Symptom Control in Palliative Care

6th Edition (2022)

Dr Benjamin Thomas with Dr Roger Cole

Palliative Care Service
Illawarra Shoalhaven Local Health District

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Contents

Key: ⚠ Palliative Care Input Strongly Recommended

Introduction

This booklet has been prepared to provide medical practitioners with practical therapeutic approaches to common symptoms encountered in palliative care. It does not set out to be comprehensive, intends to be pragmatic, may be oversimplified and emphasises local practice.

The aim is to give practitioners quick and user-friendly guides to manage the majority of symptom-control problems encountered in palliative care. For detailed information, the Palliative Care Formulary, available from the Royal Pharmaceutical Society, is an excellent 'pocket' reference text with an online version available.

This edition has been prepared in 2022, with the most recent prior update in 2013. I am very grateful to Dr Roger Cole, the primary author of the 1st through 5th editions, for the opportunity to revise the text. This edition focuses on changes in therapeutics available since 2013, as well as alterations to remove deprecated therapies, dose adjustments where indicated, inclusion of new and novel agents, compatibility data, as well as inclusion of a warning label system for agents that specialist input is strongly advised prior to utilisation. Reference is made to doses in organ failure, including renal and hepatic failure where indicated. New sections on Palliative Emergencies and on MND have been incorporated.

The scope of this booklet is to outline guidelines that need individual consideration at a clinical level, and 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 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) is a recipe to successful management of someone dying comfortably 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 situations is of vital importance in achieving success. The aim, for the patient to be continually pain free or for pain to not significantly impact their quality of life, is achievable in the majority 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 which is often missed and may not respond well to traditional analgesics.

Reduce sensory input by considering a peripherally active drug (paracetamol 500–1000mg every 6 hours and/or a nonsteroidal anti-inflammatory drug [NSAID]). Choice of paracetamol SR 665mg versus IR paracetamol should be dictated by tablet load and cost, as the analgesic effect is equivalent.

If pain persists, add the following medicines (depending on the intensity & type of pain):

- an strong opioid (details below): such as morphine, oxycodone, hydromorphone, fentanyl, methadone
- an adjuvant (if non-responsive): gabapentin, pregabalin, dexamethasone, tapentadol, amitriptyline/nortriptyline, venlafaxine, amongst others.

Never depend on ‘as required’ or *pro re nata* (PRN) prescribing alone unless pain is very sporadic. 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 aperients when starting an opioid. Do **not** rely on plain docusate alone in patients on opioids, increased stimulation via prokinesis is required.

Be prepared to prescribe treatment for nausea when commencing regular opioid therapy – most patients who experience nausea are suffering an adverse reaction that can be ameliorated, not an allergic reaction. Consider haloperidol 0.5-1mg immediately then 1.5mg at night regularly to reduce the severity of this. Regular anti-emetics may not be required after the first week in these patients (see page 14).

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, buprenorphine patches, controlled-release oxycodone, modified release hydromorphone, a wider dose range and flexibility of immediate-release formulations of oxycodone, hydromorphone and fentanyl, and a growing place for the use of methadone in opioid rotation for resistant pain situations.

Traditionally regular immediate release morphine was titrated to effect, then converted to a slow-release twice-daily regimen when the appropriate dose was reached. This approach should still be considered for patients with severe or unstable pain where the opioid requirement is difficult to predict and titration is needed. It is however a reasonable practice these days for experienced practitioners to initiate treatment with a long acting opioid (slow release morphine or oxycodone) but it may necessary to co-prescribe a number of tablet, capsule or patch sizes to allow titration of the opioid. It is also important to prescribe a suitable immediate-release preparation for 'breakthrough pain', usually in **one-sixth** of the **total daily opioid requirement** (see opioid conversion table on Page 20 for guidance). The amount of opioid used for breakthrough pain gives an indication about how much to increase the long acting opioid formulation when reviewed.

This range of opioids has increased flexibility and choice with regard to appropriate prescribing. Patients who have severe side effects, e.g., nausea and vomiting, on one may tolerate another easily. A fentanyl patch is less constipating and can be preferred by patients as it doesn't have to be taken orally, however it doesn't have a readily accessible breakthrough product so immediate-release morphine, oxycodone or hydromorphone are generally used for this. Fentanyl patches are cumbersome in unstable or progressive pain situations. Buprenorphine patches are useful in

situations where a low initial opioid dose is indicated (Buprenorphine 5 ≡ 12mg morphine / 24 hours) 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 are preferred as eGFR dips below 30ml/min.

Morphine

Morphine is available in immediate release liquid and tablet forms; as well long-acting preparations including sustained-release capsules, and controlled-release tablets. The suspension has unfortunately been discontinued.

In most patients commence a long-acting preparation in combination with liquid morphine for breakthrough pain. In an opioid naïve patient, a starting maximum could be 30mg daily given as 15mg BD. Doses should be reduced in the case of elderly patients, or those with advanced frailty, such as 5-10mg BD. Most patients should also be considered for regular paracetamol.

The breakthrough dose of liquid morphine should be 1/6th of the total daily dose for most patients (eg 5mg 4-hourly PRN for a patient prescribed 30mg 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 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.

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 or tramadol without good effect.

In renal failure choose another opioid (fentanyl or hydromorphone are recommended) as active morphine metabolites can accumulate with unpleasant or dangerous side effects. If morphine is the only option, consider reducing the dose

intended by 25-75%, or increasing the interval from 4-8 hours. If the eGFR is below 30ml/min, caution is *strongly advised*.

Oxycodone

Oxycodone is available in immediate-release liquid, capsules and tablets, as well as long-acting, controlled-release formulations 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 (e.g. 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.

Oxycodone with Naloxone (Targin) is a recently introduced combination of long-acting oxycodone and naloxone. The naloxone is an opioid 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, especially in patients with liver failure, renal failure, and in higher doses. This can lead to patients with moderate to severe liver or renal failure experiencing systemic naloxone leak, causing reversal of analgesia. Additionally, rotating patients to other opioids can lead to accidental narcotisation, as the oxycodone component was to some degree reversed. Targin is **not recommended** in patients with known liver or renal disease, or in the very elderly.

Fentanyl

Fentanyl is a potent strong opioid available as long-acting transdermal patches, immediate-acting sublingual tablets and as fentanyl injections. Transdermal fentanyl works well alongside breakthrough morphine, oxycodone or hydromorphone. It may be constipating than 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, with dose adjustments taking up to 24 hours to take effect. The transdermal patches release fentanyl in a controlled manner over 72 hours, with an onset of analgesic action at 12-24 hours after 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 24 hours after removing the patch. Patches are changed every 3 days. Patients should be advised that the first dose and any subsequent dose increase will not be effective for 12-24 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 multiple strengths. The daily oral morphine equivalent can be estimated by multiplying the fentanyl patch strength by 3, for example, a Fentanyl 12 patch would be approximately equivalent to 36mg of oral morphine daily (12 x 3), or 6mg every 4 hours. The actual conversion is a range, and the above calculation provides a dose which errs towards the more conservative side. These figures can be used to calculate the appropriate breakthrough doses of pain (usually 1/6th the calculated daily oral morphine dose).

For opioid naïve patients, fentanyl should be started with caution, as the lowest patch (the 12) is at minimum equivalent to 36mg oral morphine daily, 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).

Fentanyl sublingual tablets are now available on the PBS (for palliative care patients with cancer pain) for breakthrough pain. They are soluble and have an effect in a short number of minutes, then wear off within 1-2 hours for the majority of patients. There is no equivalent morphine dose for these, due to variable buccal absorption. It is reasonable to start at 100-200mcg q2hrly and titrate to effect.

Hydromorphone

Hydromorphone is a synthetic derivative of morphine and is available in a long-acting modified-release tablet and as instant-release tablets. The oral liquid has been discontinued and is difficult to source affordably. Hydromorphone is also available in injectable form. Its efficacy and side-effects are similar to morphine, although it has a higher potency (1mg hydromorphone ≡ 5mg of morphine). Hydromorphone has less active metabolites than morphine with respect to neurological toxicity and is a better choice of analgesic in patients with renal failure, particularly as eGFR falls below 30ml/min.

Hydromorphone is not typically recommended in the opioid-naïve patient due to its potency, with the lowest dose of slow release being equivalent to 20mg of daily morphine, unless circumstances dictate otherwise. Rotating an established patient to slow-release hydromorphone is practical; a crossover period of 12 hours is recommended as unlike other slow-release oral opioids, there is a substantive time delay to efficacy. For patients requiring breakthrough analgesia for whom the tablets are impractical – they are not easily split – local practice is becoming a mixture of oxycodone or morphine liquid, depending on tolerance and renal function, with IR hydromorphone tablets being reserved for patients on 12mg or more slow release daily.

In the elderly and the opioid naïve who do not tolerate 4mg of slow-release hydromorphone, it may be better to cautiously use slow-release morphine or oxycodone and be mindful of side effects, rather than risk the potential for narcotisation.

Methadone ⚠

Methadone is a drug with some complicated characteristics, available as tablets, syrup and injections. Methadone can be used in the place of other strong opioids such as morphine, oxycodone or hydromorphone for the management of cancer pain and also indicated as an anti-tussive in refractory cough.

Methadone is a synthetic compound with multiple-receptor binding affinity. It is an opioid receptor (mu and delta) agonist, as well as a serotonin reuptake inhibitor and an NMDA-receptor antagonist. This combination allows for analgesia, as well as the potential prevention of tolerance and opioid-induced hypersensitivity. Complicating matters further, methadone has a biphasic half-life, where in early non-steady states it is eliminated in several hours (alpha phase), but once at steady state (beta phase) half-life can range anywhere from 15-60 hours, and even up to 120 hours! Reaching this steady state can take multiple days to a week or more of continuous dosage: as such methadone should be prescribed by the experienced practitioner and under close supervision. Importantly, methadone can prolong the QT interval on ECG, although evidence in the palliative care setting is that this is not usually harmful, it is worth considering monitoring in patients at risk of prolonged QT from other causes such as electrolyte disturbance and other prolonging drugs. Consider obtaining an ECG before commencing methadone, especially in the context of other QT prolonging medications such as haloperidol..

Initiating Treatment with Methadone

For the opioid naïve patient, the starting daily dose of methadone should be maximum 15mg in divided dosing (such as 5mg TDS). For the elderly, the unwell and the frail, consider reducing this dose by 50%. Doses should be titrated upwards to effect, with 1-2 day gaps between dose titration to allow for accumulation.

