

# Symptom control in cancer management

**Lucy: I missed school yesterday because I had a cold.....**

**Peanut: There must be something going around. Lots of kids have been getting colds.**

**Lucy: Mine was a lot worse though.**

**Peanut: Why?**

**Lucy: Because it happened to me!**

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Pain and symptom control is paramount to optimising comfort and quality of life for patients with a distressing illness – be it early or advanced. The key to symptom control is understanding that all symptoms are expressed perceptions, and perceptions are multi-dimensional. Such perceptions are subjective and are influenced or modified by physical, emotional, psychological, social and spiritual factors. Every person is unique.

Management extends beyond just physical relief, and therefore flexibility is the key to managing cancer patients.

## General principles

Any pain/symptom may be caused by:<sup>1,2</sup>

- the cancer itself (61%)
- the treatment (5%), e.g. radiotherapy
- the debility of the cancer (12%), e.g. muscle spasm, constipation
- a concurrent disorder (22%), e.g. degenerative bone disease.

Principles of pain and symptom management:<sup>1,2</sup>

- Take an accurate and detailed history.
- Perform a detailed examination.
- Do not wait for a patient to complain – question and observe.
- Do not delay the start of treatment.
- Administer drugs regularly in doses titrated to each individual.
- Reassess regularly and repeatedly.
- Empathy, understanding, diversion and elevation of mood are essential adjuncts – drugs are only part of the overall management.

## Pain control

Pain is one of the most feared symptoms. Pain and cancer are, however, not synonymous. Pain occurs in approximately 25% of patients with newly diagnosed cancers, 33% of patients undergoing treatment and 75% of patients with advanced disease.<sup>3</sup>

In patients with pain, multiple concurrent pains are common – 20% have only one pain and 80% have two or more pains (35% of whom have 4 or more pains). The frequency of pain as a symptom in cancer:<sup>1</sup>

- bone/prostate: 80%
- breast/colon: 70%
- lymphoma: 20%
- leukaemia: 5%.

Types of pain:<sup>1</sup>

- somatic, e.g. bone metastases
- visceral, e.g. pancreatic carcinoma
- neuropathic, e.g. brachial plexopathy
- sympathetically maintained, e.g. reflex sympathetic dystrophy.

Methods of pain control:<sup>1</sup>

- explanation – discuss causes and therapeutic options with patient
- increasing pain tolerance, e.g. relaxation techniques, treatment of emotional distress
- modification of tumour or pathology, e.g. radiotherapy

## Pain and symptom control is paramount to optimising comfort and quality of life for patients with a distressing illness – be it early or advanced.

- modulation of pain transmission, e.g. analgesics, acupuncture
- interruption of pain pathways, e.g. destructive nerve blocks.
- Use a specific drug for a specific pain.
- Choose an appropriate route of administration.
- Titrate the dose.

Principles of analgesic use are:<sup>4</sup>

- Preferably give by mouth – easy, effective route.
- Give by the clock, i.e. not as required (prn), but according to the duration of action of the drug, which is usually 4-hourly. With respect to pain control, prn stands for *pain relief nil*.
- Give by the WHO ladder.
- Give for the individual, i.e. titration of dose.
- Perform regular review.
- Use adjuvant drugs where necessary.

When starting an analgesic:<sup>1,5</sup>

- Set realistic goals and aim for graded relief, e.g. initially a good night's rest, then pain free at rest and finally pain free on movement (not always possible).

- Provide for rescue doses in the event of breakthrough pain.
- Anticipate and treat side-effects, especially when commencing opioids.
- Keep regimen simple to aid compliance.

The WHO ladder<sup>4</sup> provides a stepwise guideline to pain control (Fig. 1).

Shortcomings of the WHO ladder:

- Gives the impression that all pain is opioid sensitive, which is incorrect.
- Gives the impression that paracetamol is not necessarily an effective analgesic, which is incorrect.
- Drug therapy is the cornerstone of pain management, however, the role of other modalities should not be forgotten.

Morphine is the opioid of choice<sup>1,3-7</sup> – by mouth no other strong opioid shows a clear advantage. It is a versatile drug because it can be given intravenously (IV), intramuscularly (IM), subcutaneously (SC), per rectum (PR), or orally (PO). It has no ceiling effect and there is no danger of drug accumulation, except in renal failure. The only limiting factor would be that imposed by adverse side-effects.

