Drug Management of Pain
Core Knowledge

e-LfH
e-Learning for Healthcare

NHS
Health Education England

Inspected and rated
Outstanding ☆
Care Quality Commission

Learning Objectives

By the end of this session you will be able to:

- Represent the WHO analgesic ladder in diagram form
- Give examples of drugs used at each stage of the ladder and why they are used
- Outline some of the uses and limitations of the analgesic ladder
- Define and list some common adjuvant analgesics used in pain management
- Recognise other pain management interventions that can be used in conjunction with drugs on the analgesic ladder

Introduction

Symptom management of pain in cancer and many non-cancer conditions starts with a thorough clinical assessment and diagnosis, based on the understanding of the pathophysiology of the pain. Pain may have more than one cause. It may be malignant, non-malignant or due to treatment. Often the most effective symptom control measure is that aimed at removing or treating the underlying cause e.g. palliative radiotherapy.

Drug management of pain should not be delayed while waiting for disease-modifying treatment. It is often continued during and after such treatment, either because medication is still required for the original cause, albeit at smaller doses, or for other causes of chronic pain. For others, drugs will be the mainstay of management; for example, if the cause of pain is not clear and the burden of further investigations/treatment outweighs the potential benefits to that patient.

This session discusses how clinicians can use the WHO analgesic ladder to help them manage pain, using a few widely known pain relieving drugs. It explains the place of adjuvant drugs and gives information about starting and titrating morphine. Finally, the session shows how an integrated approach to pain management also incorporates addressing psychosocial, spiritual and emotional concerns.

The WHO Analgesic Ladder
The Principles

The WHO analgesic ladder was originally developed as a pragmatic three-step approach for cancer pain. It provides a simple framework for non-specialist clinicians to consider a limited number of drugs in a systematic manner, tailored to the patient's needs.

The analgesic ladder is now also widely used for the management of persistent chronic non-malignant pain.

Question: What do you think are the key principles of the WHO method to relieve pain?

Answer: The key principles include:

Treating the symptom of pain promptly with analgesics
Giving analgesia on a regular basis rather than only when pain occurs; with 'as needed' pro re nata (PRN) doses available for breakthrough pain
Using adequate doses
Giving analgesia via the oral route when possible
Titrating analgesia for the individual
Reviewing and reassessing analgesia
Keeping it simple, using the ladder
You can consider the use of adjuvant analgesia at each stage

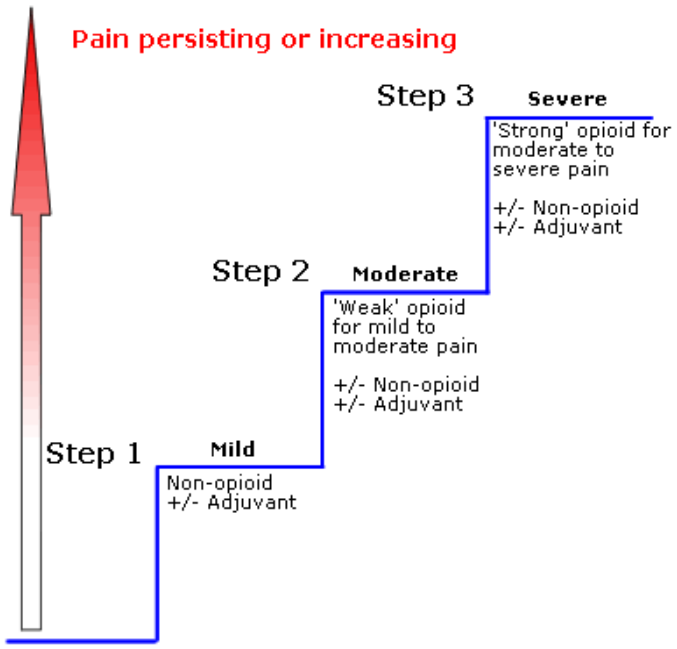


Image The WHO analgesic ladder, 1996 (adapted)

The WHO Analgesic Ladder
The Three Steps

For patients with mild to moderate pain, start at step 1 of the analgesic ladder and titrate upwards until the patient is comfortable. Review regularly to assess the response to treatment, and step the treatment up or down the analgesic ladder as necessary.

