Safe and effective prescribing for symptom management in palliative care

ABSTRACT

Palliative and end of life care forms an important part of the role of any doctor in training, and an awareness of a structured approach to managing common symptoms and end of life care is essential. Common symptoms include pain, nausea and vomiting, constipation, and breathlessness. Anticipatory prescribing of the 4 A's (analgesic, anti-emetic, anxiolytic, and anti-secretory) is a proactive approach to ensure medication is available, if required, for common symptoms in the last hours to days of life, such as pain, upper airway secretions, anxiety, and agitation. Prescribing or medication errors in relation to symptom control in palliative care can relate to individual errors, poor communication, poor care coordination, equipment and care planning. There are some important key points relating to prescribing to consider, for example, using recognized conversions when changing between opioids and from the oral to syringe drivers route; that diamorphine and morphine are not equipotent; prescribing liquid opioids in milligrams not millilitres where there are multiple concentrations available; making the indication for steroids clear when used, as they are multiple possible indications (and also their intended duration, to avoid unintended longer term sequelae of steroid use); and avoiding the use of oxygen for symptomatic relief of breathlessness in the absence of hypoxia.

Palliative care is an approach that improves the quality of life of patients facing life-threatening illness, through management of pain and other problems, physical, psychosocial and spiritual (World Health Organization, 2019).

Over 50% of people in the UK will die in hospital, and it is estimated that up to a third of hospital inpatients at any given time are in the last year of life (Clark et al, 2014). Each doctor in training, on average, will be involved in the care of 40 patients who die and a further 120 patients close to the end of life each year (Faull and Woof, 2002).

Use of opioids and other medication provides effective symptom control, with syringe drivers commonly used to ensure medication delivery when oral medication cannot be taken. However, around 20% of patient safety incidents in palliative care relate to medication errors (Yardley et al, 2018). There are five themes which commonly underlie medication incidents:

1. Individual (e.g. an individual administration error)
2. Communication (e.g. poor handover between hospital and community or vice versa)
3. Poor care coordination and delivery
4. Equipment (e.g. malfunction of a syringe driver)
5. Care planning (e.g. failure to consider that a patient may have breakthrough pain and prescribe as required analgesia in anticipation) (Yardley et al, 2018).

This article provides some top tips to promote safe and effective prescribing in palliative care, many of which are encompassed by following general principles in the approach to symptom management in palliative care (EEMMA) (Twycross and Wilcock, 2018):

Evaluation

History and examination are needed to ascertain the likely cause of each symptom before instigating any management; reverse any reversible cause.

Explanation

Careful explanation of treatment to the patient and those close to them (including likely side effects of any pharmacological measures) is important to ensure management is consistent with the patient's wishes. Explanation to colleagues is also important, e.g. giving clear indications for drugs or medication changes on prescription charts and in the clinical notes.

Management

Ensure there is individualized treatment using pharmacological and non-pharmacological approaches.

Monitoring

Regularly re-review the patient (especially medication, to minimize polypharmacy), use the lowest effective dose(s) of medication, take into account the altered physiology of people with advanced disease (e.g. renal or liver impairment).

Attention to detail

Do not make assumptions about the patient's wishes or preferences – ask them. Seek help (e.g. local specialist palliative care team) for complex symptoms and cases where symptoms are not improving. Seek and use local guidelines (they are there to help you). Before adding medication check what has been tried previously and why it was stopped.

Pain

Pain is common in patients with malignant disease and other life-limiting non-malignant conditions (up to 80% of all patients) (Harris, 2014). Pain management in the palliative care context should follow the principles of the World Health Organization (2018) analgesic ladder (*Figure 1*):

- By the mouth (oral route where feasible)
- By the clock (regular analgesia if pain is frequent)
- By the ladder
- For the individual (individual dose titration)
- With use of adjuvant analgesics if appropriate
- Attention to detail (review regularly and adjust accordingly) (Watson et al, 2011).

