Opioid use in palliative care: New developments, clinical guidelines, and common concerns

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The correct use of opioids is the mainstay of effective management of pain in palliative care. The authors describe the available analgesic options, review recent evidence and guidelines, and explore common concerns for patients and doctors associated with their use.

Introduction

In palliative care, pain can be alleviated or modified in most patients. Adequate pain relief is essential to ensure quality of life and the ability to carry out the activities of daily living. A thorough pain assessment leads to more effective management; many patients are affected by pain at more than one site and often from multiple aetiologies, consequently each pain should be evaluated separately.

To establish the cause of the pain it is essential to take a careful history, noting:

• the site of pain and any radiation

• the type and severity of pain

• when the pain started and any subsequent changes

• exacerbating and alleviating factors.

Physical examination often confirms the diagnosis, and imaging may be necessary.

It is easy to focus exclusively on the physical issues causing pain – psychological, social and spiritual factors can also influence pain.

Treatment with analgesics – guidelines and overview

The use of opioids has had a major impact on the management of pain in patients with advanced disease, yet pain can still be managed poorly. Unsubstantiated fears about the use of strong opioids, ignorance of the way in which opioids should be prescribed and an inability to recognise pain that is opioid resistant contribute to this problem. A recent Cochrane review notes that 19 out of 20 people who are given opioids for moderate to severe pain, and who can tolerate opioids, will have their pain reduced within 14 days. However, the quality of evidence is low, many trials are small with a high risk of bias. There is also inconsistent reporting of adverse events. Some studies are sponsored by pharmaceutical companies and only demonstrate non-inferiority, usually to morphine [1].

The World Health Organization (WHO) describes a three-step ladder for the prescribing of analgesics (see Figure 2). This is a framework rather than a rigid protocol, allowing considerable flexibility in the choice of drugs. It is one component of a comprehensive strategy for managing pain. There is limited research evidence regarding utility of the WHO pain ladder. [1] The principles are that analgesics should be prescribed

regularly and that inadequate pain control at one step of the ladder normally requires moving to the next step rather than using an alternative drug of similar potency.

The 2012 European Association of Palliative Care (EAPC) guidelines state that when paracetamol or NSAIDs are insufficient, the addition of any step 2 weak opioid may achieve good pain relief or that a low-dose step 3 opioid (e.g. 30mg morphine or 20mg oxycodone in 24 hours) may be used instead. [2]

The Palliative Care Formulary (PCF6) recommends that 'because cancer pain typically has an inflammatory component, it is generally appropriate to optimize pain control with a NSAID and an opioid before introducing adjuvant [co-]analgesics'. Co-analgesics can, however, be used at any step for non-inflammatory pain e.g. to treat chemotherapy-induced neuropathic pain or muscle spasms. [3]

When treatment is initiated there should be a clear understanding regarding doses and preparations of opioid to be used. Limits should be defined regarding the amount of breakthrough medication. There needs to be slow titration and a regular assessment of efficacy and side effects. It is important to address any psychological influences on the patient's experience of pain. [4]

Oral morphine is the mainstay Step 3 opioid for the treatment of pain in advanced disease and is NICE-recommended as first line. [5]. It is safe, predictable and reliable when prescribed effectively, and this can be achieved by adhering to the following;

• morphine should be given orally where possible

• it should be prescribed regularly to pre-empt pain (use on an as required basis only may result in worse pain control and higher dosages overall)

• extra doses for episodic pain (breakthrough, incident and/or end-of-dose failure) should be prescribed

• should be given an adequate trial at an adequate dosage

• side-effects should be anticipated so that they can be treated

Opioids - choice of opioid

STEP 2 OPIOIDS - Codeine and Tramadol

The step 2 opioid, codeine, is recommended for mild to moderate cancer pain [2] although there is limited evidence for its effectiveness in cancer pain. The maximum dose of codeine of 240 mg in 24 hours is equivalent to morphine sulphate 24 mg, consequently many palliative care practitioners find its use limited [1]. Tramadol, a synthetic centrally-acting analgesic with both opioid and non-opioid properties, is widely used for non-cancer pain.