Transferring from Morphine

There are multiple methods of transferring patients from other strong opioids to methadone. The first step should be to calculate the oral morphine equivalence, prior to starting methadone. The two most common local variations on how to commence methadone are described here:

Classic Conversion

1. Stop regular short-acting opioid when starting the methadone. If switching from a slow-release formulation give the first dose of 6 hours after the last dose of the 12-hourly preparation, or 12 hours after the last dose of methadone a 24-hour preparation. This should be timed with the loading dose below.
2. Give a loading dose of 1/10th the previous total 24-hour oral morphine dose, up to a maximum of 30mg of methadone. If very elderly or cachectic, omit the loading dose. Round dose down to the nearest 5mg.
3. Give 1/3rd of the loading dose q6-hourly regularly, maximum dose 10mg, round down to nearest 5mg, then commence regular dosing.
4. Use the previous breakthrough medication (i.e. morphine, oxycodone, etc).
5. Make a daily phone call or review daily to assess progress.
6. Continue current dosing if the patient is in pain for 24-48 hours. Reduce interval but *not dose* if patients become pain free, initially to q8-hourly, and then consider changing interval to BD if patient remains pain free 24-48 hours after. This anticipates accumulation of methadone, and attempts to avoid drowsiness
7. If patients remain in pain without drowsiness after 48 hours, increase dose by approximately 50%, but watch carefully for drowsiness.
8. Once patients are pain free or at a tolerable point for 48 hours, the total daily dose can be divided to BD or TDS dosing, whichever is most convenient and provides good analgesic benefit to the patient.

NB: if the patient becomes persistently drowsy, this is unlikely to wear off in less than 24 hours. Stop methadone and recommence at ~50% the prior dose, then titrate according to pain and drowsiness.

Mathematical

Calculate the initial daily methadone dose. Locally both the Nomogram Method, and the BJR Equation are used, which can provide similar results. The dose calculated should be *rounded down* to the nearest 5mg.

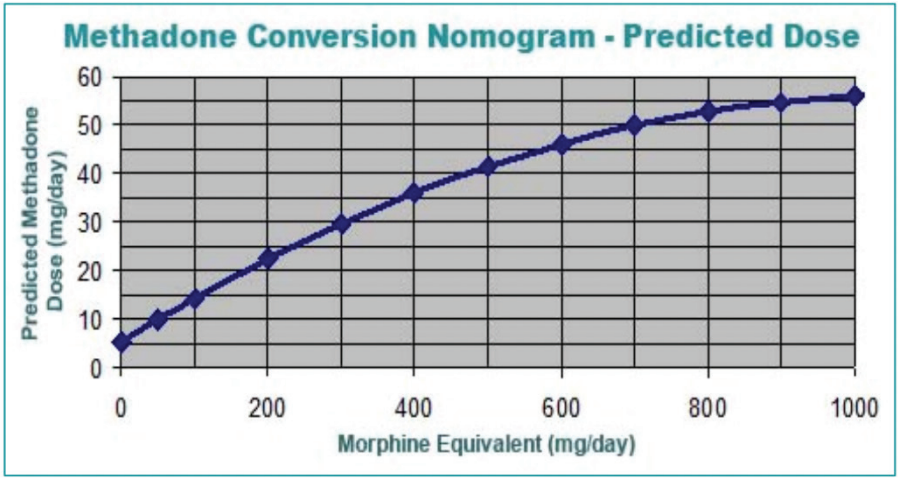

Figure 1. Methadone nomogram, from Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. Med J Aust. 2000 Nov 20;173(10):536–40.

$$\text{methadone (mg)} = \left(1.5 \times \sqrt{\text{morphine (mg)}} \right) + 15$$

Figure 2. BJR equation from Baumrucker. A new mathematical approach to methadone conversion. J Pharmacol Pharmacother. Medknow Publications; 2016 Apr 1;7(2):93–5. 7

1. Stop regular short-acting opioid 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. Divide the calculated methadone dose into either q6-hourly or q8-hourly dosing, whichever is simpler. This is the regular starting dose
3. Give a loading dose of three times the regular starting dose as calculated above, then commence regular dosing.
4. Use the previous breakthrough medication (i.e. morphine, oxycodone, etc).
5. Assess daily (in person or telephone) for progress.
6. Continue current dosing if the patient is in pain for 24-48 hours. Reduce interval if patients become pain free, initially to q8-hourly, and then consider changing interval to BD if patient remains pain free 24-48 hours after. This anticipates accumulation of methadone, and attempts to avoid drowsiness
7. If patients remain in pain without drowsiness after 48 hours, increase dose by approximately 50%, but watch carefully for drowsiness.
8. Once patients are pain free or at a tolerable point for >48 hours without bothersome side effects, the total daily dose can be divided to BD or TDS dosing, whichever is most convenient and provides good analgesic benefit to the patient.

NB: if the patient becomes persistently drowsy, this is unlikely to wear off in less than 24 hours. Stop methadone and recommence at ~50% the prior dose, then titrate according to pain and drowsiness.

Buprenorphine

Buprenorphine is an interesting drug, being a mixed opioid agonist and antagonist. Despite this, it does not seem to have a significant ceiling to its analgesic effect. It is available in transdermal patches, and in subligual tablets – the tablets are not subsidised on the PBS.

Buprenorphine has been more commonly prescribed over the past few years, particularly in the elderly, as the side effect profile seems to be kinder with respect to constipation and hyperalgesia. The dose equivalence for buprenorphine patches are also significantly lower than fentanyl, making it much safer in the opioid naïve.

The major limitation of buprenorphine patches in palliative care is the long time to effect; the patches are changed weekly, and take a minimum 24 hours (and up to 72

hours) to have a clinical effect. For patients with unstable or escalating pain, they are therefore unsuitable for use. They do have a place in patients with more chronic and stable pain, and are particularly useful in the Residential Aged Care setting.

The daily morphine equivalence can be estimated by multiplying the patch strength by 2.4, so a 5mcg/hr Norspan patch is approximately equivalent to 12mg oral morphine daily. 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 opioid 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.

Tapentadol

Tapentadol is a relatively new analgesic available in Australia. The slow release tapentadol is currently subsidised on the PBS, while the IR is not. Similar in concept to tramadol, it works primarily as a noradrenaline reuptake inhibitor, with a small effect on the opioid receptor. Tapentadol is often described as an "equivalent analgesic" in terms of potency, however it is essential to note that while it might have equivalent effect, much of its analgesia does not come from its opioid subcomponent. Conversions that rely on converting tapentadol to oral morphine equivalent often require adjustment, as there is a substantial risk of side effects.

Tapentadol is still finding its place in palliative medicine but may be considered as an adjunct for patients with neuropathic pain, for those with poor opioid tolerance, or for those suffering bone-pain related to malignancy who have a contraindication to non-steroidal or steroidal anti-inflammatories.

It does not typically replace the need for strong opioids in the management of cancer pain.

Tramadol

Tramadol is a dirty drug that is metabolised by the liver into two components an opioid receptor agonist (M1) and an SNRI similar but not identical to venlafaxine, causing enhanced serotonin and noradrenaline neurotransmission. The ratio of M1:SNRI is unpredictable; like codeine it is dependent on CYP2D6 metabolism, and can vary from practically none to substantial. The interaction profile and risks of side effects of tramadol such as serotonin syndrome and high incidence of withdrawal are substantial. It is no longer recommended for use in the palliative care setting.

To convert tramadol to another agent, a safe ratio is 100mg tramadol = 10mg oral morphine.

Nonsteroidal Anti-inflammatories

NSAIDs are commonly utilised in the community but are often neglected in palliative or cancer pain management. Alone they may not be sufficient to control pain but they can provide very good adjuvant analgesia, especially for patients with metastasis in bone, local oedema or irritation, and in combination with opioids. Consider prescribing a PPI when using an NSAID to prevent gastric irritation.

Orally, consider **celecoxib** 200mg daily for 5 days and assess response, this can be given as 100mg twice daily if preferred. Other oral agents commonly used locally include naproxen, ibuprofen, and meloxicam, although PBS restrictions may dictate preference. NSAIDs are considered to be roughly equianalgesic, with the side effect profile and dose intervals varying.

Parenterally, consider **ketorolac** as a short acting NSAID with significant potency, given 10-20mg SC three to four times daily. Be mindful that ketorolac is associated with rapid development of renal failure with ongoing use. For patients requiring regular NSAID, consider **parecoxib** 40mg SC once daily, increasing to twice daily if unsatisfactory response. Both agents can also be administered via SC infusion, although compatibility is limited.

Neuropathic Pain

Neuropathic pain may not respond fully to the approaches described above. It may be due to compression or infiltration of nerves by tumour, or to painful peripheral

neuropathy secondary to causes such as chemotherapy, organ failure or diabetes. It may be associated with clinical evidence of deafferentation (abnormal or absent sensation in the painful area). The following approaches should be considered in addition to the use of opioids and peripherally active analgesics.

- Steroids are recommended for a rapid response, while
- Adjuvants such as amitriptyline, gabapentin and pregabalin have been shown to be effective in clinical trials, with a trend to benefit of amitriptyline > gabapentin > pregabalin.
- Using gabapentin and amitriptyline together has not been shown to have significant extra benefit, although it is sometimes trialled in particularly refractory cases.
- 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.
- In the elderly, gabapentin is often better tolerated than pregabalin

In local practice, our three most commonly utilised neuropathic agents are amitriptyline, gabapentin, and dexamethasone. The choice of neuropathic agent may also vary depending upon other symptoms, such as the preference for amitriptyline in patients with insomnia, clonidine for patients with hallucinations, or valproate for patients with irritability or seizure risk. For dose guidance, see below.

Nerve root compression/infiltration:

Dexamethasone: Give 8mg immediately then 8mg in the morning daily OR 4mg morning & midday 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 another adjuvant for long-term control. Consider addition of a proton pump inhibitor for gastrointestinal cover whilst on high doses of dexamethasone (over 4mg), or on prolonged courses.

Anticonvulsants

Pregabalin (Lyrica) is now PBS-listed and so may be the drug of choice for some patients. Start with 50-75mg 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, and is likely more effective than pregabalin; however it is not listed on the PBS scheme 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 at 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). It is not generally recommended to increase the dosage when titrating by more than 200mg every 24 hours. If there has no response at 1200mg/daily, there are not many patients worth pushing further. See appendix for dosing patients with renal failure.

Carbamazepine (Tegretol) 100-400mg every 12 hours (but high frequency of side effects) may also be considered. Good efficacy in trigeminal neuralgia, and should be the first line agent for this indication.

