A practical approach to symptom management in palliative care

Doctors in all specialties will be involved in the care of patients with terminal malignant and non-malignant disease where the aim is palliation rather than cure. An understanding of the principles of symptom management in this context is therefore a generic skill that all doctors require. This article provides practical guidance on how to manage common physical and psychological symptoms encountered in palliative medicine.

Palliative care is defined as the 'active total care by a multi-professional team of patients whose disease is not responsive to treatment. Control of pain, of other symptoms, and of psychosocial, social and spiritual problems are paramount. The goal of palliative care is achievement of the best quality of life for patients and their families' (World Health Organization (WHO), 1990).

Symptom control is a major part of palliative care for patients with malignant or non-malignant disease (patients with end-stage non-malignant disease suffer from as many distressing symptoms as those with cancer; Gore et al, 2000; McKinley et al, 2004). Common physical symptoms include pain, nausea and/or vomiting, and breathlessness whereas anxiety, depression and confusion are common psychological symptoms.

General principles of symptom control are:

1. Assessment: history, examination and investigations (if appropriate)
2. Consider potential causes: symptoms may be directly related to cancer, related to cancer treatment, indirectly related (e.g. pain from a pressure ulcer) or unrelated (e.g. pain from pre-existing osteoarthritis)
3. Reverse any reversible cause
4. Palliate the irreversible.

Table 1. The World Health Organization analgesic ladder

Step 1	Mild	Non-opioid (e.g. paracetamol) +/- adjuvant
Step 2	Mild–moderate	Weak opioid (e.g. codeine, dihydrocodeine, co-codamol 30/500) +/- non-opioid +/- adjuvant
Step 3	Moderate–severe	Strong opioid (e.g. morphine, fentanyl, oxycodone) +/- non-opioid +/- adjuvant

From World Health Organization (1990)

Dr Dylan Harris *is Specialist Registrar in Geriatric and General Medicine, Department of Adult Medicine, Royal Gwent Hospital, Newport NP20 2UB and* **Dr Simon Noble** *is Palliative Care Consultant, Royal Gwent Hospital, Newport and Senior Lecturer in Palliative Medicine, Cardiff University*

Correspondence to: Dr D Harris

Physical symptoms

Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Hall and Sykes, 2004). Pain is experienced by up to 70% of patients with advanced cancer and about 65% of patients dying from non-malignant disease (Fallon and McConnell, 2006).

Of the patients with cancer who experience pain, one third have a single pain, one third have two pains and one third have three or more pains (Watson et al, 2005). Pain may be:

- Related to the cancer itself (e.g. metastatic bone pain)
- Treatment related (e.g. neuropathy secondary to chemotherapy)
- Related to cancer and debility (e.g. constipation)
- Unrelated (e.g. long-standing lower back pain) (Watson et al, 2005).

A thorough pain history is necessary to guide appropriate management and the PQRST tool is helpful (Skaer, 1998):

- Provocative factors
- Quality
- Radiation
- Severity
- Temporal factors.

Using the WHO analgesic ladder can alleviate pain in over 80% of patients (Fallon et al, 2006): starting at a level most appropriate to the patient's pain and increasing in steps until adequate analgesia is achieved (*Table 1*). Adjuvant analgesics may be used at any point based on the type of pain the patient is experiencing; an adjuvant analgesic is a drug whose primary indication is for something other than pain but that has an analgesic effect for certain types of pain (Fallon et al, 2006) (*Table 2*).

Opioids (e.g. morphine) should be used for severe pain in patients with active disease, and may even be required earlier in the illness if symptoms dictate. When introducing morphine remember basic principles (Scottish Intercollegiate Guidelines Network (SIGN), 2000; Hall and Sykes, 2004; Glasgow Palliative Care Network, 2005; Fallon et al, 2006):

- Give morphine 4-hourly
- Prescribe a rescue dose (one-sixth of total daily dose, recalculated as the baseline dose increases)
- Titrate doses upwards by 30–50% until pain is controlled
- There is no arbitrary upper dose limit
- Treat side effects with a laxative and anti-emetic
- Observe for opiate toxicity (e.g. hallucinations, drowsiness, confusion, pinpoint pupils)
- When pain is controlled convert to a slow release form (divide the total 24-hour dose of morphine by two to give the equivalent 12-hour dose) with an immediate release preparation available for rescue pain
- To convert from oral morphine to subcutaneous morphine divide the total daily dose by three to give the equivalent dose of diamorphine.

