it would be wise to dilute the adrenaline 2-3 fold. There are no guidelines for this and systemic absorption is possible.

The last days of life

Assessment

It is important to recognize when someone is dying to ensure that every comfort is provided for the patient and relatives. This includes the withdrawal of unnecessary medications, the assessment and provision of specific medications for symptom control, and medical communication with the patient (if possible) and relatives about what is happening.

Palliative treatment should be offered as a positive and active intervention rather than giving the impression that we are doing nothing for the patient. With skill and kindness this engages relatives and caregivers in the process, and doesn't leave them anxious that they should have more investigations and treatment. Likewise, they should not be left with the feeling that they have 'chosen' to let their loved-one die, which may happen if you ask them if they want medications to be withdrawn or to have sedative drugs started.

It is better to inform them, to listen and to guide them along the kindest path, imparting the feeling that this is the best medicine. This is particularly pertinent to settings where elderly patients deteriorate with multiple co-morbidities in acute hospitals and nursing homes. It is an opportunity to create good memories for the caregivers of a compassionate process and peaceful death, which has a huge impact on supporting their bereavement.

Management

- Stop all unnecessary oral medications
- Assess all current symptoms, some of which will be reported by nurses or care assistants, such as pain or calling out when moved or turned
- If the patient is having difficulty swallowing change to parenteral (subcutaneous) and rectal medications ([see page 27](#) for guidelines on how to change currently prescribed pain and symptom control medications from the oral to SC route of administration).
- Knowledge of six drugs is sufficient to manage nearly all dying (and especially elderly) patients comfortably. Morphine (alternatively use hydromorphone in 1/5th the morphine dose) and ketorolac for pain, haloperidol for nausea and delirium, midazolam or clonazepam for sedation and hyoscine for respiratory secretions (it is also a sedative, an anti-emetic and an anti-spasmodic). It is very useful to have access to a syringe-driver for continuous SC infusions.

- Determine whether the patient is comfortably dying without the need for any medical support, or whether there is the need for pain management or control of other symptoms, and whether there is a need to sedate to manage restlessness or delirium.
- If the patient appears comfortable ensure there are PRN orders for:
 - Morphine 2.5-5mg SC every 4 hours (or one-twelfth of the daily oral morphine dose or a dose-equivalence in relation to other prescribed opioids, e.g. fentanyl patches [\[see page 11\]](#))
 - Haloperidol 2.5-5mg SC every 8 hours
 - Midazolam 5mg SC every 2 hours, or clonazepam oral liquid 0.25-1mg sublingual every 6 hours
 - Hyoscine hydrobromide 0.4mg SC every 4 hours, or hyoscine butylbromide 20mg SC every 8 hours. Initiate either drug and then given regularly at the first sign of respiratory secretion retention (noisy breathing).
- If the patient is uncomfortable, in pain, agitated or affected by other specific symptoms refer to the appropriate sections of this book. In general the following combination works well subcutaneously via a syringe-driver over 24 hours backed up by the PRN orders above (ie if you're not sure what to do try this!):
 - Morphine 2.5-5mg SC statim, then 10-30mg over 24 hours, beginning with 10mg in an opiate-naive patient (see morphine conversions on [page 11](#) for appropriate doses in patients already on opioids).
 - Midazolam 2.5-5mg SC statim, then 15-30mg over 24 hours, beginning with 15mg unless the patient is extremely agitated. In a very agitated patient give midazolam 5mg SC repeated at half-hourly intervals until settled (check that urinary retention or rectal faecal impaction isn't the cause of the agitation first!) while starting the infusion
 - Clonazepam oral liquid (when midazolam is not available for the syringe-driver) 0.25-2mg sublingually every 6 hours, beginning with 0.25mg unless the patient is extremely agitated in which case I would commence the regular 2mg dose from the start (and not less than 1mg).
 - Haloperidol 2-5mg SC statim, then 2-5 mg over 24 hours
 - Add hyoscine hydrobromide 0.4mg SC statim, then 2.4mg over 24 hours OR hyoscine butylbromide 20mg SC statim, then 40-60mg over 24 hours at

the first sign of noisy respiratory secretions. Use the hydrobromide preparation if more sedation is desirable.

