# Palliative care

**After completing this tutorial, you will be able to:**

- Describe how opioid and non-opioid analgesics are used in the management of pain in a palliative setting.
- Outline how common symptoms such nausea, vomiting and constipation may be treated in patients with a life-limiting illness.
- Advise on the continuous subcutaneous administration of medicines using a syringe driver.

## Why this subject matters...

Palliative care aims to improve the quality of life of patients and their families facing the problems associated with life-threatening illness (World Health Organisation [WHO] definition). It involves a holistic assessment of a patient's needs and effective symptom control, often with medicines, is an important part of this. Palliative care may extend for many months and is not confined to the final days of life.

As a pharmacist you may be asked to advise on the use of medicines for patients receiving palliative care such as those living with cancer, organ failure (e.g. heart failure) or a neurological diagnosis (e.g. multiple sclerosis). Clinical problems may range from managing side effects and drug interactions to troubleshooting administration issues.

This tutorial briefly describes the management of some commonly encountered symptoms in adults.

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Before reading on watch Lucy, and Joe and Melita share their stories on the impact that **good palliative care** has on their quality of life. A second family share their experience of the value of **end of life care.** A further video interview with a **specialist nurse** in a community hospice explains what it is like to work in a palliative care setting.

## WHO pain ladder

Pain is a complex phenomenon. It has been shown that people with advanced disease have many different types of pain and several factors can influence their pain, such as anxiety. It is important to diagnose the underlying cause and severity of each pain before choosing treatment. Some pain responds only partially or poorly to opioids (e.g. neuropathic pain).

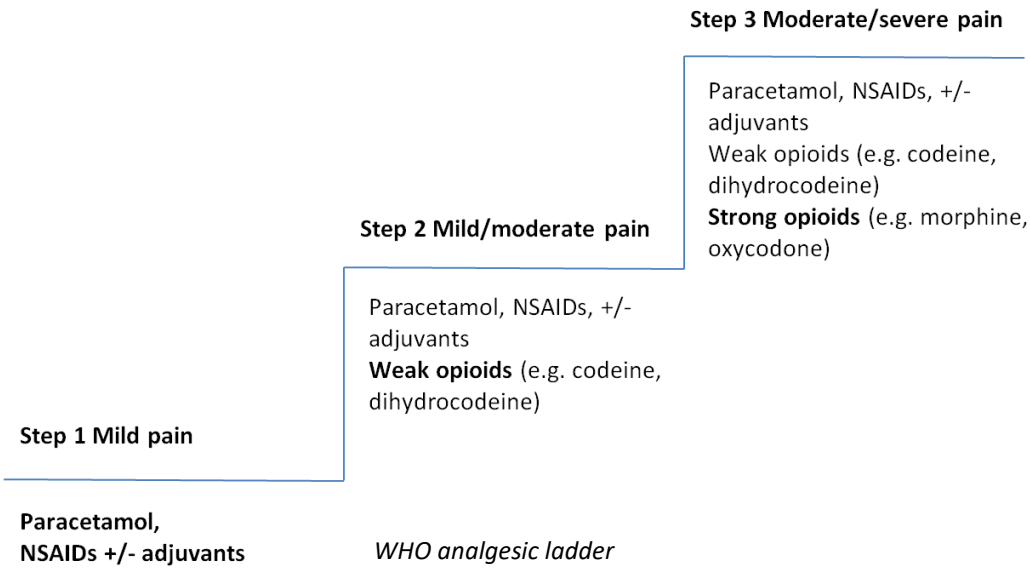
The WHO pain ladder, introduced in 1986 for the management of cancer pain, divides analgesics into three groups:

- **Non-opioids** are essentially NSAIDs and paracetamol.
- **Opioids** range from weak ones (e.g. codeine, dihydrocodeine) to strong (e.g. morphine, oxycodone).
- **Adjuvants** help to relieve pain in certain *specific* circumstances (e.g. dexamethasone for bone pain, amitriptyline for neuropathic pain).