Sodium valproate (Epilim) is accessible and easy to prescribe, starting with 200mg at night, increasing to 1G if no benefit after 3 days (start with 100mg in the elderly, quickly increasing to twice daily if well tolerated). The evidence for sodium valproate is less robust.

Antidepressants

Amitripyline is a reasonable first choice with plenty of evidence based research to support its use. However nortriptyline and imipramine are also considered effective if it is not well tolerated. Of the other classes of antidepressants the SNRI drugs venlafaxine and duloxetine have the most evidence to support their use at this time, although a number of SSRI drugs may be effective. Of these sertraline or citalopram are recommended for their lower incidence of side-effects.

Amitriptyline: commence 10mg nocte, increasing by 5-10mg 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. Amitriptyline should be given in the early evening rather than at bedtime, as it takes 4 hours for peak concentration to be achieved, and later dosing results in worsened morning side effects of dry mouth and fatigue. If **no benefit** is seen at 30mg, it is unlikely worth pushing the dose to 50mg.

Nortiptyline & Imipramine: as for amitriptyline above.

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.

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.

Others

Clonidine is an alpha-2 receptor agonist widely utilised for its blood pressure effects at the alpha-1 receptor that has benefit in neuropathic pain due to disinhibition on pain transmission in the spinal horn, amongst other central effects. Because of the antihypertensive effect, it is recommended to go slowly. Commence at 25mcg three times daily, with an increase of 25mcg per dose every 1-2 days, as long as tolerated. If no effect at 100mcg three times daily, benefit is unlikely to be achieved with further dose escalation.

Intractable Pain

Ketamine ⚠

Ketamine, an anaesthetic induction agent, had an established role in control of intractable pain including reported efficacy with neuropathic pain, incident pain (i.e. 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, although patient selection and pain types have made the generalisation of the study findings unclear. We utilise ketamine for severely escalating pain, refractory to other agents, with neuropathic components in the inpatient setting. There is also

developing evidence that ketamine has anti-depressant properties, and potentially its use in this setting is assisting the management of total or existential pain. It is also useful for reducing the symptoms of opioid-induced hyperalgesia.

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 haloperidol 2-3mg OR 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 opioid 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; 150mg/24 hours in severe pain/more robust patient. 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). Our service has gone higher than 500mg, although we have not 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 has a bitter taste 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-houlry (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 opioid dose through improved analgesia. Bear in mind that your patient may become excessively drowsy or develop hallucinations due to opioid 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.

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, or giving daily dexamethasone priming to the driver site.

Lidocaine ⚠

There is developing evidence around the use of subcutaneous lidocaine (lignocaine) via infusion, for complex or refractory pain particularly with neuropathic components. Most palliative care physicians would occasionally consider the introduction of a lignocaine infusion when severe residual neuropathic symptoms persist despite the above measures, as well as the failure to control symptoms with ketamine and/or opioid rotation to methadone. It is noted here that the place of ketamine is now controversial, and many units have moved to utilising lidocaine. In the most severe cases a subcutaneous infusion of lignocaine can be trialled with maintenance on oral flecainide or mexilitene (not used locally). Each patient should be considered on an individual basis and practitioners are requested to consult with MIMS with regard to risk factors. We always order an ECG prior to lidocaine infusion to assess the QT interval.

Lignocaine infusion: Give 50mg SC statim, followed by 200-300mg by continual SC infusion over 24hrs. If pain persists the next day, increase by 100-200mg/24 hours. The maximum dose is theoretically 1800mg/24 hours, although we rarely prescribe over 1200mg/24 hours. If pain is well-controlled, stop lidocaine and commence oral flecainide 50mg twice daily, increasing to 100mg twice daily after 4 days if symptoms

return, up to a maximum of 150mg twice daily. If pain not well-controlled, abandon the trial of local anaesthetic infusion. Side effects of concern include perioral paraesthesia, dizziness, metallic taste and drowsiness, as there are signs of initial toxicity that could worsen towards seizure and potential cardiorespiratory collapse.

Dexmedetomidine ⚠

The novel sedative dexmedetomidine is finding increasing interest as a sedative in palliative care, however it also has analgesic benefits worth commenting on. Similar to clonidine, it is an alpha-2 receptor agonist, but is far more potent. Its analgesic uses fall into two primary spaces: a procedural analgesic, where its unique sedative profile allows for interactive sedation with opioid sparing analgesia, and neuropathic/opioid sparing analgesia. It may also have some use in the areas of hyperalgesia and hypersensitisation.

Significant dosing information is not provided here as it is not currently recommended outside the hospital setting, but for interest, it is dosed per kilogram, with a dose between 0.5-1.0microg/kg subcut statim sufficient to provide sedoanalgesia to the majority of patients. Doses up to double this should be safe, under close observation.

Visceral Pain

Like neuropathic pain, visceral pain is relatively insensitive to opioids. It is related to pain within the organs, and in the cancer setting can be due to tumour infiltrating into organ space. Unlike somatic pain, the pain is often more vague and feels like a deep ache or pressure pain. The following treatments are recommended:

- Hepatic pain which is secondary to capsular distension: dexamethasone 8mg daily (often 4mg morning and midday) in addition to other analgesic measures for 3 days, then reduce, similar to nerve root compression.
- Genito-urinary pain (dysuria, bladder spasms, renal colic, see page 24)
- Gastrointestinal colic (see page 19)

Epidural and Intrathecal Pain Control ⚠

Patients with intractable pain (especially neuropathic) may only respond to epidural or intrathecal infusions of opioids, local anaesthetics, clonidine or ketamine. Specific guidance is not included her, as it is substantially outside of scope, however it is

useful to know the basic medications utilised for success and safety, though consultation with a pain specialist is essential. Medications utilised may include morphine and bupivacaine. 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 opioids to prevent toxicity.

Interventional Procedures ⚠

Patients with complex pain (especially visceral or neuropathic) may find interventional injections beneficial, which may help escalating systemic analgesics and worsening side effect profiles of strong opioids. In principal a temporary block with local anaesthetic +/- corticosteroid is often performed to assess effect, before proceeding to a semi-permanent block via neurolytic agents such as ethanol or phenol. Neurolysis usually last for 3-6 months before nerve budding occurs.

A common example is **coeliac plexopathy** seen in upper GI tumours like pancreas cancer, presenting with deep pain radiating to the back and wrap-around discomfort around the lower thorax. This may respond to guided injection of local anaesthetic and corticosteroid, which can be performed endoscopically by gastroenterologists, via fluoroscopic imaging by interventional radiologists, and by some pain specialists.

Some patients with mesothelioma benefit from a paraspinal block, especially those with **diaphragmatic irritation**.

Fractures may also be amenable to intervention analgesia, to minimise need of systemic agents.

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 myoclonus, coma and respiratory depression over the next 48 hours. With alternate opioid 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, with excretion being both hepatic and renal. 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 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 bioavailablity in liver failure. This doesn't usually present clinical problems in patients already stabilized on opioid analgesics, although it might be a cause of increasing drowsiness or other toxicity in patients with deteriorating liver function. If opioids are introduced for patients with marked liver dysfunction, careful introduction of lower-than-usual initial doses are recommended.

As detailed elsewhere, there is particular concern around the use of combination oxycodone/naloxone in patients with moderate-severe hepatic failure as naloxone can bypass hepatic metabolism and enter circulation, providing analgesic reversal

and complicating opioid efficacy. The combination should be avoided in these patients, or in patients with potential to develop such complications (such as patients with liver metastases, or cirrhosis for example).

Intravenous Drug Users

Reluctance to prescribe adequate analgesic doses of opioids 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. For patients who are maintained on opioid replacement therapy with methadone, a reasonable practice is to treat their pain as if they were opioid naïve whilst maintaining their methadone background. For patients who are maintained on opioid replacement therapy with buprenorphine/naloxone, consultation with Drug & Alcohol services in the first instance is recommended.

Opioid Conversions

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 morphine. To convert between other opioids you can work back from their morphine equivalence. Conversions from oral to parenteral routes of administration are also given for the drugs where relevant, although note that injectable oxycodone is very difficult to source, and that injectable fentanyl is rarely recommended due to rapid tachyphylaxis.

	Morphine	**Oxycodone**	**Hydromorphone**	**Codeine**	**Fentanyl**
Oral	15mg	10mg	3mg	120mg	*
Injectable	7.5mg	5mg	1.5mg	*	75microg

As can be seen from the above table, local practice is to halve the dose of the oral medication to ascertain the injectable dose, although in elderly patients and patients who are pain free at conversion, consider a PO:SC ratio of 3:1 instead of 2:1,

.

SC, IM and IV doses are equivalent, however the SC route is almost always preferred

Conversions from patches (fentanyl, buprenorphine) can be found earlier in the relevant segments. Briefly:

- Multiply fentanyl patch by **3** to get **total daily morphine equivalence**
    - e.g. Fentanyl 12 = morphine 36mg/day
- Multiply buprenorphine patch by **2.4** to get **total daily morphine equivalence**
    - e.g. buprenorphine 5 = morphine 12mg/day

Recall that for breakthrough pain, the recommended dose is 1/6th the total daily opioid dose

Gastrointestinal Symptoms

Nausea and Vomiting

Common causes of nausea and vomiting in the palliative care setting may include:

- Metabolic problems (including opioids)
- Drug-induced
- Upper gastrointestinal inflammation
- Raised intracranial pressure
- Constipation
- Bowel obstruction

The choice of anti-emetic depends on the cause as there are three primary areas where drug therapy may be effective:

1. Chemoreceptor trigger zone (CTZ; D2 and 5HT3 receptors): haloperidol, prochlorperazine metoclopramide, ondansetron
2. Gastric emptying: domperidone, metoclopramide, erythromycin
3. Vomiting centre (H1 and cholinergic receptors): promethazine, cyclizine, hyoscine hydrobromide

Other agents include the broad-spectrum neuroleptics olanzapine and levomepromazine (which work in multiple areas), and the NK-1 inhibitors aprepitant and netupitant.

Chemoreceptor Trigger Zone Blockade

For metabolic, opioid and other drug-induced nausea:

Haloperidol: 0.5-1mg immediately orally or SC, then 1.5mg orally at night. Haloperidol has the advantage of a long half-life enabling successful control with once-daily administration. Depending on response, can increase up to 3mg/24 hours. If poor control can give as BD divided dosing. Can be utilised as its own PRN medication, usually at 0.5-1mg TDS.

Metoclopramide: 10-20mg orally or SC, then every 4–8 hours orally, maximum 60mg/24 hours (typically 30-40mg).

Ondansetron: 4-8mg orally or SC, then every 8–12 hours orally

Prochlorperazine: 10-25mg every 4–8 hours orally. Whilst prochlorperazine can be given subcutaneously, it has a high risk of tissue necrosis and is best avoided if possible.

