

DRUG UPDATE

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OPIOID ANALGESIA IN CANCER

Oral morphine is still recommended as the first-line strong opioid for use in the control of cancer-associated pain despite the introduction of non-morphine opioid analgesics and novel formulations. There is no consistent evidence to support the use of non-morphine opioid analgesics for first-line opioid therapy. There is only limited evidence for a benefit of switching between opioid drugs in patients experiencing adverse effects, tolerance or inadequate analgesia, although this may be the only practical option in some situations.

What are opioid analgesics?

The World Health Organisation (WHO) pain control algorithm recommends a step-wise approach to the introduction of analgesics.¹ This principle continues to be the basis for the development of current pain control guidelines in patients with cancer.² Opioid analgesics considered in this review include only those in step 3 of the WHO guidelines such as morphine, buprenorphine, hydromorphone, fentanyl, and oxycodone.^{1,3} These drugs are available in a wide range of formulations including modified-release (MR) preparations, transdermal (TD) patches, buccal tablets, and granules for suspension.³ Parenteral administration is not considered in this review.

Which opioid should be used to control cancer pain?

Oral morphine continues to be the most widely used strong opioid analgesic and is the recommended opioid in the European Association of Palliative Care guidelines and at step 3 of the WHO pain ladder when strong opioid analgesics are introduced for the relief of moderate to severe pain.^{1,2} Titration of morphine doses to individual patient needs is relatively straightforward^{2,3} and it is the most cost-effective option compared with alternative strong opioids.

Few robust randomised clinical trials have compared morphine MR with other strong opioids for the control of cancer pain.⁴ There is no compelling evidence to support the use of a non-morphine opioid for first-line analgesia in cancer² therefore any decision to use an alternative opioid should principally be determined by adverse effects experienced with morphine.

Transdermal fentanyl

Compared with morphine, TD fentanyl is a costly option yet it accounted for over one fifth of primary care prescriptions for strong opioid analgesics in England in the financial year 2007/08.⁵ A 2007 systematic review of morphine included three studies that compared morphine MR with TD fentanyl in cancer pain.⁴ No differences in efficacy were found although other differences were observed: more patients required rescue medication in the fentanyl group and the fentanyl dose required titration upwards more commonly. Fentanyl did however appear less sedating than morphine both during the day and at night, and patients on fentanyl were significantly less constipated.⁴

Factors to consider when using TD fentanyl:

- It usually takes 36 to 48 hours to achieve steady-state plasma concentrations, during which time other analgesic cover will be required.³
- Once a patch has been removed drug elimination occurs slowly with a terminal half life ranging from 22 to 25 hours and significant blood levels persist for at least 24 hours.^{3,6}
- TD fentanyl is therefore inappropriate for unstable pain and dose titration should proceed cautiously.^{3,6}
- Despite a reduced dose frequency of 72 hours vs. a typical 12-hour interval with morphine MR there is no evidence of improved compliance with TD fentanyl in cancer pain.
- Despite an apparent reduction in the incidence of constipation,⁴ individual patient responses are highly variable. It is not often possible to avoid morphine entirely, e.g. for breakthrough analgesia.
- Fatalities and life-threatening adverse effects have been reported with incorrect use of TD fentanyl. Patients should be counselled on correct patch application and dose. The passage of fentanyl through skin is affected by temperature and patients should be advised to avoid excessive heat sources.⁷

Other non-morphine opioids

A meta-analysis of three studies (combined n = 129) compared oxycodone MR with morphine MR in cancer pain.⁸ The pooled results did not identify any significant differences in efficacy or adverse effects with the exception of dry mouth, which was less common with oxycodone (odds ratio, 0.56; 95% confidence interval, 0.38 to 0.83).⁸

A systematic review of hydromorphone for acute and chronic pain included only two studies involving a comparison with morphine MR, both in patients with cancer pain.⁹ No statistically significant differences in any parameter of efficacy or safety were observed in the larger study (n = 89), whereas the smaller study (n = 49) reported higher pain scores, a greater use of rescue analgesia, incidence of diarrhoea, and withdrawal rate with hydromorphone MR.⁹

