Pain Management
in Palliative Care

Pain in palliative care

Pain assessment in palliative care

Strategies for pain management

Other symptoms

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Pain Management in Palliative Care

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Contents

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Key messages

- **Adopt a systematic whole person approach to total pain assessment and management**
- **Administer regular analgesia in accordance with the WHO analgesic ladder**
- **Use appropriate adjuvant therapies as specifically indicated at any time during the illness**
- **Liaise with the Palliative Care team as soon as it becomes apparent that specialist advice may be needed**
- **Maintain involvement with the patient throughout their illness**

Professor Rod MacLeod

Lessons Learned

We asked Rod, Conjoint Professor of Palliative Care at the University of Sydney and Senior Staff Specialist in palliative care for HammondCare, what lessons for primary care he had learned on his journey from rural practice in East Anglia, UK to his present day work in North Sydney, Australia. His reply was that he had come to understand that for patients receiving palliative care, maintaining relationships and continuing normal daily activities are just as important, if not more so, than symptom control. This understanding is the cornerstone of successful palliative care.

Both palliative care and primary care are about people and their families, listening to them and learning what is most meaningful in their lives. Primary care clinicians have the advantage over those who work solely in palliative care of being able to build up high levels of expertise about their individual patients through years of shared experiences and mutual trust.

For patients receiving palliative care, maintaining relationships and continuing normal daily activities are just as important, if not more so, than symptom control. This premise is the cornerstone of successful palliative care.

Rod feels that general practitioners and others working in primary care often underestimate both how much they know about their patients and the importance of their role in caring for people receiving palliative care. He is not just talking about peoples' physical wellbeing and how they respond to ill health but the context of their lives and what is most meaningful to them. The sadness is when people are admitted to a hospice or hospital this expertise is often no longer available to guide patient care.

Approximately 90% of palliative care takes place in the home and there is a growing body of evidence that people who are cared for at home by a team that includes the patient's own general practitioner achieve good outcomes with significantly reduced hospital admissions. The key attributes to making this work are communication, competence and confidence.

Communication with patients is what general practitioners are good at. Communication with other health professionals can be more problematic. Often busy-ness gets in the way. Rod hopes that GPs will see this guide as an aid to providing best possible care when and where it is needed.

Competence in managing the common symptoms associated with palliative care is not difficult to achieve for most situations. Uncomplicated approaches to the physical aspects of pain, dyspnoea and nausea are usually successful but management of the fear and distress that often accompanies these symptoms needs a more intimate and individualised approach.

Confidence grows with knowledge and the experience of working alongside other members of the primary and palliative care teams. The early establishment of working relationships and pathways will ensure clinicians are not left isolated and can readily obtain advice when they need it.

These attributes enable primary care clinicians to improve the quality of life of people receiving palliative care by helping them to maintain relationships and continue with normal daily activities as well as achieving good symptom control.

Pain in palliative care

Palliative care involves assessing and managing pain that may:

- **Be persistent**
- **Have multiple aetiologies, one or more of which are incurable**
- **Impair function**
- **Threaten independence, and,**
- **Invoke fear of further suffering and death**

Pain will trouble over half of patients with advanced cancer, AIDS, cardiac disease or neurological disorders. However, pain is not inevitable in these diseases. Approximately 30% of patients with advanced cancer will not get severe pain, 80% of those who do can achieve good pain relief by the systematic use of oral analgesia, appropriate adjuvant therapies and multi-faceted supportive strategies.

The aim is to optimise quality of life right up to the moment of death.

Pain assessment in palliative care

A whole person approach to pain assessment can be assisted by considering four components of the pain experience:

1. The stimuli that cause it

2. The mind's perception of those stimuli

3. The person's interpretation of these unpleasant sensations, and,

4. The impairments they produce

The column on the left of Figure 1 summarises the factors that contribute to the components of pain. All four components require careful assessment to determine the most appropriate interventions, or method of pain control.

Heavy reliance on analgesics without the use of other appropriate interventions may produce pain relief at the cost of significant loss of quality of life.

	Contributors to pain		**Pain control**
Physical	Primary disease Disease complications Pre-existing disease Therapy related	**Stimulus**	Cause often determines adjuvant therapies Cause may be curable
Psychological	Individual sensitivity Physical resilience Mood and morale Modulation	**Perception** **Interpretation**	Analgesic ladder Supportive therapies Complementary therapies
Spiritual	Misconceptions Cultural beliefs Expectation Meaning	**Impairment**	Psychological/spiritual interventions Open discussion Therapeutic relationships
Social	Normal daily activities Relationships Sense of self Physical capability		Multi-faceted support

Figure 1: Total pain assessment and management

Painful stimuli

Accurate identification of sources of painful stimuli guides the choice of adjuvant therapies. These are pharmacological or non-pharmacological interventions that relieve pain but are not analgesics. However people with advanced disease often have more than one pain and some may mask others. For example it has been estimated that 50% of patients with cancer will have three or more pains. Therefore all of the following areas need consideration when searching for sources of painful stimuli even when the source seems immediately obvious:

- **Primary disease related (e.g. bone metastasis, liver distension in heart failure)**
- **Complications of the primary disease (e.g. peptic ulcer, pulmonary embolus)**
- **Related to general debilitation (e.g. muscular pains from minor trauma to wasted muscles)**
- **Pre-existing or other diseases (e.g. osteoarthritis, toothache)**

About two thirds of patients with cancer will experience pain at some stage of the disease. The prevalence depends on the stage of the disease and the type of malignancy. Of patients undergoing treatment for cancer, 30-40% will have pain and this will increase to 70-90% of patients with advanced disease.