In general, all patients with persisting moderate to severe pain should receive a trial of morphine +/- a non-opioid, +/- adjuvant, regardless of the cause of the pain.

Step 1

Step 2

Step 3

The WHO Analgesic Ladder
The Three Steps

Step 1

Give paracetamol and/or a nonsteroidal anti-inflammatory drug (NSAID) +/- adjuvant analgesic.

Non-opioids are analgesic drugs that have principally antipyretic and anti-inflammatory actions. They:

- Do not bind to opioid receptors
- Have a known ceiling effect on their analgesic efficacy balanced against adverse effects
- Do not produce tolerance or physical dependence and are not associated with abuse or addiction

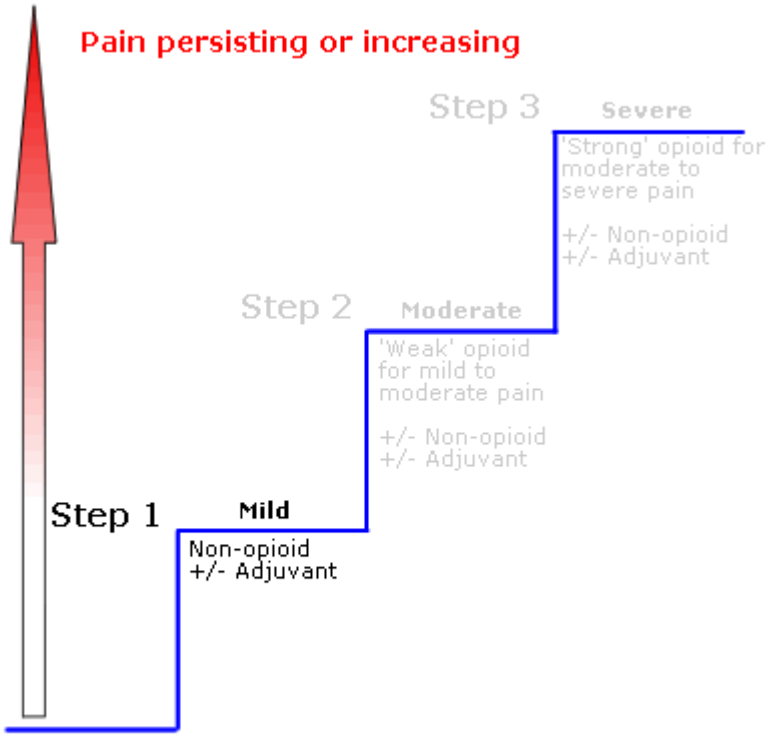


Image 1 Step 1 of The WHO analgesic ladder

Step 2

Give a full dose of 'weak' opioid (e.g. codeine) +/- non opioid +/- adjuvant.

'Weak' opioids are so called because they have a known ceiling effect on their analgesic efficacy balanced against adverse effects. In other words, the agonist effects on receptor sites increase linearly with increasing doses of the drug until they reach a plateau, and no longer continue to increase with further increases in dose. 'Weak' opioids are given at step 2 of the WHO analgesic ladder.

Examples of 'weak' opioids include codeine, dihydrocodeine and tramadol.

There is little evidence to show that switching from one 'weak' opioid to another provides significant improvement in pain control.

Remember to think about what prn opioid you will want to prescribe at this stage.

