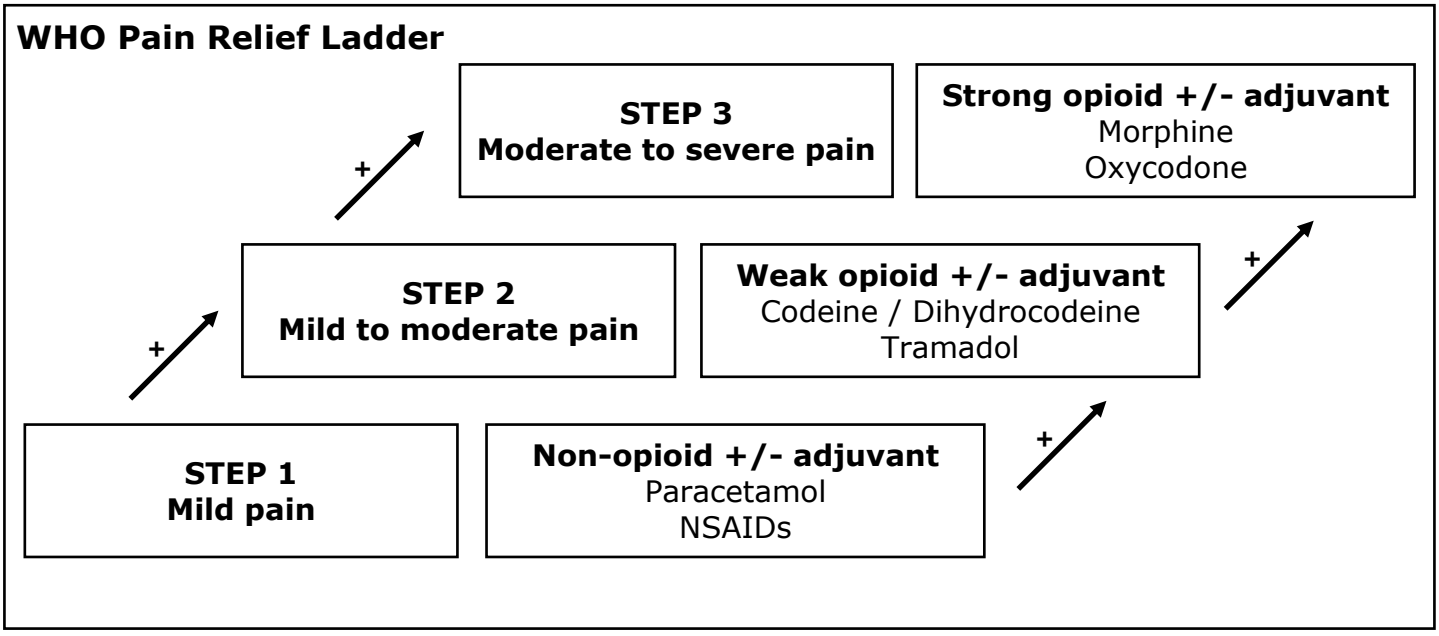
Palliative Medicine - Pain

General principles for prescribing analgesia

Use the WHO three step analgesic ladder when prescribing pain relief.



Step 1: Mild pain

- Paracetamol:
  - The maximum daily dose is 1 gram PO QDS.
  - Reduce the maximum daily dose in patients who weight less than 50kg.
  - Use with caution in patients with hepatic impairment.
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):
  - Examples include: Ibuprofen 400mg PO TDS or Naproxen 500mg PO BD.
  - All NSAIDs are associated with gastrointestinal toxicity, including increasing risk of bleeding, therefore use with caution in patients with any gastrointestinal risk factors and consider co-prescription of a proton pump inhibitor.
  - All NSAIDs are associated with a small increased risk of thrombotic events. Use the lowest effective dose for the shortest period of time to control symptoms and regularly review the need for long term prescriptions.
  - Prescription of NSAIDs is potentially inappropriate in elderly patients. See STOPP/START criteria for further information.
  - NSAIDs should be avoided where possible in patients with renal impairment.

