

Choosing and Changing Opioids

Introduction

Opioids are used for [pain](#) and [breathlessness](#). Most patients with palliative care needs respond well to titrated oral morphine.

- For frail/elderly patients, consider a lower starting dose of opioid.
- Seek specialist advice if the patient is in moderate to severe pain with frequent use of breakthrough medication, in other words more than three doses in 24 hours.

A small number of patients may need to be changed to another opioid if:

- oral route is not available
- pain is responding but the patient has persistent intolerable side effects (consider reducing the dose and titrating more slowly or adding an adjuvant analgesic before changing opioid)
- moderate to severe liver or renal impairment
- poor compliance with oral medication
- complex pain (consider adjuvant analgesics/other pain treatments).

Preparations

Choosing an opioid

When an individual's pain is not being managed effectively by paracetamol (with or without an adjuvant), the World Health Organization (WHO) Analgesic Ladder suggests moving to an opioid from Step 2 or 3. The opioids within Steps 2 and 3 are described below.

Opioids come in different dose forms (oral/transdermal/transmucosal/injectable) and with different release characteristics (immediate release and modified release). Modified release (MR) preparations tend to be used to control background pain over a 24 hour period. Immediate release (IR) preparations can be prescribed and given 'as required' for breakthrough pain. Oral immediate release preparations act quickly, for example oral morphine will start to have an effect within 20-30 minutes with peak effect at approximately 60 minutes. Titration of the background modified release opioids is guided by how much immediate release opioids are required.

Refer to [Pain Management](#) guideline.

Opioids for mild to moderate pain

Codeine

- Available as codeine phosphate tablets 15mg, 30mg and 60mg and as liquid preparations 15mg/5ml and 25mg/5ml.
- Also available in combination with paracetamol 8mg/500mg, 15mg/500mg, 30mg/500mg.
- Codeine must be metabolised to morphine to achieve most of its analgesic effect.
 - 5 to 10% of people lack the liver enzyme which enables this to happen (CYP2D6) and therefore pain relief will not be achieved but adverse side effects still occur.
 - In contrast, ultra-rapid metabolisers produce more morphine and are more prone to toxicity.
- Several active metabolites are renally excreted.
- Avoid in stage 4 and 5 Chronic Kidney Disease.
- Maximum oral dose: 240mg/24 hours.

Dihydrocodeine

- Similar to codeine in structure and analgesic effect.
- Available as 30mg tablets
- Dihydrocodeine is metabolised by the liver enzyme CYP2D6 to an active metabolite.
- No evidence to suggest that analgesic effect is affected by an individual's ability to metabolise dihydrocodeine.
- Active metabolites are renally excreted.
- Avoid in stage 4 and 5 Chronic Kidney Disease.
- Maximum oral dose: 240mg/24 hours.

Tramadol

- Oral and injectable dose forms available.
- Chemically unrelated to morphine. Opioid and non-opioid properties.
- Renally excreted.
- Use with caution in stage 4 and 5 Chronic Kidney Disease and severe liver failure. Consider increasing the dosage interval of the immediate release preparation to 12 hourly and to avoid the modified release preparation.

- Tramadol requires the liver enzyme CYP2D6 to help with its metabolism and can therefore be poorly tolerated by some individuals.
- Contra-indicated in individuals taking Monoamine Oxidase Inhibitors (MAOIs) or in those with epilepsy.
- Avoid or use with caution in individuals taking Selective Serotonin Reuptake Inhibitors (SSRIs) or Tricyclic Antidepressants (TCAs) due to risk of serotonin syndrome and of lowered seizure threshold.
- Maximum oral dose: 400mg/24 hours

Buprenorphine Patches

- Available as a 7-day patch (for example Butec®). At low doses (5micrograms to 20micrograms/hr) is used to treat moderate pain.
- Buprenorphine patches are contra-indicated in patients with acute (short-term) pain and in those who need rapid dose titration for severe uncontrolled pain.
- Undergoes hepatic metabolism to norbuprenorphine which has little clinical activity and does not cross the blood-brain barrier.
- Unchanged buprenorphine is excreted through the biliary system.
- Buprenorphine does not accumulate in renal impairment and therefore may be a good Step 2 Opioid in stage 4 and 5 Chronic Kidney Disease.