The PCF6 notes there is no pharmacological need for step 2 / weak opioids in the WHO analgesic ladder. [9] [10] It is also suggested by some specialists that step 2 should be omitted from the WHO analgesic

ladder. [1] However, in some countries, step 2 opioids have a role as oral morphine and other opioids may have limited or no availability. [3]

Morphine Sulphate – the 'Gold standard' Step 3 opioid

Morphine sulphate is regarded as the 'gold standard' and first-choice step 3 analgesic due to familiarity, availability and cost, rather than proven superiority. Morphine is available as an immediate-release preparation (up to four-hourly; tablets and liquid given regularly) with immediate release morphine as required up to hourly and modified-release preparation (once- and twice-daily) available as capsules, tablets and dissolvable granules. Diamorphine has previously been a first-choice subcutaneous opioid however subcutaneous morphine is now used more commonly, partly because of more limited availability of diamorphine.

The 2012 EAPC guidelines state that there is no significant difference between morphine, oxycodone, and hydromorphone in terms of analgesic superiority and recommend that any of these drugs could be used first line for moderate to severe cancer pain. [2] NICE, however, does not recommend oxycodone first-line because of cost. [5]

Oxycodone

Oxycodone is available in immediate-release (including liquid) and modified-release preparations. Orally it is about 1.5-2 times more potent than morphine. Oxycodone is thought to have fewer clinically important active metabolites and can be used in patients who cannot tolerate morphine [6]. Oxycodone is used in some centres as an alternative to morphine in mild to moderate renal impairment where dose adjustment may be indicated, e.g. smaller doses of immediate-release preparations are easier to titrate and control and may be preferred to modified-release preparations [7]. Many centres favour fentanyl as analgesia for patients with severe renal impairment (eGFR <30) [8].

Transdermal Fentanyl

Fentanyl is available as a transdermal patch changed every 72 hours. This is particularly useful in patients who cannot swallow, have GI absorption problems or who are poorly compliant with medication. It is metabolised to inactive metabolites by the liver and is a useful drug in patients with renal impairment.

Buprenorphine

Buprenorphine is a weak opioid agonist and a partial antagonist to morphine. At lower doses it can be considered a step 2 opioid and at higher doses acts as a step 3 opioid. It is normally used as a transdermal patch but also comes as a sublingual preparation. There are different buprenorphine patches with different dosing schedules. The patch requires changing once per week and can be considered in chronic non-malignant pain.

Transdermal Fentanyl and Buprenorphine – additional information

Transdermal fentanyl and buprenorphine have long half-lives and take days to reach steady state so cannot be titrated quickly. The EAPC guidelines note that, given patient preference and fewer side-effects of constipation, transdermal fentanyl and buprenorphine may be preferred initial step 3 opioids for some patients [2].

NICE guidance states that transdermal patch preparations should not routinely be offered as first-line treatment to patients for whom oral opioids are suitable; if oral opioids are not suitable and analgesic requirements are stable, transdermal patches 'with the lowest acquisition cost' should be considered [5]. In practice, many clinicians are reluctant to use transdermal fentanyl patch preparations in opioid-naïve patients, especially as even the lowest dose fentanyl 12 micrograms / hour patches are approximately equivalent to 45mg / 24 hours of oral morphine.

Switching between transdermal preparations and other opioids can be difficult – conversion tables are only a guide – as the conversion equivalents are wide, for example, a fentanyl 25 micrograms / hour patch approximates to 60-90mg oral morphine.

Buccal, sublingual, and nasal opioids

Fentanyl is also available as a lozenge, sublingual tablets and a nasal spray for the management of episodic pain in patients already receiving maintenance opioid therapy for pain. These preparations are intended for oral transmucosal, sublingual or intranasal use. Patients require intact oral mucosae and sufficient saliva. These preparations have a rapid onset of action, which is advantageous for incident pain, such as during washing or dressing changes. However, they have a shorter duration of effect and they need individual titration. They are also expensive.

Hydromorphone

Hydromorphone is similar to morphine but 7.5 times more potent. It is available as a high-concentrate injection so a high dose can be delivered in a small volume, however this is not listed in the BNF and is available only by special order on a named patient basis. In countries where diamorphine is not available, hydromorphone can be used in syringe drivers, especially when high doses are required. [11]

Methadone

Methadone is a long-acting opioid which may have a role in neuropathic pain due to its purported action as an NMDA antagonist. [12] It has around an 18-hour half-life but this is unpredictable and it accumulates in tissues with repeated use. Side effects such as sedation may appear only when significant amounts of the drug have accumulated. Following dosage adjustment, it can take some time for the drug to be cleared. It should, therefore, only be used by experienced practitioners. In practice, it is more likely to be used for moderate to severe cancer pain when other step 3 opioids are inadequate [2].