Step 2: Mild to moderate pain

- For pain that persists or increases despite prescription of a non opioid (+/- adjuvant) add in a weak opioid. (For patients with chronic non-cancer pain, the addition of a weak opioid should be assessed carefully and done on an individual patient basis.)
- Codeine phosphate:
  - **Oral codeine phosphate is approximately 1/10th as potent as oral morphine.**
  - The maximum daily dose is 60mg PO QDS.
  - Combination preparations of codeine phosphate and paracetamol (co-codamol) are available.
  - Avoid or dose reduce in patients with renal impairment.
- Dihydrocodeine:
  - **Oral dihydrocodeine is approximately 1/10th as potent as oral morphine.**
  - The maximum daily dose is 60mg PO QDS.
  - Avoid or dose reduce in patients with renal impairment.
- Tramadol:
  - **Oral tramadol is approximately 1/10th as potent as oral morphine.**
  - The maximum daily dose is 50-100mg PO QDS.
  - Tramadol is a centrally acting weak opioid with both opioid and non-opioid properties. In overdose it is only partially reversed by naloxone.
  - Avoid in elderly patients or those with epilepsy and avoid or dose reduce in patients with renal impairment.

Step 3: Moderate to severe pain

- For pain that persists or increases despite prescription of a weak opioid (+/- adjuvant) a strong opioid is required. (For patients with chronic non-cancer pain, the addition of a strong opioid should be assessed carefully and done on an individual patient basis.)
- Morphine is the first choice oral opioid. See section 14.1.2 Initiating oral morphine therapy for further information.

Adjuvants

- See Adjuvant treatments for specific types of pain for further information.

Initiating oral morphine therapy in the palliative setting

Morphine is the 1st choice oral opioid. Seek specialist advice for patients who have significant hepatic or renal failure, are on dialysis or are stopping dialysis*.

Titrate the dose of morphine using an immediate release preparation:

- STEP 1: Choose an appropriate immediate release preparation. Either morphine sulfate liquid 10mg/5ml (Oramorph®) or Sevredol® tablets**.
- STEP 2: Start with 5-10mg every four hours (note that lower doses i.e. 1.25 - 2.5mg may be required in patients who are opioid-sensitive, frail, elderly, small or with renal impairment).
- STEP 3: Write up the same opioid at 1/6th of the total daily dose, to be given PRN (up to 1 hourly) for use in the event of breakthrough pain.
- STEP 4: Reassess after 24-36 hours. Establish the analgesic response and any side effects. If pain control is inadequate, for example more than three breakthrough doses required in a 24 hour period, increase the regular and PRN dose by 30-50% (30% in the elderly or at higher doses).

Example:
In a patient receiving 5mg Oramorph® 4 hourly, who has received 3 PRN doses of 5mg in the last 24 hours:

- The total daily oral morphine dose = 45mg
- With a dose titration of 50%, the new dose will be Oramorph® 7.5 mg 4 hourly with PRN Oramorph® 7.5mg up to 1 hourly

When the pain is well controlled, convert to a modified release preparation:

- STEP 1: Calculate the total daily dose of immediate release morphine.
- STEP 2: Calculate the dose of modified release morphine sulfate by dividing the total daily dose by two.
- STEP 3: Prescribe an immediate release preparation to be given PRN for breakthrough pain.