Side-effects and precautions with opioid analgesia:

- Constipation occurs in almost all patients, therefore co-prescribe laxatives.
- Nausea/vomiting is usually transient – use metoclopramide or haloperidol.
- Sedation is usually mild and transient.
- Confusion/hallucination is more common in the elderly, especially if the starting dose is too high.
- Myoclonus is a sign of morphine accumulation, e.g. in renal failure. Decrease the dose or change to a different opioid.
- Allergy is extremely rare.

The usual starting dose is 10 - 15 mg 4-hourly if stepping up from a weak opioid, except in the elderly when you start with 5 mg 4-hourly. Titrate the dose up in the event of uncontrolled pain or progressive disease. It is increased by dosage increments of 30 - 50%, allowing 24 hours between dosage increases to obtain a steady state. The patient should always be advised of morphine dose for breakthrough pain, usually the equivalent 4-hourly immediate release morphine. Up to 70% of patients never need more than 200 mg in a day.<sup>1</sup>

Morphine does not cause clinically significant respiratory depression in patients with pain, for two reasons:

- tolerance to respiratory depression develops rapidly when opioids are titrated effectively, and
- to a lesser extent pain is a respiratory stimulant and also a physiological antagonist to CNS-depressant effects of morphine.

In any event, the first effect of the drug is pain relief, then sedation and finally respiratory depression, which is reversible with Narcan.

The transdermal route, e.g. the Fentanyl patch, is not suitable for rapid dose titration. It is used for relatively stable chronic pain. However, allowances should be made for breakthrough pain when it is used. Pain not relieved by morphine will not be relieved by Fentanyl.

All partial opioid antagonists, e.g.

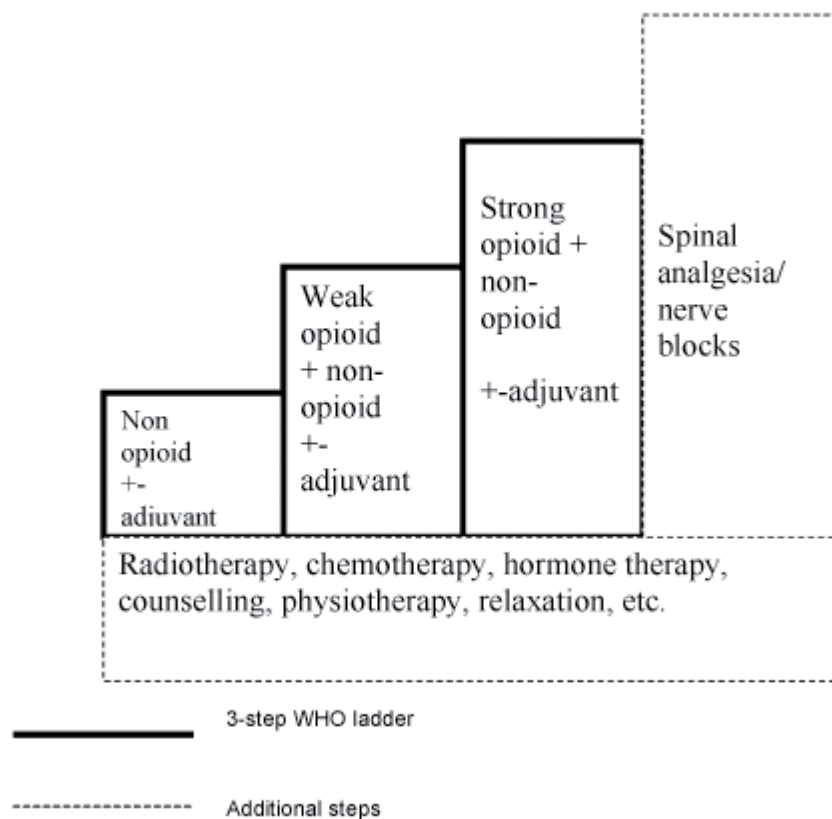


Fig. 1. The stepwise approach to pain relief.

## The response to radiotherapy usually depends on the dose delivered and the duration of the response may be better with higher doses.

buprenorphine, and mixed opioid agonists/antagonists, e.g. pentazocine, have a ceiling analgesic effect. That is, there is a dose at which any increase in the drug only results in an increase in adverse effects.

