

Opioid Prescribing Guidelines for Non Cancer Pain

Pain Ladder		
Step 1	<p>Regular Paracetamol (use throughout pain ladder)</p>	
Step 2	<p>1st Line: Consider adding Codeine</p>	
	<p>2nd Line: Switch to Tramadol if codeine is ineffective</p>	
	<p>On specialist recommendation only Buprenorphine Patches ○ Butrans Only for patients with stable persistent pain who have <u>swallowing difficulties</u> or <u>cannot tolerate other options</u>. Not to be used for any other patient group.</p>	
Step 3	<p>1st Line:</p> <ol style="list-style-type: none"> 1. Morphine <ul style="list-style-type: none"> ○ <u>Modified Release:</u> Zomorph Capsules (<i>can be opened if swallowing difficulties</i>) or Morphgesic tablets. ○ <u>Standard Release:</u> Sevredol tablets or Oramorph liquid 	<p>ONLY change from 1st line treatment with Morphine if side effects are intolerable (NB nausea may lessen after a few days) or rarely for a trial of opioid switching. Only use more than one prolonged release opioid on specialist advice. Doses over 120mg-180mg of morphine (or equivalent) daily should be referred to a specialist.</p>
	<p>2nd Line:</p> <ol style="list-style-type: none"> 1. Oxycodone <ul style="list-style-type: none"> ○ Modified Release: Longtec ○ Standard Release: Shortec 2. Fentanyl Patches * <ul style="list-style-type: none"> ○ Fencino 	<p>Oxycodone is the first choice of these treatments, to be used only if patient is intolerant to morphine. Note: Oxycodone is roughly double the potency of morphine</p> <p>*Fentanyl patches would be the next choice IF the patient has stable pain and is unable to take medication orally, making the other options unviable. Please note that fentanyl is a very strong opioid, e.g. 50mcg/hr patch = 120mg morphine daily (see table in fentanyl section for full dose equivalents)</p>
Break Through Pain	<p>Standard release morphine (Sevredol or Oramorph) or standard release oxycodone (shortec)</p>	

Co-codamol or co-dydramol may also be an option.

Key Points

- Morphine should be considered first-line if a strong opioid is indicated.
- The BNF states that oxycodone has an efficacy and side effect profile similar to morphine. Oxycodone may be considered an alternative to morphine in the small proportion of patients who develop intolerable adverse effects.
- Buprenorphine patches are broadly as effective as codeine or tramadol but much more expensive. Reserved for use on specialist advice only for patients who have swallowing difficulties and cannot tolerate other options
- Fentanyl patches should only be used in patients with stable pain who cannot take oral opioids. They should only be use at stage 3 as a secondary option. Fentanyl patches contain a very strong opioid; care must be taken when selecting the correct strength of patch.
- Opioids can be effective in the management of somatic, visceral and neuropathic pain.
- Opioids are prescribed to reduce pain intensity. Data demonstrating sustained analgesic efficacy in the long term are lacking.
- Complete relief of pain is rarely achieved with opioids. The goal of therapy should be to reduce symptoms sufficiently to support improvement in physical, social and emotional functioning.
- 80% of patients taking opioids will experience at least one adverse effect. These should be discussed with the patient before treatment begins.
- Opioids should not be used as first line pain therapy if other evidence-based interventions are available for the condition being treated.
- Drugs with demonstrated efficacy for persistent pain syndromes (e.g. tricyclic antidepressants and antiepileptic drugs for neuropathic pain) should always be prescribed before starting opioids.

The context in which opioids should be prescribed

Improvements in quality of life are unlikely to be achieved unless opioids are prescribed as part of a broader approach to improve patient function.

It is important that patients are adequately informed of the risks and benefits of opioid therapy. It is helpful to supplement discussions regarding treatment with written information. Patients presenting to secondary care services with either acute exacerbations of chronic pain or those with persistent painful symptoms following pain relieving operations are frequently started on opioids to facilitate their discharge from hospital. It is important that these individuals have their pain assessed by an experienced professional and that the pain management plan be in accordance with best practice. If opioids are considered the most appropriate therapy, arrangements must be made to monitor and follow-up treatment appropriately.

There must be clear communication of ongoing therapy and follow up to patient's general practitioner. If opioids have been started in secondary care, there should be clear agreement between the hospital and the patient's GP regarding where and by whom the patient will be assessed and who should provide the repeat prescriptions.

