Guidelines for analgesic treatment of chronic pain

Introduction

- Adequate assessment and accurate diagnosis is essential for specific treatment options to be pursued.
- The three-step World Health Organisation (WHO) analgesic ladder (1986) which was originally produced for the treatment of cancer pain, but the principles can equally well be applied to non malignant pain.
- Pharmacological interventions should be increased to full therapeutic and tolerated dose before switching to a different agent.
- All treatment strategies need to be individualised to specific patient requirements and tolerance.
- Pain is a biologically complex phenomenon and there is a rationale for combining drugs with different mechanisms of action.
- For a small number of patients with chronic stable pain who do not respond to the drug choices below consider if there is neuropathic pain and consider a trial of tricyclic antidepressant (e.g. amitriptyline) or antiepileptic (e.g. carbamazepine/gabapentin). See separate guidelines for the management of neuropathic pain.

Drug Choices and Doses – see SPC for full details and additional notes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Max Daily Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 1 - Paracetamol</strong></td>
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<tr>
<td>Paracetamol</td>
<td>1g qds</td>
<td></td>
<td>Take for at least one week at adequate dose</td>
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<tr>
<td><strong>STEP 2 - substitute Non-Steroidal Anti-Inflammatory Drug (NSAID)</strong></td>
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<tr>
<td>- Ibuprofen</td>
<td>400mg tds</td>
<td>1200mg*</td>
<td>May be appropriate for bone pain or inflammation after due consideration of the risks and benefits and need for gastroprotection. *In a recent meta-analysis, high-dose ibuprofen (2400mg per day) significantly increased the risk of major coronary events, but its safety requires further study as there were many fewer relevant vascular events.</td>
</tr>
<tr>
<td>- Naproxen</td>
<td>250mg bd</td>
<td>500mg bd</td>
<td></td>
</tr>
<tr>
<td><strong>STEP 3</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Combination of paracetamol and NSAID</td>
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<tr>
<td><strong>STEP 4 - Full dose weak opioid plus paracetamol and/or NSAID</strong></td>
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<tr>
<td>Codeine Phosphate</td>
<td>30mg qds</td>
<td>240mg daily</td>
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<tr>
<td>Dihydrocodeine</td>
<td>30mg qds</td>
<td>240mg daily</td>
<td>Use immediate release to establish dose before switching to modified release (MR)</td>
</tr>
<tr>
<td>Dihydrocodeine MR</td>
<td>60mg bd</td>
<td>120mg bd</td>
<td></td>
</tr>
<tr>
<td><em>Prescribe paracetamol and opioid separately to allow flexibility of dosing and titration of analgesic effect.</em></td>
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<tr>
<td><strong>STEP 5 – Alternative weak opioids plus paracetamol and/or NSAID</strong></td>
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<tr>
<td>Tramadol caps</td>
<td>50-100mg qds</td>
<td>400mg daily</td>
<td>Use immediate release to establish dose before switching to MR</td>
</tr>
<tr>
<td>Tramadol MR tabs</td>
<td>100mg bd</td>
<td>200mg bd</td>
<td><em>Price variation in brands in primary care</em></td>
</tr>
<tr>
<td>Fentanyl patch</td>
<td>12microgram/hour every 72 hours</td>
<td></td>
<td>NB. ONLY for patients who are unable to tolerate oral preparations.</td>
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<tr>
<td><strong>STEP 6 - Strong Opioids</strong></td>
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<tr>
<td>Oral morphine</td>
<td>Starting dose depends on current opioid dose – see table below</td>
<td></td>
<td>Start with immediate release morphine sulphate or sustained release as clinically appropriate.</td>
</tr>
<tr>
<td>Fentanyl patches</td>
<td>25microgram/hour every 72 hours</td>
<td>100mcg/hour hour</td>
<td>NB. ONLY for patients who are unable to tolerate oral preparations</td>
</tr>
</tbody>
</table>

Referral to pain management clinics - Only refer patients for whom pain cannot be controlled after trying all the above steps unless there are concerns about diagnosis where an earlier referral should be made.
Step 1  
- Paracetamol is a suitable first choice as it is well tolerated, effective and inexpensive.  

Step 2  
- Due to the possible adverse effects from NSAIDs, they should be used at the lowest effective dose for the shortest time necessary to control the symptoms. Ibuprofen (1200mg per day or less) and naproxen (1000mg per day or less) are considered to have the most favourable cardiovascular safety profiles of all non-selective NSAIDs. In a recent meta-analysis, high-dose ibuprofen (2400mg per day) significantly increased the risk of major coronary events, but its safety requires further study as there were many fewer relevant vascular events.  
- NSAIDs should generally be avoided in patients with a history of serious upper gastrointestinal complications or at high risk of developing these. They may worsen asthma, hypertension, renal impairment or heart failure.  
- Where NSAIDs are contraindicated, not recommended or not preferred, weak opioids are an alternative.  
- Avoid diclofenac because of the increased risk of serious cardiovascular events and the potential correlation with its use and the incidence of Clostridium Difficile.  
- Selective cox-II inhibitors have not been included because they have not been shown to have significant and consistent benefits over non-selective NSAIDs. They are also associated with a small increased risk of serious cardiovascular events.

Step 3  
- Due to different mechanisms of action, a combination of paracetamol and an NSAID may achieve improved analgesia; however there is no trial evidence for this.