Tapentadol

Tapentadol is a centrally-acting step 3 opioid which has both mu-agonist and noradrenaline re-uptake inhibitor activity. It is around 3 times less potent than morphine. There are few studies comparing it with less expensive strong opioids; it is not recommended for use in acute pain. It may be useful for patients with chronic and non-malignant pain who do not respond to morphine [13].

Alfentanil

Alfentanil is an injectable opioid that is commonly used in severe renal impairment and in syringe pumps. Caution is needed in hepatic failure, as it can accumulate. Care is needed with conversions; it is 30 times more potent than oral morphine. As there is no oral formulation available and SC alfentanil has a short duration of action, immediate-release oxycodone (PO or SC) may be used for breakthrough pain.

Prescribing Opioids in Palliative Care

Opioids in acute pain in patients with advanced, progressive conditions

Acute pain requires rapid action. Established practice was that rapid titration of dosage against pain was best achieved with four-hourly immediate-release opioid preparations, followed by a switch to a modified-release preparation when pain stabilised.

Where clinicians are confident in using modified-release preparations, they too can be used as first line agents, particularly when opioids are being initiated in the community. The EAPC advises that both immediate-release and modified-release preparations can be used for dose titration. [2] NICE guidance emphasizes patient empowerment and informed choice and suggests that patient preference is important [5] [14]. Similarly, Cochrane concludes 'it is possible to titrate with oral morphine of any formulation'. [1]

Immediate- and modified-release preparations can both be used to manage 'background pain'. They should be supplemented with immediate-release opioids as rescue/breakthrough analgesics for episodic pain which 'breaks through' the background analgesia or when there is end of dose failure. The rescue or breakthrough dose is calculated as one-sixth of the modified-release, or background dose. Frequent daily use of breakthrough analgesics usually implies that the regular dosage is inadequately controlling pain and consequently the regular dose should be increased.

It is important to distinguish breakthrough pain from incident pain. Analgesics for incident pain should be prescribed for episodic pain that is precipitated by painful 'incidents', e.g. when washing or during dressing changes. Unlike analgesics for breakthrough pain, this does not imply that the background pain is not being controlled and the regular dosage of opioid should not necessarily be increased. Oral transmucosal or intranasal preparations of fentanyl can be useful for incident pain . NICE emphasizes that these fast-acting fentanyl preparations are not first-line for breakthrough analgesia [5] and cost may need to be considered [14]. The PCF6 notes that oral morphine performs well in studies comparing it with short-acting preparations of fentanyl. [15]

Increases in regular dosage can be made by calculating the amount of breakthrough medication used in the previous 24 hours and incorporating it into the regular dosage for acute pain this step should be repeated until optimal analgesia is achieved).

Opioids in chronic cancer pain

Ideally, the steps outlined for acute pain should be followed. For some patients, especially in an outpatient setting, it may be possible and more practical to titrate with modified-release preparations. Immediate release doses for breakthrough pain should also be prescribed.

Opioids used in palliative care for non-cancer pain

This can be a controversial issue. Opioids may be appropriate for patients with advanced, progressive non-malignant disease with short prognoses. It is acknowledged that a proportion of people with long-term pain will benefit from opioids. However, there is little evidence that opioids are effective in treating long-term / chronic pain i.e. no data to show that opioids improve key outcomes regarding pain management, including level of functioning, mood and quality of life. [16] Given this lack of evidence for positive effects, the possibility of long-term harm is important. Opioids should be discontinued if not effective, even if no other treatment is available. [4]

[4]Opioid switch/rotation

Opioid switching or opioid rotation refers to the practice of substituting one step 3 opioid for another. This is common practice when analgesia is inadequate and / or troubling side-effects outweigh benefits. A Cochrane review could not identify any randomised controlled trials to support this practice [12], but evidence from other studies enabled the EAPC to make a weak recommendation for this practice. [2] ()

It is believed that drug tolerance can develop in long-term use in some patients, diminishing opioid effect. Tolerance can also cause problems when assessing relative potency of different opioids. Caution is therefore advised when switching opioids – the new opioid may be more potent than anticipated. Dose reduction is therefore recommended. Regular follow-up is important in titrating doses accordingly.