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 may have an additive effect when used with other drugs that act on the CTZ.

Increasing Gastric Emptying

For gastric stasis (the aetiology in up to 10% of opioid-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

Erythromycin: 75mg oral elixir every 8 hours (this may be useful in patients with denervated stomachs, eg following oesophagectomy)

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:

Cyclizine: 25-50mg orally or SC, then 25-50mg every 8-12 hours orally or SC (the tablets are available on the special access scheme in Australia, or OTC in small packets as a trial). Usually requires hospital dispensing

Hyoscine hydrobromide: 0.3–0.6mg every 8 hours orally or 0.2-0.4mg SC every 8–12 hours

Promethazine: 10–25mg orally, then every 12 hours orally

Broad-Spectrum Anti-Emetic

Recommended as a third line antiemetic, or where other measures are unsuccessful, these medications impact multiple receptors including dopaminergic, histamine and serotonin. The most common side effects are sedative and dry mouth:

Olanzapine 5mg nocte (2.5mg in frail/elderly), increasing to maximum of 10mg nocte. Not subsidised for this indication on PBS. The oral wafer is well tolerated; the IM injection can be given SC.

Levomepromazine ⚠ 6-12.5mg PO or SC stat, then every 6-12 hours. Levomepromazine is only available on the special access scheme in Australia. Doses above 20-25mg begin to favour sedation over antiemesis.

Important Points

For intractable symptoms consider:

- Faecal loading or impaction (P.R. examination, x-ray)
- Hypercalcaemia. Consider treatment with pamidronate 30-90mg IV, or Zoledronic acid (Zometa) 4-8mg IV. Denosumab 60-120mg SC may provide sustained benefit. Pamidronate can be infused subcutaneously on the palliative care unit.
- Upper GI inflammation. All PPIs may assist here, we tend to utilise pantoprazole orally (20mg – 40mg once daily). Esomeprazole can be given by SC injection (20-40mg)
- Bowel obstruction. Avoid bowel stimulants such as metoclopramide, senna, bisacodyl; see below for guidance on medical management
- Raised intracranial pressure. Use steroids - dexamethasone 8-16mg daily and consider further investigation if within goals of care
- Poor oral tolerance: consider 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. Haloperidol Is the typical first line antiemetic, as a once or twice daily bolus SC injection of 1-1.5mg can be quite effective. All medications that can be given as bolus injections described above can be given as equivalent syringe driver infusions (e.g., cyclizine 25mg TDS can be 75mg via syringe driver), but compatibility with other medications may vary

- Consider rehydration with SC fluids, using 1-2 litres of normal saline or 4% dextrose and 1/5th normal saline, if desirable, if not within terminal phase of life

Constipation & 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, with or without rectal measures.

Prophylaxis When Commencing Regular Opioids

It is recommended that all patients on opioid treatment receive prophylaxis, even when reporting 'normal' bowel habit. The use of plain docusate is **not recommended** without the use of a stimulant, as docusate alone has been shown to provide no benefit in opioid-induced constipation.

The following stepwise approach is recommended:

1. **Docusate with senna**: 2 tablets initially at night time, if ineffective add in two tablets in the morning. It is reasonable to prescribe senna alone, however it is harder to aquire. If ineffective after 48 hours, proceed to the next step.
2. **Bisacodyl**: 5-10mg. If effective, continue with this and consider reducing the dose if it causes abdominal pain or diarrhoea. If ineffective after 48 hours, proceed to the next step.
3. **Glycerine** or **bisacodyl suppository** immediately. Increase docusate sodium with senna or bisacodyl to 2-3 tablets twice-daily. If ineffective after 48 hours, consider addition of a macrogol or trial of methylnaltrexone.

Evaluation of the Constipated Patient

- 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 disimpaction of the rectum if indicated following adequate analgesia and sedation (e.g. midazolam 2.5–5mg plus an opioid, both by SC injection).

Management of the Constipated Patient

Consider the rationale for constipation, and address appropriately if possible

1. For opioid induced constipation, see above for agents used in prophylaxis. The addition of more stimulant (as the opioids decrease prokinesis) as well as ensuring there are no hard stool in the rectum is the first approach. For severe constipation with opioid use, trial **methylnaltrexone** adjusted for weight and renal function
    a. For patients >62kg, give 12mg SC
    b. For patients between 38 – 62kg, give 8mg SC
    c. For patients below 38kg, give 0.15mg/kg SC
    d. Reduce dose by 50% if moderate renal impairment
    e. Repeat dose after 2 days if minimal effect. Some patients may require regular dosing.
2. Consider use of a **macrogol 3350** in addition to **senna** or **bisacodyl**. These agents act as iso-osmotic medications, and do not have a substantial effect on body hydration, although the brand **Movicol** can cause electrolyte dyscrasia in renal impairment and **Osmolax** or **Clearlax** may be preferred.
3. Low dose bowel-preparations similar to colonoscopy medicines can be tried. Oral fleet drops (5-10mls of **Fleet Phosphate** solution) given 1-2 times daily can be quite efficacious, although there is a need to be mindful of hyperphosphataemia in chronic use. Oral **sodium picosulfate** drops (1-2mls ducolax) given BD can be similarly effective.
    a. Oral **Epsom salts** 5-10gm (1-0 teaspoons) twice daily dissolved in less than 40mls of water provides a potent alternative to the above.

4. If needing rectal intervention, trial **Microlax** enema initially, and proceed to fleet if poor response

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.

Lactulose is less preferred in palliative care patients, outside those with liver cirrhosis who require it to assist in prevention or management of encephalopathy, due to its propensity to cause bloating and abdominal discomfort. If its use is desired, I tend to start at 10mls TDS and titrate gradually to effect.

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 2-3 times daily; or docusate sodium 240mg 3 times daily
2. Try **macrogol** 3350 as a bowel flusher. Begin at 2 sachets twice daily, increasing up to 4 sachets twice daily if minimal effect.
3. Consider addition of a low-dose bowel preparation agent, oral **fleet phosphate** 10mls twice daily, or **sodium picosulfate** 2.5mls twice daily. Epsom salts 10g twice daily (2 teaspoons) can be used as substitute
4. If unsuccessful with the above, consider full-dose bowel preparation agent, and repeat if necessary
5. If opioid use is a contributor, consider addition of **methylnaltrexone** as described above.

After success, commence an aperients regimen, which must be more aggressive than previous (failed) aperient regimen. 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 **docusate** with **senna**.

For high colonic loading with 'soft' faeces or with an empty rectum on PR, the following steps are recommended:

- Evacuation: Try **macrogol** as described above. If insufficient, consider addition of fleet phosphate or **sodium picosulfate** as above, or **Epsom salts** as substitute.
- If opioid use is a contributor, consider addition of **methylnaltrexone** as described above.

These approaches may be inappropriate in the last days of life when bowel management should be dictated by symptoms and common sense.

Diarrhoea

Diarrhoea in the palliative setting can be complex to manage. Excluding contributing factors such as faecal impaction leading to overflow as described above is crucial, to ensure a hidden constipation is not missed. Modern cancer therapeutics can cause an inflammatory diarrhoea which is best managed acutely by oncologists, and often requires high dose steroids and sometimes monoclonal antibodies.

For patients with bowel resection, particularly those with significant loops of bowel gone, diarrhoea can be incredibly challenging to manage, as there are not sufficient receptors present for pharmacological agents to have impact. Regular nursing care, dietary modifications and stoma input (if stoma present) can be the mainstay in these patients.

In patients with pancreatic insufficiency due to prior surgery or tumour, who present with fatty diarrhoea, ensure adequate provision of Creon at mealtimes, titrating to effect. Patients suffering neuroendocrine tumours may require somatostatin injection to assist in diarrhoea control. Specific dose guidance for these patients is outside the scope of this book.

If anti-motility agents are required, consider the following:

Loperamide 2-4mg statim and then regularly as required, typically 3-4 times daily.

Diphenoxylate/Atropine (Lomotil) 2.5-5mg 3 times daily, up to 4 times daily if poor control.

Codeine phosphate 30-60mg every 4 hours.

Malignant Bowel Obstruction

Malignant bowel obstruction (MBO) is common, particularly in GI primary cancers, although many other malignancies can result in an MBO due to metastasis. Increasing peritumoural oedema or a metastatic deposit can 'trap' the bowel resulting in a twisting and trapping. Sometimes this can wax and wane, with intermittent transit of intestinal contents – this is a partial obstruction. Complete obstruction tends to result in obstipation with altered bowel sound pitch. The most common symptoms that occur with an MBO are nausea, abdominal pain, bowel changes and distention.

Surgical Management

This should be considered first. Generally surgical treatment 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.

Medical Management

The goals of management are to:

- Reduce nausea and vomiting using antiemetics by the injectable route. Some patients may continue to experience vomiting once or twice a day in the absence of nausea.
- Reduce high secretory volumes with octreotide or hyoscine butylbromide. If there is ongoing high volume output, consider a nasogastric tube for symptomatic relief in the amenable patent.
- Reduce abdominal pain and colic utilising analgesics and anti-peristaltic agents
- Reduce peritumoural oedema with high dose corticosteroids.

Consider the following approach:

1. Add **dexamethasone** 8mg subcutaneously daily, or 4mg twice daily, to assist with pain and decrease peritumoural oedema
2. Utilise **haloperidol** as the first line antiemetic, either via regular SC injection or via syringe driver. Avoid metoclopramide as it can worsen colic, unless trying to "push through" a partial obstruction. Cyclizine can used but be aware that it will slow kinesis further.
3. **Hyoscine butylbromide** 40mg daily via infusion will assist with colic, can utilise 60-80mg if secretory control is desired
4. If secretions persist despite hyoscine, add **octreotide** 500mcg/24 hours via syringe driver. This can be increased to 1000mcg if minimal effect, but increasing further is rarely beneficial.
5. Manage pain with **opioids** added to the syringe driver as needed: if the patient is already taking oral opioids convert to infusion and add as appropriate. If opioid-naïve, consider 10-15mg of morphine over 24 hours as a starting dose.

For patients with refractory nausea despite the above, we prefer **levomepromazine** as discussed earlier. Patients will hopefully become free of nausea but may still vomit. 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 or intravenous fluids may be required.

If recurrent obstructions become a feature and prognosis is reasonable, consideration of a venting gastrostomy (a "backwards PEG tube") may be beneficial for symptom control, and allow patients to self-empty their gastric contents (or with assistance) rather than requiring ongoing nasogastric tube placement. These can be done in consultation with interventional radiology, which can be very useful in patients who are high risk for endoscopic procedure.