Note that the World Health Organization ladder was originally designed for cancer patients, and may not be as applicable in

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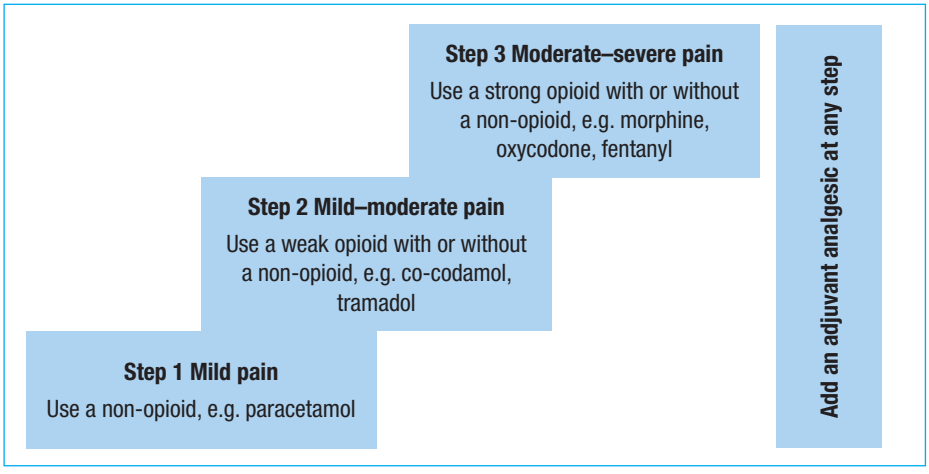

Figure 1. The analgesic ladder. From World Health Organization (2018).

patients with non-cancer pain (e.g. escalation of opioids is not recommended in current guidelines for patients with chronic pain).

At step 3 of the analgesic ladder, morphine is recommended as the first-line option in the absence of significant renal impairment (Harris, 2008; National Institute for Health and Care Excellence, 2012). The recommended starting dose for patients with no renal or hepatic impairment is 10–15 mg oral sustained release morphine twice daily with 5 mg oral immediate release morphine for breakthrough pain (National Institute for Health and Care Excellence, 2012). This is a guide starting dose, and should be determined for the individual patient by prior opioid requirements (both regular and as required).

The dose can be titrated for the individual, depending on response and side effects. This is usually done by reviewing the response and amount of breakthrough medication the patient has required on average per day, and if this remains frequent (e.g. average 3–4 or more per day) recalculating the background doses to include the average amount of breakthrough medication that has been required (or, by increasing in increments of around 30% if the patient has not been given, or appropriately requesting as required doses) (Watson et al, 2011). For patients with moderate pain (step 2), low-dose step 3 opioids may also be considered (such as low dose morphine or oxycodone), or the original step 2 opioids (codeine, tramadol) (Caraceni et al, 2012).

As an approximate guide the short-acting opioid (used as required for breakthrough pain) is commonly dosed at around 1/6 of the background dose (e.g. 10 mg immediate release morphine as required for a patient taking 30 mg modified release oral morphine twice daily) (Watson et al, 2011). Dosing should be individualised for each patient (Caraceni et al, 2012).

Short-acting strong opioids are often used in liquid form: this will depend partly on the dose and partly on patient preference (some may prefer tablets or capsules while others prefer liquids, with poor manual dexterity a barrier to practically measuring the latter). If liquid preparations are used always prescribe the intended dose in milligrams and not millilitres, as there are different concentrations.

For example, a patient prescribed 5 'ml' of immediate release morphine liquid could be given 10 mg if the 10 mg/5ml concentration liquid is dispensed or 100 mg if the 100 mg/5ml strength is used.

In some circumstances it may be appropriate to use an alternative background strong opioid, e.g. oxycodone in patients with moderate renal impairment (Harris, 2008). Transdermal patches (e.g. fentanyl or buprenorphine) may be appropriate in some circumstances, e.g. dysphagic patients (those with head and neck cancer or neurodegenerative diseases), patients with poor gastrointestinal drug absorption or malabsorption, or patients who have poor compliance with oral medication (e.g. those with advanced dementia) (Twycross et al, 2018). Generally opioid patches are only suitable when a person is on a stable opioid dose because of their long half-life and time to peak plasma concentration (Twycross et al, 2018).

Use local guidelines where available or the online Palliative Adult Network Guidelines (www.book.pallcare.info, an open access guideline resource and opioid dose calculator; Watson et al, 2011) to guide appropriate prescribing when converting between different opioids (e.g. from morphine to oxycodone) or between different routes (e.g. from oral morphine to subcutaneous diamorphine in a syringe driver).