If needed, advice is available from the pain team via the email advice line:

oxonpainadvice@nhs.net

There should be standard communication between hospital and primary care team.

Morphine

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.

Titration of Morphine

- Titrate immediate release morphine (Sevredol or Oramorph) 10 mg every 4 hours (elderly or renal impairment 5mg).
- Titrate (i.e. increase dose) to achieve pain relief every 2-3 days. Increase dose by no more than 50% every 3 days.
- Do not continue to escalate dose if there is no functional gain.
- Keep a log of morphine consumption. (Stop and call doctor if intolerant of side effects.)
- Once pain is stable a longer acting preparation (Zomorph or Morphgesic) equivalent to the total daily dose can be prescribed.
- At this point, ensure that immediate release morphine is now only used for 'breakthrough' pain and not continued at previous levels.

Evidence

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.

A meta-analysis of three studies (combined n = 129) compared oxycodone MR with morphine MR in cancer pain.⁵ 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).⁵

Most studies comparing oxycodone and morphine have been with m/r preparations, and have involved only small numbers of patients. Trials suggest that m/r oxycodone is as effective as m/r morphine at controlling cancer pain, with little difference in overall tolerability.

The doses compared were titrated according to pain control as inter-individual variability in sensitivity to analgesic and adverse effects from different opioid analgesics has been observed. This may explain why some, but not all, studies have reported less nausea and vomiting with oxycodone than with morphine. Some small studies have also found that oxycodone does not cause hallucinations, even in patients who have had hallucinations with morphine. A small study involving 13 cancer patients who had acute delirium while receiving oral or s/c morphine, found that switching to an equivalent dose of oxycodone given by s/c infusion provided effective analgesia, improved mental state and reduced nausea and vomiting. However, this has not been demonstrated in large RCTs, and switching opioids is just one of several options for patients experiencing side effects with morphine.

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 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.

Fentanyl Patches

Fentanyl patches can be used in patients with stable pain who cannot take oral opioids.

They should only be use at stage 3 as a secondary option.

Indications for their use include:

- Patients who have difficulty swallowing or pain on swallowing
- Intolerable undesirable side effects with morphine or oxycodone that cannot be mitigated
- Persistent nausea and vomiting
- Gastrointestinal obstruction
- Tablet phobia or poor compliance with oral medication

Pain not relieved by morphine will not be relieved by fentanyl. If in doubt seek specialist advice before prescribing fentanyl patches.

Do **NOT** use fentanyl patches in patients who need titration of their analgesia for severe uncontrolled pain.

MHRA have received a number of reports from healthcare professionals, patients, and carers of life-threatening adverse reactions and death after fentanyl overdose in people who were using the patches to control malignant and non-malignant pain.

These reports also provide some evidence of inappropriate prescribing of fentanyl patches, including prescribing in unlicensed indications and in opioid-naïve patients.

Fentanyl patches contain a very strong opioid; care must be taken when selecting the correct strength of patch. The dose equivalents below are from page 21 of the BNF 68 (prescribing in palliative care).

72-hour fentanyl patches are <u>approximately</u> equivalent to the following 24 hour doses of oral morphine	
30 mg morphine salt daily	Fentanyl 12mcg/hr patch
60 mg morphine salt daily	Fentanyl 25mcg/hr patch
120 mg morphine salt daily	Fentanyl 50mcg/hr patch
180 mg morphine salt daily	Fentanyl 75mcg/hr patch
240 mg morphine salt daily	Fentanyl 100mcg/hr patch
Note: Conversion ratios vary and these figures are a guide only. Doses have been approximated to allow comparisons with preparations available.	

Buprenorphine patches

Buprenorphine patches at lower doses (BuTrans) are broadly as effective as codeine or tramadol but much more expensive (see appendix 1). Recent studies show small benefits of transdermal buprenorphine over placebo⁷. Another showed patients on buprenorphine patches plus paracetamol used considerably less escape medication than those on codeine plus paracetamol⁸. One study did compare buprenorphine patches with modified release tramadol and found them broadly equivalent in effect⁹. The OCCG pain guideline follows the

review published by Midlands Therapeutic Review Committee on Butrans and Transtec in chronic non cancer pain¹⁰. This guideline takes on board their consideration to have clear criteria on who is suitable for buprenorphine patches and the fact that it should be implemented by a specialist.