Table 1: Causes of pain in patients with cancer

Pain due to direct effects of the cancer (70%)	Organ infiltration	Bone Nerves Viscera Liver Soft tissue
	Remote effects	Neuropathies Myopathies
Pain syndromes from cancer therapy (25%)	Radiation	Fibrosis Neuropathy Lymphoedema
	Surgery	Incision pain Phantom pain
	Chemotherapy	Neuropathies Necrosis Polyarthritis
Pain unrelated to cancer (5%)	Low back problems Osteoarthritis Peripheral neuropathy Spinal stenosis Unknown cause	

Although a quarter of pains are therapy related, most of these are directly related to the intervention and of short duration, for example the pain associated with surgical procedures.

Identifying the sources of painful stimuli

Clinicians need to draw on all their learning and experience to identify the source of painful stimuli. Here are some simple reminders that may be useful.

• **Pain of acute onset or sudden exacerbation is a palliative care emergency.**
It may represent a wide range of conditions that are amenable to prompt treatment such as GI perforation, fracture, bleeding into a solid organ or spinal cord compression. However, the confirmation of a diagnosis should not delay the provision of effective analgesia.

• **Well localised pain is likely to be somatic in origin.** This may be arising from cutaneous or musculoskeletal tissues. The deeper the tissue the duller the pain is likely to be. Remember however, that irritation of the peritoneum or pleura will produce well-localised sharp pain even though the original site of inflammation may be the abdominal or thoracic viscera (e.g. pulmonary embolus).

• **Maintain a high index of suspicion for neuropathic pain.** Neuropathic mechanisms are involved in about 40% of cancer pain syndromes. The pain may be disease related (for example, infiltration or compression of nerve tissue by tumour mass) or therapy related (for example post-surgery neuropathy or chemotherapy induced polyneuropathy).

Neuropathic pain is commonly described as burning, cold, numb, or stabbing, in the distribution of a peripheral nerve or nerve root. It may be accompanied by paraesthesia, hypersensitivity or allodynia (pain on light touch). Involvement of the sympathetic system is indicated by a vascular distribution of the pain accompanied by localised pallor, flushing and/or disturbances of sweating.

Pain perception

Many of the drugs used in the analgesic ladder (discussed later) have their major action on modifying pain perception. Complementary therapies such as acupuncture may also help with pain perception and, although many of these have no scientific basis, in palliative care it is the outcome for an individual patient that is important.

This physiological modulation is influenced by a patient's mood and morale and their general health and resilience. As these are often low in people with advanced disease, these patients can be particularly vulnerable to pain. Additional interventions (pharmacological and non-pharmacological) should be aimed at improving mood, morale, general health and personal resilience and also at decreasing sensitivity to pain.

Evaluation of these contributing factors is an essential component of pain assessment. Effective interventions in these areas can make major contributions to pain management. The wide range of appropriate interventions is not always the preserve of the clinician. Spiritual, cultural, social and family based strategies are often important.

The effectiveness of interventions for pain control can only be evaluated by measuring the severity of the pain. The subjective nature of pain means that only the patient can do this.

Probably the simplest and most useful method of measuring pain severity is a verbal rating scale. Ask "How do you rate the severity of the pain on a scale of 0 to 10 with 10 being the worst pain you could ever imagine?" and write down the response. This scale is only suitable for temporal comparisons of pain severity for single patients. It is not suitable for comparing pain between patients.

"How do you rate the severity of the pain on a scale of 0 to 10 with 10 being the worst pain you could ever imagine?"

Pain interpretation

In the higher centres, pain interpretation is influenced by prior experiences, knowledge, and cultural values, etc. People attempt to put the pain into a framework they can understand and that gives it some meaning. This interpretation is often influenced by misconceptions and results in unrealistic fears and expectations that may add to suffering.

Assessment of pain interpretation hinges on good therapeutic relationships and honest but tactful discussions.

Open questions are essential. A useful question is "What does this pain mean to you?" This may highlight misconceptions such as "the cancer is about to burst" or "death is near". It may lead to a spiritual or metaphysical discussion or maybe something very practical but important to the patient, for example, "It means I cannot sit at the table with the rest of my family at meal times".

"What does this pain mean to you?"

Impairment that accompanies ongoing pain

Often a focus for a patient and their family is planning and preparing for death. This may be important but should not overshadow planning for life. Optimising quality of life up until the moment of death is the main focus of palliative care.

Ongoing pain often impairs relationships and the ability to continue the normal activities of daily life. It can distort a person's sense of self. For example, back pain may restrict a patient to their bed and isolate them from the rest of the family.

Moving the bed into the living room could allow the patient to remain an active family member. Unless the clinician asks good open questions this part of the suffering of pain may never be revealed. A good opening question is "What is the worst thing about the pain?"

"What is the worst thing about the pain?"

By identifying impairments and working with patients, their families (immediate and extended families), and other members of the caring team to overcome them, clinicians can help patients to regain control of their lives and optimise the quality of their remaining days.

Strategies for pain management

A thorough assessment of pain in palliative care enables the development of strategies to manage the pain and optimise quality of life. These may include:

- **Regular analgesic administration according to the WHO analgesic ladder**
- **Use of appropriate pharmacological and non-pharmacological adjuvant therapies**
- **A wide range of strategies to improve mood, morale, general health and resilience**
- **Open discussions arising from strong therapeutic relationships to assist in appropriate pain interpretation**
- **Multi-faceted interventions to overcome impairment to relationships, normal activities of daily life, the sense of self and physical capability**

This booklet focuses on the pharmacological strategies most useful for primary care.

The WHO analgesic ladder

The WHO analgesic ladder (Figure 2) is a schema to guide symptomatic pain relief.
Up to about 90% of cancer patients will receive adequate pain relief from implementation of this ladder.

General principles

- **Analgesics should be given regularly, usually by mouth.**
- **If one drug on a step does not provide pain control, move up a step rather than trying another drug on the same step.**
- **Use adjuvant therapy for specific indications on any step of the ladder.**

Step 1 Non-opioid (e.g. paracetamol) ± adjuvant (e.g. nortriptyline for neuropathic pain)

A non-opioid is used for analgesia on the first step of the ladder. This is usually paracetamol at a dose of 1 gram every 6 hours. If it is not effective at this dose move to step two.