Table 1 illustrates some common opioid conversions. These provide an approximate not absolute guide (because of inter-individual variation in opioid pharmacokinetics related to age, ethnicity, renal and hepatic function, the direction of opioid switch, and other concurrent medication) (Twycross et al, 2018). There can therefore be slight variation in the ratios depending on the source used and, regardless of this, the ratios are not a substitute for clinical assessment or clinical judgement.

A fentanyl 25 mcg/hour patch is roughly equivalent to 90 mg oral morphine, for example. So even the lowest dose fentanyl patch (12 mcg/hour) is a relatively high starting opioid dose if the patient is opioid naïve. Also be aware (and explain to the patient) that the rate of absorption may be increased if the skin under the patch becomes vasodilated (e.g. in febrile patients, if the patient takes a hot bath or if hot water is applied) (Twycross et al, 2018).

Side effects

Constipation is a common and persistent side effect of all opioids; always make sure that the patient has a laxative available. Other side effects (e.g. nausea and neurocognitive effects such as a 'spaced out' feeling) are more likely to be transient on initiation or after dose titration and it is worth explaining this to the patient (Twycross et al, 2018). There are some implications for driving when taking opioids (as well as a number of other medications commonly used for symptom control such as benzodiazepines) and this should form part of your discussion with the patient about side effects. Your organization is likely to have a patient information sheet that you can use to explain this (an example is given at https://xerte.cardiff.ac.uk/play_10223).

Adjuvant analgesics

Adjuvant analgesics (other non-opioid medications for specific pain types) can be used alongside opioids at any step in the pain ladder. Common examples are:

Table 1. Conversion ratios of common opioids

Convert			Example	
From	**To**	**Ratio***	**From**	**to**
Codeine or tramadol	Morphine (oral)	÷10	Tramadol 100 mg four times a day	Morphine 40 mg/day (e.g. morphine modified release 20 mg twice daily)
Morphine (oral)	Oxycodone (orally)	÷ 2 (or by 1.5)	Morphine modified release 40 mg twice daily (80 mg/day)	Oxycodone 40 mg (e.g. oxycodone modified release 20 mg twice daily)
Morphine (oral)	Diamorphine (subcutaneously)	÷ by 3	Modified release morphine 15 mg twice daily (30 mg/day)	Diamorphine 10 mg/24 hours subcutaneously
Morphine (oral)	Morphine (subcutaneously)	÷ by 2	Modified release morphine 15 mg twice daily (30 mg/day)	Morphine 15 mg/24 hours subcutaneously
Oxycodone (oral)	Oxycodone (subcutaneously)	÷ by 1.5 (or 2)	Modified release oxycodone 30 mg twice daily (60 mg/day)	Oxycodone 40 mg/24 hours subcutaneously
Buprenorphine (transdermal patches)	Morphine	x 100	Approximate equivalence/relative potency to oral morphine: Buprenorphine 5 mcg/hour patch ~ oral morphine 12 mg/24 hours 10mcg/hour patch ~ 24 mg oral morphine/24 hours 20mcg/hour patch ~48 mg oral morphine/24 hours	
Fentanyl (transdermal patches)	Morphine	x 150 (or 100)	Approximate equivalence/relative potency to oral morphine: Fentanyl 12 mcg/hour patch ~ 43 mg oral morphine/24 hours 25mcg/hour ~ 90 mg oral morphine/24 hours 50mcg/hour ~ 180 mg oral morphine/24 hours 75mcg/hour ~ 270 mg oral morphine/24 hours 100mcg/hour ~ 360 mg oral morphine/24 hours	

**The recommended conversion ratios vary – the ratios used in the Palliative Care Adult Network Guidelines opioid calculator (www.book.pallcare.info) are given here.*

- Amitriptyline or nortryptyline and/or gabapentin or pregabalin for neuropathic pain
- Non-steroidal anti-inflammatory drugs or steroids for liver capsule pain
- Non-steroidal anti-inflammatory drugs for bone pain
- Anti-spasmodic drugs for smooth muscle spasm (e.g. hyoscine butylbromide)
- Muscle relaxants for painful skeletal muscle spasm, e.g. benzodiazepines, baclofen
- Steroids for pain from tissue compression or infiltration.

