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## PHARMACOLOGICAL MANAGEMENT OF PAIN IN PRIMARY CARE (2): OPIOIDS

- 👉 **Opioids are effective for the treatment of severe pain, including cancer pain**
- 👉 **As patients vary in their response to opioids, there should be an individualised approach to their use**
- 👉 **The use of opioids combined with non-opioids can reduce the dose of opioids required**
- 👉 **The use of opioids in chronic non-cancer pain is more controversial and should be managed in a specialist setting**

### INTRODUCTION

Pain directly impacts on a substantial proportion of the population, becoming more common with increasing age. A recent survey showed that approximately two thirds of pain sufferers visit their general practitioner because of pain<sup>1</sup>. This, the second of three bulletins on pain, will deal with the use of opioids for the management of non-malignant pain in primary care. The third bulletin will deal with the overall management of cancer pain.

### PRINCIPLES OF PAIN MANAGEMENT

As discussed in the previous bulletin<sup>2</sup>, the World Health Organisation (WHO) devised an analgesic ladder, originally designed for analgesia associated with cancer pain<sup>3</sup>, which can be adapted for the management of all types of pain. Table 1 details the recommended stepwise approach to use of analgesic therapy.

Table 1: Adapted from WHO's pain ladder<sup>4</sup>

#### Step 1: Non-opioid medication

- The use of paracetamol is the drug of choice for mild pain (4g/24 hours). A non-steroidal anti-inflammatory drug (NSAID) can be added or substituted in those with pain that is not relieved by this treatment.
- The decision on which analgesic to use should be based on a risk/benefit analysis for each individual patient.

#### Step 2: Weak opioid +/- non-opioid

- A mild opioid such as codeine, dihydrocodeine or tramadol should be the next step when a non-opioid is insufficient for the patient's pain.
- If the effect of a weak opioid is inadequate, do not change to another weak opioid. Move to Step 3 of the analgesic ladder.

#### Step 3: Strong opioid +/- non-opioid

- The drug of choice for severe pain is morphine. The oral route is the recommended route, and should be used whenever possible. The starting dose is usually 5-10mg 4-hourly. The starting dose should be lower in elderly or frail patients.
- Alternatives to morphine include fentanyl, hydromorphone, methadone and oxycodone.

### PHARMACOLOGY

Opioids are a group of naturally occurring and synthetic substances, whose pharmacologic actions mimic the endogenously produced endorphins. It has been well established that the analgesic effects of opioids arise from their ability to bind to opiate receptors and inhibit directly the ascending transmission of nociceptive information from the spinal cord, and to activate central pain control circuits, which modulate pain<sup>5</sup>. There are 3 types of opiate receptors - mu, delta and kappa; most opioids act at the mu receptors<sup>4</sup>. Almost all opioids in current use are full agonists i.e. increasing doses gives increasing analgesia until the pain is relieved, or adverse effects intervene. There are opioid preparations available for administration by several routes - IV, IM, sublingual, transdermal, rectal, as well as oral. Most opioids are absorbed from the GI tract, but bioavailability is variable, due to first-pass metabolism in the liver. Lipophilic opioids such as codeine or methadone may be absorbed through the skin or buccal mucosa; they are also reported to cross the blood-brain barrier more rapidly, compared with morphine<sup>5</sup>. The shape of the time-effect curve also varies with the route of administration, with parenteral administration giving a more rapid onset of effect of shorter duration, compared with the oral route. Opioids are metabolised in the liver and excreted via the kidneys, therefore compromised hepatic or renal function requires a reduction in dosage. The dose and route of administration to be used depend on the patient's condition and whether rapid onset of pain relief (as in acute severe pain) is needed<sup>6</sup>. For the patient who is not systemically ill a non-parenteral route should be employed wherever possible.

**Morphine remains the standard against which other opioid analgesics are compared<sup>7</sup>.** It is often not possible to achieve equi-analgesic effects with weaker opioids (such as codeine) because of the occurrence of side effects (especially constipation) at higher doses. However, concomitant use of non-opioids (paracetamol or NSAIDs) may reduce the dosage requirement of an opioid, enabling effective use of weaker opioids<sup>6,8</sup>. (See Table 1).

**Side effects and their management.** While opioids are primarily used clinically for their pain-relieving properties, they produce a host of other effects, due to the wide distribution of opiate receptors, both in the brain and in the periphery<sup>5</sup>. This explains the many, usually unwanted, effects that occur with use of opioids.