An alternative to paracetamol on step one is a non-steroidal anti-inflammatory drug (NSAID). The choice of drug is based on a risk/benefit assessment for each individual. NSAIDs are particularly indicated for bone pain and may be taken as an adjuvant therapy on any step of the ladder. Patients receiving NSAIDs who are at risk of gastrointestinal side effects will receive some protection from the addition of a proton-pump inhibitor once daily half an hour before breakfast with a glass of water.

Other adjuvant therapies (pharmacological or non-pharmacological) may be indicated at any time during step one.

Step 2 weak opioid (e.g. codeine)
+ step one analgesic
± adjuvant

For step two, a weak opioid such as codeine is added to the analgesic used in step one. This usually means adding codeine to the regular paracetamol already being taken. However compound paracetamol and codeine preparations are not recommended as the amount of codeine is too small. The recommended dose of codeine is 30-60 mg every four hours up to a maximum of 240 mg daily. Codeine has a ceiling analgesic dose of 240 mg daily; dose-related adverse effects continue to worsen if this dose is exceeded. Therefore in most situations there is no benefit in taking codeine at doses greater than 60 mg four times a day.

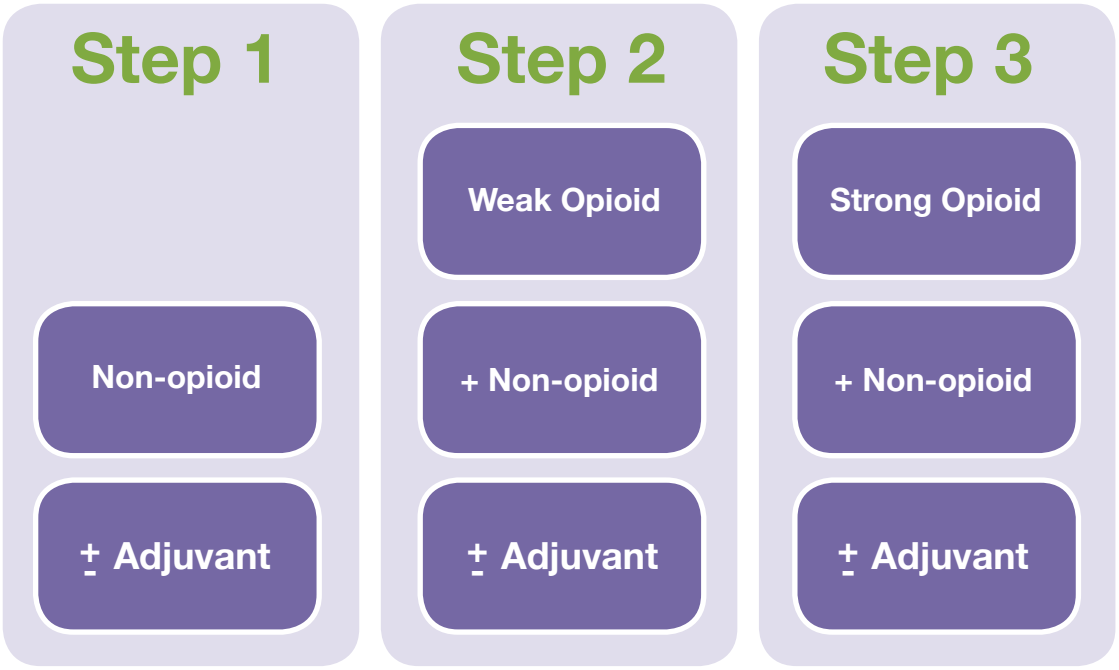

Figure 2: The WHO analgesic ladder

Most of the action of codeine is dependent on hepatic metabolism which converts it to morphine by CYP2D6. Up to 10% of the population have deficiencies in this enzyme and respond poorly or not at all to codeine.

An alternative to codeine on step two is dihydrocodeine available as controlled release tablets; maximum dose 120 mg twice daily.

Tramadol has opioid like actions and is effective in moderate pain but can cause troublesome nausea and occasionally CNS excitation.

If pain is not controlled with codeine at maximum doses do not switch to dihydrocodeine (or vice versa); move onto step 3 of the analgesic ladder

Constipation is inevitable with opioid use. Starting a laxative at the same time as the opioid reduces future problems with faecal impaction. A combination stimulant plus softener laxative is recommended.

Starting a laxative at the same time as the opioid avoids future problems with faecal impaction

Step 3: strong-opioid (e.g. morphine) + non-opioid ± adjuvant

Morphine is the first choice for moderate to severe pain because of its availability, cost and the body of experience in its use. Morphine is combined with the non-opioid used in step 2 plus any indicated adjuvant therapies. Alternative opioids for moderate to severe pain are oxycodone, fentanyl, hydromorphone and methadone.

Starting oral morphine

Morphine is started with morphine elixir or normal release* as tablets. Effective pain control is achieved by giving the morphine regularly (four hourly) without waiting for the previous does to wear off.

- **For an adult who has pain on the regular weak opioid used in step two an appropriate starting dose is 5 mg every four hours. The weak opioid is stopped when the morphine is started.**
- **In patients who are not currently taking an opioid (opioid naïve) the dose is normally reduced to 2.5-5 mg every four hours.**
- **Elderly or very cachectic patients or those with renal impairment, also usually start with 2.5 mg every four hours.**
- **Keeping a written record (i.e. in a diary) of rescue doses is important.**

*"Normal release" is the same as "immediate release" referred to in some texts.

Constipation - provide a laxative and review regularly.