Refer to [buprenorphine information sheet](#)

Note: A 3-day patch (35microgram, 52.5microgram and 70microgram/hr) and a 4-day patch (35microgram, 52.5microgram and 70microgram/hr) are available. At higher doses (greater than 20microgram/hr), buprenorphine is used to treat moderate to severe pain.

Opioids for moderate to severe pain

First-line opioids

Morphine (refer to morphine information sheet)

- Immediate and modified release oral preparations (ensure correct preparation is prescribed); subcutaneous (SC) injection and in [CME T34 syringe pump](#) for continuous subcutaneous infusion (CSCI).
- Renally excreted, active metabolites – titrate morphine slowly and monitor carefully in stage 1 to 3 Chronic Kidney Disease.

- Use alternative opioids in stage 4 and 5 Chronic Kidney Disease and patients undergoing dialysis to avoid toxicity. Refer to [End Stage Renal Disease](#) guideline.
- Consider low doses and slow titration in liver impairment.

Diamorphine

- Highly soluble opioid used for SC injection and in a [CME T34 syringe pump](#) (CSCI).
- Use for high-dose SC breakthrough injections (above morphine SC bolus injections of 60mg [2ml]). Powder preparation is soluble in a small volume of water for injections.
- As with morphine, cautious use in renal and liver impairment. Avoid in stage 4 and 5 Chronic Kidney Disease.

Second-line opioids

Oxycodone (refer to [oxycodone information sheet](#))

- For moderate to severe pain if morphine/diamorphine are not tolerated.
- Immediate and modified release oral preparations (ensure correct preparation is prescribed); SC injection; [CME T34 syringe pump](#) (CSCI).
- Lower concentration preparation limits dose for SC injection to 20mg (2ml). (In some NHS boards, a 50mg/ml injection is available – check local guidance.)
- Avoid in moderate to severe liver impairment, where clearance is much reduced.
- Mild to moderate renal impairment: reduced clearance so titrate slowly and monitor carefully.
- Avoid modified release preparations in stage 4 and 5 Chronic Kidney Disease. Immediate release preparations may be used with caution for breakthrough pain.

Fentanyl (refer to [Fentanyl patches information sheet](#) and consider seeking specialist advice)


- Transdermal patch lasting 72 hours; use if oral and SC routes are unsuitable.
- Consider only if tolerant to opioids as this is a very potent opioid. A 12 microgram/hour fentanyl patch is equivalent to about 30mg to 60mg of oral morphine in 24 hours. Inappropriate use can cause fatal overdose <https://www.gov.uk/drug-safety-update/serious-and-fatal-overdose-of-fentanyl-patches>.
- For **stable pain** if morphine not tolerated; dose cannot be changed quickly.
- No initial dose reduction in renal impairment but may accumulate over time as it is cleared through the kidneys. Consider changing every 96 hours if eGFR<30ml/min, pain is well

controlled but the patient has shown signs of mild toxicity. Consider seeking specialist advice in this situation.

- Liver impairment; dose reduction may be needed in severe liver disease.
- Do not initiate at the end of life when the oral route is no longer available (can take too long to reach steady state) – refer to [Fentanyl Patches](#) information sheet. If a patient is already on a fentanyl patch and in the last days of life, refer to [Fentanyl Patches](#) information sheet.

Third-line opioids (seek specialist advice)

Alfentanil (refer to [alfentanil information sheet](#))

- Alfentanil is a potent opioid: 1mg of alfentanil is roughly equivalent to 30mg oral morphine.
- Short-acting, injectable opioid for SC injection and in a [CME T34 syringe pump](#) (CSCI).
- In episodic/incident pain, it can be given sublingually (an unlicensed  spray is available) or subcutaneously.
- Dose does not need to be reduced in renal disease including stage 4 and 5 Chronic Kidney Disease.
- Clearance may be reduced in liver impairment; reduce dose and titrate.
- Drug of choice if eGFR<30ml/min and syringe pump required
- Useful if severe pain and toxicity.
- Please seek specialist advice when switching from a CSCI of alfentanil to an alternative opioid.

Fentanyl sublingual/buccal/intranasal

- These are potent preparations. Before rapid acting fentanyl is used, patients must have been on a stable dose of a regular opioid for approximately 7 days equivalent to a minimum of 60mg oral morphine or 30mg of oral oxycodone in 24 hours or a 25 micrograms/hour fentanyl patch.
- In episodic/incident pain, fentanyl can be given sublingually (Abstral[®], Effentora[®]), buccal (Effentora[®]) or intranasally (Pecfent[®], Instanyl[®]) – check local guidance for preferred preparation and refer to [Abstral[®]](#), [Effentora[®]](#) or [Pecfent[®]](#) guidelines. These products are not interchangeable due to different absorption profiles.