The original version of the WHO guidelines also included a suggested pain ladder as shown below, which can be used as a general guide to pain management based upon pain severity. Subsequent updates to the guidelines have highlighted the need to tailor analgesics according to the individual patient's needs.

Therefore patients should start on the step of the ladder most appropriate to their level of pain. If a drug fails to relieve the pain, patients should move up one step rather than across the ladder (e.g. don't swap from codeine to dihydrocodeine). Consider the additional use of adjuvants at all steps, and continue with regular paracetamol and NSAIDs at each step if effective and safe.

Analgesics should ideally be given by mouth and administered at appropriate fixed intervals of time, taking into account the patient's waking hours and bedtime.




**Step 1**: *Regular* paracetamol is the first-line analgesic for patients with mild pain. NSAIDs are especially valuable in patients with an inflammatory component to their pain (e.g. bone pain), but come with side effects that need to be taken into account. The combination of both paracetamol and an NSAID can be particularly effective.

**Step 2**: There is some debate about the need for this step as there is no pharmacological need to prescribe a weak opioid before progressing to a strong opioid.

However, in some situations weak opioids may provide sufficient analgesia; and in others it may be useful to include step two to help manage the beliefs held by some patients about the use of strong opioids. If regular paracetamol has helped to control a patient's pain, then compound paracetamol-opioid preparations may be prescribed if they contain therapeutic doses of opioid (e.g. co-codamol 30/500).

If step two is omitted then the patient will need to be started on a lower dose of a strong opioid.

**Step 3**: Morphine is often the strong oral opioid of choice for the management of severe pain. The combined use of regular modified-release and 'when required' immediate-release morphine allows effective symptom control for most patients. There is no maximum morphine dose as long as it is titrated carefully, and that increased doses give increased pain relief without unacceptable side effects.

# Opioids for pain

Often patients are initially managed on a regular dose of an immediate-release morphine product such as Oramorph solution every four hours. When pain control is stable, they are then switched to a modified-release formulation that is usually given twice daily. The initial dose of modified-release morphine can be calculated by adding up the total amount of oral morphine over 24 hours. This includes regular four hourly doses plus any 'when required' doses prescribed for breakthrough pain.

For example, a patient, Paul, has required 10mg oral morphine solution every four hours with two 10mg 'when required' doses, for a few days. His 24-hour morphine requirement is 80mg.

Therefore his starting dose of modified-release morphine would be 40mg every 12 hours or 80mg every 24 hours.

The BNF advises that the first dose of the modified-release preparation can be given at the same time as the last dose of the immediate-release preparation, or within 4 hours of it. However, in practice there might need to be more of an overlap while the modified-release preparation starts to work. Immediate-release morphine should continue to be prescribed 'when required' for breakthrough pain and can be given every 2-4 hours (up to hourly may be needed if pain is severe or in the last days of life). The 'when required' dose should be about one-sixth to one-tenth of the total daily dose of modified-release morphine.

Additional doses of opioids may also be required when breakthrough pain is predicted such as during a dressing change.

> For our patient Paul on modified-release morphine sulphate 40mg every 12 hours, the 'when required' dose of immediate-release morphine would be around 10mg every 2-4 hours.

If a patient's condition declines and they become unable to swallow, a change in route of administration should be considered. Morphine is often the preferred parenteral opioid given continuously using an infusion device called a syringe driver. Diamorphine is also sometimes used; it is more soluble in water compared to morphine and can be dissolved in a smaller volume. In practice in the UK, the subcutaneous route is used in preference to the intravenous route. This is in part because inserting an intravenous access device can sometimes be difficult in a palliative context (e.g. if the patient is restless, and/or has poor venous access). In addition, the intravenous route is associated with a broader range of complications compared to the subcutaneous route (e.g. phlebitis, extravasation). Also if access is lost, there may be more of a delay in inserting a new intravenous cannula which is a more specialist skill compared to a subcutaneous access device, which may lead to loss of symptom control. Subcutaneous administration also allows for greater patient mobility, as they are less restricted by the presence of a peripheral intravenous cannula usually in an arm vein.