- Add ketorolac 10-30mg SC every 12 hours if the patient still appears to be in pain. Use this from the beginning if there is a lot of musculo-skeletal pain, especially in a cachectic patient. Alternatively prescribe an indomethacin suppository 100mg every 12-24 hours.
- If no syringe-driver is available:
 - Give one-sixth of the total oral daily morphine dose every 4 hours SC (note that this is the same as the oral dose, which is twice as potent parenterally, so give a lower dose of 1/12th to 1/6th if pain is not an issue), or start a fentanyl 12 or 25mcg/hour patch. If you elect to use the patch remember that you will have to give morphine (or its equivalent) regularly 4-hourly for the first twelve hours while the patch 'kicks in'. Then keep the morphine order PRN.
 - Use the clonazepam option as above
 - Give 2mg haloperidol SC every 12 hours
 - Use SC ketorolac or indomethacin suppositories as above.
 - Give hyoscine hydrobromide 0.4mg SC every 4 hours OR hyoscine butylbromide 20mg SC every 8 hours.
- Please contact your local palliative care service if you are still having difficulties in achieving patient comfort.

Appendix: Renal Failure Doses

Acknowledgement

We are grateful to the renal palliative care service at St George Hospital for their permission to reproduce the following table.

DRUG	Action in end of life care	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure GFR	Adult Dose with Renal Failure	Dose/interval change in renal replacement Rx			NEPHRO TOXIC? (Y/N)	OTHER COMMENTS
						PD	HF	HD		
Amitriptyline (Enderp)	Neuropathic Pain	Metabolised in the liver.	D < 5% excreted unchanged in urine	No change to normal doses.	Starting dose 10mg nocte. Increase dose according to response and tolerability.	Not dialysed	Unknown	Not dialysed	No	Contraindicated in Glaucoma, recent AMIs. Has multiple drug interactions (see MIMS; The Renal Drug Handbook.) Side effects - Antihistamine effect - sedation; Anticholinergic effect - dry mouth, blurred vision, constipation, urinary retention.
Buprenorphine (Norspan) patches	Pain management	Norbuprenorphine (weakly A)	Renal M - 33% in urine D - 1% unchanged Faecal D - 66% unchanged	10-50 ml/min No change <10 ml/min Patches 5mg minimum dose changed every 7 days Injection & S/L: Reduce dose by 25-50%. Avoid large single doses	Starting dose - 5mg patch changed every 7 days	Dialysed – dose as for GFR<10mls/min	Dialysed – dose as for GFR<10mls/min	Dialysed – dose as for GFR<10mls/min	No	Can cause urinary retention and oedema (non - renal) CAV/VVHD – not dialysed – dose as GFR 10-20ml/min "There is a lack of evidence about longer term use in ESRD" Brown E et al 2007, p. 99 "...it may be a potentially useful analgesic for use in patients with CKD, although until there are onger term studies the authors remain cautious about recommending it" Davison EJ et al (eds) <i>Supportive Care for the Renal Patient</i> 2010, 2nd ed, OUP.
Buscopan (see Hyoscine Butylbromide)										
Ceftriaxone	Lower respiratory infection			Normal dose	1g daily IVI	Not dialysed	No data	Not dialysed		