Colic

Often associated with bowel obstruction above. If an MBO is suspected, should investigate and manage as above, otherwise consider cessation of stimulant laxatives and switch to liquid paraffin 30mls two-three times daily, considering enemas if required, until bowels move well.

Utilise SC **hyoscine butylbromide** 20mg every 4-8 hours, via syringe driver if needed.

Once the oral route is manageable and bowels are opening, consider an oral antispasmodic such as **Lomotil** 2.5-5mg three times daily, or **mebeverine** 135-270mg three times daily. Can also continue oral hyoscine butylbromide 20mg four times daily, although this is poorly bioavailable. May benefit from **hyoscine hydrobromide** 0.3mg every 8 hours instead.

Squashed Stomach Syndrome

This condition is characterised by dyspeptic symptoms associated with compression of the stomach from hepatomegaly or an upper abdominal tumour. Symptoms include: fullness, early satiety, epigastric pain, flatulence, nausea, vomiting, heartburn, hiccups. Treatment is as follows:

- Antiflatulent: **mylanta** 10mL every 4–6 hours; **simethicone** 100-200mg with meals or every 6 hours.
- Acid reduction: PPI at effective dose in the morning, **esomeprazole** 20mg equivalent or higher.
- 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. The evidence for pharmacological management is poor, with signals only and recent trial evidence non-promising. Appetite stimulation may be possible, but weight loss will typically continue. Referral to dietician may be helpful. The best management is often reassurance and

permission to eat foods that provide joy, rather than attempting to hit nutrient goals. If desired, pharmacological 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.

Mirtazepine 15mg at night (start at 7.5mg for frail/elderly), increasing to up to 30mg at night - higher doses lose appetite and sleep benefits.

Megestrol acetate 160mg –800mg daily (may require the largest dose to be effective)

Hiccups (Singultus)

The aetiology of hiccup is complex and may be multifactorial. Causes may include gastric distention, diaphragmatic or phrenic nerve irritation, cerebral oedema from brain tumours, and infection. We attempt to remove any stimulating issues if possible, and consider the following pharmacological options. Local practice would be to typically consider haloperidol as a first line agent, followed by gabapentin. Baclofen is considered particularly in suspicion of oesophageal spasm. Other cases are outlined below.

Haloperidol 1-1.5mg statim then 1.5mg at night is a good starting point, especially for patients who have nausea, to decrease the hiccup reflex. SC doses can be given in the distressed patient who is struggling to swallow. Can increase up to 3mg at night for maintenance if needed

Chlorpromazine 12.52-25 statim, then up to 25mg every 8 hours orally can be used as an alternative to haloperidol. Chlorpromazine 25mg IV may be used in a distressed patient if access is available.

Gabapentin 100-300mg at night, lower doses in the elderly.

Baclofen may be beneficial although it can be sedating or cause postural hypotension even in small doses. Start with 10mg statim then 5mg three times a day, can gradually increase with caution up to 10-20mg three times daily if needed.

Dexamethasone 8-16mg PO if raised intracranial pressure from tumour suspected or seen on imaging, reduce as tolerated to a maintenance dose as able.

Metoclopramide (20mg orally or SC) plus antiflatulent (e.g. mylanta 20mL or simethicone 200mg) can be utilised to promote gastric emptying, with maintenance of 10mg three times daily as required.

Pharyngeal stimulation: swallow 2 heaped teaspoons of granulated sugar or 2 glasses of a liqueur; drink from 'wrong' side of a cup

Notably patients on dexamethasone may experience hiccup *secondary* to commencing the steroid medication, thought to be due to lowering the reflex arc associated with hiccup. It is more common with higher doses, i.e. more than 4mg of dexamethasone daily. If this is a consideration, we recommend withdrawal of dexamethasone and substitution with another steroid medication, if ongoing steroids are necessary for other symptom control. Our preference is to utilise prednisone at a 1:5 ratio (so 1mg of dexamethasone is approximately 5mg of prednisone).

Respiratory Symptoms

Introduction

Respiratory symptoms are very common in palliative care patients, and particularly those with primary lung pathologies like cancers or obstructive airways disease. Breathlessness is the commonest symptom at the end of life, regardless of pathology, and an ordered and stepwise approach to its management is crucial in providing good palliative care.

Breathlessness

Dyspnoea is commonly multifactorial in the palliative care setting. There may be a reversible or organic cause, but equally patients who are losing weight and energy may just as easily experience worsening dyspnoea due to muscle fatigue and general deterioration.

For patients where death is not imminent, we should consider appropriate investigation and treatment of underlying causes of dyspnoea to improve quality of life. Specific investigations and treatments are not included here; however some of the more frequent causes of dyspnoea that we see in palliative care include:

- Bronchospasm
- Cardiac failure occasioning fluid overload
- Pulmonary infection
- Pleural effusion
- Pericardial effusion
- Anaemia
- Chronic airways limitation (CAL)
- Lymphangitis carcinomatosis
- Superior vena cava obstruction (SVCO)

The pharmacological management of breathlessness can be considered to fall within four main areas, with opioids for dyspnoea modulation, anxiolytics for panic-associated breathlessness, oxygen for hypoxic states, and targeted therapies for specific areas. These are outlined below.

Opioids

There is good evidence for the use of low-dose opioids, particularly morphine, in the treatment of symptomatic dyspnoea. Perceptions associated with breathlessness are processed in areas of the brain including the insula, cingulate, sensory cortices and amygdala which are all rich in opioid receptors. Opioid-mediated pulmonary vasodilation may also play a role. There has been a persistent wariness about prescribing opioids in patients particularly at risk of hypercapnia, however at low doses morphine has been proven relatively safe.

Not all dyspnoea will respond to opioids, and it is notable that dyspnoea from pulmonary hypertension has negative evidence for relief from opioids, and dyspnoea from cardiac failure has evidence that is at best equivocal.

Morphine is the drug of choice in patients that can tolerate it, as it has the best evidence of all the opioids for dyspnoea. Low-dose regular oral morphine is typically effective. In patients without pain, commence at 2mg immediate release every 4 hours (half dose for the elderly), and consider titration up to 5mg every 4 hours. Doses higher than this (30mg / daily) will rarely provide relief from dyspnoea if there has been no benefit already observed. Slow release morphine can also be prescribed as a once-nightly capsule, starting at 10mg, to a maximum of 30mg, if this would be well tolerated. For patients for whom morphine must be used with caution (especially renal failure), consider dose reduction and interval increases.

In patients with pain, if they are taking an opioid other than morphine, especially oxycodone, consider rotation to morphine as a first step. If pain has been troublesome on other regimens, it is possible to utilise morphine as an adjuvant for dyspnoea in a similar fashion above, watching for toxicity with caution.

Other opioids have very mixed evidence in the management of dyspnoea. **Oxycodone** has negative evidence and has been shown to be worse than placebo. **Fentanyl** may work but only has evidence as a nebuliser. **Hydromorphone** has some positive evidence but is very difficult to source. It is reasonable to trial low-dose opioids in equivalence to morphine above (10mg/day OMED) however it is reasonable to abandon these if they do not show benefit with early dosing. 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.

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. Counselling 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 for patients who have experienced acute attacks of dyspnoea in the past. For a pharmacological approach, we utilise the following:

Lorazepam is the benzodiazepine most commonly used for dyspnoea, at 0.5-1mg PRN, and up to three times daily regularly + PRN if needed. Reduce doses in the elderly and frail to 0.25mg, or if patients are particularly sedate. Lorazepam can be given sublingually or orally, as the tablet will disintegrate.

Clonazepam is a longer-lasting benzodiazepine that comes in both tablets and liquid formulation. 0.25-0.5mg as an initial dose is reasonable, followed by twice daily maintenance dosing of up to 1mg.

Diazepam can be given at 2-5mg initially, titrating up to 10mg if required. Usual interval is two to three times daily.

Midazolam or Clonazepam can be given by injection or infusion if the parenteral approach is required, further detail below.

Oxygen

Most patients should not require continuous oxygen where there has been optimal management with morphine and anxiolytics. Studies have shown that in non-hypoxic patients (saturations over 90%) a high-pressure electrical, hand-held fan is equally effective in the management of dyspnoea. Other studies have shown that air is as effective when delivered via nasal prongs as oxygen in the non-hypoxic, and in patients with cardiac failure oxygen has no real benefit over airflow. Oxygen is however often prescribed due to the difficulty in providing pressured air.

The criteria in our local service for prescription of oxygen via the palliative care service typically includes a short-term prognosis of less than 3 months, with pharmacological management in situ. Smoking must not occur in the vicinity of the oxygen concentrator.

For patients with a longer-term survival, it may at times be more appropriate to refer oxygen prescriptions via respiratory specialists or via ENABLE.

Cough

Cough is another respiratory symptom with multiple potential causes. For fit patients, consider treatable options rather than solely depending on suppressive therapy. Such options may include:

- Mucolytics for 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 should be considered for all patients with persistent symptoms. The following options are available:

Reduce pharyngeal stimulation using e.g. simple linctus 10ml, cough lozenges, or 1-2 teaspoons of honey.

Opioids for central cough suppression. Consider a trial of **codeine linctus** 30mg every four hours PRN, or of **morphine elixir** 2-3mg every four hours PRN, to suppress the cough reflex. If morphine is beneficial, can consider slow release dosing once-twice daily with the appropriate formulation. It can be argued that morphine should be utilised over codeine, given that codeine is a morphine prodrug; however some patients do find the linctus formulation soothing in and of itself. **Pholcodine** is less used in our service although is available. **Methadone** ⚠ can be used for cough suppression in low dose, consider 2.5mg at night time and increase if minimally effective to 5mg at night or to 2.5mg twice daily. Be mindful of drowsiness and be prepared to withhold or reduce doses.

Paroxetine 5-20mg has been reported to be very effective though its site of action is unknown, particularly in dry cough secondary to tumours within the thorax.

Local anaesthetic blockade of cough receptors may be used in patients whose symptoms persist despite central suppression. Options include: **lidocaine** 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.

Secretions occasioning cough. Consider **amitriptyline** 10-20mg at night, **glycopyrrolate** 0.2mg initially, then 1.2-2.4mg by SC infusion per 24 hours, or **hyoscine butylbromide** 20mg initially then 40-60mg by SC infusion per 24 hours.

Dexamethasone 8mg orally daily for 5 days, reducing to 4mg daily as maintenance, may be a useful adjunct in patients with lymphangitis carcinomatosis or upper airways compression.