Fentanyl and buprenorphine are useful alternatives that can be given as transdermal patches if the patient's pain is stable and their dose is unlikely to change rapidly. However serious harm including fatalities have been reported with transdermal opioid preparations due to accidental exposure in the case of fentanyl and medication errors with buprenorphine, and so extra care is required if these are prescribed.

Guidance on conversion between oral morphine and other opioids is given in most palliative care resources. Interpret dose conversion factors with care as they are only approximations, and there is a great deal of inter-patient variability.

Anticipation and management of the side effects of analgesics is an important part of optimising therapy. Nausea and vomiting, sedation and constipation are the most common side effects observed in patients taking opioids. However nausea and vomiting are usually transient and improve after several days. Patients should take long-term laxatives regularly to minimise the risk of constipation.

# Nausea and vomiting

As with pain, there are many causes of nausea and vomiting (e.g. constipation, severe pain, hypercalcaemia, intestinal obstruction, drugs). It is important to identify the most likely cause as this determines the treatment.



Antiemetics can be categorised according to their pharmacological group, effect on a specific neurotransmitter, or likely site of action.

When initiating an antiemetic, the patient should be reviewed every 24 hrs; it may be necessary to substitute the antiemetic or add in another drug from a different class (e.g. haloperidol and cyclizine work in different ways). A single drug is normally sufficient to control symptoms but using two drugs from different groups may be required in resistant patients. Remember to think laterally when using combination antiemetic therapy; don't use drugs that may antagonise one another (e.g. cyclizine inhibits the prokinetic actions of metoclopramide). Adjuvant agents such as corticosteroids may also be helpful.

The oral route is suitable for prophylaxis where there is mild nausea and vomiting; non-oral routes should be used for moderate to severe symptoms.

In practice cyclizine, haloperidol or a prokinetic such as metoclopramide or domperidone are often used as first-line antiemetics. Levomepromazine is also used as an antiemetic in palliative care. You do need to be careful about the contraindications to each antiemetic, and assess their relevance to the individual patient.

# Other symptoms

## Constipation

This is a common symptom in patients with terminal illness due to loss of appetite, dehydration, immobility, drugs, and disease involving the gastrointestinal tract.
Patients on morphine and other constipating drugs should be prescribed regular prophylactic laxatives. Regular administration of a faecal softener and a peristaltic stimulant is often recommended. The dose should be titrated to enable patients to pass a stool easily every one to three days.

## Diarrhoea

Diarrhoea is less common than constipation in patients with terminal illness. The diagnosis must be made carefully to exclude 'overflow diarrhoea' which is liquid faecal matter seeping past impacted faeces. Common causes of diarrhoea include excessive laxative use, side effects of drug therapy (e.g. chemotherapy, antibiotics), infections (e.g. *C. difficile*) and initiation of enteral feeds.

Agents such as loperamide and codeine may provide symptomatic relief. Treatment for specific conditions include octreotide in patients with a carcinoid tumour which stimulates water and electrolyte absorption and inhibits water secretion in the small bowel.