Cimetidine (Magicul. Formerly manufactured as Tagamet)	Pruritus (Histamine H ² receptor antagonist)	Inactive metabolites	1/2 life in ESRD 5 hours	Dosage should be reduced according to <i>creatinine clearance (MIMS)</i> 0-15 ml/min 200mg BD (<i>Chambers et al recommend 100-200mg BD</i>) 15-30 ml/min 200mg TDS 30-50 ml/min 200mg QID >50 ml/min normal dose	Commence 100mg bd; maximum dose - 200mg bd	Insignificant dialysability. No change to dosing regime	Unknown	Dialysable (10-20%) Recommended that dosing occurs post dialysis		Works as an antihistamine. H ² receptors in the skin Be aware of drug interactions (see MIMS) Accumulation caution in RF
Clonazepam (Rivotril)	Benzodiazepine	7-amino-clonazepam (I) 7-acetylamino-clonazepam (I) 3-hydroxy-clonazepam (A)	Renal (D) <1% unchanged	No dose adjustment required *INCREASED RISK OF SEDATION IN RENAL FAILURE	Commence 0.25 - 0.5 mg nocte	Dose as normal renal function Unknown dialysability	Dose as normal renal function	Dose as normal renal function Not dialysed	No	Caution in renal failure. Midazolam infusion may be preferable.
Codeine	Weak Opiate	C6G (A), Norcodeine 20-50 10-20 <10 (?), Morphine (A) M3G (I) M6G (A)	Renal (D,M)	20-50 - normal dose 10-20 - 75% normal dose <10 - 50% dose	Maximum Panadeine Forte dose (each contain 30mg codeine) is 4 / day. See commentary in 'Other' column.	dose Unknown so as <10	dose Unknown so as <10	dose Unknown so as <10	No	Unknown dialysability "We advise caution with chronic use of codeine in CKD patients and suggest limiting doses to 120mg or less per day." Davison S, Ferro CJ Management of Pain in CKD. <i>Progress in Palliative Care</i> 2009; 17:186-195.
Cyclizine	Antiemetic (centrally acting)		<1% excreted unchanged in urine	No change to normal doses.	50mg tds po/sci/ivi	Unknown	Unknown	Unknown	No	Increased cerebral sensitivity in patients with renal failure. Not recommended in the terminal phase.
Dexamethasone	Breathlessness Appetite	65% (I)	8% unchanged eliminated in urine Renal (D,M)	GFR <10ml/min Normal dose tapered to minimum effective dose	Dosing according to indication. Typical commencing dose - 4mg mane. If using more than one daily dose use mane and midi dosings only.	Not dialysed	Not dialysed	Unlikely removal Normal dose	No	"Does not require dose adjustment, but may be complicated by fluid retention" (Yorkshire Group, 2006. p.9) For anorexia should consult Renal Dietician. Be aware of the significant side effects of Dexamethasone in intermediate to long term use, including and increased susceptibility to infections, proximal myopathy, impaired glucose tolerance, hypertension and osteoporosis.
Fentanyl (Durogesic) patch	Opioid	Norfentanyl (I)	D – 9% faecal D,M - 75% renal	20-50 - normal dose 10-20 - 75% normal dose <10 - 50% dose	Minimal commencing dose - 12mcg/hour patch changed every 3 days.	Dose as for GFR <10	Dose as for GFR <10	Dose as for GFR <10	No	Not dialysed. If converting from other opioids to Fentanyl and vice versa consult opioid conversion charts or the Pain or Palliative Care teams.