Example:
In a patient receiving 10mg of Oramorph® 4 hourly, who has received 2 PRN doses of 10mg in the last 24 hours:

- The total daily oral morphine dose = 80mg
- The modified release dose is Morphine Sulfate MR 40mg BD (80mg ÷ 2)
- The breakthrough dose is Oramorph® 10-15mg PRN (80mg ÷ 6) up to 1 hourly

The breakthrough dose will be 1/6th of the total daily dose.
We recommend this titration process with normal release preparations, especially for the inpatient setting. **Alternatively and with sufficient experience you can initiate morphine therapy with a modified release preparation.** For patients with no renal or hepatic comorbidities, offer a typical total daily starting dose of 20-30mg of oral morphine (e.g. 10-15mg modified release morphine BD) plus 5mg immediate release morphine PRN. Monitor and titrate treatment as described in section 14.1.3.

* Morphine undergoes renal excretion
In general, morphine should be avoided in patients with severe renal failure (chronic kidney disease [CKD] stage 4/5; estimated GFR < 30mL/min or creatinine > 150micromol/L) whereby an alternative opioid should be used. Patients with mild/moderate renal failure (CKD stage 2/3; estimated GFR 30 – >60mL/min) should be monitored closely. In these patients the dose may need to be reduced +/- the dose interval increased, or an alternative opioid be considered to prevent toxicity. Consider discussing with your ward Pharmacist, the renal team and Specialist Palliative Care team. See section 14.1.4 Alternative Opioids.

** Oramorph® is available in two different strengths: Oramorph® oral solution and Oramorph® Concentrated oral solution. To avoid confusion, **ALWAYS prescribe the dose in MILLIGRAMS.** Due to tablet strength, the smallest dose of Sevredol® which can be administered is 5mg; therefore Oramorph® will be required when smaller doses are prescribed.

Monitoring and titrating oral morphine therapy

Monitoring:

- When a patient is admitted on a strong opioid use two independent sources to confirm the current dose and the preparation used.
- Monitor the efficacy of the current regime by:
  - Questioning the patient
  - Using pain scales or scores where appropriate
  - Checking the number of PRN doses used in a 24 hour period
  - Monitor for side effects or dose limiting toxicity

Titrating:

- If more than three breakthrough doses are required in a 24 hour period, increase the regular dose by 30-50% (30% in the elderly).

Example:
In a patient receiving 30mg morphine sulfate M/R capsules BD who has required 4 PRN doses of 10mg Oramorph® in the last 24 hours:

- Increase the M/R dose by 30-50% e.g. morphine sulfate M/R 40mg BD
- Increase the breakthrough dose following an increase in the M/R dose e.g. Oramorph® 10-15mg PRN up to 1 hourly

• Ensure that a new breakthrough dose is calculated following any dose increase.

Incident pain

- 'Incident pain' occurs as a direct and immediate consequence of a movement or activity e.g. dressing change, getting up to use the toilet.
- This type of pain can be difficult to plan for as the normal release preparations of morphine and oxycodone need 30-60 minutes to take effect.
- In cases where this is a particular problem it may be appropriate to use an **immediate release fentanyl preparation.** These preparations take around 15 minutes to achieve their full effect, and have a duration of effect of 1-2 hours.
  - **Fentanyl sublingual tablets** (Abstral®) should only be used in cancer patients who are already on a daily minimum of 60mg morphine (or equivalent) and must only be prescribed on the recommendation of the Specialist Palliative Care Team.
  - Once initiated, the dose must be titrated according to the Abstral® dose titration chart (click to open).
  - If patients regularly require ≥4 doses of Abstral® in a 24 hour period, it is usually necessary to increase the background analgesia.

Alternative opioids

Situations where an alternative opioid may be appropriate:

- Intolerable side effects with current opioid
- Inadequate analgesia despite dose titration
- Difficulties with the current method of administration
- Renal failure or significant hepatic failure

General considerations when switching to an alternative opioid:

- Not all opioids are equipotent. Use the opioid dose conversion guide (click to open) when switching to an alternative opioid. Be aware that conversion doses are approximate dose equivalents only.
- Consider a dose reduction of 25-50% for the first 12-24 hours of commencing an alternative opioid, particularly when the patient is on a high dose. Always ensure the patient has access to appropriate breakthrough medication.
- Monitor closely and with extra care if the patient is frail, elderly or has renal or hepatic impairment.
- The decision to switch opioids may be best supported by discussing with the ward pharmacist or the Specialist Palliative Care Team.