Adjuvant analgesics for neuropathic pain have a similar efficacy, so choice is guided by potential drug interactions or side effects or other potential benefits (e.g. amitriptyline if low mood and poor sleep as well as neuropathic pain, although note that the starting dose for neuropathic pain is lower than the antidepressant dose). Pregabalin and gabapentin require a 'controlled drug prescription' (e.g. total quantities to be dispensed must be specified in words and figures). In some patients opioids may be effective monotherapy for neuropathic pain: if a patient is already taking an opioid for another pain, assess the response to that for the neuropathic pain before automatically adding an adjuvant.

Non-pharmacological options

Considering non-pharmacological options for pain is as important as the pharmacological treatments in an overall holistic approach, e.g. transcutaneous electrical nerve stimulation (TENS), heat (hot water bottle or heat pad), radiotherapy (e.g. for cancer-related bone pain at a single site), nerve block, or physiotherapy (for positioning and/or splinting) (Harris, 2014).

Complex pain situations with patients with multiple comorbidities, renal and hepatic impairment and multiple types of pain are increasingly common in the ageing population. Navigating a careful balance between acceptable pain management, side effects and drug interactions can be challenging, so clinicians should have a low threshold to involve the local specialist palliative care team: that is what they are there for.

Nausea, vomiting and constipation

Nausea and vomiting are common symptoms in advanced disease (prevalence of up to 70% in advanced cancer and up to 50% in non-malignant advanced disease) (Harris, 2010). Although the two symptoms are commonly associated, they should be assessed separately. Be careful to clarify what the patient means (e.g. 'vomiting' may be used by the patient to also describe expectoration of sputum and regurgitation).

Different anti-emetics act on different receptors or parts of the emetogenic pathway (the efferent and afferent pathway through the 'chemoreceptor trigger zone' and 'vomiting centre' in the brainstem). Current guidelines recommend that the initial anti-emetic prescribed should be guided by clinical assessment of the likely cause of the nausea or vomiting (Harris, 2010) (*Table 2*):

- Metoclopramide and cyclizine in theory should not be routinely prescribed together (as the pro-kinetic effect of metoclopramide is antagonised by cyclizine)
- Be careful using multiple anti-emetic drugs which affect dopamine receptors as this may precipitate drug-induced parkinsonism (e.g. metoclopramide, haloperidol, levomepromazine), and avoid in patients with Parkinson's disease or who have Parkinsonian syndromes. Domperidone is an alternative pro-kinetic to metoclopramide, which does not cross the blood–brain barrier, and extrapyramidal effects are therefore less likely (Harris, 2010).
- A number of symptom control drugs may have more than one indication (e.g. haloperidol may be for nausea and/or delirium; an opioid may be for breathlessness and/or pain). Make it clear in the clinical notes and drug chart what each drug is being prescribed for, and if for multiple symptoms then clearly state this.

Table 2. Preferred anti-emetics for different causes of nausea or vomiting

Cause of nausea or vomiting	Example
Drug or metabolic causes (e.g. nausea secondary to starting an opioid or hypercalcaemia)	Haloperidol or metoclopramide
Delayed gastric emptying (e.g. squashed stomach syndrome from liver metastases)	Domperidone or metoclopramide
Vestibular or intracranial causes (e.g. nausea secondary to brain metastases)	Cyclizine
Chemotherapy or radiotherapy related	Ondansetron
Nausea from multiple causes or if other options failed	Levomepromazine

Most anti-emetics can be given via a syringe driver (domperidone being one exception). The dose used is generally the same as the oral dose, e.g. metoclopramide 30 mg/24 hours via syringe driver if taking metoclopramide 10 mg three times a day orally. In theory, haloperidol and levomepromazine require a lower dose subcutaneously (because of higher subcutaneous compared to oral bioavailability), although it has to be noted that in reviews of clinical practice many centres use 1:1 initially and review (Twycross et al, 2018).

Constipation is a common symptom in patients with advanced disease and usually multifactorial (e.g. opioids, reduced fluid intake, poor mobility). There is no significant difference in efficacy between different laxatives (Twycross et al, 2018), and a combination of a stimulant and softener is generally recommended. Use of several different laxatives concurrently adds to medication burden, and makes it difficult to assess which actually works best for each individual patient.