DRUG	Action in end of life care	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure GFR	Adult Dose with Renal Failure	Dose/interval change in renal replacement Rx			NEPHRO TOXIC? (Y/N)	OTHER COMMENTS
						PD	HF	HD		
Gabapentin (Neurontin)	Neuropathic pain Uraemic Pruritus Restless Legs Syndrome		Renal (D) eliminated unchanged in urine	GFR <15ml/min (dialysis) Usual maintenance 100-600mg/day or alternate daily according to effect.	Minimum commencing dose - If on dialysis - 100mg post dialysis. Titrate does by 100mg increments. If on a conservative non-dialysis pathway - (a) If eGFR >50 commence 100mg tds and titrate up by 100mg increments according to tolerability and response. See 'Other Comments' column. (b) If eGFR 30-49 commence 100mg nocte - 100mg bd and titrate up by 100mg increments according to tolerability and response. See Other Comments column. (c) If eGFR 15-29 commence 100mg nocte and titrate up by 100mg increments according to tolerability and response. See Other Comments column. (d) If eGFR < 15 commence 100mg every second night and titrate up by 100mg increments according to tolerability and response. See Other Comments column.	Dose as for GFR <15	Dose as for GFR <15	Dialysed: Load 300-400mg then 200-300mg after each HD	Yes	Dialysis 3x per week lowers the 1/2 life by 60%. Give as evening dose or post dialysis. May supplement 50% dose post dialysis if essential Can cause false positive urinary protein Interacts with Cimetidine * Please note that authoritative cautions has been expressed in the use of Gabapentin in patients with ESRD managed conservatively: "In the Stage 5 CKD without dialysis it is preferable not to use" (Murtagh FEM, Weisbord D. Symptom Management in renal failure. In: Chambers EJ et al (eds). <i>Supportive Care for the Renal Patient</i> . 2nd ed. 2010. OUP, p. 123.) Please also note the recommendations of the <i>Palliative Care Formulary</i> (3rd edition, 2008). The authors recommend the following doses (starting and maximum doses at specific levels of eGFR) - >80: 300mg tds - 800mg tds; 50-79: 200mg tds - 400mg tds; 30-49: 300mg daily - 300mg bd; 15-29: 300mg daily; <15: 300mg alternate days (starting and maximum dose). After every 4 hours of haemodialysis - supplementary single dose of 200-300mg. As a general rule they advise commencing smaller doses in the elderly. Also in patients with eGFR <15 to "further reduce daily dose in proportion to the creatinine clearance."
Glycopyrrolate (Robinul)	Respiratory secretions (Terminal)	No data	D = 48.5% renal remainder unchanged in bile	No data	200-400mcg q 2 - 4 hrs sci	No data	No data	No data	No	Recommended for terminal secretions in renal Dose is titrated against effect. Accumulation possible
Haloperidol (Serenace)	Agitation, confusion, nausea	Hepatic metabolism Hydroxyl-haliperidol (A)	(M) mainly eliminated via bile, faeces and urine	GFR <10ml/min or dialysis. Begin with low end of dose range and titrate according to response	Minimal commencing dose - 0.5 mg. Typical commencing doses for: * Nausea - 0.5 mg bd * Delirium - 1mg bd	Not dialysed Dose as for GFR <10	No data	Not dialysed Dose as for GFR <10	No	Elderly should use low doses to avoid extrapyramidal reactions INCREASED RISK OF SEDATION IN RENAL FAILURE 50% of normal dose recommended (Douglas et al 2009)