Step 4  
- Weak opioids may be considered early in the management of chronic pain.  
- There is evidence that adding full dose opioid (e.g. dihydrocodeine 30mg) to paracetamol increases analgesia.  
- Dihydrocodeine may be preferred to codeine because there is some evidence that up to 25% of the population will not respond optimally to codeine.  
- There is no good evidence that the low dose combinations (co-dydramol 10/500mg) are any more effective than paracetamol alone and side effects are increased, especially constipation, and should not be prescribed.  
- High dose combinations may be prescribed e.g. co-dydramol 20/500mg, however flexibility is lost and patients must take the full dose of opioid to get the full dose of paracetamol.  
- Side-effects with opioids for mild to moderate pain include nausea, drowsiness and constipation. Regular laxatives may be required.  
- Headaches are associated with chronic regular use of opioids and they should be avoided in patients with a history of headache problems including migraine.  
- The All Party Parliamentary drug Misuse Group Inquiry into Physical Dependence and Addiction to Prescription and Over-the-counter Medication (January 2009) issued the following recommendations:  
  - When GPs prescribe drugs which are known to have the potential to cause physical dependence or addiction, they must explain these potential risks to the patient.  
  - When GPs prescribe such drugs, they should set up procedures to monitor the patient. The practice of repeat prescription without review for these drugs must end.

Step 5  
- Tramadol produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. Psychiatric reactions have been reported.  
- The BNF states that it has fewer typical opioid side effects notably less respiratory depression, less constipation and less addiction potential, however there is no evidence that it is any more effective than other weak opioids and its safety profile is problematic so its place in therapy is limited.  
- Transdermal preparations: Fentanyl 12microgram/hour patch has been included as second line alternative for patients with chronic severe pain who cannot tolerate large oral, regular doses of weak opioids or non-opioid + opioid combination analgesics. They are also a useful alternative for any patient with a high potential for addiction.  
- Buprenorphine transdermal patches are ONLY recommended for:  
  - restricted use in palliative care if the patient is unable to swallow
OR
- for patients with dementia who require opioid analgesia and cannot tolerate or swallow oral formulations in accordance with the local ‘Hospital Dementia Pain Prescribing Pain Pathway – For Use for patients with Dementia or Delirium or Both’ – see APC website.

The view of the APC is that buprenorphine transdermal patches are expensive, have abuse potential, may cause dependence and are therefore NOT included in this guideline.

- The Scottish Medicines Consortium have assessed buprenorphine patches and decided that their use is not recommended for treatment of severe opioid responsive pain conditions which are not adequately responding to non-opioid analgesics.

**Step 6**

- Strong opioids are superior to weak opioids for pain relief but a review concluded that the majority of patients using opioids for chronic non-malignant pain experience at least one adverse event and that a significant proportion stop using them because of an adverse event.
- The National Patient Safety Agency\(^\text{15}\) issued action to be taken to reduce dosing errors with opioid medicines, specifically errors occurring when a patient's dose or preparation is changed. This advice must be followed by all healthcare practitioners when prescribing opioid medicines.
- The BNF warns about the risk of confusion when generic titles are used for some modified release preparations including morphine sulphate preparations where there have been incidents of incorrect supply in the past. There have also been incidents relating to once daily and twice daily preparations being confused and the patient being inadvertently given too high a dose. Consequently Worcestershire APC advises that all clinicians prescribe modified release morphine sulphate by brand name and avoid mixing once daily and twice daily preparations.
- Worcestershire Acute Hospitals NHS Trust (WAHT), as part of a regional contract will be stocking Morphgesic® SR Tablets rather than MST Continus® tablets. These are a twice daily formulation with similar appearance to MST and are available in primary care. WAHT does not stock MXL once daily preparation.

- When converting to step 7, use the following dose conversions:

<table>
<thead>
<tr>
<th>Morphine Dose Equivalents</th>
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<tbody>
<tr>
<td><strong>Converting from current opioid</strong></td>
</tr>
<tr>
<td><strong>Example 60mg dihydrocodeine</strong></td>
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<tr>
<td>60mg qds –240mg in 24 hours</td>
</tr>
<tr>
<td>Oral dihydrocodeine/codeine</td>
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<tr>
<td>Oral tramadol</td>
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</tbody>
</table>

**Transdermal Preparations**- Transdermal analgesics offer limited advantages and should only be used in patients who have specific problems with oral therapy. They are not suitable for use in acute pain.
- Fentanyl patches are in the Worcestershire Area Prescribing Committee (APC) formulary, but for patients unable to tolerate oral morphine preparations as an alternative to a diamorphine syringe driver.
- Fentanyl ‘25’ patch is equivalent to 90mg morphine salt daily. Manufacturer recommends use only in opioid tolerant patients due to the risk of severe respiratory depression.
- The MHRA\(^\text{16}\) issued drug safety advice on the use of fentanyl patches regarding their use and advice to be given when a patch is prescribed. Key points are:
  - Monitor patients using patches for increased side effects if fever is present
  - Avoid exposing patch site to external heat (may increase absorption and adverse effects)
  - Only use in opioid tolerant patients due to the risk of severe respiratory depression.
  - Ensure patients and caregivers are aware of the signs and symptoms of fentanyl overdose – i.e. trouble breathing or shallow breathing, tiredness, extreme sleepiness or sedation, inability to think, walk or talk normally; and feeling faint, dizzy or confused.
References

8. Personal communication with pain consultants and data from Napp.