- The effective dose of transmucosal fentanyl cannot be predicted from the background dose of opioid. Start at the lowest dose and titrate upwards to determine the effective dose.
- 100microgram fentanyl is approximately equivalent to 15mg of oral morphine.

Fourth-line opioids (specialist use only)

Hydromorphone (refer to [hydromorphone information sheet](#))

- Potent opioid for specialist use only.
- Frail or elderly patients need smaller doses, less frequently with slower titration.
- Liver impairment, reduced clearance. Start at a lower dose and closely monitor.
- Renal impairment, reduced excretion. Titrate slowly and closely monitor. Avoid in stage 4 and 5 Chronic Kidney Disease.
- At higher doses, consider medicines burden of breakthrough dose

QT *Methadone¹ (refer to [methadone information sheet](#))*

- Potent opioid for specialist use only.
- Oral methadone is used by specialists for complex pain where other opioids have inadequate efficacy.
- Available in oral tablet and liquid form. Methadone can also be given by injection.
- Dosing is difficult due to the potentially long and unpredictable half-life.
- Partial renal and biliary excretion occurs therefore dose reduction may not be required in Chronic Kidney Disease.
- Half-life is prolonged in severe liver disease.
- Conversion from other opioids to methadone is complex and inpatient admission is advised.

Cautions

Opioid toxicity

- Can be precipitated by several factors, including rapid dose escalation, renal impairment, sepsis, electrolyte abnormalities, drug interactions.
- Wide variation in the dose of opioid that can cause symptoms of toxicity.
- Prompt recognition and treatment are needed. Symptoms include:

¹ QT Indicates this medication is associated with QT prolongation

- persistent sedation (exclude other causes)
 - vivid dreams, hallucinations, shadows at the edge of visual field
 - **delirium**
 - muscle twitching/myoclonus/jerking
 - abnormal skin sensitivity to touch (opioid induced hyperalgesia, OIH).
- If the pain is controlled, reduce the opioid dose by a third. Ensure the patient is well hydrated. Seek advice.
 - If pain is uncontrolled, consider reducing opioid dose by a third. Consider adjuvant analgesics, alternative opioids or both. Seek advice.
 - Naloxone (in small titrated doses) is only needed for life-threatening respiratory depression (refer to [Naloxone](#) guideline).

Dose and administration

Changing opioid – seek specialist advice if uncertain

- These doses/ratios are **approximate** (\approx) and not exact equivalent doses and should be used as a **guide**.
- Dose conversions should be conservative and doses are usually rounded down (Note – check available strengths).
- Adjust and monitor doses closely, extra care with: opioid toxicity; frail and elderly patients; renal or hepatic impairment.
- Always prescribe an appropriate drug and dose for breakthrough pain:
 - 1/6th to 1/10th of the 24 hour regular opioid dose as required.

Conversions from weak opioids to oral morphine		
Weak opioid dose	Equivalent oral morphine dose	Conversion factor from weak oral opioid to morphine
Oral codeine or oral dihydrocodeine 240mg/24hrs	\approx Oral morphine 24mg/24hrs	Divide by 10
Tramadol 400mg/24hrs*	\approx Oral morphine 40mg/24hrs	Divide by 10
Nefopam 90mg/24hrs*	\approx Oral morphine 30mg/24hrs	Divide by 3
Buprenorphine 7-day Patch 5micrograms/hr**	\approx Oral morphine 12mg/24hrs	

* Not generally recommended for use in palliative care.