## Dyspnoea

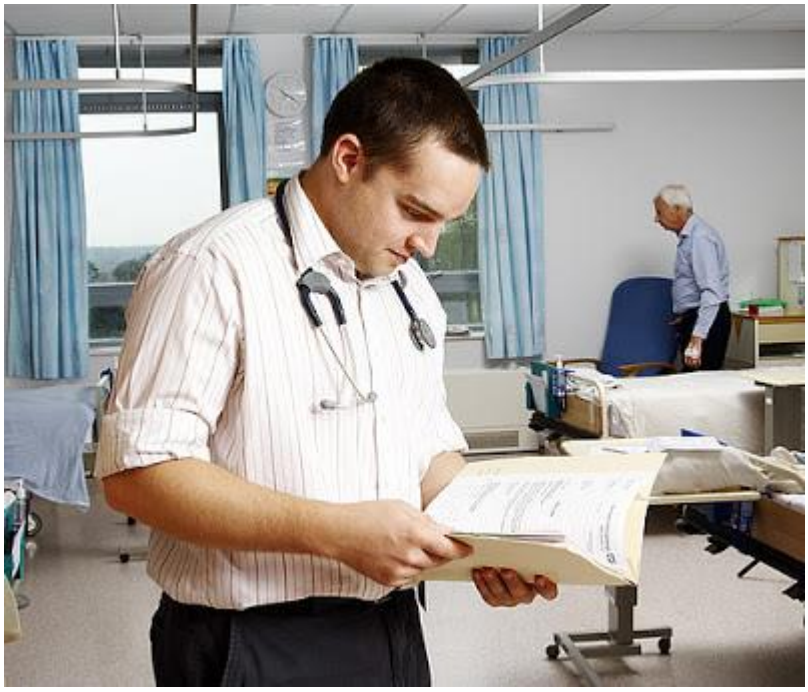
Dyspnoea is an unpleasant sensation of being unable to breathe easily. It is common in patients with advanced disease. It is important to ensure that any underlying co-morbidities, such as COPD, are optimally managed. Opioids can help to relieve the sensation of breathlessness and tend to be more beneficial in patients who are breathless at rest. Often lower doses are required compared with pain, for example starting with immediate-release morphine 1-2mg every four hours and titrating according to response. Benzodiazepines can be used in the management of breathlessness associated with anxiety.

## Confusion

This may be managed by treating the underlying cause e.g. hypercalcaemia. If this fails, consider antipsychotics such as haloperidol or olanzapine. In terminal restlessness midazolam, levomepromazine and haloperidol may be administered as continuous subcutaneous infusions via syringe drivers.

## Excessive respiratory secretions

These can be reduced by subcutaneous injection of hyoscine hydrobromide, hyoscine butylbromide or glycopyrronium bromide. However, hyoscine hydrobromide crosses the blood-brain barrier and is often not used as a first-line antisecretory unless sedation is desirable.





**Intestinal obstruction**

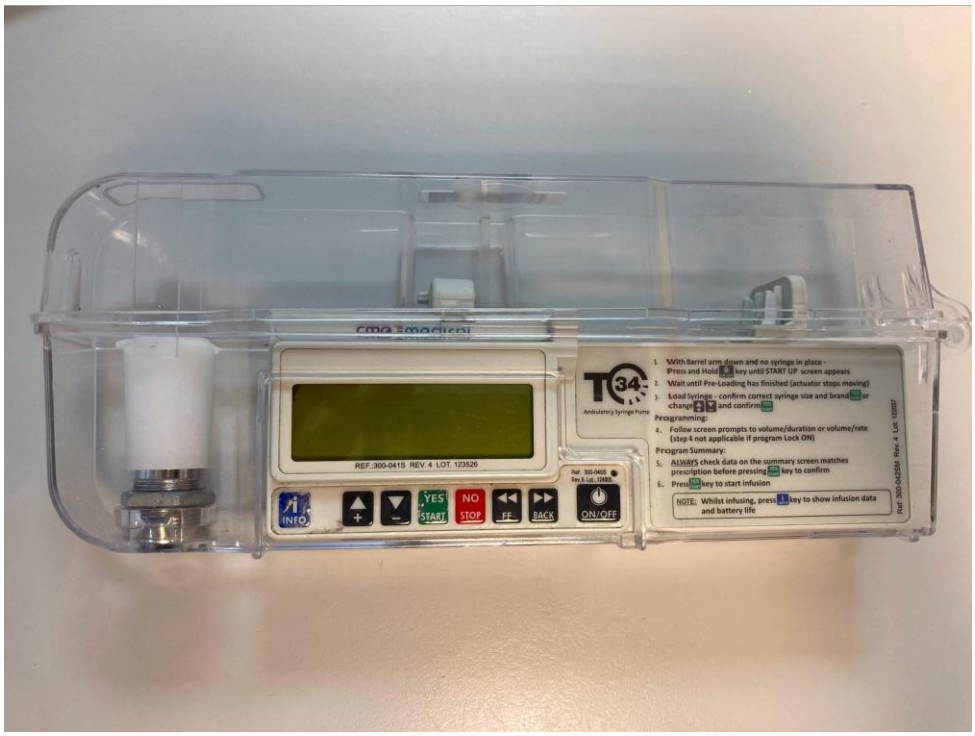
Intestinal obstruction occurs when there is a partial or complete obstruction of the gut lumen and/or peristaltic failure. The patient may suffer a range of symptoms depending upon the severity and location of the obstruction, but they may include vomiting, constipation, constant abdominal pain and colic.