The most serious side effect is the **risk of respiratory depression**. Opioids cause respiratory depression by acting directly on respiratory centres, and this occurs more rapidly with lipophilic opioids. **Patients with impaired respiratory function, including asthma, are at increased risk of this occurring and should be monitored carefully<sup>9</sup>.** Individual titration and careful monitoring

of the dose will reduce the risk of respiratory depression. Moreover, it has been shown that pain may act as a natural antagonist to this effect<sup>10</sup>. Tolerance to this effect generally occurs with repeated use of opioids<sup>9</sup>. Respiratory failure resulting in death can occur following overdose. Naloxone is a selective opioid antagonist, and is life-saving in those patients with respiratory failure due to opioid overdose. The half-life of naloxone (1 hour) is shorter than most opioids and repeated doses may be required.

Other adverse effects of opioids include:

- **Nausea and vomiting:** 30-60% of patients taking opioids for the first time will experience nausea and/or vomiting. This is due to a direct stimulation of the chemoreceptor trigger zone for emesis within the brain<sup>5</sup>. Treatment with an anti-emetic such as cyclizine may be required, particularly when opioids are used for acute pain<sup>6</sup>. Tolerance usually develops within 5-10 days when they are used in the management of chronic/cancer pain<sup>11</sup>.
- **Constipation:** Opioids act on many sites of the gastrointestinal tract and spinal cord, producing a decrease in peristalsis and intestinal secretions, resulting in constipation<sup>9</sup>. Constipation occurs early in opioid treatment, especially with some opioids, e.g. codeine<sup>12</sup>. Patients should be managed from initiation of therapy with regular prophylactic laxatives, including a combination of a stimulant and a softening laxative<sup>11</sup>.
- **Drowsiness:** This needs to be carefully monitored in case the patient develops respiratory depression<sup>7</sup>. In those patients with cancer pain, it can occur for the first few days after opioids are introduced and also following dose increases. Patients should be warned of the risks of driving and operating machinery. These effects can be increased if other CNS depressant drugs are used<sup>11</sup>.
- **Urinary retention:** Opioids increase smooth-muscle tone, cause bladder spasm and increase sphincter tone, resulting in urinary retention, which occurs more commonly in the elderly<sup>9</sup>.
- **Alteration of Mood:** Patients frequently experience euphoria and tranquility; however dysphoria may also occur<sup>10</sup>. These effects are thought to be due to an opioid effect distinct from the analgesia mechanism of action.
- **Effects on cognition:** These are common when treatment is started, or with dose changes. The cognitive effects of long-term opioids are less clear<sup>13</sup>.
- **Opioid-induced neurotoxicity:** This is a recently recognised syndrome, which occurs in patients receiving high-dose or prolonged opioid administration, and in patients who have decreased renal function or previous borderline cognition. There is wide individual variation in the dose of opioid that causes neurotoxicity. Signs include agitation, visual and auditory hallucinations, nightmares, vivid dreams, confusion and myoclonic jerks. Reducing the dose of opioid, ensuring adequate hydration and treating the confusion with haloperidol orally or subcutaneously should manage treatment of opioid neurotoxicity<sup>11,14</sup>.
- **Drug interactions:** Care should be taken when prescribing opioids in those patients on CNS depressants as they may exhibit an additive depressant effect. Opioids should be avoided in patients on monoamine oxidase inhibitors or within two weeks of their withdrawal due to potential adverse effects on blood pressure<sup>15</sup>. Interactions with other medications can also occur and the individual summaries of product characteristics (SPCs) (available on [www.medicines.ie](http://www.medicines.ie)) should be consulted.
- **Other side effects:** Occasionally, administration of an opioid may trigger release of histamine, resulting in urticaria, vasodilatation (and hypotension) and bronchoconstriction<sup>6,7</sup>. In severe acute pain, these symptoms may be hard to differentiate from the underlying cause of the pain. Dry mouth can be troublesome and patients should be encouraged to use simple measures such as frequent sips of cool drinks, ice cubes etc. Less commonly reported side effects include sweating, pruritus, hallucinations, myoclonus and unsteadiness<sup>11</sup>.