Parenteral opioid administration

Some patients are unable to tolerate oral morphine due to dysphagia, nausea and vomiting, or unresponsiveness towards the end of life. Injectable opioids such as subcutaneous morphine, diamorphine, oxycodone, fentanyl or alfentanil can be used instead. When converting patients from oral to parenteral opioid, refer to the BNF or the PCF, and consider specialist advice.

Subcutaneous injection is the preferred route for most patients because it is less invasive than intravenous administration. If the patient has become unable to take a modified release preparation or requires regular injections a subcutaneous infusion pump should be used (see Figure 1 and Table 1). As the PCF6 emphasizes, subcutaneous infusion is **not** equivalent to a **'**step 4' on the analgesic ladder [18]. NICE recommends 'subcutaneous opioids with the lowest acquisition cost for patients in whom oral opioids

are not suitable and analgesic requirements are unstable'. [5] The choice of subcutaneous opioid used should take into account patient's previous opioid preparations and doses.

Other medications can be mixed with the subcutaneous opioid as needed. For symptom management at end of life these are commonly antiemetics, e.g. cyclizine, haloperidol, or low-dose levomepromazine; sedatives e.g. midazolam and/or levomepromazine; and anticholinergics to reduce secretions e.g. hyoscine butylbromide, hyoscine hydrobromide or glycopyrronium. Note that the prescription needs to state which drugs are to be 'mixed'.

The EAPC guidelines suggest that IV infusion should be considered when rapid pain control is necessary and when SC infusion is contraindicated (due to peripheral oedema, coagulopathies, or the need for high volumes of medication). [2] In clinical practice this is rarely necessary.

For the compatibility of drugs to be mixed within a subcutaneous infusion pump see tables in the PCF6 and online.

Opioid side-effects

Many patients will experience side-effects from opioids. Around 1 in 10 people require an alternative analgesic agent as a result [1]. It is important to inform patients about potential side effects and their management. Common side effects are constipation, nausea and drowsiness.

Constipation

Constipation occurs in approximately 95 per cent of patients using opioids and it is important to discuss that it can be managed with good adherence to laxatives. [14] Prophylactic regular laxatives, such as a macrogol or senna, can be prescribed. There is no evidence for recommending one laxative over another [2]. To encourage compliance, check what is acceptable to the patient and what s/he has tried before. Some patients may require a combination of laxatives with different modes of action. NICE stresses that laxatives should be optimised before an opioid switch is considered. [5] [14]When oral laxatives at maximum tolerated doses are not effective, peripherally selective opioid antagonists (oral naloxegol or subcutaneous methylnaltrexone) may be considered. These decrease the constipating effect of opioids by acting selectively on the bowel without affecting the central analgesic action. [2] NICE notes that these mu-opioid receptor antagonists are safe and effective but that there is limited evidence for their efficacy in a palliative care setting, especially when compared with optimized laxative therapy. [14]

Nausea and vomiting

Nausea and vomiting occur in approximately 20 per cent of patients. This side effect is usually self-limiting within days. [5] It is not necessary to prescribe regular anti-emetics prophylactically but useful to prescribe on an 'as required' basis. Suitable anti-emetics for opioid-induced nausea include haloperidol (1.5-3mg once daily), cyclizine (50mg three times daily) or metoclopramide (10mg three times daily).

Drowsiness

NICE recommends warning patients that they may experience mild drowsiness or impairment of concentration on starting opioids, but that this is usually self- limiting. The PCF gives guidance on drugs and fitness to drive, and an example of a patient advice leaflet. There is no evidence of increased risk with chronic use opioids once on a stable dose for more than one week but breakthrough doses may cause transient impairment [17]. If CNS side-effects persist, clinicians can consider a dose reduction or an opioid switch. [5] EAPC guidelines make a weak recommendation for using methylphenidate as a psychostimulant in such cases. This is, however, used rarely in clinical practice. Dose reduction or opioid switching may need to be considered if patients develop delirium or troublesome hallucinations. [2]

Fears about use of strong opioids

Practitioners and the public may have concerns about the use of opioids. Clear communication with patients is important to allay anxiety, and written as well as verbal information may be helpful. It is best to anticipate these concerns and discuss fears openly when initiating opioids.