The aim is to find a laxative the patient can tolerate and take regularly (e.g. some prefer senna and magnesium hydroxide because of smaller volumes; others may prefer macrogol sachets even though they are a bigger volume). To support compliance take into account the patient's preferences, e.g. tablet or liquid and volume, and also what he/she has tried previously.

Breathlessness

Breathlessness is a common symptom in patients with advanced malignant and non-malignant disease (>50% with increasing prevalence as disease progresses) (Watson et al, 2011). The overall approach is treating any reversible or correctable component (e.g. optimizing inhaler therapy for advanced chronic obstructive pulmonary disease), and pharmacological and non-pharmacological options to relieve symptoms of breathlessness.

Symptomatic pharmacological approaches may involve use of opioids. Guidelines advocate lower doses than for pain (e.g. starting dose of immediate release morphine 2.5 mg as required; Watson et al, 2011) and usually not titrating higher than around 30 mg morphine/24 hours (Twycross et al, 2018).

A benzodiazepine is sometimes considered if there is an anxiety component directly relating to the breathlessness, but the evidence for benefit is limited, and they should not be used routinely in this context. Seek advice if unsure (Watson et al, 2011).

Non-pharmacological options may include breathing exercises, use of a hand-held fan or complementary therapy.

Oxygen is a drug. Not all patients with advanced disease and breathlessness will be hypoxic by pulse oximetry (oxygen saturations <91%), but may report a subjective benefit from oxygen. Those patients are likely to find a handheld fan just as beneficial (randomized controlled trials have not found a difference between oxygen or air for subjective benefit, unless the patient is hypoxic) (Watson et al, 2011).

Steroids in palliative care

Steroids are commonly used in palliative care and have a number of potential indications: as an adjuvant analgesic for pain (4–8 mg daily), and at higher doses (8–16 mg daily) for cerebral oedema, malignant spinal cord compression and lymphangitis carcinomatosis. They are also used in short courses for appetite or fatigue (usual dose 2–4 mg dexamethasone daily), but the effect may only last a few weeks and should be balanced against the potential side effects (Watson et al, 2011).

In view of all the potential side effects, steroids are intentionally usually used just as a short-term measure (with the dose reduced by 2 mg (or a 25–50% reduction) every 5–7 days), while other aspects of management are changed or take effect. Dexamethasone is most commonly used because of its lower tablet burden.

In most situations it is appropriate to discontinue steroids when someone is entering the last hours to days of life. In some circumstances it may be of benefit to continue them (e.g. poorly controlled fitting from cerebral oedema secondary to a brain tumour). Dexamethasone can be given via a syringe driver, but is not compatible with

TOP TIPS

- Use recognized conversions when changing between opioids and appreciate the relative potency between them (either from your local guidelines or formulary or validated online resources, e.g. www.book.pallcare.info).
- Always prescribe the dose of short-acting opioid liquids (e.g. morphine, oxycodone) in mg and not ml as there are different concentrations.
- Diamorphine and morphine are not the same (diamorphine is more potent) and should not be used interchangeably.
- A number of anti-emetics can be given via a syringe driver. The dose used is generally the same as the total oral dose.
- Metoclopramide and cyclizine in theory should not be routinely prescribed together.
- Constipation is common. There is no significant difference in efficacy between different laxatives: the aim is to find a laxative the patient can tolerate and take regularly.
- Steroids have a number of potential uses in palliative care: make the indication and intended duration clear, and prescribe them in the morning or at lunchtime.
- If an opioid is being used for breathlessness make that clear (otherwise it may be stopped inadvertently because the patient does not have 'pain').
- Remembering the 4 'A's for anticipatory prescribing for end of life care (Analgesic, Anti-emetic, Anxiolytic, Anti-secretory).

CURRICULUM CHECKLIST

This article addresses the following requirements from the general internal medicine training curriculum

- Managing end of life and applying palliative care skills

many other drugs and an alternative is to give as a once-daily subcutaneous injection (as it has a long duration of action). The long duration of action also means that once daily (oral dosing) is preferable, as steroids cause insomnia if taken late in the day.

Always make the intended steroid duration and indication clear as patients can inadvertently end up remaining on steroids unnecessarily.