Nausea and drowsiness also commonly occur at the commencement of morphine use. However these are usually transient and settle within one week. Some clinicians prefer to combine the first week of morphine treatment with an antiemetic (see later). Patients should be advised not to drive for one week after starting morphine or after increasing the dose.

Morphine titration

The dose of morphine is titrated slowly upwards to achieve effective pain control. There is no upper dose for morphine use unless the patient suffers from distressing and uncontrollable adverse effects.

Pain perception is reviewed regularly with the aid of the verbal rating scale and if needed the dose is increased by 30-50 % every four hours. The incremental percentage decreases as the dose increases. As there is no maximum dose of morphine the dose can be increased, if tolerated, as long as stronger analgesia is required and there is certainty that it is opioid-sensitive pain. Opioids are, of course, only useful for opioid-responsive pain.

Switching to slow release morphine

Switching to slow release (long acting) morphine involves using the same daily dose as is needed to achieve good pain control with normal release morphine. For example a person achieving good pain control with 20 mg of normal release morphine every four hours is taking 120 mg of morphine per day. They will need 60mg of slow release morphine every 12 hours.

Opioid tolerance and dependence

"If I am on morphine now, what happens when the pain get worse?"

Patients and care givers may be concerned about opioid addiction (psychological dependence) and loss of effectiveness over time (tolerance). These potential barriers to effective pain relief are not justified. Patients on opioids for cancer pain do not become addicted in the same way as those with long term heroin dependency.

Withdrawal symptoms may be experienced if doses are missed for any reason but this is a normal physiological process to chronic opioid use for pain and is not related to addiction. The need for increased doses for pain relief usually relates to a change in the disease process (rather than tolerance). Patients and care givers can be reassured that increased opioid doses are available and will be effective if pain worsens.

Breakthrough and incident pain

Breakthrough pain is pain which "breaks through" the base level of analgesia. This can occur during dose titration or when pain is normally controlled by slow release morphine. In both cases rescue doses of normal release morphine are required. If doses of normal release morphine are required consistently they are incorporated into the long acting, twice daily dose.

Incident pain is pain on movement or activity (e.g. movement of a fractured limb). If the action or movement stops, the pain stops. Doses of normal release morphine can be given when the aggravating event occurs or before any activity that is known to bring on the pain. When morphine is given regularly for this type of pain there is a high risk of adverse effects due to the possibility of excessive doses and because the duration of action of morphine exceeds the duration of the activity related pain. Management needs to be decided on a case-by-case basis. Doses for incident pain are not added to the total daily doses of slow release morphine.

Rescue doses of normal release morphine should be available for all patients for the treatment of breakthrough or incident pain. However the patient needs to be warned to avoid repeated doses for incident pain, because of the concerns discussed in the previous paragraph. The dose is the same as that needed for a four hourly dose of normal release morphine, or 1/6th of the total daily dose. For example, for a patient taking 240 mg of slow release morphine per day (e.g. 120 mg twice daily) the rescue dose for breakthrough pain is 40 mg. If there is no response, the dose can be repeated after one hour. The next regular dose is taken at the normal time without waiting for the rescue dose to wear off.

When a rescue dose is taken for breakthrough pain, the next regular dose is given at the normal time.

Managing opioid-induced adverse effects

Constipation with opioids is inevitable and persistent. It is recommended that a combination laxative with both stool softening and stimulant properties is taken regularly as soon as opioid medication is started. Coloxyl with senna is a stimulant laxative and faecal softener. Movicol™ is a useful addition and may be used regularly for opioid induced constipation.

The dose of laxative should be titrated to maintain the patient's normal pattern of bowel opening.

Nausea and vomiting usually resolve within a few days

Up to two-thirds of patients experience nausea and/or vomiting at the start of treatment with morphine. This usually resolves within a few days and can be covered by an anti-emetic for the first week of treatment. If it continues it may be due to a mixture of drug induced and pathological causes. A search for a remedial cause should be made; otherwise an anti-emetic can be continued. Suitable antiemetic drugs and doses include:

- **Haloperidol, 0.5 - 1.5 mg at night is an appropriate first choice.**
- **Metoclopramide is particularly useful if gastric stasis is a factor. Start with 10mg three to four times daily and increase if necessary. However it can increase pain if intestinal colic is present such as in bowel obstruction. Avoid metoclopramide in this situation. Use only for short-term treatment (≤2 weeks)**
- **Cyclizine, 25 – 50 mg three times daily, is particularly useful if symptoms are aggravated by movement or the nausea/vomiting is of central nervous system origin (e.g. brain tumour).**

Effects on cognitive function

These are usually minimal for patients on stable doses of morphine. Patients just starting morphine or who have had a dose increase should be warned that sedation and drowsiness can occur. They should avoid driving for the first week after starting treatment or increasing the dose.

Opioid toxicity

Classic signs of opioid toxicity include pinpoint pupils, hallucinations, drowsiness, vomiting, respiratory depression, confusion and myoclonic jerks.

This can occur when:

- **Doses are increased too rapidly.**
- **Renal impairment is present.**
- **A patient is poorly responsive to opioids and high doses are used in an attempt to get a response.**
- **An adjuvant pain relieving intervention such as chemotherapy or radiotherapy has recently occurred and has given pain relief, and the baseline morphine has not been reduced.**

If toxicity occurs the opioid should be stopped and one or more regular doses omitted. When signs of toxicity have subsided, the opioid may be recommenced at a lower dose or an alternative opioid given at a lower equivalent dose. If the opioid is morphine and there is a mild renal impairment – stop the slow release morphine and when the toxic signs and symptoms are reducing, introduce normal release morphine at longer intervals than the usual four hours. Morphine toxicity can be reduced more quickly if the patient is hydrated (e.g. by giving 1 litre of normal saline subcutaneously over 12 hours). The delirium symptoms of toxicity may be treated with haloperidol while the toxicity is resolving.