**Tolerance and dependence.** **Tolerance** (i.e. the drug loses its effectiveness over time, requiring increased doses to produce the same response) and **dependence** (changes occur in the homeostatic mechanisms in the body so that discontinuation of the drug results in disturbance in homeostasis = **withdrawal**) are reported to occur with prolonged use of opioids. Animal studies suggest that tolerance develops due to interaction between other neurotransmitters and the opioid pathway, and that dependence is closely related to tolerance. **These are physiological responses noted in all patients and are not predictors of addiction**<sup>5</sup>. Clinically, opioids can be discontinued in dependent patients by gradually tapering off the dose (e.g. reduction by 10-20% every other day until zero) to prevent the occurrence of withdrawal<sup>5</sup>.

## CLINICAL USES OF OPIOIDS

Opioids are particularly useful for the management of moderate to severe pain. Studies suggest that nociceptive pain is especially responsive to opioids<sup>16</sup>. Opioids can be used in the management of severe acute somatic pain or for acute visceral pain such as acute chest or abdominal pain<sup>6</sup>. Opioids may also be used in the management of chronic pain, including neuropathic pain, however there is controversy as to their effectiveness for this indication<sup>17</sup>. Opioids however are not effective in every patient with pain<sup>18</sup>. Individuals vary in their response to opioids and the opioid dosage needs to be modified according to each patient's response. Individuals will also vary in their response to different opioids<sup>19</sup>.

Morphine is the "gold standard" opioid for the management of **acute severe pain**; it may need to be administered parenterally if the patient is unable to take it by the oral route<sup>6</sup>. For opioid-naïve patients with acute pain, frequent monitoring of pain relief, sedation, respiratory rate, and blood pressure are required. Dose titration involves incremental increases until a favourable balance between analgesia and side effects is found. All opioids have the potential for side-effects as discussed and there is no single ideal drug. Respiratory depression is always a major concern<sup>6</sup>.

**Opioids are the cornerstone in the management of cancer pain in patients**<sup>20</sup>, where the aim is to relieve pain and improve the patient's quality of life<sup>20</sup> - this will be discussed in more detail in the next bulletin.

**The use of opioids in chronic non-cancer pain is more controversial, with concerns regarding the effectiveness and side-effects in this group of patients.** It has also been reported that there is a lack of good quality research regarding the benefits and risk of opioids for persistent non-cancer pain<sup>21</sup>. A recent study suggests that opioids provided pain relief for both neuropathic pain, including postherpetic neuralgia and diabetic neuropathy, and for musculoskeletal pain, including osteoarthritis<sup>18</sup>. They should only be considered after the use of other established therapies have been tried, and ideally after specialist assessment of any underlying cause of the pain. A treatment plan should be developed between the patient and health care professionals before starting opioid therapy in this group of patients. It is advised that where possible the use of opioids on a long-term basis should be monitored by pain specialists<sup>7,21</sup>.

**There is no strong evidence, which supports the superiority of one opioid over another**<sup>22</sup>. Morphine is the most commonly prescribed opioid in use for chronic/cancer pain. There is increasing clinical experience in the use of alternative opioids, particularly when morphine is ineffective or is causing too many side-effects<sup>23</sup>. Opioid switching may be required in order to select an opioid with the most favourable balance between analgesia and side-effects<sup>18</sup>. Specialist advice should be sought before switching strong opioids as the dose ratios may vary<sup>21</sup>. Injectable opioids are rarely appropriate in the management of persistent non-cancer pain<sup>13</sup>. Table 2 outlines practical advice for prescribing opioids.

**Table 2: Practical Advice for prescribing opioids** <sup>11,19</sup>

- Before starting a patient on an opioid particularly for chronic/cancer pain, explain to the patient and their family the need for the opioids, the expected result and the commonly experienced side-effects.
- The oral route is the route of choice, especially for chronic pain.
- Patients vary in their response to various opioids: individual titration is needed.
- Regular stimulant and stool-softening drugs should be co-prescribed for all patients.
- Nausea and vomiting often resolve within days of commencing treatment.
- Initiate morphine treatment using normal release preparations, start with 5-10 mg every 4 hours. This may need to be reduced, particularly in those patients with renal impairment where accumulation of morphine metabolites can occur.
- Once the patient has adequate pain control on the normal release preparation, consideration should be given to converting to the same total daily dose of controlled release morphine. This can be commenced at the time that the next normal release formulation was due.
- Specialist advice should be sought for chronic opioid use, or if parenteral administration is considered necessary.
- Sustained release preparations of opioids should be swallowed whole and not broken, chewed or crushed as this can lead to a rapid release and absorption of a potentially fatal dose.
- The underlying cause of the pain should be sought and treated if possible.