Oral alternatives to morphine:

- Oral oxycodone:
  - Oral oxycodone is approximately 1.5 times as potent as oral morphine.
  - Available in both immediate release and modified release generic preparations.
  - Oxycodone is metabolised in the liver to mostly inactive compounds. However due to renal excretion of oxycodone and its metabolites, the potential for accumulation in patients with significant renal impairment remains. It should therefore be avoided if the estimated GFR <15mL/min. In this situation, seek advice from the ward pharmacist or Specialist Palliative Care Team.

Example:
In a patient receiving oral morphine sulfate M/R 40mg BD plus Oramorph® 10-15mg PRN for breakthrough pain, the equivalent oral oxycodone dose would be:

- Morphine sulfate M/R 40mg BD ÷ 1.5 ≈ oxycodone M/R 25mg BD
- Oramorph® 10-15mg PRN ÷ 1.5 ≈ oxycodone I/R 5-10mg PRN up to 1 hourly (except in CKD Stage 5)

    - Oxycodone is contraindicated in moderate to severe hepatic impairment.

Subcutaneous alternatives to oral morphine:

- Subcutaneous morphine:
  - **Subcutaneous morphine is approximately twice as potent as oral morphine.**
  - To calculate the 24 hour dose for a continuous subcutaneous infusion via syringe pump (s.c. syringe pump), calculate the total daily oral morphine dose and divide by two.
  - To calculate the breakthrough dose of subcutaneous morphine, divide the total daily subcutaneous morphine dose by six and prescribe this dose PRN up to 1 hourly.
- Subcutaneous oxycodone:
  - **Subcutaneous oxycodone is approximately three times as potent as oral morphine.**
  - To calculate the 24 hour dose for a s.c. syringe pump, calculate the total daily oral morphine dose and divide by three.
  - To calculate the breakthrough dose of subcutaneous oxycodone, divide the total daily subcutaneous oxycodone dose by six and prescribe this dose PRN up to 1 hourly.
- Subcutaneous alfentanil:
  - **Subcutaneous alfentanil is approximately thirty times as potent as oral morphine.**
  - Alfentanil is metabolised in the liver and its inactive metabolites are renally excreted, making it an appropriate alternative to morphine in patients with severe renal impairment.
  - It has a rapid analgesic effect and short duration of action (1-2 hours) which limits it use as a PRN medication.
  - Always seek Specialist Palliative Care Team advice when prescribing alfentanil.
- Subcutaneous diamorphine:
  - **Subcutaneous diamorpine is approximately three times as potent as oral morphine.**
  - As diamorphine is highly soluble in water, high doses can be administered in small volumes. This makes it a particularly useful substitute where high doses of morphine are required in a s.c. syringe pump.
  - Due to ongoing shortages, diamorphine should only be prescribed where the 24 hour dose of subcutaneous morphine in a syringe pump exceeds 135mg or where the PRN dose of subcutaneous morphine exceeds 20mg.
  - Always seek Specialist Palliative Care Team advice when prescribing diamorphine.

Transdermal alternatives to oral morphine:

- Indications for transdermal opioid preparations:
  - Difficultly with the oral route (e.g. due to difficulty swallowing, vomiting or poor oral absorption).
  - Unacceptable side effects with other opioids
  - Renal impairment
  - Poor compliance with oral analgesia
  - Patient preference

- General considerations and cautions for transdermal opioid preparations:
  - Transdermal preparations are suitable for **stable pain** only.
  - Depending on the drug, transdermal preparations may take up to 72 hours to reach steady state in terms of analgesic effect, meaning they are not an appropriate option for fast dose titration or rapidly changing pain.