Hydromorphone (Dilaudid)	Opioid	Dihydro- <10 isomorphine (A), dihydromorphone (A), H3G (I)	Renal(D,M) Metabolites renally excreted but inactive	20-50 Normal dose 10-20 Reduce dose <10 Reduce dose	If opioid naïve typical commencement dose - 0.5 - 1mg mg q 4hours orally (or 0.25 - 0.5 mg sci) Titrate according to pain / dyspnea.	Unknown so dose as for GFR<10	Unknown so dose as for GFR<10	Unknown so dose as for GFR<10	No	Start at low doses in renal failure. "Small risk of accumulating drug/active metabolite" (Yorkshire Group 2006, p.10) <i>If converting from other opioids to Hydromorphone and vice versa consult opioid conversion charts or the Pain or Palliative Care teams.</i>
Hyoscine Butylbromide (Buscopan)	Colicky pain, terminal secretions, malignant bowel obstruction	Unknown	D - 50% renal excretion	Normal dose	Typical commencement dose 20mg tds - qid po/sci. Maximum daily dose - 240mg.	Dialysed - dose as for GFR<15mls/min	No data	Dialysed - dose as for GFR<15mls/min	No	Recommended for terminal secretions in renal. No dose adjustment required.
Hyoscine Hydrobromide	Inhibit Excessive Secretions	Apo-hyoscine	Excreted in urine, metabolised in liver (s/c only 3.4% D excreted in urine in 72 hrs)	30-60 Normal Dose 10-30 Normal dose <10 or on dialysis, Normal dose Not recommended in ESRD (crosses blood/brain barrier)		Dialysable Normal dose	No data on dialysability Normal dose	Dialysable Normal dose	No	Anticholinergic - Can cause urinary retention Not recommended in the terminal phase. Uraemia causes increased permeability of the blood brain barrier to centrally acting agents. This may result in Hyoscine hydrobromide causing paradoxical agitation. (Douglas C, Murtagh FEM et al. <i>Palliative Medicine</i> 2009;23:103-110).
Ketamine	Neuropathic pain	Nor-ketamine (A) dehydronor-ketamine (I)	a) Ketamine and norketamine - Renal 5% in urine unchanged + 5% unchanged in faeces b) Inactive metabolites renally excreted	No change	Best be used under the supervision of the Pain or Palliative Care teams. Usual practice is to give a test dose of 10mg sci. Monitor for any psychomimetic effects. After two hours, if tolerated, commence 100mg sci in a syringe driver over 24 hours and titrate up by 100mg/day according to efficacy and side effects.	Unlikely to be dialysed dose as for normal renal function	Not dialysed - dose as for normal renal function	Unknown dialysability dose as for normal renal function	No	NMDA Receptor antagonist. Can cause urinary retention and oedema (non - renal) CAV/VVHD - not dialysed - dose as in GFR 10-20ml/min 20-50% protein bound Can cause profound psychomimetic effects.
Levomopromazine (Nozinam)	Restlessness, confusion, agitation, nausea	a) sulphoxide metabolite b) glucuronides	Majority excreted in urine as M D- small amount unchanged in urine and faeces	GFR 10-50 - No change GFR <10 ml/min - start with small dose INCREASED RISK OF SEDATION IN RENAL FAILURE	Minimal dose - 6.25 mg. Typical commencement dose - 6.25 mg bd. Doses are best adjusted according to symptoms.	Not dialysed - dose as for GFR <10 ml/min	No data	Not dialysed - dose as for GFR <10 ml/min		Started cautiously and at low doses, and titrated according to response and side effects (Yorkshire Group 2006, p.8) Can be added after Midazolam for terminal agitation if symptoms persist (Douglas et al 2009, p.106)