Fear of addiction

Addiction characterized by psychological dependence and craving rarely occurs in patients who do not have a history of misuse of drugs. Where pain is being controlled by other means, for example a bone metastasis treated with radiotherapy, withdrawal of the opioid should be gradual as chemical dependence does occur.

Fear of tolerance

Tolerance is the progressive increase of dosage required to achieve the same effect. The evidence for tolerance to the analgesic effect of morphine is limited. This is reinforced by experience in long-term cancer pain management in patients treated with opioids; the rate of rise in dosage is slow and there may be long periods without dosage increase. Increasing dosages of morphine in cancer patients often reflect disease progression.

Fear of respiratory depression

In cancer patients where the opioid dosage is titrated against the patient's pain, clinically significant respiratory depression rarely occurs. Of note, pain appears to be a physiological antagonist of the depressant effects of opioids on respiration. Respiratory depression can and does occur if the underlying cause of the pain is suddenly removed and the opioid dosage is not adjusted accordingly, for example following a nerve block. When other approaches, such as chemotherapy or radiotherapy, are used to provide analgesia, opioids may need to be gradually titrated down to compensate.

Fear that opioids hasten death

Morphine is often not started until the patient is extremely unwell, hence the misconception that morphine hastens death. Early prescribing of morphine may prolong life and certainly improves quality of life by enabling the patient to sleep, eat, and increase physical activity. Patients and families may misinterpret a prescription for morphine as being an unspoken signal that death is imminent. They may also

mistakenly associate use of a syringe pump with causing or hastening death. It is therefore important to explain the reasons for prescribing opioids, and the value of using a subcutaneous infusion. [18]

Unfortunately, these misconceptions are fuelled by reports in the press. This was recently highlighted following the Gosport War Memorial Hospital enquiry. Opioids were prescribed incorrectly in multiple cases, almost certainly precipitating deaths. [19] Opioids were used without clinical indication; there was anticipatory prescribing with a wide dose ranges; inappropriately high doses were used; and continuous subcutaneous infusions via syringe pumps were used inappropriately. [20] This was an extreme example of bad practice and patients and families should be reassured that "research has shown that opioid medication does not shorten lives, and may even prolong lives due to good pain relief." [21]

Failure of opioid therapy and opioid-resistant pain

There are many reasons why opioids fail which include:

- inadequate dosage
- too long an interval between doses
- wrong route of administration (e.g. oral route in a patient who is vomiting)
- compliance issues
- regimen too complicated

However, probably the most common reason for failure is the use of an opioid when the pain is opioid resistant or only partially sensitive. In these circumstances co-analgesics should be considered.

Use of co-analgesics

The likelihood of opioid insensitivity should be assessed. Table 2 lists common opioid-resistant pain aetiologies and suggests management strategies.

In situations where opioids do not result in adequate pain control, co-analgesics can be considered. In some instances, opioids have no role at all. The EAPC guidelines make a strong recommendation that amitriptyline or gabapentin should be considered for patients with neuropathic pain once opioids have been optimised. It is especially important that extra care is taken with titration when both drugs are used in combination, otherwise the combination may cause increased CNS adverse events. [2]

Conclusion

This article has focused on the management of pain with opioids. However, pain is invariably a complex symptom. Patients who are facing life-threatening or life-limiting illness are likely to have emotional, social and spiritual factors influencing their symptoms. A comprehensive history is key. A holistic management strategy that addresses all the needs of the patient is required to achieve good pain control; this may include a wide range of non-pharmacological interventions.

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Images

Figure 1 – keep from original

Figure 2 – latest version of WHO analgesic ladder. We should put in latest version as at http://www.who.int/cancer/palliative/painladder/en/

Table 1 – keep from original but some changes and reference [21]:

- Dysphagia (neuromuscular weakness / tumour obstruction)
- Persistent nausea and vomiting
- Drowsiness / coma
- Absorption problems in GI tract (rare)
- Bowel obstruction
- *With caution* when pain responds better to injections than to oral opioids / patient preference

Table 2 – keep from original