Oral analgesics should be used as first line therapy in chronic non-cancer pain, however there is a place for buprenorphine patches for **patients with stable persistent pain who cannot swallow or cannot tolerate other options. It should not be used in any other group.** The patches are unsuitable in acute or unstable pain due to the need for slow titration of doses; it may take up to 72 hours to achieve a stable blood level after a change in dose.

The table below of buprenorphine patch strength equivalents to morphine, is from page 21 of the BNF (prescribing in palliative care).

Buprenorphine patches are <u>approximately</u> equivalent to the following 24-hour doses of oral morphine	
12 mg morphine salt in 24 hours	Buprenorphine 5 micrograms/hr
24 mg morphine salt in 24 hours	Buprenorphine 10 micrograms/hr
48 mg morphine salt in 24 hours	Buprenorphine 20 micrograms/hr
84 mg morphine salt in 24 hours	Buprenorphine 35 micrograms/hr
126 mg morphine salt in 24 hours	Buprenorphine 52.5 micrograms/hr
168 mg morphine salt in 24 hours	Buprenorphine 70 micrograms/hr
Note: Conversion ratios vary and these figures are a guide only. Doses have been approximated to allow comparisons with preparations available.	

Recommendations for Prescribing Opioid Patches

All prescribers must follow this advice when prescribing fentanyl or buprenorphine patches.

- Healthcare professionals, who prescribe and dispense opioid patches, must fully inform patients and caregivers about directions for safe use:
 - follow the prescribed dose
 - follow the correct frequency of patch application
 - ensure that old patches are removed before applying a new one
 - patches must not be cut
 - avoid touching the adhesive side of patches and wash hands after application
 - follow instructions for safe storage and disposal of used or un-needed patches
- This information is given in the SPC for prescribers and in the package insert for patients
- Increased body temperature, exposure of patches to external heat sources, and concomitant use of CYP3A4 inhibitors may lead to potentially dangerous rises in serum buprenorphine/fentanyl levels.
- Concomitant use of other CNS depressants might also potentiate adverse effects from opioids
- Healthcare professionals, particularly those who prescribe and dispense patches, should ensure that patients and caregivers are aware of the signs and symptoms of opioid 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. Patients and caregivers should be advised to seek medical attention immediately if overdose is suspected

- Patients who experience serious adverse events should have the patches removed immediately and should be monitored for up to 24 hours after patch removal

Prices of Opioid Patches

In 2014/15 Oxfordshire CCG spent around £79,500 on buprenorphine patches. They were prescribed 2,547 times. In the same time period approximately £265,000 was spent on fentanyl patches, which were prescribed 8,393 times. The cost of these products is very high and must only be prescribed in accordance to the pain ladder. See Appendix 1 for a breakdown of the costs of opioids in OCCG.

Prices of Buprenorphine and Fentanyl Patches (Aug 2015)

Drug and Strength	Pack Size	Brand	Duration of Release	Price
Buprenorphine 5mcg/hr Patches	4	BuTrans	7 days	£17.60
Buprenorphine 10mcg/hr Patches	4	BuTrans	7 days	£31.55
Buprenorphine 20mcg/hr Patches	4	Butrans	7 days	£57.46
Buprenorphine 35mcg/hr Patches	4	Transtec	4 days	£15.80
Buprenorphine 52.5mcg/hr Patches	4	Transtec	4 days	£23.71
Buprenorphine 72mcg/hr Patches	4	Transtec	4 days	£31.60
Fentanyl 12mcg/hr Patches	5	Fencino	3 days	£8.46
Fentanyl 25mcg/hr Patches	5	Fencino	3 days	£12.10
Fentanyl 50mcg/hr Patches	5	Fencino	3 days	£22.62
Fentanyl 75mcg/hr Patches	5	Fencino	3 days	£31.54
Fentanyl 100mcg/hr Patches	5	Fencino	3 days	£38.88

Formulation

Where possible, modified release opioids administered at regular intervals should be used in the management of patients with persistent pain.

Clinical experience suggests that immediate release preparations are more associated with tolerance and problem drug use.

Use of flexible dosing regimens using immediate release preparations (alone or in combination with modified release preparations) can, in some circumstances, provide effective symptomatic relief and allow an overall reduction in opioid dose.

Use of such regimens may be justified when :

- the pain is intermittent and short-lived;
- pain intensity has significant diurnal variation; and
- background pain is well controlled with modified release preparations but the patient has infrequent, short-lived episodes of increased pain.