If opioid toxicity occurs consider reducing the dose, ensure adequate hydration or switch to an alternative opioid at a lower equianalgesic dose (Fallon et al, 2006). Alternative opioids to morphine (e.g. oxycodone, hydromorphone) should also be considered if there are unacceptable side effects (substituting opioids may reduce side effects in ≤75% patients), in renal failure, for patients in whom the route of administration needs to be changed and if the patient expresses a preference (Cairns, 2001; Watson et al, 2005).

Up to 40% of cancer-related pain may have a neuropathic component which may be treated with: tricyclic antidepressants (e.g. amitryptiline), anticonvulsants (e.g. gabapentin), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), topical preparations (e.g. capsaicin cream), radiotherapy and acupuncture (Mehta, 2005; Watson et al, 2005). Neuropathic pain may also be opioid responsive.

Finally, non-drug treatments for pain should also be considered e.g. TENS (transcutaneous electrical nerve stimulation), physiotherapy, acupuncture and relaxation techniques, herbal medicine and homeopathy (Colvin et al, 2006; Fallon et al, 2006).

Table 2. Adjuvant analgesics

Drug type	Indications
Non-steroidal anti-inflammatory drugs, e.g. diclofenac 50 mg three times a day	Bone metastases, liver capsule pain, soft tissue infiltration
Steroids, e.g. dexamethasone 8–16 mg daily	Raised intracranial pressure, soft tissue infiltration, liver capsule pain, nerve compression
Anticonvulsants/antidepressants, e.g. gabapentin 100–300 mg nocte, amitryptiline 25 mg nocte	Nerve compression or infiltration, paraneoplastic neuropathies
Bisphosphonates, e.g. pamidronate	Malignant bone pain

From Watson et al (2005); Colvin et al (2006); Fallon and McConnell (2006)

Nausea and vomiting

Nausea is an unpleasant sensation experienced in the back of the throat and the epigastrium that may or may not culminate in vomiting (the forceful expulsion of the contents of the stomach through the oral and/or nasal cavity) (Rhodes and McDaniel, 2001). Nausea and vomiting occur in 50–60% of patients with advanced cancer (Baines, 1997).

Numerous neurotransmitter receptors are involved in transmitting the impulses connected with nausea and vomiting to the vomiting centre and chemoreceptor trigger zone (CTZ) in the mid brain.

Chemical triggers (such as drugs, metabolites and toxins) are detected at the CTZ, whereas the vomiting centre receives input from stretch receptors on nerve terminals (e.g. from liver capsule stretch by metastatic disease or bowel dilatation as a result of obstruction) as well as input from higher mental centres (e.g. pain, fear memory) and integrates these with input received from the CTZ (Mannix, 2006).

Different anti-emetics block different receptors and the choice of anti-emetic should be guided by the underlying cause of vomiting (*Table 3*). For example, haloperidol blocks central dopamine receptors in the CTZ, cyclizine blocks histamine receptors and muscarinic receptors in the brainstem, and domperidone and metoclopramide block peripheral dopamine receptors in the stomach and upper small bowel. Levomepromazine is a useful second-line antiemetic because of its broad spectrum action on a range of receptors (histamine, dopamine, acetylcholine and 5HT2 receptors). Ondansetron and granisetron block 5HT3 receptors and are very receptor specific. They therefore do not have wide application in palliative care and their principal use is the prevention of chemotherapy-induced nausea and vomiting or third-line therapy for nausea and/or vomiting secondary to bowel obstruction (Rhodes and McDaniel, 2001).

In summary, when managing a patient with nausea and vomiting:

- Identify possible causes
- Consider probable pathways and neurotransmitters involved to guide use of the most appropriate anti-emetic

Table 3. Pharmacological management of nausea in palliative care

Cause of vomiting	Choice of anti-emetic
Drug, toxin or metabolic	Haloperidol, levomepromazine
Radiotherapy	Haloperidol
Chemotherapy	Ondansetron, dexamethasone, metoclopramide
Bowel obstruction	Cyclizine, hyoscine butylbromide, octreotide
Delayed gastric emptying	Metoclopramide, domperidone
Raised intracranial pressure	Cyclizine, dexamethasone

From Baines (1997); Glasgow Palliative Care Network (2005); Watson et al (2005)

- Use an anti-emetic regularly, titrate the dose, considering alternatives to the oral route if necessary
- When using combinations of drugs remember potential interactions, e.g. metoclopramide and cyclizine have an antagonistic effect, haloperidol and metoclopramide may causes restlessness and Parkinsonism
- Finally, consider non-pharmacological measures, e.g. relaxation, acupuncture, providing small frequent meals which do not have extremes of taste or smell.

Breathlessness

Breathlessness is an unpleasant sensation of difficult, laboured breathing and occurs in 21–79% of terminal cancer patients (Davis, 1997; Ripamonti, 1999).