Do not use regular doses of meperidine for chronic pain in view of its active metabolite, which is a CNS-stimulant and can cause agitation, tremor and seizures.

Neuropathic pain occurs when nerves are damaged and this may be secondary to nerve compression, nerve injury or sympathetically maintained pain. Although clinical experience has demonstrated that many neuropathic pains will respond to opioids, in some situations adjuvant analgesics need to be used.

In the case of nerve compression, corticosteroids, e.g. dexamethasone, with an initial starting dose of 8 - 24 mg daily, may reduce peri-tumoural oedema, thus reducing compression.

In the event of nerve injury pain:<sup>2,7</sup>

- Step 1 – if dysaesthetic type pain, start with a tricyclic antidepressant, e.g. amitriptyline 10 - 25 mg tds and titrate up.
  - if shooting type pain then commence with an anticonvulsant, e.g. carbamazepine 100 mg tds or gabapentin 100 - 200 mg tds.
- Step 2 – add the one drug to the other, i.e. tricyclic to anticonvulsant or vice versa.
- Step 3 – if no response, try class 1 cardiac anti-arrhythmic, e.g. mexiletine or ketamine.
- Step 4 – failing the above, use a spinal analgesic/nerve block if pain is localised to a specific site.

As sympathetically maintained pain does not respond to secondary analgesics, sympathetic nerve blocks are required.

Radiotherapy helps by reducing oedema, decreasing inflammation and production of pain-producing kinins, reducing the size of the tumour and slowing progression. Indications for the use of radiotherapy in pain control are:

- bone metastases – hemibody irradiation may help if multiple metastases are present
- local tumour with mass effect
- brain metastases

- adjunct to surgery in pathological fractures that will not heal when active tumour is present
- nerve compression.

The response to radiotherapy usually depends on the dose delivered and the duration of the response may be better with higher doses. Side-effects are variable and dependent upon the area being treated.

### Common symptoms

Some of the more common and distressing symptoms encountered in cancer patients are discussed below.

#### Nausea/vomiting

This symptom is common and is encountered in 40 - 70% of patients. The causes are often multifactorial and can usually be determined from a careful history and clinical examination. This step is crucial when choosing an appropriate anti-emetic. Determine whether the potential causative factor is acting on:<sup>2,5,7,8</sup>

- vomiting centre (VC)
- chemoreceptor trigger zone (CTZ)
- via vagal stimulation
- via vestibular apparatus
- via cerebral cortex, e.g. oedema, or
- via limbic system, i.e. taste, smells.

Anti-emetics are predominantly neurotransmitter-blocking agents acting on different receptor sites and therefore treat different causes of vomiting (Fig. 2).<sup>9</sup>

Simplistically you could choose a specific anti-emetic for a specific trigger site, for example:

- CTZ – haloperidol, 5HT<sub>3</sub> antagonist or metoclopramide
- VC – cyclizine
- vestibular apparatus – cyclizine, H<sub>1</sub> anti-histamine
- vagal stimulation – cyclizine
- cerebral cortex – dexamethasone for oedema, benzodiazepine for psychological stimuli.

At times more than one anti-emetic is needed and then combinations with complementary actions should be used, e.g. cyclizine and haloperidol. Avoid combinations with antagonistic actions, e.g. a prokinetic with an anticholinergic drug, as the final common pathway for prokinetic drugs is cholinergic, resulting in a blockage of their action by anticholinergics.<sup>8</sup>

In the recent ASCO guidelines (Update 2006)<sup>10</sup> for anti-emetic usage, the recommendation for chemotherapy-induced vomiting is:

- a 3-drug combination of 5HT<sub>3</sub> serotonin receptor antagonist, dexamethasone and aprepitant on day 1 for chemotherapy agents with a high emetic risk, e.g. anthracyclines, high-dose cyclophosphamide
- a 2-drug combination of 5HT<sub>3</sub> antagonist and dexamethasone for chemotherapy with moderate emetic risk.

To prevent delayed emesis in patients receiving cisplatin and other high emetic risk agents, dexamethasone and aprepitant is recommended on day 2 and 3 as well.