Choosing appropriate medicines to manage these problems is sometimes difficult due to their effects on gut motility. For example, as a prokinetic, metoclopramide may be helpful in a patient with nausea and vomiting who has gastric stasis, but it couldn't be used if the patient also has colic because it might make it worse. Morphine may be helpful for constant abdominal pain, but if the patient also has peristaltic failure then an agent with a lower risk of constipation such as fentanyl should be considered.

Erratic or poor oral absorption of medicines may also present a problem in patients with intestinal obstruction, and the use of non-oral options may be necessary such as patches or syringes drivers.

# Syringe drivers

A syringe driver is a small portable battery-operated pump that administers drugs subcutaneously by continuous infusion. It is not something that is used by every patient in palliative care, but it can be very useful. Syringe drivers are indicated when other routes become inappropriate or difficult. They are generally programmed to deliver their contents over 24 hours.



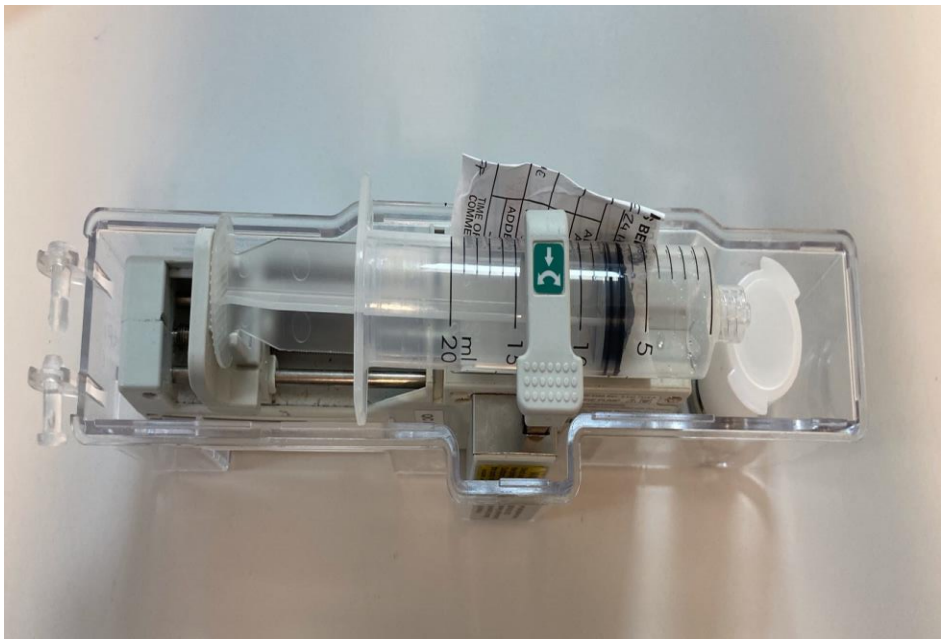

*An empty syringe driver*

Morphine, midazolam and cyclizine are common examples of drugs given in this way, but not all medicines are suitable to be administered via a syringe driver. For example an injection needs to be formulated in a relatively small volume to be given via this route. In addition, products that are irritant (e.g. prochlorperazine, diazepam) are less suitable because of the risk of injection site reactions. Similarly, products that are very acidic or very alkaline may also increase the risk of local irritation.

Most medicines given via continuous subcutaneous infusion are **not licensed** to be given in this way, and mixing them with other medicines in a syringe driver is also unlicensed. However it is common practice in a palliative care setting, and often several medicines may be given using a single device.