Breathlessness is also a common symptom in a number of advanced progressive illnesses such as end stage heart failure and end stage chronic obstructive pulmonary disease (COPD).

In patients with cancer breathlessness may be:

- A direct effect of the cancer (e.g. pleural effusion)
- Related to cancer treatment (e.g. radiation pneumonitis)
- Unrelated (e.g. caused by pre-existing heart failure).

A thorough history is fundamental in the approach to the breathless patient and examination may reveal signs of the underlying cause, e.g. pleural effusion, lung consolidation, anaemia, deep venous thrombosis in the leg (and therefore pulmonary embolus) and evidence of underlying pre-existing lung disease (e.g. COPD).

In all patients consider underlying reversible causes and their treatment, for example:

- Exacerbations of COPD: nebulized bronchodilators and steroids
- Pleural effusion: therapeutic aspiration (and pleurodesis if a malignant effusion as these are likely to recur)
- Pulmonary emboli: anticoagulate (usually with low molecular weight heparin rather than warfarin in the palliative care setting)
- Lymphangitis carcinomatosa: corticosteroids
- Superior vena cava obstruction: steroids, palliative radiotherapy
- Symptomatic anaemia: blood transfusion, erythropoietin (EPO) in certain circumstances, e.g. anaemia secondary to chemotherapy (Watson et al, 2005; Brown, 2006).

General treatment options include:

Opiates, e.g. oromorph 2.5 mg as required

If used inappropriately, opioids cause respiratory depression (determined by prior exposure, rate, route and dose administered and coexisting pathology) (Davis, 1997). However, low dose oral opiates can relieve breathlessness (without measurable reductions in respiratory rate or oxygen saturations) by reducing the central perception of the symptom, reducing associated anxiety and reducing sensitivity to hypercapnia (Davis, 1997; Ripamonti, 1999; Brown, 2006). There is no significant evidence favouring benefit of nebulized opioids.

Benzodiazepines, e.g. lorazepam 0.5–1 mg or diazepam 2–5 mg as required

Benzodiazepines are particularly useful in patients in whom panic and hyperventilation are contributing but may also be useful in patients without prominent anxiety (Davis, 1997). In the terminal phase subcutaneous opiates and benzodiazepines (e.g. midazolam 2.5 mg subcutaneously or 5–10 mg over 24 hours in a syringe driver) may be used treat breathlessness as well as other symptoms such as anxiety and agitation (Brown, 2006).

Oxygen

Even in non-hypoxic patients, oxygen appears to have symptom benefit without physiological benefit: this in part may be related to placebo effect (Ripamonti, 1999; Morrison and Meier, 2004). However, patients can become highly psychologically dependent on oxygen which may actually impair their quality of life, only a small number of patients should therefore require continuous oxygen (Davis, 1997).

Corticosteroids, e.g. dexamethasone 4–8 mg daily

Corticosteroids are useful where there is bronchospasm or partial obstruction (e.g. stridor as a result of tracheal obstruction and lymphangitis carcinomatosa).

Non-pharmacological management

This can include relaxation techniques, directing a stream of cold air over the face, repositioning in the bed, physiotherapy input for breathing exercises, and explanation and reassurance.

Using syringe drivers

In patients who are unable to use the oral route for medication consider alternatives, e.g. transdermal, rectal or subcutaneous infusion. Patients often experience multiple symptoms and syringe drivers facilitate administration of concomitant drugs simultaneously, however, this is not suitable for all drugs and combinations (*Table 4*). Principal syringe driver indications are:

- Severe dysphagia
- Patient too weak to swallow oral drugs
- Reduced level of consciousness
- Intractable vomiting
- Poor patient compliance (Mehta, 2005).

Psychological symptoms

Anxiety

Anxiety is apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnoea unattached to a clearly identifiable stimulus (Dirckx, 1997).

Anxiety may be severe and may also exacerbate other symptoms such as pain and breathlessness. It is impor-

Table 4. Practical considerations when using syringe drivers

Drugs compatible with diamorphine	Cyclizine
	Haloperidol
	Hyoscine
	Metoclopramide
	Octreotide
	Midazolam
	Ondansetron
Drugs which should be administered with a separate syringe driver	Dexamethasone
	Phenobarbital
	Diclofenac
	Ketamine
Drugs not suitable for subcutaneous use	Diazepam
	Chlorpromazine
	Prochlorperazine

From Mehta (2005); Watson et al (2005)

tant to address underlying factors such as pain or drug withdrawal (including alcohol withdrawal).

Psychological (cognitive) therapy can help patients to identify the thoughts that cause them distress and find ways of challenging them before the anxiety escalates (Cathcart, 2006).