With respect to radiation-induced emesis:<sup>10</sup>

- For high-risk patients, e.g. total body irradiation, it is recommended that a 5HT<sub>3</sub> serotonin receptor antagonist with or without corticosteroid is given before each fraction and for at least 24 hours thereafter.
- For moderate emetic risk, a 5HT<sub>3</sub> antagonist is given before each fraction only.

The potential causes of nausea are depicted in Fig. 2.

#### Anorexia/cachexia syndrome

This is a complex syndrome that combines anorexia, chronic nausea, weight loss and lethargy. Dietary advice and nutritional supplementation are key to the management of this syndrome. Prokinetic drugs can be used for nausea. Prednisolone 10 - 30 mg or dexamethasone 2 - 4 mg daily may help anorexia but response is usually short lived. Progestational drugs such as medroxyprogesterone or megestrol acetate provide another option.

#### Constipation

Constipation is a common cause of distress and is inevitable after commencing an opioid. A combination of a stool softener with a peristaltic stimulant should be used, e.g. lactulose with a senna preparation. The aim is to obtain a soft bowel motion every 3 - 4 days.

**Pain is one of the most feared symptoms. Pain and cancer are, however, not synonymous.**

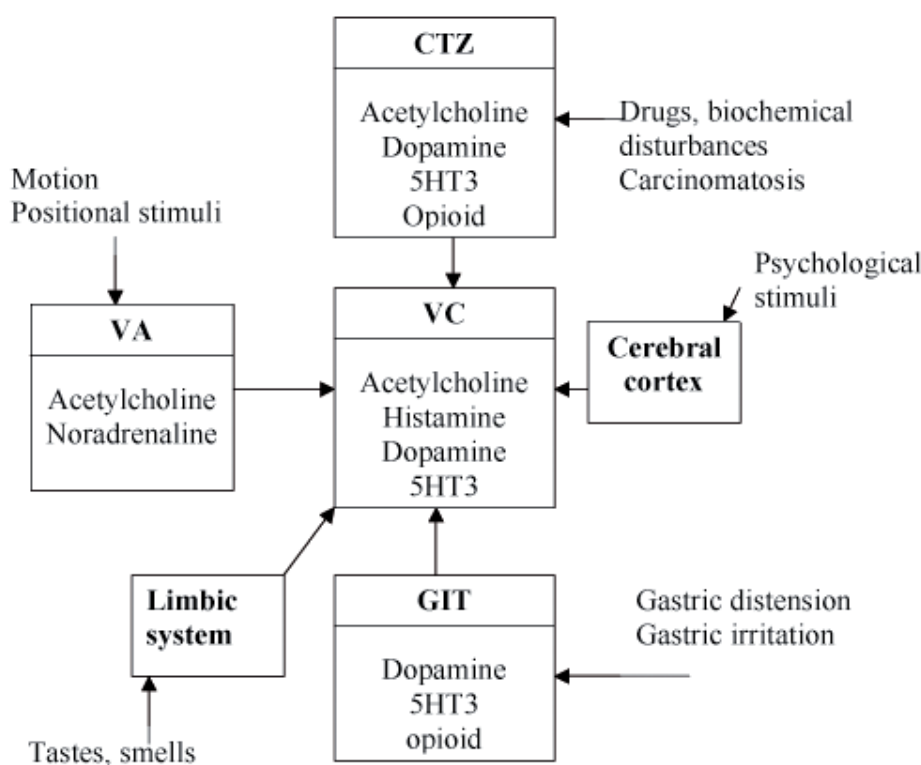


Fig. 2. The potential causes of nausea. CTZ = chemoreceptor trigger zone; VA = (vestibular apparatus); VC = vomiting centre; GIT = gastrointestinal tract.

### Malignant ascites

This condition is generally associated with peritoneal metastases but other causes include hypoalbuminaemia, portal hypertension, hyperaldosteronism. Tense ascites can be uncomfortable and distressing.

Depending on the type of malignancy and the performance status of the patient, systemic or intraperitoneal chemotherapy are options.

In the case of mild ascites or asymptomatic ascites commence with 100 mg spironolactone, increasing to 300 mg daily, and 40 - 80 mg furosemide. Once a satisfactory result has been achieved, discontinue furosemide. Beware of intravascular volume depletion.

In the event of tense ascites, symptomatic ascites or failed medical therapy an abdominal paracentesis should be done. Tap to dryness. Repeat as required. Shunts are not often used in malignant ascites.