- On removal of a transdermal patch, a reservoir of drug will remain under the skin meaning significant blood levels will persist for up to 24 hours.
- Patients receiving a transdermal patch should always have access to breakthrough analgesia, usually in the form of oral morphine or subcutaneous morphine if the oral route is not possible. Refer to the opioid dose conversion guide for the appropriate PRN dose.
- Drug absorption may increase if the patient has a fever. Monitor for signs of opioid toxicity.
- Do not use heat pads or hot water bottles over skin with a transdermal patch in situ as this will also increase drug absorption.
- Do not apply to damaged or irritated skin (e.g. recently irradiated or shaved skin, lymphoedematous skin).
- Watch for the development of erythema under the patch, which may indicate a skin reaction.
- Always rotate the patch to a different site when changing.
- While in hospital check patch skin adherence daily.

• Buprenorphine:
- **Transdermal buprenorphine is approximately 100 times more potent than oral morphine.**
- Buprenorphine is metabolised in the liver by the CYP3A4 pathway. Administered together with inhibitors or inducers of CYP3A4 pathway, the efficacy of buprenorphine may be intensified (by inhibitors) or weakened (by inducers). Examples include antifungals, macrolides and anticonvulsants.
- Buprenorphine or its metabolites are not renally excreted; there is no need to adjust dose in renal failure (CKD 3-5)
- Buprenorphine is only partially reversed by naloxone, in overdose specialist advice should be sought.

• Fentanyl:
- **Transdermal fentanyl is approximately 100 times more potent than oral morphine.**
- Opioid naive patients should be commenced on oral or parenteral opioids and dose-titrated until adequate pain control is achieved before converting to a fentanyl patch.
- Only patients who are already receiving regular opioids and have stable pain are suitable for conversion to a fentanyl patch.
- Commencing a fentanyl patch:
  - STEP 1: Calculate the appropriate dose fentanyl patch using the opioid dose conversion guide.
  - STEP 2: Apply the fentanyl patch and continue the previous opioid until the fentanyl patch has had time to take effect (approximately 12 hours). More specifically:
    - *For a patient on four hourly immediate release oral opioids:* take the regular four hourly dose when the fentanyl patch is first applied. Take a further dose of immediate release oral opioid at 4 and 8 hours post fentanyl patch application. Then stop the regular oral opioid.
    - *For a patient on regular 12 hourly modified release oral opioid:* apply the fentanyl patch at the same time as the last dose of oral modified release opioid.
    - *For a patient receiving opioids via a s.c. syringe pump:* apply the fentanyl patch and continue the syringe pump for a further 8 hours before removing
  - STEP 3: Ensure appropriate breakthrough analgesia is prescribed. This should be immediate release oral morphine or immediate release oxycodone (where the eGFR <30mls/min). Subcutaneous opioids may be considered where the oral route is not possible. The breakthrough dose should be 1/6th of the equivalent 24 hour total morphine dose.
- Continuing and adjusting a fentanyl patch:
  - Patches should be removed after 72 hours and a new patch applied in a new site on clean, dry skin.
  - Do not adjust the dose of the patch until at least 48 hours have elapsed on the current patch strength.

    - Adjustments in patch dose should be made according to breakthrough use, usually in increments of 12-25 micrograms/hr.
- Stopping a fentanyl patch and starting an alternative opioid:
    - *Switching to a 12 hourly modified release oral opioid:* remove the fentanyl patch and after 12 hours start the new oral opioid. Ensure an immediate release opioid at an appropriate dose is available for breakthrough pain.
    - *Switching to a s.c syringe pump:* remove the fentanyl patch and after 12 hours commence the s.c syringe pump at the full equivalent dose. Ensure an immediate release opioid at an appropriate dose and route is available for breakthrough pain.
- For patients on a fentanyl patch who have entered the dying phase and require additional analgesia:
    - It is simplest to continue the fentanyl patch at the current dose.
    - Add a s.c. syringe pump with morphine or oxycodone (where the eGFR <30mls/min) to manage additional analgesia requirements.
    - Remember to adjust the PRN dose to take into account both the fentanyl patch and the amount of opioid in the s.c. syringe pump.