** Note buprenorphine is measured in micrograms and morphine is measured in milligrams.

Conversions from oral strong opioids to other strong opioids		
Oral morphine dose	Equivalent opioid dose	Conversion factor from oral morphine to other opioid
Morphine 10mg	≈ SC morphine 5mg	Divide by 2
Morphine 10mg	≈ SC diamorphine 3mg	Divide by 3
Morphine 10mg	≈ Oral oxycodone 5mg	Divide by 2
Morphine 10mg	≈ SC oxycodone 2mg to 3mg	Divide by 4
Morphine 30mg to 60mg	≈ Fentanyl patch 12 micrograms/hour	Refer to: Fentanyl
Morphine 60mg to 90mg	≈ Fentanyl patch 25 micrograms/hour	Refer to: Fentanyl
Morphine 30mg	≈ SC alfentanil 1mg*	Divide by 30 Refer to: Alfentanil
Morphine 10mg	≈ Oral hydromorphone 1.3mg	Divide by 5 to 7.5
Morphine 15mg	≈ SC hydromorphone 1mg*	Divide by 10
Oral oxycodone dose	Equivalent opioid dose	Conversion factor from oral to SC
Oxycodone 5mg	≈ SC oxycodone 2mg to 3mg	Divide by 2
Oxycodone 5mg	≈ Oral morphine 10mg	Multiply by 2
Oxycodone 5mg	≈ SC diamorphine 3mg	Divide by 1.5
Oxycodone 15mg to 30mg	≈ Fentanyl patch 12 micrograms/hour	Refer to: Fentanyl
Oxycodone 30mg to 45mg	≈ Fentanyl patch 25 micrograms/hour	Refer to: Fentanyl
Oxycodone 15mg	≈ SC alfentanil 1mg*	Divide by 15
Oxycodone 5mg	≈ oral hydromorphone 1.3mg*	Divide by 4

*Use only with specialist palliative care input

Dose advice for “as required” prescriptions

- Patients on a regular opioid will require an opioid prescribed as required for breakthrough pain. An appropriate as required dose is typically 1/6th to 1/10th of the regular opioid dose.
- The as required dose is usually increased appropriately when the dose of regular opioid is increased.

- For most as required opioids a prescribing interval equivalent to the duration of expected onset of action for the route administered is permitted, particularly if pain is severe to allow for dose titration whilst monitoring for toxicity. The prescription should also identify that if 3 or more doses have been given within 4 hours with little or no benefit urgent advice or review should be sought. If more than 6 doses are required in 24 hours advice or review should be requested.
- Refer to [Care in the Last Days of Life](#) guideline.
- Seek specialist advice when prescribing rapid acting fentanyl preparations or refer to the medicine information sheet if familiar with the product - [Fentanyl Sublingual \(Abstral\)[®]](#), [Fentanyl Buccal \(Effentora\)[®]](#) and Fentanyl Nasal Spray ([Pecfent[®]](#)).

Dose conversions

A guide to dose conversions *FROM* morphine *TO* second-line opioid analgesics used for moderate to severe pain

Use the tables above as a guide. The doses are approximate (\approx) and not exact equivalent doses. Breakthrough opioid doses are based on a calculation of 1/6th of the daily dose - these doses may be adjusted up or down to avoid the use of decimal points and to allow a practical dose to be administered. Some patients may require a smaller 4-hour breakthrough dose of 1/10th of the daily dose. Initiate dose with caution depending on clinical condition and judgement.

- Opioid bioavailability (particularly for oral morphine) and response are highly variable.
- It is important to exercise caution when switching opioids. Start low and titrate gradually.
- Always prescribe an appropriate drug and dose for breakthrough pain: 1/6th to 1/10th of the 24 hour regular opioid dose as required.
- Opioid conversions and ratios may vary depending on the resource used. The conversions used in these guidelines are based on consensus of use across Scotland and reference sources.
- **Consider reducing the dose by up to 30% and re-titrating:**
 - when changing opioid because of differences in pharmacokinetics and pharmacodynamics, including incomplete cross tolerance
 - if the patient is opioid toxic, frail or elderly.
- Check the information about individual drugs if the patient has renal or liver impairment.

- Particular care is needed when changing between opioids at higher doses or when the dose of the first opioid has been rapidly increased as these patients are at greater risk of adverse effects.
- Morphine and oxycodone doses can be measured accurately in 1mg dose increments. **Decimal places are not recommended.**
- Fentanyl: Refer to [Fentanyl Patches](#) information sheet for dose conversions.
- Alfentanil: Refer to [Alfentanil](#) information sheet for dose conversions.
- The effective sublingual/buccal dose of Fentanyl cannot be reliably predicted from the background maintenance opioid dose and individual titration for a patient is required, always starting at the lowest dose.

Monitor the patient carefully. If in doubt, seek advice.

Practice points

- Morphine injection is available in a maximum concentration of 30mg/ml.
- Oxycodone injection may only be available as 10mg/ml (50mg/ml injection may be available in some NHS boards).
- When giving SC opioid injections, the maximum volume is 2ml. If a patient needs a dose that is in an injection volume above 2ml – seek advice.

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