For twice-weekly TD buprenorphine (Transtec[®]) efficacy has only been demonstrated in placebo-controlled randomised studies.¹⁰ It is not clear how it compares with other opioids and use is not recommended in preference to less costly options. No good evidence exists for use of once-weekly BuTrans[®] patches in cancer pain, with no randomised studies identified.¹¹

Breakthrough pain

Various opioid preparations are available for breakthrough pain in patients on maintenance opioid analgesia. These include oral solutions of morphine and oxycodone, immediate-release morphine tablets, oxycodone or hydromorphone capsules, and fentanyl lozenges.²

Recent additions are buccal (Effentora[®], Cephalon) and sublingual (Abstral[®], Prostrakan) fentanyl tablets.¹² These products have only demonstrated efficacy for breakthrough cancer pain in placebo-controlled trials.^{13,14} In the absence of active-comparator studies they are not recommended in preference to less costly alternatives.

How safe are opioid analgesics?

Adverse effects of opioid drugs include constipation, nausea, vomiting and sedation.^{1,3} The majority of these effects can be managed using adjunctive treatments, e.g. regular

use of laxatives or anti-emetics.^{1,3} A systematic review of oral morphine use in cancer pain reported that although adverse effects were common this was not associated with a high discontinuation rate (4%),⁴ suggesting that adverse effects can be managed adequately in most patients. Renal impairment may affect opioid selection, with the excretion of many opioids and their active metabolites dependent on renal function.³

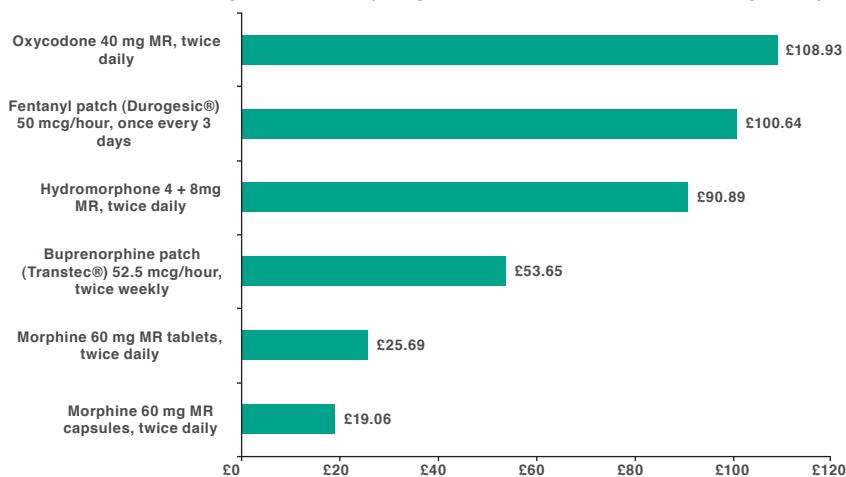
Summary

Pain control is highly subjective and it is essential that treatment is tailored to individual patient needs.¹ Evidence to support switching to an alternative opioid is generally anecdotal or based on observational and uncontrolled studies.¹⁵ However, opioid switching may be the only practicable option for patients who experience inadequate analgesia or intolerable and unmanageable adverse effects. There is insufficient evidence to recommend a specific sequencing of opioids.¹⁵

Opioid drugs are the mainstay of management of moderate to severe cancer-associated pain.¹ Morphine is the recommended first-line treatment option. Other opioid drugs should only be used for patients who cannot tolerate or fail to achieve adequate analgesia with morphine. TD preparations may be useful for the small number of patients without oral access.

How much do they cost?

Cost for 30 days treatment (Drug Tariff and NHS dm+d, February 2009)



N.B. Doses shown are for general comparison and may not equate to therapeutic equivalence.³

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