## INDIVIDUAL OPIOIDS

Opioids have traditionally been classified as weak or strong, although this division is thought by some to be artificial. The weak opioids include codeine, dihydrocodeine, meptazinol and tramadol (tramadol may behave as a weak or strong opioid depending on the dose used). The strong opioids include morphine, oxycodone, hydromorphone, pethidine, fentanyl, buprenorphine, methadone and tramadol <sup>21</sup>. **The initial starting dose depends on whether the patient is opioid naive, the age of the patient, presence of renal impairment, the patient's previous analgesic requirement and the severity of the pain.** Full reference must always be made to the SPC.

Table 3 outlines the most commonly prescribed opioids in primary care in Ireland based on GMS data from December 2005. Table 4 outlines other opioid preparations currently licensed in Ireland.

**Table 3 : Commonly prescribed opioids in primary care in Ireland** \* <sup>7,11</sup>

Drug	Analgesia Indications	Dose (oral)
Morphine # • Normal release • Controlled release • SC/IM/IV also available - dose will need to be reduced	Severe pain	5-10 mg every 4 hours (normal release) - the dose needs to be adjusted individually dependent on the patients analgesia history and response
Codeine #	Mild to moderate pain	30 - 60 mg every 4-6 hours (max 240mg daily)
Tramadol #	Severe pain	50-100mg 4-6 hours (total daily dose 400mg)
Dihydrocodeine # • Normal release • Controlled release	Moderate to severe pain	30 mg every 4-6 hours 60mg every 12 hours
Oxycodone # • Normal release • Controlled release	Severe opioid responsive chronic pain conditions	Initial dose 5mg 4-6 hourly

\* Based on GMS data for December 2005

# Please refer to SPC for full details of these medications prior to commencing

**Morphine** - remains the most valuable opioid analgesic for severe acute pain, and is regarded as the standard against which other opioid analgesics are compared <sup>7</sup>. Morphine affects the initial perception of pain and the emotional response to it. Patients with severe pain rarely experience euphoric sensations from morphine but may become drowsy and relaxed, partly because of decreased distress. Morphine is recommended as a standard by the WHO because of its wide availability and low cost <sup>24</sup>. In opioid naive patients with acute pain, it provides analgesia at a dose that does not severely alter consciousness. Where possible the oral route should be used.

**Codeine** - is a weak opioid, which binds to mu receptors. It is metabolised by the liver and 10% is converted to morphine. Its analgesic effect is due to its conversion to morphine. It is effective for the relief of mild to moderate pain, however constipation limits its long-term use. Large doses of codeine cause excitement, and dependence can also occur, but less so than that seen with morphine <sup>5</sup>. It is commonly combined with non-opioids.

**Tramadol** - is a synthetic codeine analogue with mixed mu receptor agonist activity. Its analgesic effect is also produced by inhibition of the reuptake of noradrenaline and by promoting the release of serotonin. It is licensed for severe pain in adults. The side effects are similar to those seen with the other opioids. At equivalent doses it has been reported to cause less respiratory depression than morphine and less constipation than codeine <sup>25</sup>. Seizures have been reported in patients taking tramadol, and it may exacerbate seizures in those patients with pre-disposing factors. Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances <sup>12</sup>.

**Dihydrocodeine** - is a semisynthetic opioid with a potency between codeine and morphine <sup>26</sup>. It may be used to relieve moderate acute and chronic pain. It can cause histamine release and should not be used in patients with hyper-reactive airways <sup>27</sup>.

**Oxycodone** is a powerful mu-receptor agonist and is as effective as morphine in achieving pain control in patients with cancer<sup>28</sup>. It can be considered in patients unable to tolerate morphine. Oral oxycodone is twice as potent as oral morphine. It is available in normal release and controlled release formulations<sup>11,29</sup>.