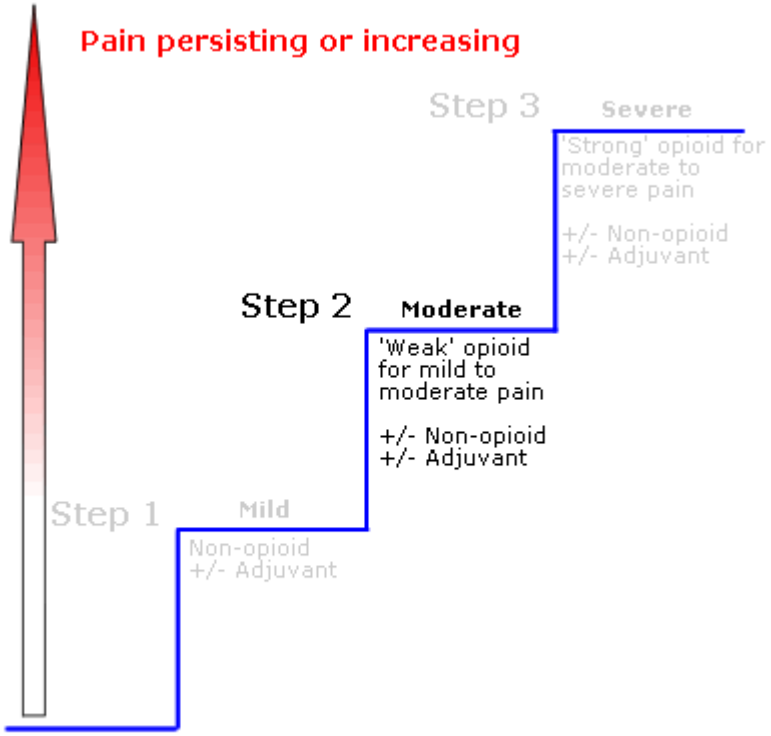


Image 2 Step 2 of the WHO analgesic ladder

Step 3

‘Strong’ opioids such as morphine are given at step 3 of the WHO analgesic ladder. At this step give morphine +/- non-opioid, +/- adjuvant.

‘Strong’ opioids are so called because they have no known ceiling effect for analgesia. However, their efficacy must be balanced against adverse effects in each individual patient.

When there is partial pain relief, but intolerable side effects will not permit increasing the morphine dose further, it may be beneficial to switch from one opioid to another. This is known as opioid switching.

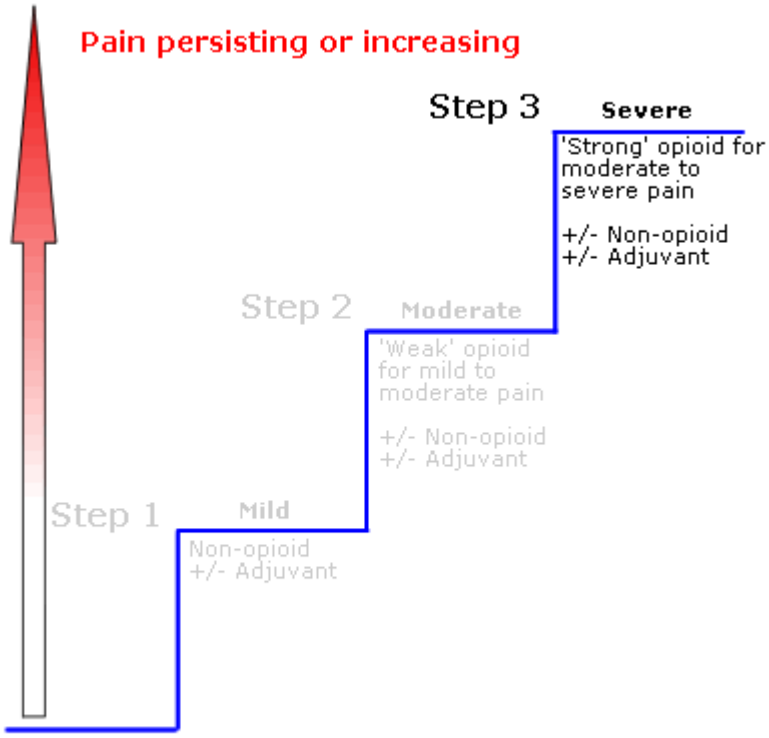


Image 3 Step 3 of the WHO analgesic ladder

The following are the key drugs used in pain management.