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

Haemoptysis

Simple or low-volume 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: Local practice is to commence at 1gm every 8 hours, and then continue for 48 hours after bleeding ceases. If the bleeding recurs with withdrawal of tranexamic acid, consider instituting maintenance dosing of 500mg two-three times daily. Can be given subcutaneously (the intravenous formulation) if required.

Massive bleeding at the end of life via the airway is a palliative emergency, and is discussed in that section, on page 35.

Death Rattle

Death rattles or terminal secretions describes the rattling noise produced during respiration when secretions are retained in large airways, in patients too weak to expectorate effectively. It is thought to be due to a combination of saliva and airway

secretions. Patients are often moribund but relatives, other patients and staff may be distressed by it. There is limited data on how affected patients are, although local research implies some distress may be present. Counselling relatives is usually advisable to reassure them that the patient is not suffering. Pharmacological treatments have evidence as prophylaxis in prevention of secretory build up, however use after secretions have already developed tends to be inefficacious.

Any of the following treatment options may be considered:

Hyoscine butylbromide 20mg SC initially, then 60-80mg SC infusion per 24 hours. Theoretical maximum is 100mg per 24 hours although unclear if much benefit over 80mg.

Glycopyrronium 0.4mg SC initially, then 1.2-2.4mg SC infusion per 24 hours.

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 (same dosing as glycopyrronium)

If severe symptoms are present, we typically ensure sufficient sedative medication is on board – see the End of Life care section for details.

If associated with purulent sputum consider a statim subcutaneous injection of **ceftriaxone** (1g reconstituted in 3.75 mls 2% lignocaine, in two injection sites.

Urinary Symptoms

Introduction

Urinary problems in palliative care can be a significant limitation on quality of life. There is an increased prevalence as the end of life approaches, with many patients proceeding to requiring catheterisation to relieve bladder retention.

Frequency and Urgency

For patients suffering from frequency or urgency, should consider reversing treatable causes whenever possible, including:

- Bladder outlet obstruction, irritation or compression by pelvic tumour:
    - TURP for prostatomegaly in the fit and well
    - Dexamethasone 8mg daily for 5 days followed by 4mg maintenance where pelvic tumour is implicated.
    - Chemotherapy or radiotherapy may be options in the appropriate patient
- Infection, consider trial of appropriate antibiotics
- Diuretic therapy, wean back on over-diuresis
- Oversedation leading to loss of control
- Polyuria which will not respond to the treatment options outlined below (check BSL in patients on steroids or with upper-GI tumours)

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, local practice prefers **amitriptyline** first line, starting at 10mg nocte and titrating up to 25mg if minimal improvement. These doses will generally not result in urinary retention but be mindful of the potential side effect and

consider the need to bladder scan. **Propantheline** 15-30mg every 6-8 hours can be an alternative, particularly in the diaphoretic patient. Consider **oxybutynin** as a patch in patients with poor oral tolerance although this can cause skin reactions, and has the potential to make the frail more likely to fall. **Solinefacin** can be trialled at 5mg at night if the above is ineffective, it is unfortunately not subsidised on the PBS.

NSAIDs can be used, although there is a small risk of aggravating haematuria. Choice depends on prescriber preference, locally we utilise **celexocib** 200mg daily as our first line NSAID. Be cautious in renal failure, although short courses of NSAIDs should not be avoided if considered beneficial as they are usually well tolerated with only transient effects.

Mirabegron is a beta$_3$-adrenoreceptor agonist that may be more effective than anticholinergic medicines, but is not currently on the PBS. Start at 25mg once daily, consider increasing to 50mg once daily if needed and if well tolerated.

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, and can occur in both catetherised and non-catheterised patients. 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 an NSAID such as naproxen 250–500mg every 12 hours + morphine if required every 4 hours titrated upward until there is effective relief of pain

Anticholinergic drugs, consider amitriptyline at night time as a first line choice. Oxybutinin orally 5-10mg twice daily (2.5mg in the elderly) can be helpful. Mirabegron is useful in patients with overactive or as a patch can

Amitriptyline 10–50mg at night is recommended as a first line. Can consider trialling **oxybutynin**, **solinfacin**, **propantheline** or **mirabegron** as described above although evidence is more limited.

Consider **hyoscine butylbromide** 20mg SC twice daily (or 40mg via infusion).

Nerve blocks may be trialled by intervention radiology, with intervention possible at the inferior hypogastric plexus.

Change the catheter if one is present, and consider decreasing the gauge to prevent spasm recurrence.

Hesitancy

Consider treatable causes including:

- Withdrawal of drugs with anticholinergic side effects
- Opioid induced hesitancy may respond to changing the opioid, 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 0.5–1mg once or twice daily. Mode of action is sympathetic antagonism, which promotes voiding

Tamsulosin 400mcg once daily. Same mode of action as prazosin but more selective for receptors in the bladder. Also more expensive unless the patient qualifies for the RPBS scheme, although generics are now available.

Dutasteride 500mcg daily, this is given in combination with tamsulosin. Potentially useful in male patients with prostatomegaly; alters levels of serum testosterone.

Haematuria

The primary medication utilised in our setting is tranexamic acid. Consider 1gm three times daily until bleeding has ceased, then stop and evaluate. If bleeding returns, the patient may need a maintenance dose of 500mg two to three times daily. Half doses in patients with severe renal failure. There is a theoretical risk of clot retention in the bladder although this has not been seen locally.

For patients with ongoing severe bleeding with clots, urological input is required to consider continuous bladder irrigation for severe bleeding and clots.

Retention at the End of Life

Urinary retention at the end of life is common, likely due to a combination of iatrogenic factors from medications utilised, as well as from general physical decline and frailty. The primary concern is discomfort leading to severe restlessness in the otherwise poorly responsive patient who is too unwell to void, which may lead to inappropriate treatment with sedatives and tranquilisers.

For patients at the end of life, regular examination of the lower abdomen, preferably with non-invasive bladder scan, is recommended, with progression to an indwelling catheter strongly recommended in patients who demonstrate increasing urinary volumes without relief. Proactive discussion with family members and with patients themselves when able will often make this process less distressing.

Use of low dose midazolam as an amnestic (consider 2.5mg subcut) to aid in passing a catheter is quite reasonable in this setting.

Itch & Ulcers

Itch

Itch is a very complicated pathology with multiple aetiologies. There are dozens of potential pathways involved in palliative care patients, including serotonin, substance-P, hyperbilirubinaemia, uraemia, and histamine.

Dry skin

Dry skin is among the commonest causes of pruritus in patients with advanced cancer. Itch should also be treated when present in patients with pruritus of other origins.

Locally applied emollients are the mainstay of successful management. Substantial evidence does not exist for one agent over another, with plain **sorbolene** being reasonable to start. **Paraffin** or other oil-based emollients may prove helpful if simple moisturisers are ineffective.

Histamine-mediated

Histamine is often blamed but uncommonly responsible for itch in palliative care patients. Only about 10% of palliative care patients with itch will have a beneficial response to antihistamine therapy. Some predictors of positive response include recent commencement of opioids (although this is rare), allergy and prior history of dermatitis.

Trial **loratadine** 10mg daily, or **promethazine** 25mg at night if sleep is disrupted. Consider a brief course of steroid medications, topical over systemic. Deeper sedatives may be required if itch does not respond, including benzodiazepines.

Cholestasis

Itch is due to build-up of bilirubin deposits in skin, leading to jaundice. The itch may be present before significant jaundice is observed but hyperbilirubinemia is seen on bloods and scleral icterus may be developing.

Trial **sertraline** 25mg at night, titrating up to 50mg if poor response (can go to 100mg in some patients). Can also trial **paroxetine** 10mg at night, up to 20mg.

Rifampicin 150mg daily initially if available and increase to 150mg twice-daily if needed, can work second line.

Methylnaltrexone 4mg to 8mg SC second daily can assist some patients, without reversing analgesic benefits of opioids.

Can consider either **cholestyramine** 4gm twice-daily or **ursodeoxycholic acid** 10mg/kg/day (rounded to nearest tablet) at night although both **cholestyramine** and **Ursofalk** are poorly tolerated.

Antihistamines do **not** help in this setting.

Uraemia

Consider and optimise renal function as able, correct iron deficiency and hyperphosphatemia in patients with renal failure to lessen symptom impact.

Consider **capsaicin** cream if itch is local only, 0.025% up to four times daily – this is often poorly tolerated.

For systemic therapy, the first line choice should be a gabapentinoid. Start **gabapentin** at 100mg at night and titrate up slowly, or **pregablin** at 25mg. In patients on haemodialysis, give the gabapentinoid three times a week on the night *after* dialysis. Be prepared to dose reduce depending on severity of renal failure, as gabapentinoids accumulate.

Evening primrose oil tablets (Blackmore's) can help some patients.

Antihistamines do **not** help in this setting.

Opioid-Induced

If early (or spinal intervention), give stat dose of a H1-antagonist like loratadine or cetirizine. Consider **opioid-rotation** if ongoing issues, use of low-does **methylnaltrexone**, or **ondansetron** 8mg twice daily.

Malignant Itch

Cancer can drive itch especially in lymphoma and paraneoplastic syndromes.

First line trial a gabapentinoid, prefer **gabapentin** 100mg twice-daily and titrate to effect.

If there is ongoing itch, **aprepitant** 165mg every three days can resolve this rapidly, although expense and availabity may limit access.

Mirtazapine 7.5mg at night, increasing to 15mg, can assist.

SSRIs as above, sertraline or paroxetine, can assist.

Lidocaine by infusion can help with refractory itch, particularly in the malignant setting. Consider 100mg/24 hours via syringe driver, increasing by 100mg daily with caution, This option would not be recommended outside the palliative care unit.

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 to put across is the importance of managing and preventing odours when ulcers have a necrotic base and are infected by anaerobic bacteria.

Metronidazole 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 suspending 100mg of the intravenous formulation in 10gm of hydrogel (can use lubricant gel) and applying to the wound surface. This can also be combined with **morphine** (10mg/10g gel) for local pain relief and/or **sucralfate** 1gm tablet crushed and mixed in the gel for haemostasis. Care should be taken not to have topical contact with metronidazole preparations.

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.

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 clinically 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, consider:

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: 500mg tablet crushed and mixed in lubricant gel, applied locally 3 times a day. This can also be used in refractory epistaxis or in vaginal bleeding, using a gel and applicator.

Systemic tranexamic acid: 1g every 6-8hours orally, reducing to 500mg every 8 hours if effective.

Topical adrenaline: 1:10,000 adrenaline-soaked non-adherent gauze dressings applied to wound surface. For large areas it is wise to dilute the adrenaline 2-3 fold. Note that systemic absorption is possible from this method, so proceed with caution.