**Table 4: Other Opioids licensed in Ireland<sup>7</sup>**

Drug	Analgesia Indications	Dose
Fentanyl # • Transdermal patch • Lozenge	Severe opioid responsive pain conditions Breakthrough pain	Refer to SPC - transdermal Initial dose 200 mcg - buccal (Refer to SPC)
Buprenorphine # • Transdermal patch	Severe opioid responsive chronic pain conditions	Refer to SPC - transdermal
Hydromorphone # * • Normal release • Controlled release	Severe opioid responsive pain conditions	Initial dose 1.3mg 4 hourly (oral)
Pethidine # *	Acute pain (not suitable for severe continuing pain)	50-150mg 4 hourly (oral) 25-100mg repeated after 4 hours (SC/IM)
Meptazinol # *	Short term treatment of moderate pain	200mg 3-6 hourly (oral)
Methadone # *	Severe opioid responsive pain conditions - as a substitute for morphine	Refer to SPC

# Please refer to SPC for full details of these medications prior to commencing

\* Minimal/no usage based on GMS figures for December 2005

**Fentanyl** is a powerful mu-receptor agonist, which is **100 times more potent than morphine**<sup>5</sup>. It is used for acute postoperative and chronic pain management. It is highly lipid soluble and rapidly crosses the blood-brain barrier. Respiratory depression is similar to that observed with other mu receptor agonists, but the onset is more rapid. There is a patch delivery system formulation of fentanyl, which is indicated in the management of chronic intractable pain in patients requiring opioid analgesia. It can be used in patients as an alternative to morphine in those with stable pain<sup>11</sup>. **It is recommended that advice from a pain relief specialist should be sought before prescribing or transferring to transdermal fentanyl**<sup>11,30</sup>. There is also a formulation available which permits rapid absorption of fentanyl through the buccal mucosa - this is used in cancer patients on maintenance opioid therapy who require management of breakthrough pain.

**Buprenorphine** - has both opioid agonist and antagonist properties (a partial mu receptor agonist and a kappa receptor antagonist). It is **25-50 times more potent than morphine**<sup>5</sup> and has a longer duration of action. Its effects are only partially reversed by naloxone due to its high receptor affinity. It may antagonise the analgesic effects of other opioids and can precipitate withdrawal symptoms. The transdermal route is licensed for severe opioid responsive pain. Buprenorphine is metabolised to norbuprenorphine by CYP3A4, and care should be taken in those patients who are also taking known inhibitors of CYP3A4 (e.g.azole antifungals and macrolide antibiotics), as well as drugs which induce CYP3A4 activity (e.g. anticonvulsants and rifampicin)<sup>5</sup>.

**Hydromorphone** is a powerful mu-receptor agonist and may be used as an alternative to morphine particularly in those patients where morphine is causing cognitive impairment or is poorly tolerated<sup>11</sup>. **It is approximately 7.5 times more potent than oral morphine**<sup>5</sup>, and is available in normal release and controlled release formulations.

**Pethidine** - may be used for acute moderate and severe pain. It was commonly used in the past, however it is less commonly used now<sup>9</sup>. It produces prompt, but short-lasting analgesia. It is metabolised to norpethidine which has pharmacological activity and can accumulate in renal impairment. Overdose or use in patients with renal dysfunction (e.g. the elderly) can cause central nervous system stimulation (myoclonus, convulsions) due to norpethidine<sup>27</sup>. Seizures have also been observed in patients with normal renal function<sup>9</sup>.

**Methadone** is a synthetic drug structurally and pharmacologically similar to morphine, which acts mainly at the mu receptor. Methadone has a long duration of action and its analgesic effects may last as long as 24 hours. It can be used as a substitute for morphine in the management of severe chronic pain such as cancer, in the occasional patient who experiences excitation (or exacerbation of pain) with morphine. However advice from a specialist should be sought concerning dose conversion and titration when prescribing methadone in cancer pain<sup>11</sup>. Care is required when escalating the dose because of the prolonged half-life and its tendency to accumulate over a period of several days with repeated dosing.

**Meptazinol** - demonstrates mixed agonist and antagonist activity at opioid receptors. It also appears to display central cholinergic activity, which contributes to its analgesic effect. It is useful for the short-term treatment of moderate pain.<sup>31</sup>

## SUMMARY

Opioids are effective analgesics<sup>24</sup> and are essential tools in pain management. They are widely used for acute severe pain and cancer pain. They are also increasingly used in chronic severe non-cancer pain, which requires specialist supervision. Opioids have a well-described toxicity profile, the most important of which is the risk of respiratory depression. Patients vary in their response to various opioids, and an individualised approach is required for all patients prescribed opioids. There are many opioids available, however morphine is the gold standard and is the most commonly prescribed opioid. When switching opioids it is essential to get specialist advice as there are variations in the dose ratios. It is also important to appreciate that not all pain responds to opioids.

*References available on request.* Date prepared: May 2006

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet or summary of product characteristics (SPC), also available on [www.medicines.ie](http://www.medicines.ie) for specific information on drug use.

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