### Malignant bowel obstruction

In patients unsuitable or unfit for surgery, the conventional 'drip and suck' is an uncomfortable long-term management of malignant bowel obstruction. Medical management should keep the majority of these patients free of nausea and pain with about one emesis a day unless they have a high bowel obstruction, e.g. gastric outlet obstruction. This is achieved by using a syringe driver containing a combination of haloperidol or cyclizine, morphine and hyoscine butylbromide. This obviates the need for a nasogastric tube. However, in a relatively

high bowel obstruction it may be necessary to re-insert a nasogastric tube or percutaneous gastrostomy to avoid ongoing vomiting.

### Dyspnoea

This condition is distressing and frightening for both patient and family/carers. It occurs in up to 70% of patients with advanced disease. General principles of management include:<sup>2,5,7</sup>

- reassurance and explanation
- optimal patient positioning
- relaxation techniques
- treatment of reversible causes.

Therapeutic options include:

- blood transfusion if the patient is anaemic
- thoracocentesis with or without pleurodesis for pleural effusion
- oxygen if hypoxic (debatable)
- trial of high-dose steroids for lymphangitis carcinomatosis
- stenting, laser therapy, brachytherapy for endobronchial disease.

Drug options for a patient with dyspnoea depend on the cause and include:

- Mist morphine – if not previously on an opioid, low doses (5 - 20 mg) are often all that is needed. If the patient is already on an opioid, increase the dose by 50% for 2 - 3 days and if there is no subjective improvement then go back to the original dose.
- Diazepam 5 - 10 mg daily or lorazepam 1 mg tds/prn sublingually if the patient is anxious.
- Dexamethasone 4 - 8 mg daily by mouth may be helpful if there is bronchospasm or partial obstruction of airway.
- Midazolam 5 - 10 mg IM or slowly IV is effective, with rapid onset of action, for respiratory panic.

### Hiccoughs

There are innumerable potential causes of hiccoughs. Effective drugs to treat this condition include:

- a prokinetic agent for gastric stasis
- a muscle relaxant, e.g. baclofen 5 mg tds or midazolam 2 - 10 mg IV if the hiccoughs are severe
- a central suppressant of hiccough reflex, e.g. chlorpromazine 10 mg tds – beware of drowsiness and cardiac effects in the elderly.

### Delirium/confusion

The prevalence of this symptom ranges from 20% to 70%.<sup>5</sup> The cause is usually multifactorial and a search for treatable causes should always be made. Common causes include:

- drugs
- infections
- metabolic disturbances
- renal/hepatic failure
- cerebral anoxia
- disease progression
- alcohol withdrawal.

Management involves:<sup>5</sup>

- treating any infections and correcting metabolic abnormalities
- reviewing medication
- reassuring and orientating the patient
- only using sedative drugs, e.g. haloperidol or midazolam, if the patient is very restless and agitated.

**Morphine is the opioid of choice – by mouth no other strong opioid shows a clear advantage.**

## Symptom control

Discussion and management of symptomatic emergencies such as spinal cord compression, superior mediastinal syndrome and metabolic abnormalities are beyond the scope of this article.

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## In a nutshell

- Management of pain and symptoms extends beyond just physical relief.
- Approach requires evaluation, explanation, individualised treatment, supervision and attention to detail.
- Causal factors include cancer, treatment, debility and concurrent disorder.
- Treatment depends on the underlying pathological mechanism.
- Flexibility is key to managing cancer patients.
- Morphine is the opioid of choice.
- Choose drugs carefully as their side-effects can also compromise quality of life.

## single suture *The secret of Lance Armstrong's success*

It may be that Lance Armstrong is such a good athlete because of his liver function. Enormous amounts of lactic acid are produced during endurance sports by muscle cells. Lactic acid is removed from the body by enzymatic conversion and depends mainly on the capacity of the hepatic gluconeogenesis that converts lactic acid to glucose. Enhanced hepatic gluconeogenesis may lead to Armstrong experiencing less muscle pain during exercise as well as providing extra energy. The authors of the paper hypothesise that Armstrong's increased hepatic capacity is a result of his training programme as a young man, when he swam 10 000 m and cycled 32 km daily. Another argument for enhanced hepatic gluconeogenesis is his extraordinary recovery from metastatic testicular cancer. The cancer cells produce large quantities of lactic acid.

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