Respiratory depression

Serious respiratory depression is unlikely unless very excessive doses of morphine have been given. If it is life-threatening the opioid antagonist naloxone can be given at a dose of 20 µg every two minutes until the respiratory rate is satisfactory. Naloxone is short acting so it is important to observe the patient and, if necessary, give further doses every 30-60 minutes. Giving naloxone may significantly increase a patient's pain. If the naloxone is titrated against respiratory rate and level of consciousness an acute pain crisis is unlikely.

Alternative opioids

There is limited evidence for the effectiveness of switching opioids in the management of cancer pain. However, an alternative opioid to morphine may be indicated in situations such as morphine intolerance, severe renal impairment, difficulties with oral administration and poor analgesic response. When the dose of 24 hour oral morphine approaches 500 mg, consider discussing with a palliative care specialist. If a switch from morphine to another opioid is indicated, inpatient unit admission is usually advisable.

Methadone

Methadone has a wider analgesic effect compared to morphine, and can be used if the side effects of morphine are not tolerated. It has a long half-life, complex and variable pharmacokinetics and can accumulate on repeated dosing. However, it is a safer alternative to morphine in renal failure. The prescribing and doses of methadone in palliative care differ from those in other disciplines of medicine. In addition it has a number of significant drug interactions and is usually administered under specialist guidance.

Oxycodone

Oxycodone is a step 3 opioid and is available in controlled release (Oxycontin) and immediate release capsule (Oxynorm) formulations. Oxycodone has high oral bioavailability and is about 1.5 to 2 times as potent as oral morphine. It can generally be used without toxic effects in patients with renal failure. Patients who are being switched from oral morphine should initially receive half the dose of oral oxycodone (10 mg oral oxycodone is equivalent to 20 mg oral morphine).

Hydromorphone

Hydromorphone is also a step 3 opioid available in short and long acting forms. It is metabolised in the liver and metabolites are excreted by the kidneys but it is safer to use than morphine in renal impairment. It can also be used subcutaneously.

Fentanyl

Fentanyl is a synthetic opioid which is available as a transdermal patch (Durogesic). This allows controlled delivery of the drug for up to 72 hours. Transdermal fentanyl is potentially useful if the patient has experienced intolerable adverse effects to morphine or is unable to take oral analgesia. Whilst effective in treating cancer pain, the fentanyl patch has a less flexible dose regimen than oral morphine and it should only be used in patients with stable opioid requirements. The onset of action is 12-24 hours so most patients will require oral morphine, oxycodone or hydromorphone for breakthrough pain when switching.

Table 2: Equivalent doses of oral morphine and fentanyl patches

Morphine dose (mg/24 hours)	Fentanyl patch (µg/hour)	Morphine does (mg/24 hours)	Fentanyl patch (µg/hour)
<135	25	585-674	175
135-224	50	675-764	200
225-314	75	765-854	225
315-404	100	855-944	250
405-494	125	945-1034	275
495-584	150	1035-1124	300

The duration of action of the patch is about 72 hours in most patients and a degree of analgesia/adverse effects will continue for 12-24 hours after removal of the patch. Fentanyl 25 µg/hour is approximately equivalent to 120 mg per day of oral morphine. This is likely to be too strong for the opioid naïve patient and lead to opioid toxicity. Fentanyl 12 µg/hour patches are also available.

Pethidine is not used in palliative care

Pethidine is a synthetic opioid drug. It has a short duration of action (2-3 hours) and is unsuitable for the management of severe chronic pain. A metabolite, norpethidine, is renally excreted and can accumulate in renal impairment and cause myoclonus, tremor and seizures. There is no place for the use of pethidine in palliative care.

Adjuvant therapies

Adjuvant therapies are used for specific indications at any stage for pain and symptom relief in palliative care. They include radiotherapy, chemotherapy, surgery and a range of drugs which are familiar to clinicians for other indications. Many of these therapies are the preserve of specialists.

Neuropathic pain

Opioids are effective, or partially effective, in some types of neuropathic pain but their efficacy is often less than optimal and adjuvant therapies may be required in combination with the opioid. The most commonly used are tricyclic antidepressants (TCAs) and antiepileptic drugs. There is no significant difference between these two classes of drugs either in their effectiveness or overall incidence of adverse effects. There is little evidence to support the use of SSRIs for neuropathic pain but SNRIs have shown some benefit. Nerve blocks may be useful.

Tricyclic antidepressants (TCA)

In practice TCAs are better tolerated than anti-epileptics and they are often preferred for superficial burning pain. They are usually effective at lower doses but may aggravate opioid induced constipation. Nortriptyline may be preferred to amitriptyline as it has fewer anticholinergic adverse effects (dry mouth, constipation, drowsiness) and has a lower potential to cause postural hypotension.

Anti-epileptics

Carbamazepine, sodium valproate or clonazepam are commonly used antiepileptics for neuropathic pain and may be more effective for shooting or stabbing pain than for burning pain. Gabapentin has been shown to be effective in cancer pain when added to an opioid and is generally well tolerated. Pregabalin is also an alternative which is gaining favour as an effective agent.

A TCA and an antiepileptic can be used in combination but additive adverse effects may occur. If combination therapy is used introduce one drug at a time. The combination of a TCA and antiepileptic drug may increase drowsiness.

Anti-arrhythmics

Mexiletine and flecainide are not routinely used as adjuvant therapy because of a high incidence of adverse effects.