Motor Neurone Disease

Introduction

MND is perhaps best thought of as a heterogeneous syndrome overlapping with a number of other diseases. It is due to degeneration of the upper and lower motor neurones, and can result in progressive weakness of bulbar, limb, thoracic and abdominal muscles. Cognitive function can be affected in 20-50% of patients, with around 5% developing a dementia (typically FTD). The median survival is about 30 months, although can be very variable from short months to a number of years. It usually takes over a year to diagnose once symptoms develop, and the vast majority (almost 95%) are not genetically related. Symptoms associated with poor prognosis are respiratory symptoms at diagnosis, with rapid progression, and cognitive impairment.

This section details some of the more common symptoms associated with MND in palliative care.

Sialorrhoea / Bronchial Secretions

Sialorrhoea due to impaired swallow rather than over-production, and can be quite disabling. There are two main kinds of saliva, thin and watery (seen in drool) and thicker, more bronchial secretions. Involvement of the allied health team for swallow technique (Speech Pathology), cough management (physiotherapy) and head and neck support (occupational therapy) should be done. Consider barrier creams to support skin, portable suction units, and side sleeping to reduce pooling.

It is important to clarify the type of secretions as treatment for thin/watery can make thick/bronchial secretions even more difficult to expectorate.

For thin/watery secretions: Pharmacological options include **amitriptyline** 10mg at night, increasing up to 50mg. Can use up to 50mg three times daily in refractory cases. **Atropine** drops (ophthalmic) can be given orally, the 1% formulation, 1-2 drops three times daily (poor lip seal can limit use). Can also utilise **glycopyrronium** (available from the hospital pharmacy) 200mcg three times daily initially up to 1mg three time daily. Other options include **hyoscine hydrobromide** patches which can

be started as a half patch daily behind the ear and titrate to effect – noting that these patches are Special Access only.

Interventional options can include **botulinum A** toxin injections to the salivary glands, which can last up to three months although be mindful this can make dysphagia worse. **Radiotherapy** to the parotid and/or submandibular glands may assist and can sometimes be repeated. Consider the use of a portable suction device.

Bronchial secretions can occur throughout the airway, with typically thick mucus secretions causing difficulty coughing or swallowing, and sometimes partial airway blockage with a feeling of choking. This can be worsened by dehydration, mouth breathing and non-invasive ventilation.

Improving oral hygiene can assist, as can rehydration. Avoidance of mouth breathing should be attempted, although for bulbar patients this may not be practical. Some patients find **papaya** or **pineapple** juice with a meal helpful (has enzymes to help breakdown the secretions. Sucking on lozenges can assist, as can nebulised saline or humidifiers. Consider mucolytics like **bromhexine** 16mg three times daily, or nebulised **acetylcystine** (available from the hospital pharmacy).

Spasticity

Consider non-pharmacological interventions to spasticity including minimisation of precipitating factors like tight clothing, constipation, postural discomfort in wheelchairs, orthotics. This is regardless of site of spasticity due to autonomic nervous pathway feedback loop. Hydrotherapy and movement therapy from physio is helpful.

Pharmacological treatments vary depending on level of muscle tone. The critical question is whether muscle tone is important for mobility/transfers as anti-spasticity medications risk loss of useful muscle tone and compromising mobility. If muscle tone is important (patient not bedbound), **Gabapentin** is the typical first line choice, start 100mg three times daily and titrate to effect. Consider benzodiazepines; **diazepam** 5mg two times daily is reasonable, titrate gradually. If no muscle tone or the patient is bedbound, consider **baclofen** 5mg two-three times daily, up to 20mg three times daily with cautious titration. In select patients, low doses can be used nocte only to balance symptom control nocte and maintaining mobility. Can also consider **dantrolene**.

Cramp

Consider non-pharmacological interventions similar to above. Can trial **quinine sulphate**, 200mg BD.

Dysphagia

Gradually occurs as disease progresses. Earlier in bulbar disease. Initially, speech pathologist input is recommended as well as dietician. Consider a good trigger for advance care planning and goals of care discussion as a hallmark of progressive decline

In the later stages, supplemental nutrition may become necessary. PEG or RIG may be necessary, ideally patients should be referred before weight loss of >10% body weight and should have a vital capacity of 50% or greater. Earlier intervention is better, particularly where there is risk of respiratory deterioration as this may limit the ability to go through the procedure.

Respiratory Failure

As MND progresses, the development of respiratory muscle weakness progressing to failure is a common trajectory leading to death. Clinical features that enhance suspicion of this developing include orthopnoea, nocturia and frequent awakenings during sleep, as well as early morning headaches, increasing daytime somnolence, and memory/concentration deficits. Respiratory symptoms typically worsen, with exertional dyspnoea, tachypnoea, accessory muscle use and weakened cough potentially developing. Patients may also develop syncope, confusion, hallucinations, diaphoresis, tachycardia and weight loss, among other symptoms.

Respiratory insufficiency can be worsened by aspiration and pneumonias, with nocturnal oximetry being useful. Muscle function can be measured with vital capacity and sniff nasal pressure, although these are not helpful if there is severe bulbar weakness.

The best symptomatic management of respiratory failure in MND is **ventilation**, usually non-invasive although invasive does occur. **BiPAP** or bilevel positive airway pressure improves survival, eases symptoms and improves quality of life, with a median survival of 7 months. Notably around a third of patients do not tolerate

BiPAP, and compliance can be limited in patients with cognitive or bulbar dysfunction.

It is important to have advanced care discussions with patients developing respiratory symptoms and progressing to failure, as the pathway away from ventilation is often the provision of sedation while withdrawing ventilator support, and this should be discussed prior to initiation or even referral for ventilator assessment.

Notably, **oxygen therapy is not recommended** in patients with MND and respiratory muscle weakness, as impaired breathing effort and oxygen provision can lead to hypercapnia and progress to further respiratory depression and hasten death. If patients are hypoxic, oxygen may be considered with close monitoring under specialist support, and often requiring regular arterial monitoring.

Delirium and Seizures

Introduction

Delirium is very common in palliative care patients, particularly approaching the end of life. Organ failure leading to biochemical abnormalities, disease progression, medication side effects and general frailty can all contribute to this state. Management differs based on the clinical trajectory.

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.

The Non-Terminal Patient

The approach above of investigating and reversing causes as appropriate should be followed, and management will often be dictated by investigations and results. For symptomatic control, consider the following

Benzodiazepines for relaxation, although there is some evidence these can worsen the symptoms of delirium. Consider **clonazepam** 0.25-0.5mg at night time, or **lorazepam** 0.5mg three times daily.

Neuroleptic medications will not resolve delirium but may have a settling effect on paranoia. Consider **haloperidol** 1-2mg stat and then twice daily, or **olanzapine** 2.5-5mg at night time. For refractory cases, **chlorpromazine** 12.5-25mg three times daily may be helpful.

Clonidine shows promise in the treatment of delirium without dementia, due to decreasing catecholamines within the central nervous system. Consider starting at 150microg at night time, to aid in both sleep and as a relaxant. It can be increased by 50mcg at a time to a maximum of 300mcg if desired. Be mindful of potential postural blood pressure changes.

Sodium Valproate may help resolve agitated behaviours in some patients. Consider starting at 100mg twice daily, increasing gradually up to 300mg twice daily if needed.

Dexmedetomidine ⚠ may prove helpful by infusion, although most of the experience in its use has been in the terminal-adjacent setting. 0.3-0.5mcg/kg/hour subcutaneously via infusion is a reasonable dose for delirium treatment.

The Terminal Patient

Terminal Delirium, also referred to as terminal agitation, terminal restlessness, and hyperactive delirium at the end of life. Management is focussed on relieving agitation and reducing distress. The focus is classically sedative, with parenteral medication delivery. There is a recent shift towards cooperative sedative medications, which are discussed towards the end of this section, but these are specialist in nature.

Benzodiazepines are the traditional first line choice. **Midazolam** 2.5-5mg statim subcutaneously, then followed by 15-20mg via continues infusion initially and titrated to effect. Rapid tachyphylaxis can develop with midazolam and for patients with prolonged dying it may be necessary to increase dosing. Doses in excess of

100mg are used in some centres, although locally we rarely exceed 60mg over 24 hours. **Clonazepam** may be used as an alternative or as an adjunct to midazolam, and may be administered either as regular injection or via syringe driver. When prescribed via syringe driver, 1mg/24 hours is 'lost' to PVC absorption, so we typically overprescribe to compensate. Consider 1-2mg as a loading dose subcutaneous statim, then 4-5mg (3-4mg actual) as a starting dose over 24 hours. This can be increased up to 15mg over 24 hours if needful, although escalating dose of either benzodiazepine without relief is often a sign other sedatives are required. If combining the two benzodiazepines, consider 20-30mg of midazolam and 6-8mg of clonazepam over 24 hours.

Levomepromazine ⚠ is a broad-spectrum neuroleptic similar to chlorpromazine. It is an SAS scheduled agent in Australia, but has a streamline (SAS-C) code for agitation at the end of life. It is an excellent tranquiliser in many patients who respond poorly to benzodiazepines alone. Consider 25mg SC statim and repeat at 60 minutes if poor response, then start 150-200mg SC infusion over 24 hours depending on response. Maximum infusion should be 250mg/24 hours; levomepromazine can be given as a 2-4 hourly breakthrough dose for agitation if required.

Phenobarbital ⚠ is an older highly sedative barbiturate utilised as a third-line sedative, which provides deep relaxation that is especially useful in patients who may be poorly responsive to the above agents. Consider especially patients who have intracranial disease like leptomeningeal carcinomatosis, prior severe epilepsy, prior heavy benzodiazepine or neuroleptic use, etc. Local practice is to give a loading dose of 400mg (IM is preferred over SC), and commence a separate syringe driver of phenobarbital of 1800-2400mg depending on prior agitation and response to loading dose. Some patients may require a second loading dose of another 200-400mg after 1-2 hours if still significantly unsettled. The infusion can be titrated up to 3200mg over 24 hours if required and agitation persists.

Dexmedetomidine ⚠ has local evidence for the management of terminal delirium with reasonable communication, for patients who do not yet wish to be deeply sedated and wish potential communication to continue with families/loved ones. It is not currently recommended outside of specialist palliative care settings, however statim doses of 0.5mcg/kg subcut, as well as infusions of 12-18mcg/kg over 24 hours have reasonable efficacy.