DRUG	Action in end of life care	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure GFR	Adult Dose with Renal Failure	Dose/interval change in renal replacement Rx			NEPHRO TOXIC? (Y/N)	OTHER COMMENTS
						PD	HF	HD		
Lignocaine	Difficult to manage Neuropathic pain	Active metabolites accumulate during prolonged infusions		No change	Should be used under the supervision of the Pain or Palliative Care teams.	Unlikely	No data	Not dialysed	No	Caution in prolonged infusion in renal failure-dose modification if adverse effects
Lorazepam (Ativan)	Breathlessness, anxiety	(I) 70-75% as glucuronide metabolites	Renal (88%) Faecal (7%)	GFR <10ml/min or dialysis. Begin with low end of dose range and titrate according to response	0.5-1mg bd-tds (sublingual or po)	Normal dose	Normal dose	Normal dose	No	CNS adverse effects may be more pronounced in patients with renal impairment
Methadone	Pain Intractable cough	(I) 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine, 2-ethyl-3, 3-diphenyl-5-methylpyrrolidine (liver)	(M) in faeces and urine	GFR 10-50 Normal dose GFR <10 50% of normal dose	Should be used under the supervision of the Pain or Palliative Care teams. Only recommended to be used by knowledgeable physicians (Mid-Atlantic Renal Coalition and the Kidney End-of-Life Coalition. <i>Clinical Algorithms to Treat Pain in Dialysis Patients</i> . 2009.) There are several recommended dosing schedules. Given its metabolism - high oral bioavailability and it accumulates with repeated dosing - it requires care and clinical experience to use safely. If converting from another opioid the commencement dose is calculated according to the current background opioid dose. Accordingly a commencement dose should be individualised. For pain, a typical commencing dose is 2.5mg qid and then adjusted carefully under the supervision of the Pain or Palliative Care teams. For intractable cough commence 5mg - if cough is mainly nocturnal 5mg nocte; if cough is day and night 5mg bd.	Not dialysed Dose as for GFR <10	No data	Not dialysed Dose as for GFR <10	No	"Methadone is well cleared in renal failure, but has a very long half life, even when renal function is normal" (Yorkshire Group 2006, p.10). Use if unable to control pain with Hydromorphone or Fentanyl (opioid - allergy, adverse events or refractory pain). (Mid-Atlantic Renal Coalition and the Kidney End-of-Life Coalition. <i>Clinical Algorithms to Treat Pain in Dialysis Patients</i> . 2009.) Beware of multiple drug interactions.
Metoclopramide (Maxolon)		Hepatic Metabolites (I)	Predominantly renal (D,M)	GFR 20-50: Normal dose GFR 10-20: 75-100% of normal dose GFR <10: 50-100% of normal dose (10mg q8-12h titrated to response)	Minimal dose 5 - 10 mg. Typical commencement dose - 5-10mg tds half an hour prior to meals	Not dialysed Dose as for GFR <10	No data	Not dialysed Dose as for GFR <10	No	For GFR <20, start at low doses. Increased risk of extrapyramidal reactions in severe renal impairment.
Midazolam (Hypnovel)	Agitation, End of life crisis sedation	1-hydroxymethyl midazolam	Renal (D,M) 45-57% <1% as unchanged drug	GFR 10-50 Normal dose GFR <10 50% of normal dose	Typical commencement dose 2.5 mg - 5 mg q 4 hours. Titrate dose according to symptoms.	Unlikely Dose as for GFR <10	No data	Not dialysed Dose as for GFR <10	No	INCREASED RISK OF SEDATION IN RENAL FAILURE. Dose reduction and an increased dosing interval for midazolam recommended (Douglas et al 2009, p.106)
Morphine	Pain control, breathlessness	M3G (I) M6G (A)	Renal (D,M)	20-50 25% dose 10-20 Small dose eg start with 2.5-5mg <10 Small dose eg start with 1.25 -2.5mg	Not recommended in Renal Failure. If no other strong opioid available commence with small doses (1-2mg orally tds-qid; 0.5-1mg sci tds-qid) and titrate slowly.	Dose as for GFR <10	Dose as for GFR <10	Dose as for GFR <10	No	Dialysed in HD and CAV (renally excreted, toxic metabolites)
Octreotide	Malignant bowel obstruction	(?liver)	Renal (32% unchanged)	Normal dose	Commence with 150 mcg tds sci. Can bring into syringe driver over 24 hours. Maximum dose 1500 mcg over 24 hours	Normal dose	Likely dialysed, no published data exists	Normal dose Dialysed: plasma clearance increased by around 30%. Supplemental dosing may be required	No	Haemodialysed, unknown peritoneal dialysability Elimination t1/2 sc=100minutes