Predictable opioid side effects and their management

There are several predictable side effects to morphine and other opioids which you should consider, discuss with the patient and where necessary prescribe additional symptom control medication:

Constipation:
- Patients receiving an opioid should always have access to laxatives.
- When prescribing strong opioids, prescribe laxatives **regularly**.
- Consider combination of a stimulant (senna 7.5-15mg BD or bisocodyl 5-10mg ON) and a softener (docusate sodium 100-200mg BD).
- For opioid induced constipation which has not adequately responded to laxatives consider naloxegol 25mg OD (naloxegol is a peripherally acting opioid antagonist, therefore decreases the constipating effect without altering the central analgesic effect). Please see Naloxegol for Opioid-Induced Constipation for further information.

Nausea and vomiting:
- Patients commencing on an opioid should have access to an anti-emetic (e.g. metoclopramide 10mg TDS/PRN OR haloperidol 1.5mg BD/3 mg nocte PRN).
- This side effect is often transient, typically lasting 5-7 days.

Drowsiness and sedation:
- Patients commencing opioids should be warned about possible drowsiness and sedation.
- This side effect often settles after 3-5 days on a stable dose.
- For outpatients, it is sensible to advise against driving or operating machinery for 7 days after commencing or increasing opioids or within 4 hours of a breakthrough dose. https://www.gov.uk/drug-driving-law
- If this symptom is persistent, consider dose reduction where pain is controlled or switching to an alternative opioid where pain remains uncontrolled (seek specialist advice).

Dry mouth:
- This is often worsened by any additional medication with anticholinergic side effects, therefore review drug history.
- Encourage good mouth care.
- Sugar free chewing gum, saliva substitutes and mouthwashes may be helpful.

Opioid toxicity

Recognition of opioid toxicity:

- Factors which may contribute to the development of opioid toxicity include:
  - Rapid escalation of opioid dose
  - Renal or hepatic failure leading to the accumulation of active metabolites
- Features of opioid toxicity include:
  - Persistant sedation
  - Hallucinations
  - Vivid dreams
  - Delirium
  - Muscle twitching / myoclonus / jerking
  - Confusion / agitation
  - Pinpoint pupils (poor discriminating sign)
  - Respiratory depression

Management of opioid toxicity:

- Exclude other causes of systemic deterioration (e.g. infection, hypercalcaemia)
- Check renal and hepatic function
- Treat any appropriately reversible cause
- **Mild toxicity:**
  - Reduce the opioid dose by 30-50%
  - Ensure the patient is well hydrated
  - Treat any underlying cause
  - Seek advice from the Specialist Palliative Care Team
- **Moderate toxicity:** (respiratory rate is >8/min and oxygen saturations are satisfactory)
  - Omit the next opioid dose / remove fentanyl patch / remove syringe driver
  - Ensure the patient is well hydrated
  - Seek urgent advice from the Specialist Palliative Care Team
- **Severe toxicity:** (respiratory rate ≤8/min with reduced oxygen saturations)
  - Manage as a medical emergency (full A-E assessment and management, MET call where appropriate).
  - Consider reversal of respiratory depression with naloxone (see below).
  - The aim is to reverse respiratory depression without compromising analgesia or precipitating generalised opioid withdrawal.
  - **Seek urgent advice from the Specialist Palliative Care Team**

Use of naloxone:

- **Indication: Life threatening respiratory depression**, which may be characterised by;
  - Respiratory rate (RR) ≤8/min
  - Reduced oxygen saturations
  - Reduced GCS
  - Cyanosis
- **Method of administration:**
  - Draw up a 400 microgram ampoule of naloxone in 10ml of 0.9% sodium chloride for injection.
  - Administer 100 micrograms (2.5ml) IV every 2 minutes until RR is satisfactory.
  - Further boluses may be required as naloxone is shorter acting than most opioids.
  - If repeated doses are required, consider a naloxone infusion (see A&E Emergency Prompt Cards - Naloxone Usage and Infusion for further information).
  - **Note: if no response to 800 micrograms of naloxone, opioid toxicity is unlikely. Look for another cause and contact anaesthetics / ITU for support.**

Adjuvants treatments for specific types of pain

The consideration of adjuvant analgesics is advised at every step of the WHO analgesic ladder in order to augment pain relief. A thorough pain assessment to correctly identify the nature and source of pain is essential in identifying when adjuvant treatment many be beneficial. Adjuvant treatments may be pharmacological or non-pharmacological.

Pharmacological adjuvant treatments	Non-pharmacological adjuvant treatments
Corticosteroids Antidepressants Anti-epileptics Hyoscine butylbromide Benzodiazepines Bisphosphonates Ketamine Nerve blocks	TENS Acupuncture Massage Heat Psychological support and relaxation Radiotherapy Interventional techniques (stenting etc.)

Below are some specific situations where adjuvant treatments should be considered.

Bone pain

- **Radiotherapy** is usually effective for pain from bone metastases.
- Refer for a **orthopaedic / neurosurgical opinion** where appropriate (for example where there is actual or imminent fracture or spinal cord compression).
- **NSAIDs**:
  - Naproxen 250-500mg BD (lansoprazole 30mg OD should also be prescribed for patients also taking corticosteroids or otherwise at increased risk of GI side effects.)
- **Bisphosphonates**:
  - Bisphosphonates are indicated in pain from bone metastases of any origin, where treatment with alternative analgesics, radiotherapy or surgery is either unsuccessful or inappropriate.
  - Give zolendronic acid 4mg IV in 100ml of 0.9% normal saline over 15 minutes (a dose reduction is required in patients with renal impairment, see BNF for further details).
  - Prescribe appropriate substitution of calcium and vitamin D3; monitor serum calcium levels.
  - Where there has been a good response to treatment, consider repeat doses every 3-4 weeks.

Nerve pain

- Nerve pain is described as "burning", "shooting" or "aching".
- It often requires the use of opioids and adjuvant analgesics.
- Specialist Palliative Care Team referral is advised at an early stage, but the following general approach is suggested:
  - STEP 1: Titrate to maximum tolerated dose of **opioid**.
  - STEP 2:

    Amitriptyline 10-25mg nocte, increasing every 5-7 days in increments of 10-25mg to a maximum of 75mg nocte. If ineffective discontinue gradually over a few weeks. Common side effects include dizziness, sedation, dry mouth and constipation. Amitriptyline is contraindicated where there is a history of cardiac arrhythmias.
    OR
    Gabapentin 300mg OD (100mg OD in the elderly or frail) increasing by that amount every 1-3 days to 300mg TDS. Then increase according to response in steps of 300mg daily to a maximum of 1.8g daily. Sensitive patients might require slower dose titration. Discontinue if no benefit seen after 5 days on the highest dose tolerated. Dose reduction is required in renal impairment.

OR
Pregabalin 25-75mg BD. Titrate dose every 3-7 days to a maximum dose of 300mg BD. Sensitive patient might require slower dose titration. Dose reduction is required in renal impairment.

- STEP 3: A combination of **amitriptyline AND gabapentin OR pregabalin** may be used if neuropathic pain doesn't respond to either agent given alone.
- STEP 4: **Dexamethasone** may be considered for the treatment of cancer related neuropathic pain but little evidence exists for their use. Start at 8mg mane for 3-5 days and then taper to the minimum effective dose. Stop if there is no significant improvement after 5 days.
- STEP 5: If ongoing cancer related neuropathic pain, consider oncology referral for radiotherapy.

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