The need to use immediate release opioids for persistent pain should prompt specialist review. Injectable opioids should not be used in the management of patients with persistent non-cancer pain except in extraordinary circumstances and then only after consultation with a specialised multidisciplinary pain management service.

Choice of drug depends on clinical circumstance, local experience and expertise.

There are no high quality randomised trials that compare different opioids in the management of persistent non-cancer pain.

Serotonin syndrome can occur as a consequence of excess serotonergic activity at central nervous system and peripheral serotonin receptors. This can produce specific symptoms, including cognitive, autonomic and somatic effects. The symptoms may be barely perceptible but can be more serious. Numerous drugs and drug combinations have been reported to produce serotonin syndrome; for example tramadol should be used with care in patients who are co-prescribed tricyclic antidepressants and selective serotonin reuptake inhibitors.

Drug dose

Pain treatment with opioids should start with a low dose that is titrated upwards according to analgesic effect and side effects. The patient must be warned that it may take some days to determine whether the drug is going to be effective.

The doses of opioid used for chronic non-cancer pain in well conducted controlled trials usually equate to less than 180mg morphine equivalent in 24 hours.

There are no high quality data published that inform prescribers of the safety and efficacy of higher doses.

NB If patients do not achieve useful relief of pain symptoms at doses between 120-180mg morphine equivalent in 24 hours, referral to a specialist in pain medicine is strongly recommended.

Trial of opioid therapy

A closely monitored trial of opioid therapy is recommended before deciding whether a patient is prescribed opioids for long term use.

It is good practice when assessing the patient in pain to elicit a mental health history, including screening questions relating to

- current or past history of depression or anxiety
- current or past history of substance misuse
- family history of substance misuse

The goals of therapy should be agreed before starting opioid treatment and assessed at each review. These goals should be clearly documented.

A formal opioid 'contract' can provide a useful basis for further discussion if medication use becomes poorly controlled or the agreed outcomes of therapy are not achieved. It is helpful to plan for the management of flare-ups in symptoms by means other than an increase in stable opioid dose.

Adverse effects should be documented at every assessment.

The patient may need two or three upwards adjustments of opioid dose (if tolerated) before effectiveness can be evaluated. If, after reasonable dose titration, useful pain relief is not achieved or intolerable side effects occur, the trial of opioid therapy should be considered unsuccessful. If opioid therapy is not to be continued, the dose of opioid should be stopped by gradual decrements.

Long term opioid prescribing

Following successful opioid trial, treatment may be continued until :

- the underlying painful condition resolves;
- the patient receives a definitive pain relieving intervention (e.g. joint replacement);
- the patient no longer derives benefit from opioid treatment (periodic dose tapering or cessation of therapy is recommended to confirm continued effectiveness of treatment);
- the patient develops intolerable side effects; or
- use of opioids becomes problematic

During long term opioid treatment, reviews should be conducted at least monthly in the first six months after stable dosing has been achieved.

Frequency of review thereafter can be clinically determined by the complexity of the case, but should be at least biannually.

Practical Prescribing Points

National Guidance

- Quantity prescribed should be appropriate for clinical need of patients
- DH good practice guidance recommends that prescriptions should be for a maximum of 30 days supply. If in exceptional cases, to cover a justifiable clinical need and after consideration of any risk, a longer period is supplied, the reasons for this decision should be recorded in the patient notes.

Prescriber responsibilities.