Anticipatory prescribing for the last hours to days of life

A number of common symptoms which may occur in the last hours to days of life can be predicted. Guidelines recommend anticipatorily prescribing subcutaneous medication for these symptoms for as required use when someone is recognized to be approach the end of life: the 4 'A's.

- Analgesic, e.g. diamorphine, for pain, (may also be for breathlessness)
- Anxiolytic, e.g. midazolam
- Anti-secretory (for retained upper airway secretions at the end of life), e.g. hyoscine hydrobromide
- Anti-emetic, e.g. levomepromazine.

These are prescribed for patients who do not currently have all those symptoms, in anticipation that they may develop them.

If patients are already taking oral opioids (or anti-emetics or benzodiazepines) then these will need to be converted to a syringe driver (continuous subcutaneous infusion over 24 hours). The online resource mentioned earlier (www.book.pallcare.info) can be used to calculate appropriate subcutaneous doses and check if drugs are compatible together in the same syringe driver (Watson et al, 2011).

'Death rattle' (retained secretions in the upper airways at the end of life) occurs in around 50% of people (Watson et al, 2011). Drugs such as hyoscine hydrobromide or glycopyronnium may be used to help reduce this symptom. They primarily reduce the development of further secretions rather than dissipate existing secretions and should therefore be introduced sooner rather than later where required.

Diamorphine and morphine are not the same (diamorphine is more potent) and should not be used interchangeably. To convert from oral morphine to diamorphine subcutaneously divide the total oral dose by 3 (e.g. morphine sulphate modified release 30 mg twice daily orally would be 20 mg diamorphine/24 hours via syringe driver) or divide by 2 for the equivalent morphine dose subcutaneously.

Deprescribing for patients with life-limiting illness

Reviewing and rationalising existing medication which may no longer be of benefit is just as appropriate as adding medication for symptom control, and can avoid patients building up a large tablet burden.

Polypharmacy correlates to higher risk of adverse drug reactions, and drug–drug interactions (Morin et al, 2019). Around 33% of people with known life-limiting diseases remain on drugs of questionable clinical benefit for the last 3 months of life (e.g. statins, calcium supplements, bisphosphonates, multivitamins) (Morin et al, 2019). There should be an individualised approach to deprescribing, but in particular focussing on medication that the patient was previously commenced on for primary or secondary prevention of specific conditions in the long term.

Diabetes UK produces useful practical guidance on reducing and rationalising diabetic medication (and blood sugar monitoring) for people with a limited prognosis (Diabetes UK, 2018). The British Geriatrics Society has a useful resource to help manage Parkinson's medication as a person becomes less able to take this orally (e.g. through conversion to a patch) (http://www.parkinsonscalculator.com/).

Conclusions

Palliative and end of life care is an important aspect the role of all doctors in training. The EEMMA approach (evaluation, explanation, management, monitoring, attention to detail) provides a framework to do this. Using recognized online resources and opioid conversion tools helps facilitate safe prescribing practice. Anticipating symptoms is also important, especially the 4 A's at the end of life (Analgesic, Anti-emetic, Anxiolytic and Anti-secretory). BJHM

KEY POINTS

- Prescribing or medication errors in relation to symptom control in palliative care most commonly relate to individual errors, poor communication (e.g. poor handover), poor care coordination and delivery, equipment (e.g. malfunction of a syringe driver), and care planning (e.g. failing to anticipate symptoms and prescribe 'as required' medication in advance).
- The principles of the World Health Organization analgesic ladder provides a structured approach to the management of pain in advanced disease, and morphine is the recommended first-line strong opioid.
- For nausea and vomiting, current guidelines recommend the initial anti-emetic prescribed should be guided by clinical assessment of the likely cause.
- The overall approach to breathlessness in advanced disease is to treat any reversible or correctable component, and, pharmacological (e.g. opioids) and non-pharmacological options (e.g. handheld fan) to support symptom relief of the breathlessness.
- A number of symptoms can be anticipated towards the end of life and anticipatory prescribing the 4 'A's (an Analgesic, Anti-emetic, Anxiolytic, Anti-secretory) can help ensure these can be promptly managed if needed.
- Reviewing and rationalising existing medication that may no longer be of benefit (deprescribing) is just as appropriate as adding medication for symptom control.

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