Table 3: Adjuvant therapies

Indication	Comment	Possible Treatment
Bone pain	From tumour or metastases. X-ray all to exclude fractures that may require surgical fixation	NSAIDs Biphosphonates Steroids Radiotherapy Surgical fixation of mechanical instability
Bowel or ureteric colic	All causes. Stop prokinetics and stimulant laxatives	Surgery Stents Steroids Hyoscine butylbromide
Cerebral metastases		Dexamethasone Radiotherapy Surgery
Constipation	Opioids	Combined stimulant/faecal softener Rectal emptying
Gastric distension pain	Obstruction or direct tumour effect	Antacids Prokinetics (eg metoclopramide, domperidone) Surgery
Hepatic capsular pain	Liver enlargement	Dexamethasone
Muscle spasm	Infiltration	Muscle relaxants (e.g. diazepam) LA into trigger points Heat, massage, etc
Nerve compression	All causes	Dexamethasone
Neuropathic pain	See below	TCAs, antiepileptic drugs, gabapentin, pregabalin
Skin tenderness	May progress to ulcer	Gentle massage Cushioning
Spinal cord compression	This is an emergency	Steroids Radiotherapy Surgery
Tenesmus	Involvement of rectal muscles	Dexamethasone

Suggested doses for neuropathic pain

- **Nortriptyline: The dose of nortriptyline is 10-50 mg nocte with a similar onset of action to amitriptyline.**
- **Amitriptyline: The starting dose of amitriptyline is 10 mg at night increasing to 50-75 mg at night and an effect is usually seen within 7 days.**
- **Sodium Valproate: 200 mg BD increase every few days according to response. Usual maintenance dose is 400-1200 mg daily in divided doses. May be better tolerated than carbamazepine.**
- **Carbamazepine: Start with 100 mg daily and titrate by 100-200 mg every two weeks. Usual maintenance dose is 200mg three or four time daily. Carbamazepine has many drug interactions and toxicity can be increased by concurrent treatment with drugs that inhibit the CYP3A4 enzyme (e.g. azole antifungals, erythromycin, cimetidine, fluoxetine, diltiazem). For more information on drug interactions check the appropriate reference sources.**
- **Clonazepam: 0.5-2 mg daily often best taken at night. Titrate dose slowly: 1-2 mg a day is usually adequate. May cause drowsiness and ataxia. There is little evidence to support effectiveness but it may be useful for nocturnal pain. Clonazepam is also useful for morphine induced myoclonus.**
- **Gabapentin: Start with 300 mg daily in divided doses and titrate if necessary, according to response, up to a maximum of 2,400 mg daily. For many patients the effective dose is between 900-1,800 mg daily.**
- **Pregabalin: Start with 75 mg twice daily, if required increase to 150 mg twice daily. It may take weeks to achieve maximal effect. Do not discontinue abruptly.**

Corticosteroids

Corticosteroids are useful in several types of cancer pain. They reduce oedema and inflammation, and thus the pressure associated with some tumours, by inhibiting prostaglandin production. They have complex central effects and can elevate mood, appetite and general well-being. Conversely, depression, mood swings, and psychosis can occur. Proximal myopathy is also a significant adverse effect in this group of patients.

Some of the main indications for the use of corticosteroids as adjuvant therapy (with suggested doses) are shown in Table 4.

The evidence for actual doses of steroids is poor and often it is a matter of local practice and opinion. It is helpful to clearly document the indications and plan for steroids when first introduced. They can often be down-titrated while symptom control is maintained.

Cortiscosteroids should be used for as short a time as possible. Review effectiveness after one or two weeks and reduce or stop if the effect is not significant. If they are used for appetite stimulating or an improvement in well-being then a short course of two weeks may be preferable to continued treatment.

Prednisone 10-20 mg daily can be used in an attempt to increase appetite and improve feeling of well-being but the evidence for this is scanty.

Methylprednisone is preferred to dexamethasone in some centres as the incidence of some side effects (e.g. mood disturbances) is lower.

Dose equivalents: **Dexamethasone 0.75mg**
= Prednisone 5mg
= Methylprednisolone 4 mg

Table 4: Indications for the use of corticosteroids as adjuvant therapies

Indication		Dexamethasone dose
General well-being	Appetite stimulation Increase sense of well-being Anti-emetic	2-4 mg daily
Neurological	Raised intracranial pressure	Up to 16mg daily
	Cerebral tumours	Up to 16mg daily
	Spinal cord compression	Up to 16mg daily
	Nerve compression or infiltration	4-8 mg daily
Capsular stretching	Liver metastases	4-8 mg daily
	Other visceral metastases	4-8 mg daily
Soft tissue infiltration	Head and neck tumours	4-8 mg daily
	Abdominal and pelvic tumours	4-8 mg daily
Tenesmus	Rectal pain due to invasive tumour	4-8 mg daily

Other symptoms

Dyspnoea

Patients receiving care are often distressed by dyspnoea. This may be related to primary disease or a concurrent illness. Identification of the underlying cause that may be eminently treatable, allows appropriate therapy. Examples of some treatable causes of dyspnoea are given in Table 5.

Simple non-specific measures can also produce relief. These include sitting upright in bed, oxygen (if hypoxia has been confirmed), use of a hand-held or free-standing fan, controlled breathing techniques and the management of anxiety.

Although morphine in high doses can cause respiratory depression, low doses can improve dyspnoea, probably by reducing inappropriate and excessive respiratory drive. The dose of morphine is titrated to response at much lower doses and with smaller incremental changes than for pain control.

- **For patients who are not already receiving opioids 2.5 mg morphine every four hours is a suitable starting dose.**
- **If a patient has already been taking a weak opioid e.g. codeine, a dose of 5-10 mg regularly every four hours and as required is more appropriate.**
- **If the patient is already on regular morphine for pain control, increase the dose of regular morphine by 30-50% every 2-3 days until symptoms are controlled or adverse effects prevent further dose increases.**

Table 5: Examples of some treatable causes of dyspnoea.