Non-opioids

Paracetamol

Paracetamol has antipyretic and analgesic activity, but negligible anti-inflammatory effects. It is well absorbed after oral administration and does not irritate the gastric mucosa.

It is usually well tolerated within normal recommended dose 500-1000mg qds. Beware that higher doses may be associated with risk of hepatotoxicity. Lower doses are recommended in patients with renal impairment.

Paracetamol can be utilised at every step of the WHO analgesic ladder.

Non-opioids

NSAIDs

NSAIDs have anti-inflammatory actions and are often used for pains such as musculoskeletal pain. They may worsen asthma, hypertension, renal impairment or cardiac failure.

About 60% of patients will respond to any NSAID (BNF, 2009). Whilst there is little evidence to show that switching from one NSAID to another provides significant improvement in pain control, there are large variations in individual tolerance and response.

All NSAIDs are associated with a risk of gastrointestinal adverse events, such as gastritis or ulceration. For people at higher risk of gastrointestinal adverse events with NSAIDs either:

Use paracetamol instead of a NSAID or

Use a gastroprotective agent with a NSAID if clinical judgement is that NSAID is required

Don’t forget that all NSAIDS are contra-indicated in patients with active peptic ulceration.

All NSAID use can be associated with a small increased risk of thrombotic events (e.g. myocardial infarction and stroke) (BNF, 2014).

NSAIDs can be utilised at all steps of the WHO ladder.

'Weak' opioids

Codeine

Codeine is usually the first choice 'weak' opioid for mild to moderate pain. It is frequently given as a compound analgesic preparation of higher dose codeine plus paracetamol (30/500). Codeine plus paracetamol provides more pain relief than either codeine alone or paracetamol alone.

Prescribing codeine separately to paracetamol allows flexibility of dosing and titration of analgesic effect.

Codeine is metabolised into morphine and is about one-tenth as potent as morphine. There are large inter-individual variations in efficacy, with up to 10% of people being poor metabolisers, who will gain little or no pain relief. In addition, some other drugs (such as fluoxetine and paroxetine) will block the metabolism of codeine to morphine. Some clinicians choose to use low dose morphine (step 3) rather than codeine (step 2) if step 1 analgesics have been ineffective in controlling a patient's pain.

240mg daily of codeine phosphate is equivalent to approximately 24mg of morphine a day.

Compound analgesic preparations are given at step 2 of the analgesic ladder.

'Weak' opioids

Low dose 'weak' opioids

Low dose, combined analgesic preparations of codeine with paracetamol (e.g. co-codamol 8/500) are sub-therapeutic and should not be used for pain control in patients with cancer (SIGN, 2000).

Caution: When co-codamol is prescribed and no strength is stated, the 8/500 preparation will be dispensed.

Tramadol

Tramadol is a centrally acting synthetic analgesic with both opioid and non-opioid properties. Its mode of action is not completely understood. However, it appears to act by modifying transmission of pain impulses via inhibition of noradrenaline and serotonin (5HT) re-uptake and also by weakly binding to mu-opioid receptors.

Tramadol has high oral bioavailability. It is less constipating than codeine or morphine, but nausea is a more common adverse effect.

Seizures have been reported in patients taking tramadol at and above the recommended dose. It should be avoided in epileptics and used with caution in patients on concomitant medications with lower seizure threshold, such as tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs), major tranquillisers, fentanyl.

Dose, or dose frequency, of tramadol should be reduced in severe hepatic impairment or severe renal impairment.

400mg daily of tramadol is equivalent to approximately 40mg of morphine a day.

Tramadol is usually given at step 2 of the WHO analgesic ladder.

The WHO Analgesic Ladder
Adjuvant Analgesics

Whilst opioids are often very effective for pain control they may not completely alleviate pain when administered alone.