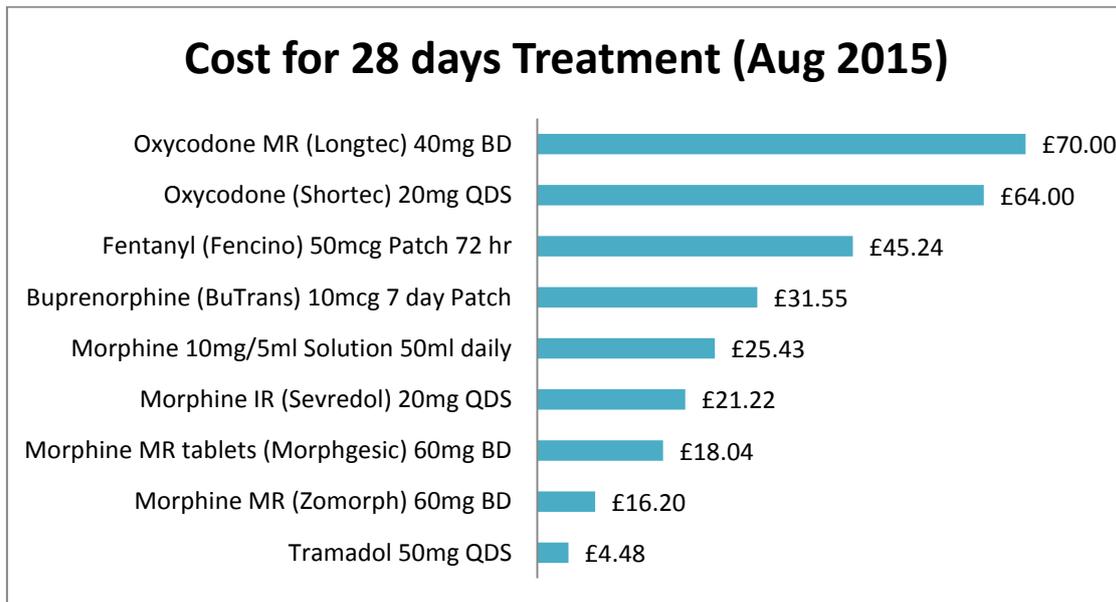
- To avoid creating dependence by introducing drugs to patients without sufficient reason
- To avoid being used as an unwitting source of supply for addicts. Be especially careful with temporary residents and consider small supplies
- See BNF for further detail (controlled drugs & drug dependence)

References:

1. World Health Organisation. Cancer pain relief with a guide to opioid 1. availability. 2nd ed. Geneva 1996 **(G)**
2. Hanks GW et al. Morphine and alternative opioids in cancer pain: the EAPC 2. recommendations. British J Cancer 2001;84:587-93 **(G)**
3. Twycross R, Wilcock A (eds). Palliative Care Formulary, 33. rd ed. Oxford 2007. Palliativedrugs.com Ltd, Nottingham, 2007
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5. Reid CM et al. Oxycodone for cancer related pain – meta-analysis of 8. randomised controlled trials. Arch Intern Med. 2006;166: 837-43 **(MA)**
6. Quigley C. Opioid switching to improve pain relief and drug tolerability. 15. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD004847. DOI: 10.1002/14651858. CD004847. **(R)**
7. Bruno R da Costa, Eveline Nüesch, Rahel Kasteler, Elaine Husni, Vivian Welch, Anne WS Rutjes. Oral or transdermal opioids for osteoarthritis of the knee or hip
8. Conaghan PG1, O'Brien CM, Wilson M, Schofield JP. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomised trial.
9. Karlsson M1, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) versus prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, parallel-group noninferiority study.
10. Midlands Therapeutic Review Advisory Committee. Buprenorphine Transdermal Patch for the Treatment of Chronic Non-Cancer Pain. January 2012.

KEY: G – Guideline, MA – meta-analysis, R – review

Appendix 1: Costs



Appendix 2: Potential Prescribing Errors with Oxycodone

Prescribers and anyone responsible for entering drugs on to the computer (e.g. from discharge sheets, outpatient letters, etc.), need to be aware that there are different oxycodone presentations available, which have different dose schedules:

Preparation	Strength	Usual Dosage Schedule
Oxycodone Capsules (Shortec)	5, 10,20mg	Every four to six hours
Oxycodone MR tablets (Longtec)	5, 10, 20,40, 80mg	Every 12 hours
Oxycodone liquid	5mg/5ml	Every four to six hours
Oxycodone concentrate	10mg/ml (50mg/5ml)	Every four to six hours
Oxycodone injection	10mg/ml	Every four hours or by infusion (see BNF)

- **When prescribing, dispensing or administering it is important to check correct formulation is selected.**
- **For liquid preparation it is essential to double check that the correct strength has been selected. The concentrate is ten times stronger than the normal liquid preparation**
- **There have been several instances where patients have been prescribed oxycodone MR tablets three or four times a day and also on a ‘when required’ basis, which is clearly inappropriate for an MR preparation. It appears that this is due to the wrong preparation being selected in error; both the standard release capsules and the MR tablets are available in 5, 10 and 20mg strengths and it is easy to select the wrong formulation.**
- **This issue has been partially addressed by using Shortec and Longtec. The difference in names is clearer and they imply the release time better than the previous brand (oxycontin and oxynorm).**

Prescribers may wish to review their prescribing of oxycodone to make sure in line with current recommendations and that the correct formulation is selected on occasions where oxycodone is indicated. Prescribers should double-check that they have selected the correct formulation