Treatment	
Anaemia	Transfusion
Congestive heart failure	Diuretic, ACE inhibitor
Chronic obstructive airways disease	Bronchodilator
Respiratory tract infection	Antibiotic
Pericardial effusion	Paracentesis, corticosteroid
Pleural effusion	Aspiration, pleurodesis
Anxiety	Reassurance, breathing exercises, benzodiazepines
Superior vena caval obstruction	Corticosteroid, radiotherapy

Benzodiazepines may be useful even if anxiety is not apparent as they have calming and muscle relaxant properties. Low doses do not cause significant respiratory depression but patient monitoring is prudent especially if they are also on opioids. Appropriate doses are diazepam 5 mg or lorazepam 0.5-1 mg by mouth. Sublingual lorazepam is useful if a rapid effect is required.

Cough

Cough may be associated with dyspnoea and settle when the dyspnoea is treated or it may occur independently. Treatable causes should always be sought and managed in the usual way. Symptomatic management is guided by whether the cough is dry or productive.

A dry cough due to malignancy can usually be managed with a cough suppressant unless dyspnoea is a feature. Suitable doses are:

- **Pholcodine. An initial dose of 30 mg (loading dose) followed by 5-10 mg four times daily. The initial loading dose is recommended because of pholcodine's long half-life.**
- **Oral morphine. At 2.5 mg every four hours, increasing up to 20 mg if needed will usually suppress cough in patients who are not already taking morphine.**
- **Methadone. This may be useful at low doses of 2 mg three times daily for patients already taking morphine.**
- **Codeine. Doses ranging from 15-30 mg 8 hourly to 60 mg 6 hourly have been recommend**ed.

If an uncontrolled dry cough is due to a tumour, a trial of dexamethasone at a dose of 6-8 mg/daily may be beneficial. A productive cough may require a trial of several approaches such as:

- **Expectorant**
- **Nebulised saline to loosen mucus, or**
- **Physiotherapy to aid cough and expectoration.**
- **Cough suppressants are generally avoided with productive coughs but may be useful to aid sleep or when a patient is dying or too weak to cough.**
- **Adding an anti-muscarinic (e.g. hyoscine hydrobromide) may help to reduce retained secretions.**

Constipation

Constipation is very common in patients with advanced cancer due to the side effects of drugs (such as opioids and anti-muscarinics), loss of appetite, immobility, poor fluid intake and disease involvement in the GI tract. It can lead to nausea and vomiting, abdominal discomfort and overflow diarrhoea. Prophylactic laxatives (stimulant plus softener) are recommended for all patients prescribed opioids or other drugs that may cause constipation. Rectal treatment may be required for a patient with faecal impaction and hard stools should be treated with a softener before purgatives are given.

Hiccups

The most common cause of hiccups is gastric distension but they can also be caused by brain tumour, uraemia, phrenic nerve irritation or infection. Intermittent hiccups can often be treated by non-drug therapy such as vagal/pharyngeal stimulation or rebreathing from a paper bag.

If hiccups are prolonged and distressing, pharmacological treatment may be required. Several medications are available.

- **Haloperidol and chlorpromazine are both effective and may cause central suppression of the hiccup reflex. Haloperidol 1.5 mg PO TDS. If hiccups are not relieved the dose can be increased by 1.5 mg each day to a maximum of 9 mg daily. Chlorpromazine 25 mg PO TDS. If hiccups are not relieved the dose can be increased by 25 mg each day to a maximum of 200 mg daily.**
- **Metoclopramide for reduction of gastric stasis or distension. Dose: 10 mg Q8H.**
- **Nifedipine or baclofen for muscle relaxation.**
- **An antiepileptic (e.g. sodium valproate, carbamazepine or gabapentin) can be tried if the hiccups are intractable.**

Retained secretions (death rattle)

This occurs when weakness prevents the patient from clearing respiratory secretions. The noisy breathing and bubbling sounds can be distressing to family and friends so it is very important to explain the situation and reassure them. If treatment is necessary, options include:

- **Repositioning the patient**
- **Exclusion of pulmonary oedema and possible treatment with a diuretic**
- **Administration of an anti-muscarinic:**
  - **Hyoscine hydrobromide is effective as a single subcutaneous dose of 400 µg. Review the response after 30 minutes. If effective, continue, using 1.2-2.4 mg as a continuous 24 hour subcutaneous infusion.**
  - **Hyoscine butylbromide (Buscopan) is more freely available, has a shorter duration of action and causes less sedation than the hydrobromide. The dose is 20 mg as a single subcutaneous injection. Review the response after 30 minutes. If effective, continue, using 60–180 mg as a continuous 24 hour subcutaneous infusion.**

Xerostomia and stomatitis

Xerostomia is often reported in patients with advanced cancer. It may be drug induced. In most cases severity of dry mouth is dose related and drug effects are additive. Alternatively it may be secondary to dehydration, mouth breathing, radiotherapy, anxiety, renal failure or infection (especially Candida). Stomatitis has similar causes and is exacerbated by reduced immunity and some chemotherapeutic drugs.

Drugs that may cause dry mouth include:

- **Morphine (often overlooked)**
- **Tricyclic antidepressants (amitriptyline, imipramine, nortriptyline)**
- **Antihistamines**
- **Antipsychotics (e.g. haloperidol, chlorpromazine)**
- **Anti-epileptics (carbamazepine, sodium valproate)**
- **Beta-blockers**
- **Diuretics**

Routine mouth care and oral hygiene is important in all patients to prevent the development of oral problems. This includes removal of debris from the oral mucosa, teeth or dentures and rinsing the mouth regularly with water or normal saline. Water or normal saline is safe, soothing and can be given as frequently as required. Warming or cooling as required may increase the soothing effect. Only use antimicrobial mouthwashes if specifically indicated or if the patient is at risk of a secondary infection.

Routine mouth care and oral hygiene is important in all patients to prevent the development of oral problems

If possible, identify and treat the underlying cause of the dry mouth. For example, change drug therapy or reduce the dose if possible, manage dehydration and anxiety. For symptomatic treatment of dry mouth, simple measures are advised such as frequent sips or sprays of cold water, sucking ice cubes or boiled sweets and applying lip balm to prevent drying and cracking. Oil or butter, used as an oral lubricant, is often very effective and can be used as often as required. Salivary stimulants such as lime juice, fresh melon or pineapple are also useful.