Pharmacological therapy includes use of benzodiazepines, e.g. diazepam 1–5 mg orally as required (WHO, 1990). Selective serotonin reuptake inhibitors may be effective for panic attacks if benzodiazepines are ineffective or alternatively tricyclic antidepressants in sub-antidepressant doses can be used (Watson et al, 2005). Complementary therapies may also be useful.

Depression

Depression is a temporary mental state or chronic mental disorder characterized by feelings of sadness, loneliness, despair, low self-esteem and self-reapproach (Dirckx, 1997).

While up to 69% of patients with advanced cancer may experience depression, under-treatment is frequent (Watson et al, 2005). Equally, depression is often overlooked in patients with advanced non-malignant disease such as end stage heart failure and COPD (Cathcart, 2006).

Many of the symptoms usually used to diagnose depression are almost universal in cancer patients (e.g. fatigue and loss of energy) and diagnosis can be difficult. Equally thoughts of death may be realistic and a basis for appropriate planning (Watson et al, 2005). A number of substitute symptoms have therefore been suggested for patients with advanced malignant disease, e.g. social withdrawal, pessimism and lack of reactivity (Endicott, 1984). The single question 'are you depressed?' has been found to have a high sensitivity, specificity and positive predictive value in some studies (Lloyd-Williams et al, 2003).

Careful thought should be given when prescribing antidepressants during the final weeks of life when there is insufficient time to achieve therapeutic effect (Lloyd-Williams et al, 1999). Low dose dexamethasone can be used to elevate mood in patients with a short prognosis or while awaiting a response from antidepressants in other patients (Watson et al, 2005).

Confusion and delirium

Delirium is characterized by global cerebral dysfunction, defined by disturbed level of consciousness, attention, thinking, memory, psychomotor behaviour, emotion and sleep-wake cycle (Watson et al, 2005).

Delirium is present in up to 42% of patients with advanced cancer admitted to palliative care units (Lawlor et al, 2000). Delirium may frequently complicate care at the end of life as patients are often unable to communicate their symptoms. Furthermore, delirium generates distress for patients and their families and impedes communication between them.

Management of patients with delirium in the palliative care setting should follow a step-wise approach:

Identify the underlying cause and its reversibility

Identifying underlying precipitating and perpetuating factors and their reversibility, e.g. rehydration and bisphosphonate to correct hypercalcaemia (*Table 5*).

Environmental strategies

Reassurance, reorientation (e.g. with clocks and calendars), the presence of familiar staff and family, limiting staff changes, reduce the level of noise stimulation and appropriate lighting levels for the time of day (Lawlor et al, 2000; Potter and George, 2006).

Pharmacological treatment

Benzodiazepines can be used if other options have failed, particularly where agitation and restlessness are prominent features. Antipsychotic agents used include haloperidol (e.g. 1.5–3 mg orally) and levomepromazine (where sedative effects desired) (Lawlor et al, 2000).

Table 5. Potential causes of delirium

Cause	Example
Metabolic	Hypercalcaemia, hyponatraemia, renal failure, liver failure, hypoxia
Infective	Bronchopneumonia, urinary tract infection
Drug related	Opioids, corticosteroids, neuroleptics, drug withdrawal (benzodiazepines, alcohol)
Cerebral pathology	Cerebrovascular accident, cerebral malignancy: primary or secondary
Miscellaneous	Urinary retention, faecal impaction, severe pain

From Lawlor et al (2000); Glasgow Palliative Care Network (2005); Watson et al (2005); Potter and George (2006)

Elderly patients should receive reduced drug doses and benzodiazepines carry a greater risk of paradoxical agitation in this group (Watson et al, 2005).

Conclusions

The aim of palliative care is to relieve suffering and improve quality of life for patients with advanced illnesses and their families. Common symptoms include pain, nausea and breathlessness, anxiety, depression and confusion. Most symptoms are amenable to treatment if a carefully structured approach is taken. Communication and exploring the patient's ideas, concerns and expectations are paramount to achieve the optimum control of symptoms whether they are biological, psychological, social or spiritual. BJHM

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KEY POINTS

- Management of symptoms is a fundamental component of palliative care for all patients with terminal disease (malignant or non-malignant disease).
- Symptoms may be physical or psychological.
- The World Health Organization analgesic ladder provides a practical tool for management of pain.
- Most symptoms can be managed by taking a careful history and examination to identify the underlying cause, its mechanism and pharmacological and non-pharmacological therapies that may remove or reduce its adverse effects.
- Depression and anxiety are common but under-treated and may aggravate physical symptoms.

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