Seizure

In the non-terminal patient, we recommend the involvement of neurology if able. Patients with brain tumour are more likely to seize due to increased cranial oedema. Consider the following:

Dexamethasone 8-16mg SC and reduce after 3-5 days to lowest effective dose

Midazolam for seizure interrupt 2.5-5mg parenterally as needed

Leviteracetam can be given via syringe driver (alone), up to 1500mg over 24 hours. Note that leviteracetam can worsen aggression and agitation in patients with frontal lobe disease.

Clonazepam 0.25-0.5mg twice to three times daily regularly as prophylaxis, titrating as needed.

For patients in the terminal phase, maintain dexamethasone dosing if present (reduce to lowest possible dose) and utilise benzodiazepines via infusion as described above for agitation. Consider **phenobarbital** for refractory seizures, 200mg as a loading dose and 3-5mg/kg over 24 hours as an infusion dose – between 500-800mg is typically sufficient for seizure prophylaxis.

Palliative Care Emergencies

Introduction

There are several non-related conditions for which crisis management in the palliative care setting is crucial, either to reverse if reversal is indicated, or to provide rapid symptom relief in the dying patient. These are outlined below.

Malignant Spinal Cord Compression

MSCC can occur with most tumour types, and should be considered where red flags exist. Severe pain in the back that wraps around to the front and is worst on lying flat is a significant cause for concern in a patient with known malignancy. Pain is almost always the first presenting symptom, and can proceed other neurological changes by many weeks. Weakness is present more than half the time at time of diagnosis but almost always follows pain. Paraesthesias or numbness are less common but still present in approximately 50% of patients. Bowel and bladder dysfunction are typically **late** signs. There needs to be a high index of suspicion to avoid **irreversible neurological damage**.

The approach is combination depending on the tumour type. If the clinical suspicion exists, **dexamethasone** should be given as a priority at 16mg PO or SC, followed by rapid imaging. MRI is recommended, as CT is often inadequate to visualise tumours. Maintain dexamethasone dosing of 8-16mg daily until a plan is developed.

Depending on findings and fitness of patient, a combination of radiotherapy, chemotherapy and neurosurgery can be considered. Radiotherapy can be offered as analgesic and stabilisation for the older and frailer, while those with chemotherapy sensitive tumour should have this expedited with their medical oncology specialist. For the younger or fitter patients with reasonable prognosis, urgent neurosurgical input is suggested.

Superior Vena Cava Obstruction

SVCO is due to the obstruction of blood flow through the SVC, through compression of the SVC by extrinsic or intrinsic tumour, from thrombosis, or from both coexisting.

Most commonly this is due to a malignancy, although it can be due to issues with long lines indwelling for treatments like chemotherapy. It is quite common in patients suffering from primary lung carcinoma, especially small cell.

SVCO commonly presents with facial and arm oedema, cough and breathlessness, as well as potentially positive Pemberton's sign

Similarly to cord compression, urgent treatment with high dose **dexamethasone** 16mg, followed by urgent imaging and oncological input is suggested. Radiotherapy can be utilised as can chemotherapy in sensitive tumours, and some tumours may be stentable.

In patients who are approaching the end of life, it is recommended to maintain high dose dexamethasone 8-16mg daily to prevent worsening dyspnoea, and manage with sedation as described below.

Terminal Distress

Severe distress at the end of life is not common but can occur due to rapid symptom decompensation, particularly breathlessness. Agitated delirium and uncontrolled pain are also potential causes of distress in the terminal phase of life. Severe distress at the end of life needs to be rapidly controlled for the benefit of the patient, their loved ones and any clinicians involved.

If a patient is suffering from uncontrolled pain at the end of life, it should be managed with parenteral opioids with rapid escalation to effect. Give subcutaneous PRN dose equivalent to their prior oral dosing every 30-60 minutes until pain control is reasonable, and then if sufficient prognosis remains commence a syringe driver to maintain efficacy. A reasonable syringe driver dose could be the dose required to gain analgesic control x 6 over 24 hours (e.g. if needed 10mg of subcutaneous morphine to become comfortable, consider 60mg/24 hours via syringe driver).

More detail on delirium management is given elsewhere in this volume (see X) but in the crisis setting, consider **midazolam** subcutaneously 2.5-5mg every 30 minutes until distress has settled prior to commencing an infusion

For patients with acute respiratory distress at the end of life with elevated respiratory rate and cyanosis, who are 'gasping' for air, the best management can be rapid sedation with some opioid for respiratory control. Provide oxygen if it is

available, and administer 10mg of morphine and 10mg of midazolam intramuscularly. Repeat at 15 minutes if the patient is still in distress; the goal is to provide adequate sedation and anxiolysis whilst alleviating consciousness. The subcutaneous route is not preferred in the crisis setting due to slower medication onset. Severe respiratory distress of this nature is typically due to obstruction of main airways (or worsening SVCO as described above) and is not compatible with life for an extended period. If symptoms settle and the patient plateaus, consider a syringe driver of their background opioid dose plus 20-30mg of morphine, as well as a minimum 20-30mg of midazolam over 24 hours.

Terminal Exsanguination

Life-threatening bleeding at the end of life can result from tumours around the airway or oesophagus, variceal ruptures, and patients with acute leukaemia in particular. They are good to anticipate as can be frightening to witness, but in clinical practice are rare. Interventions that make the most significant difference are counselling families and patients about the possibility, ensuring that if an event happens someone is with the patient at all times to provide reassurance, and provision of dark-coloured towels to disguise the bleeding.

Crisis doses of morphine and midazolam may be helpful to provide rapid sedation but there is rarely time for these to be efficacious. If they are to be used, consider **morphine** 10mg with **midazolam** 10mg IM or IV every 10 minutes until the patient is unresponsive, up to 3 doses in a row. The subcutaneous route is not recommended due to peripheral vascular compromise.

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.

Oral medications are preferred to parenteral or rectal administration of drugs in palliative care although as patients approach the end of life, swallowing difficulties develop and it may become necessary to convert existing medications to the parenteral route. Most patients cannot continue oral medications in their last 24-48 hours of life. 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

Maintaining symptomatic control and prevention of worsening symptoms is the primary goal for prescribing 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 adherence to the appropriate combination of an opioid, an NSAID and other co-analgesics (such as steroids and anticonvulsants) where these previously formed part of the oral regime. Not all medications are available in all routes, and alternatives may be required.

Nausea and vomiting control can be maintained by parenteral administration in the vast majority of cases.

Intermittent (4-hourly) or continuous SC administration of drugs via a syringe driver forms the mainstay of management.

Continuing Symptom Control

Oral **morphine** and **hydromorphone** 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). Injectable **oxycodone** is available parenterally but is expensive and hard to access; it is recommended to convert this to either **morphine** or **hydromorphone** and utilise these agents. **Methadone** can be converted to a subcutaneous infusion but the ratio is variable and it is recommended to gain specialist input.

Transdermal **fentanyl** or **buprenorphine** patches are generally continued with the addition of SC morphine or hydromorphone. It is common practice to maintain a patch and to add a SC morphine infusion to titrate the analgesic requirements. Be aware of the morphine equivalence of the patient's patch (page 13) 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<50mls/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 **parecoxib** SC 40mg once daily, or with ketorolac 10-20mg SC every 8-12 hours in patients with complex pain. We may

use ketorolac as a PRN medication in patients we feel could manage without regular. Neither of these medications works well in a syringe driver so are given as intermittent injections.

Paracetamol is available as a suppository, although is not commonly used in local practice.

If patients haven been taking steroids regularly orally, we typically continue subcutaneous dexamethasone as a once a day bolus. As a rough guide, 1mg of **dexamethasone** is equivalent to 5mg **methylprednisolone**, 6mg **prednisone** or 25mg **hydrocortisone**.

In patients taking anticonvulsants or antidepressants for neuropathic pain, we sometimes utilise ketamine or clonazepam parenterally, which has some evidence in this setting. If seizure control is desired, it is possible to give **leviteracetam** via syringe driver in a 1:1 dose to the prior oral daily dose, up to 2000mg daily, or **sodium valproate** in similar fashion. In the dying patient, we utilise injectable benzodiazepines such as **midazolam** and **clonazepam**, as well as infused **phenobarbital** in the refractory terminal setting (see page 33).

Terminal Care

Stop all unnecessary medications, taking care to counsel family member (and patients if able) that this is not a life limiting issue; the vast majority of medications taken in the community do not make a rapid difference to life expectancy. Change required medications as discussed above in order to maintain adequate symptom control,

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

Knowledge of four drugs is sufficient to manage the majority of all dying patients comfortably, particularly the elderly, in the home setting.

1. **Morphine** for pain and dyspnoea
2. **Midazolam** for distress and sedation
3. **Haloperidol** for nausea and agitation
4. **Hyoscine butylbromide** for terminal secretions

It is beneficial to be familiar with the use of **clonazepam** as an adjunct to the use of midazolam especially in the home setting as liquid formulation, and access to a syringe driver is beneficial.

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 two hours, for *pain* and/or *dyspnoea*
- **Midazolam** 5mg SC every two hours, for *distress* and/or *agitation*
- **Haloperidol** 1-2.5mg every six hours, for *nausea* and/or *agitation*
- **Hyoscine butylbromide** 20mg SC every four hours, for *secretions*

Consider orders for **clonazepam** liquid 0.5-1mg every six hours for *distress* second line to midazolam, especially in the absence of a syringe driver. In the patient who is not opioid naïve, adjust the morphine dose to be 1/6th their prior daily oral morphine equivalent, using the conversion information discussed on page 20. In the patient with known renal impairment, consider the use of hydromorphone in place of morphine, at 1/5th of the morphine doses discussed above.

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 (i.e. if you're not sure what to do try this to start!):

- **Morphine** 2.5mg SC statim, then 15mg/24 hours in an opioid-naive patient (see morphine conversion on page 10 for appropriate doses in patients already on opioids).
- **Midazolam** 2.5mg SC statim, then 15mg 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.

- **Hyoscine butylbromide** 60mg over 24 hours, as prophylaxis for terminal secretions. There is good evidence this prevents the build-up of so-called death rattles, and in the terminal patient is generally tolerated

Add **haloperidol** 2-3mg over 24 hours to the syringe driver if the patient has required regular antiemetics.

If no syringe-driver is available:

- Give **morphine** 2.5mg SC every 4 hours (in the opioid naïve patient), or the appropriate 1/6th dose of their prior opioid.
- Give **clonazepam** liquid 1mg PO every eight hours OR SC every 8 hours.
- Give **hyoscine butylbromide** 20mg SC every 8 hours

Please contact your local palliative care service if you are still having difficulties in achieving patient comfort.

Health
Illawarra Shoalhaven
Local Health District