Pruritus

This can be difficult to treat and may be caused or aggravated by malignancy, renal failure or hyperbilirubinaemia. Pain and itch often involve common pathways, for example cholestatic and uraemic itch are mediated via opioid receptors. Morphine and other opioid analgesics can also contribute to pruritus by causing peripheral release of histamine. Other causes include endocrine disease, iron deficiency, drug allergy and lymphoma.

Treatment includes:

- **Identifying and treating or removing the underlying cause**
- **Application of surface cooling agents (e.g. 0.25-1% menthol in aqueous cream), tepid showers, humid environment**
- **Using a soap substitute, e.g. emulsifying ointment**
- **Oral antihistamine, e.g. cetirizine or promethazine**
- **Bile sequestrant if indicated, e.g. Cholestyramine 6-8 g daily**
- **Doxepin**
- **Rifampicin for chronic cholestasis**
- **Anxiolytics e.g. benzodiazepines**
- **H2 antagonists (act on histamine receptors in the skin), e.g. cimetidine 400 mg daily**
- **If pruritus is associated with obstructive jaundice the best intervention is stenting the biliary tract**
- **Paroxetine**

Referral to a palliative care team or dermatologist may be indicated in difficult cases.

Delirium

Toxic confusional states, like delirium, are common in people who are dying and if they prove to be irreversible, may be an indication of impending death. They can be most distressing for patients, family and staff. Diagnosis is often made by an abrupt onset and fluctuating impairment of consciousness – the primary symptom which results in: disorientation (to time), fear and dysphoria, memory impairment (short term memory), reduced attention span to external stimuli, perceptual disturbance (illusions, hallucinations), disorganised thinking (paranoia, rambling). There are often multiple organic causes but in up to 50% of cases, specific causes are not found, despite investigations.

Treat the underlying organic causes if identifiable. Ensure there is a safe and secure environment – have adequate staffing, remove potentially dangerous objects, have the mattress on the floor, prevent sensory over-stimulation – have a single room, minimise noise and staff changes and maintain a warm and comfortable environment.

Drugs can be useful if symptoms are severe (in combination with above management):

- **Haloperidol is the drug of choice but not in AIDS delirium (HIV makes the CNS more sensitive to dopamine antagonists), hepatic encephalopathy or alcohol withdrawal where benzodiazepines only should be used**
- **Haloperidol regimen in acute delirium**
  - **Oral if compliant – s/c or i/v if not**
    - **Initial dosage – mild 0.5-1.5 mg orally**
    - **Severe 1.5-5 mg orally**
    - **Very severe 10mg s/c or i/v**
    - **Repeat and titrate every 30-40 minutes until controlled**

Alternatives included levomepromazine (methotrimeprazine), risperidone, olanzapine or quetiapine.

Sedatives should not be used alone in most cases of delirium as they may aggravate symptoms, particularly if inadequate doses are used so always use with an antipsychotic (i.e. never on their own in delirium). Benzodiazepines are most commonly used.

Syringe drivers in palliative care

A thorough assessment of pain in palliative care enables the development of strategies to manage the pain Administration of drugs via syringe drivers is complex due to the possibility of incompatibilities between drugs and diluents and the variety of administration devices available. If possible it is advisable to obtain specialist advice. The following is a brief overview.

A syringe drive is a battery driven device that delivers drugs, usually subcutaneously, over a selected time period. The main indications for subcutaneous infusion are:

- **Nausea and vomiting not controlled with oral medication**
- **Bowel obstruction (because absorption by oral route is impaired)**
- **Inability to take drugs orally (reduced level of consciousness, dysphagia, trache-oesophageal fistula)**

Continuous subcutaneous infusions often contain a mixture of drugs, e.g. morphine plus antiemetic(s). The dose of each drug should be individualised and PRN doses prescribed for breakthrough symptoms.

Incompatibilities (e.g. precipitation, particle formulation, chemical inactivation) can occur between drugs and also with diluents used to make up the infusion. The incompatibility is not always detectable by visual inspection. In most cases sterile water as the diluent is preferable to normal saline. For advice on diluents, administration and the compatibility of multi-drug combinations contact your local hospice or hospital pharmacy department.

Table 6: Examples of some drugs commonly used in syringe drivers.

Drug	Indication	Usual Dose
Morphine	Pain	One half of total daily oral dose
Haloperidol	Nausea or vomiting Agitation and confusion	1-2.5 mg over 24 hours 1015 mg over 24 hours
Dexamethasone	Usual steroid indications	4-16 g over 24 hours
Methotrimeprazine (Levomepromazine)	Nausea or vomiting	6.25-50 mg over 24 hours
Cyclizine	Nausea or vomiting	75-150 mg over 24 hours
Midazolam	Agitation, confusion and acute breathlessness	10-60 mg over 24 hours
Hyoscine butylbromide	Intestinal colic associated with bowel obstruction Excessive secretions	60-180 mg over 24 hours
Hyoscine hydrobromide	Excessive secretions	0.4-2.4 mg over 24 hours

Useful resources

MacLeod, R.D., Vella-Brincat J., & Macleod A.D. (2014).
The Palliative Care Handbook (7th ed.) Sydney: HammondPress
Available at **www.hammondcare.com.au/shop/palliative-care/the-palliative-care-handbook**.

Palliative Care Expert Group (2010). Therapeutic guidelines: palliative care (version 3). Melbourne: Therapeutic Guidelines Limited.

Australian Adult Cancer Pain Management Guideline Working Party. (2013). Cancer Pain Management in Adults, Cancer Guidelines Wiki, accessed 21 August 2014, http://wiki.cancer.org.au/australia/Guidelines:Cancer_pain_management