The risk of incompatibility generally increases with the number of drugs, and compatibility information should always be consulted **before** medicines are mixed in a syringe driver (see

Information sources). If you can't find data for the combination you have been asked about then remember that medicines with a long half-life might not need to go in the syringe driver, and could potentially be given as a once or twice daily direct subcutaneous injection (e.g. dexamethasone, haloperidol). You can also refer back to the Injection Compatibility topic on Reducing risk for some more troubleshooting tips.



*An overhead shot of a syringe driver in situ - the pump pushes the plunger on the left along the barrel of the syringe administering the medicine(s) to the patient*

Water for injection is the preferred **diluent** in the UK because there are more compatibility data for commonly used medicines. Also it is less likely to cause compatibility problems compared to sodium chloride 0.9% which can produce unpredictable results with cyclizine, and higher doses of diamorphine and haloperidol. However sodium chloride 0.9% is isotonic, and so (in theory) is less likely to cause infusion site reactions than water for injection. In practice though, because the volumes involved are low and the rates of administration are slow, site reactions are not usually a problem with water for injection.

The **final volume** of a syringe (volume of drug + volume of diluent) may depend upon the brand of syringe driver used and the time over which it is to be administered. Generally the more dilute the contents are, the lower the risk of compatibility problems and injection site reactions. Sometimes the final volume of the syringe may be too large to fit into the device and you may need to consider using more concentrated formulations or halving the volume and giving the infusion over 12 hour periods (e.g. higher doses of levetiracetam).

Finally, once set up, the infusion should be **monitored every four hours** to check for precipitation or discolouration and to ensure that the syringe driver is running at the correct rate.

Watch this video, presented by a specialist nurse in Oxfordshire, which shows how one brand of syringe driver is set up. This may not be the brand you use locally, so the detailed instructions may differ in your hospital, but the video does show the range of operational capabilities of a syringe driver.

## Suggested questions

You may be asked about a range of clinical problems in the palliative care setting, but many will relate to symptom control or compatibility of medicines in syringe drivers.

If you are asked about **symptom control** then the indication may be obvious, but ask about the likely cause, and establish what the patient has tried already. You will also usually need to find out what other medicines the patient is taking, and their other significant medical problems. You'll need to know whether they are able to take medicines orally, and if they can't what other routes are available (so the intramuscular and rectal routes may be unsuitable if they have low platelets for example).

If you are asked about **mixing medicines in a syringe driver** then you'll need to find out the dose of each medicine, the diluent used and the infusion volume (if known).

## Information sources

The BNF has a useful section on prescribing in palliative care that covers the management of a range of symptoms including pain, constipation, nausea and vomiting, and restlessness and confusion. It also includes an opioid conversion guide, helpful information about switching between fentanyl and buprenorphine patches and oral morphine and guidance on using syringe drivers.



The **Palliative Care Formulary** is a detailed guide to prescribing medicines in the palliative care setting. Its companion syringe driver compatibility database and discussion forum can be found at palliativedrugs.com.

Palliative Care Matters is an alternative website to support clinical decision-making in palliative care and also includes a syringe driver compatibility database and links to a range of guidelines.

Andrew Dickman and Jennifer Schneider's book The Syringe Driver is only available in paper form, but is a comprehensive guide to administering and mixing medicines in syringe drivers. The section on individual drugs at the beginning of the book brings together lots of really helpful information in one place.

There are a range of helpful Clinical Knowledge Summaries on the topic including pain, secretions, dyspnoea and cough.

Remember to check if you have any **local guidelines** from your palliative care team.

There's a **Medicines Q&A** from UKMi specifically about opioid conversions in the palliative setting which goes into more detail than other resources. Find it on the SPS website.

Be careful about conducting a general internet search on this subject. If you do, you may like to look at our brief guide to evaluating websites about medicines.

*[Last updated: 4 January 2021]*

# Next steps in learning...

CPPE has links to useful learning resources via its Palliative Care gateway page including an introduction to palliative care and a quiz. The resource Dealing with difficult discussions is an e-learning programme designed to help you approach difficult discussions with patients and others.

In addition, you might like to look at these resources:

- NICE has published a Clinical Guideline on Strong Opioids for Adults in palliative care.
- Explore the valuable range of information provided for the public in Scotland about palliative care by NHS Inform.