Adjuvant analgesics are drugs whose primary indication is not for pain, but for other condition(s). Examples include:

Image Adjuvant analgesics

Tricyclic antidepressants or anti-epileptics - useful for neuropathic pain

Bisphosphonates for metastatic bone pain

Corticosteroids for nerve compression (such as spinal cord compression)

Skeletal muscle relaxants for skeletal muscle spasm (alongside physical therapy and relaxation therapy)

Smooth muscle relaxants (e.g. antimuscarinics) or organ distension and colic

There is some evidence that combining opioids with adjuvant analgesics can provide enhanced pain control at lower doses, with the potential for reduced toxicity. In some circumstances, adjuvant analgesics, even when used alone, can provide pain relief. This is particularly seen with complex neuropathic pain.

The WHO Analgesic Ladder Advantages and Limitations

The advantages of the WHO analgesic ladder include:

Simplicity

Rational and consistent application of analgesic drugs

It is applicable to a wide variety of situations and users

It can be employed in countries where access to 'strong' opioids may be difficult

It incorporates the concept of using adjuvant analgesics in combination with opioids to optimise pain management

Question: What do you think are the limitations of the WHO analgesic ladder?

Answer: The limitations of the WHO analgesic ladder include:

It is confined to pharmacological options. The WHO analgesic ladder gives no guidance as to when to use non-pharmacological and/or procedural interventions

It does not give guidance as to the management of pain that is severe at the outset

Step 2, using a 'weak' opioid, is becoming less popular. There has been a trend for an earlier transition to step 3 directly from step 1, for example, low doses of recently developed 'strong' opioid analgesic preparations (e.g. buprenorphine transdermal (TD) weekly patches)

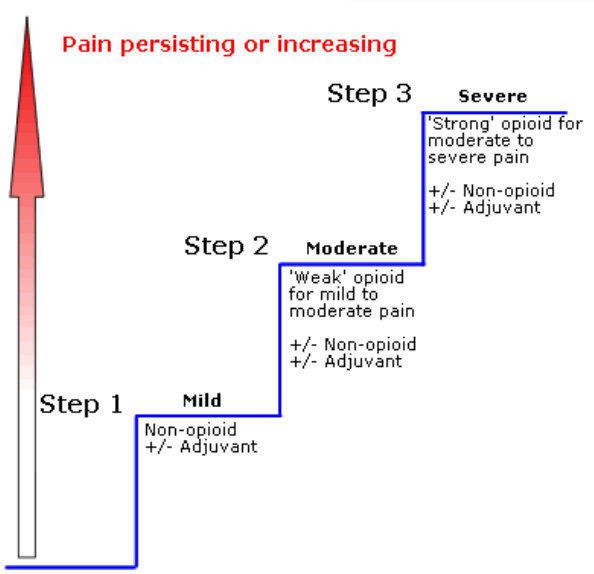


Image The WHO analgesic ladder, 1996 (adapted)

'Strong' Opioids Starting and Titrating Morphine

Morphine is the usual first choice 'strong' opioid for persisting moderate to severe cancer pain because its drug profile is well known, it is low cost and easily available. 'Strong' opioids other than morphine have, so far, not demonstrated advantages that would make them preferable as the first choice oral opioid for pain.

When starting and titrating morphine:

- Begin with a start dose. This will vary between patients
- After 1–2 days, calculate the total dose given over 24 hours (regular and PRNs). Use this to recalculate the 4-hourly dose requirement. See example
- The usual PRN dose is 50-100% of the 4-hourly dose
- Repeat this process every 1–2 days until pain is controlled

Start dose:

- If opioid-naive: use IR (short-acting) morphine solution 2.5mg every 4 hours and 'as needed' (PRN)
- If already on a 'weak' opioid: switch to IR morphine solution/tablets 5–10mg every 4 hours and 'as needed' (PRN) for breakthrough pain