DRUG	Action in end of life care	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure GFR	Adult Dose with Renal Failure	Dose/interval change in renal replacement Rx			NEPHRO TOXIC? (Y/N)	OTHER COMMENTS
						PD	HF	HD		
Ondansetron (Zofran)	Pruritus Nausea	Multiple metabolites (I)	Renal <5% unchanged in urine Hepatic	Normal dose	Commence 4mg prn. Regular dose 4-8 mg bd	Unlikely dialysability. Dose as for normal renal function	Unknown Dose as for normal renal function	Not dialysed. Dose as for normal renal function.	No	Can be used to treat uraemic Pruritus. NOTE: Ondansetron is very constipating
Oxycodone (Endone, Oxycontin, Oxynorm)	Pain - strong Opioid	Noroxycodone (A) Oxymorphone (A)	Renal (D 19%,M 65%) Faecal (D,M)	10-50 Normal dose <10 Avoid *BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE	Endone - minimal dose 2.5mg. Typical commencement doses - 2.5 mg tds-qid. Oxycontin - minimal dose 5mg Typical commencement dose - 5 mg bd	Unknown dialysability Dose as for GFR <10	Unknown dialysability Dose as for GFR <10	Unknown dialysability Dose as for GFR <10	No	Oxycodone: "There are no long term studies of chronic use in renal failure and the conflicting case reports mean there is insufficient evidence currently for a recommendation." Davison S, Chambers EJ & Ferro CJ. Management of pain in renal failure. In Chambers et al (eds) Supportive Care for the Renal Patient 2010, 2nd ed, OUP. *Used in ESRF – low doses of Oxynorm Metabolites may be more likely to accumulate and cause sedation, than hydromorphone metabolites at very low GFRs GFR<60 increased plasma concentration of active drug by 20-50%
Paracetamol	Simple pain relief	Glucuronide, sulphate 10-50 <10 and glutathione conjugates (I)	Renal (D and M, only 3% unchanged)	10-50 Normal dose <10 500mg- 1g 6-8hrs	Typical dose 1g	Dose as GFR<10		Dose as GFR<10	Yes in overdose	Not removed by PD Known to be removed by HD Normal doses are very often used in ESRD
Pregabalin (Lyrica)	Neuropathic pain Uraemic Pruritus Restless Legs Syndrome	Undergoes negligible metabolism	Renally excreted as an unchanged drug	Dosing schedule with normal renal function is a bd dose. With CKD need to reduce to a daily dose.	If on dialysis – commence 25 mg daily and titrate according to tolerability and response. (The Renal Drug Handbook, 3rd ed). MIMS recommends giving an extra 25mg after each dialysis. If on a conservative pathway – (a) If eGFR 30-60 – commence 75 mg daily and titrate according to tolerability and response. (b) If eGFR 15-29 – commence 25-50mg daily and titrate according to tolerability and response. (c) If eGFR <15 – commence 25mg daily and titrate according to tolerability and response. (The Renal Drug Handbook, 3rd ed)	Dialysed	Dialysed	50% removal after 4 hours of HD	No	Is a Gabapentanoid medication. Use with caution in patients with severe Congestive Cardiac Failure (The Renal Drug Handbook, 3rd ed)
Sodium Valproate (Epilem)	Neuropathic pain	None	Liver (D) 5% excreted unchanged in urine	GFR <10ml/min Normal dose tapered to minimum effective dose (and blood conc)	Commence - 200mg bd	Unknown dialysability Normal dose	Unknown dialysability Normal dose	Not dialysed Normal dose	No	Alter doses according to FREE serum levels INCREASED RISK OF SEDATION IN RENAL FAILURE
Tramadol (Tramal)		O-desmethyl-tramadol (A) N-desmethyl-tramadol (A)	Renal (D,M) 90% Faecal(D) 10%	20-50 Normal dose 10-20 50 -100mg 12hourly <10 Data sheet advises against use	If on dialysis commence 50mg bd; maximum 100bd. If on a conservative pathway : (a) If eGFR >30 – dose as in normal renal function. (b) If eGFR 15-30 – commence 50mg bd; maximum 100mg bd (c) If eGFR <15 – 50mg bd (maximum).	Unknown dialysability Data sheet advises against use	Unknown dialysability Data sheet advises against use	Slowly dialysed Data sheet advises against use	No	Although data sheet advises against use in PD, HD & GFR <10, Renal Drug Handbook suggests using doses of 50mg 12 hourly. Avoid using with SSRIs
Tranexamic acid	Clot stabiliser for bleeding	None	Renal (D) 90% by glomerular filtration in 24hrs (IV dose). 39% at 24hr & 41% at 48hr (oral dose), <5% as M in urine	GFR 10-30 1000-1500mg od. GFR <10ml/min 500-1000mg od after dialysis	eGFR 30 - 60 - commence 1 - 1.5g bd-tds eGFR 10-30 - commence 1 - 1.5g daily eGFR <10 - commence 500mg - 1g daily	Unknown dialysability Dose as for GFR <10	Unknown dialysability Dose as for GFR <10	Unknown dialysability Dose as for GFR <10	No	Unknown dialysability Dose as for GFR <10

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