IR oral morphine:

- Can been given in tablet or liquid formulation (e.g. Sevredol, Oramorph)
- It is quickly absorbed – usually gives pain relief within 15-20 minutes
- Is effective for 4 hours

Example

If the patient has taken a total of 60mg oral morphine in the last 24 hours:

60mg divided by 6=10mg oral morphine, given 4-hourly and PRN

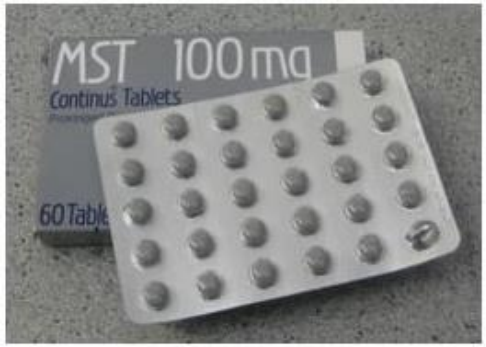
'Strong' Opioids Modified Release Morphine

Once a stable daily dosage of morphine has been reached, switch to the same total daily dose using twice-daily modified release (MR) morphine, at 12 hourly intervals.

Patients can also be successfully titrated using MR morphine (Wiffen and McQuay, 2003).

Morphine can be given parenterally (usually subcutaneously), when the oral route is not considered the most effective, such as persistent nausea and vomiting or if the patient is too weak to swallow. Subcutaneous morphine is approximately twice as potent as oral morphine.

Morphine has active metabolites, which are renally excreted and therefore accumulate in renal impairment. This can be avoided by lowering doses, giving doses less frequently and using IR morphine rather than MR morphine. With the development of alternative opioids, it is now common to switch to opioids with a more favourable renal profile in moderate to severe renal failure.



Useful facts about MR oral morphine

- MR oral morphine has slow absorption and is long lasting
- Most common are 12 hour preparations (MST, Zomorph)
- A 24 hour oral morphine preparation (morphine xtra long (MXL)) is available
- MR tablets **must not** be crushed as they lose their MR properties

'Strong' Opioids Anticipating Painful Situations

There are some people who have good pain control for most of the time but experience an escalation of pain that comes on as a result of an action or activity. This is called incident pain.

Examples of situations that can cause incident pain include:

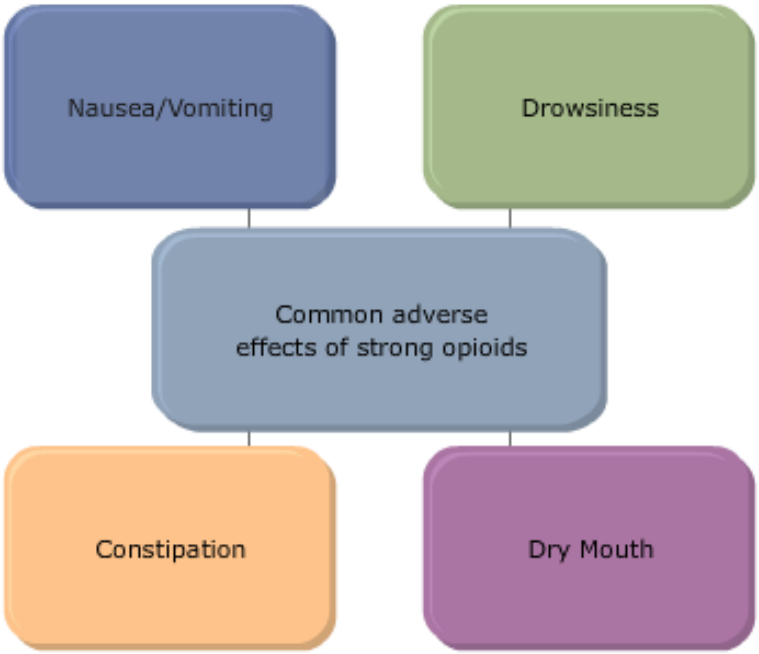
- Mobilisation
- Bathing/dressing
- Transfers
- Wound dressing changes
- Planned turns
- Manual evacuation of stool

Most of the time, these are planned procedures and the pain can be anticipated. IR (short-acting) oral or s/c morphine prescribed as PRN can be given 30-60 minutes in advance of any planned procedure to minimise any pain experienced by the patient. This helps to decrease anxiety and fear and allows patients to feel more confident about the situation.

Giving appropriate verbal information about the procedure can also help reduce anxiety and distress.

'Strong' Opioids Managing Common Adverse Effects

Adverse effects of opioids occur because there are specific opioid receptors in the brain, spinal cord and peripherally in the body. Some more common or troublesome side-effects are shown in the image. Most patients become tolerant to these side-effects within a few days, except for constipation.



'Strong' Opioids Managing Common Adverse Effects

Nausea/vomiting

About one-third of patients taking an opiod, experience initial nausea and/or vomitting.

Prescribe an anti-emetic (e.g. haloperidol 1.5mg od or metoclopramide 10mg tds).

This can be used regulary or 'as needed' for the first few days to prevent opiod-induced nausea and vomiting in sensitive patients.

Most patients then become tolerant to this effect, and do not require anti-emetics long term.

Drowsiness

Drowsiness or sedation is common, but most patients become tolerant within a few days after a dose increase.

Temporarily reducing the dose of the opioid, and slower titration, can help in sensitive patients.

Driving: Advise patients not to drive if adversely affected, but tolerance to sedative effects usually develops within a week or two of dose stabilisation.

'Strong' Opioids Managing Common Adverse Effects

Constipation

To prevent opioid-induced constipation, co-prescribe a regular stimulant laxative or stimulant laxative with a faecal softener (e.g. senna +/- docusate sodium or co-danthrusate).

Stimulant laxatives can cause abdominal colic - avoid these if intestinal obstruction is a possibility.

Dry mouth

Dry mouth can be troublesome. Patients should be encouraged to use simple measures such as:

- Frequent sips of cool drinks
- Ice cubes
- Frozen segments of fruit such as pineapple or melon
- Chewing sugar-free gum

Consider rationalising any other drugs that also cause dry mouth.

Name two pain management interventions that can be used in conjunction with drugs on the analgesic ladder.

Feedback

Utilising the WHO analgesic ladder is only one part of an integrated approach to pain management.

Apart from disease-modifying therapies, specific invasive interventional techniques, e.g. celiac plexus block and non-pharmacological measures, such as TENS can be used in conjunction with the above approach.

In addition, clinicians need to recognise that psychological, spiritual and emotional factors may also influence pain. Poorly controlled pain may adversely affect a person's mood, and psychological or spiritual distress can increase the perception of pain. Assessing and addressing these is also part of pain management.

Robert's Case Study Overview

Robert Smith, an ex army officer, returned from Cyprus two years ago. He is married to Sarah and has two young children in private school.

Eighteen months ago Robert was diagnosed with melanoma on the right upper back. This was removed with a wide excision including some axillary lymph nodes, two of which showed disease.

He has now experienced a mild, but increasing, vague dull aching discomfort in the right side of the abdomen for two weeks, that is difficult to localise. There is no radiating element to his pain. Taking two tablets of paracetamol regularly has not alleviated his pain. He visits his GP who changes his regular analgesia.

Session Key Points

- The WHO analgesic ladder provides a useful general framework for choosing drug options for pain control
- 'Strong' opioids are the mainstay of pharmacological management of persisting moderate to severe pain
- Combining analgesics can enhance pain control at lower doses, with the potential for reduced toxicity from any of the individual drugs used
- Other therapies, including disease-modifying treatment, pain intervention techniques and non-pharmacological treatments, can have important roles in pain management, as part of a multi-modal approach
- Don’t forget to address psychological and spiritual dimensions of pain