1. Introduction

Strong analgesics are essential drugs in palliative care, their use dictated by therapeutic need and response, not by brevity of prognosis. Providing the dose of an opioid is carefully titrated against the patient's pain, there are generally no absolute contraindications to the use of strong opioids for cancer pain. However there are circumstances eg renal or hepatic impairment, when it may be better to avoid the use of certain opioids and/or positively choose certain other ones.

Morphine is the strong opioid of choice for moderate-severe cancer pain but other strong opioids may be used if: morphine is not readily available, if the transdermal route is preferable or if the patient has undesirable effects with morphine. However, strong opioids are not the panacea for pain and generally require use alongside non-opioid medication and the addressing of psychosocial dimensions of suffering.

Opioids come in different dose forms (oral/ transdermal/ transmucosal/ injectable) and with different release characteristics (immediate release and modified release).

- Modified release (MR) preparations are taken regularly and are used to provide background pain control over the entire 24 hour period. Titration of the regular modified release opioids is guided by how much additional immediate release opioids are required.

- Immediate release (IR) preparations are 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.

- Due to the length of time taken to achieve steady state, the initiation of transdermal preparations (buprenorphine/ fentanyl) is contraindicated in acute pain (transient, intermittent or short-term pain) e.g. post-operative pain or when there is need for rapid dose titration for severe uncontrolled pain.

2. Scope

2.1 This guidance applies to all prescribers within UHL who are prescribing opioids for patients with the intention of achieving symptom control of pain or breathlessness in the context of a palliative approach to their care. It aims to help prescribers safely choose and manage appropriate opioids and convert patients from one opioid medication to another, when clinically appropriate, in a palliative care setting. Further information about opioid conversions and compatibility information for subcutaneous infusions of medications via subcutaneous syringe drivers is found at Palliative Care Guidelines^{Plus} at https://book.pallcare.info/index.php?op=plugin&src=opiconv or in the Palliative Care Formulary at www.medicinescomplete.com (requires subscription).

3. Recommendations, Standards and Procedural Statements

There is a lack of high quality RCT data to support switching opioids. It is crucial for prescribers to understand that conversion ratios are ***never*** more than an approximate guide due to wide inter-individual variation in opioid pharmacokinetics, dose and duration of opioid treatment, direction of switch in opioid, nutritional status and concurrent medications. Careful monitoring during drug conversion is necessary to avoid both under-dosing and excessive dosing. This is particularly important when switching at high doses or if there has been a recent rapid escalation of the first opioid. In these circumstances a dose reduction of 25-50% may be necessary. Involvement of the specialist palliative care team is strongly recommended in these circumstances. Published conversion ratios vary and recommendations from specialist palliative care sources may vary from the manufacturer's recommended ratios.

This guidance covers the general principles but individual prescribers remain responsible for their own prescribing decisions. It is expected that if prescribing or changing opioids falls outside of their personal competencies or scope of practice, that they will use the resources available to them in their place of work and check their calculations with a second person. If there is any uncertainty or specialist advice is needed, discussion with a pharmacist or the Specialist Palliative Care team is recommended.

4. Cautions:

4.1. Driving

All opioids can impair driving ability and patients should be counselled accordingly. Morphine, diamorphine and methadone are included in the Road Traffic Act in England and Wales related to driving with certain drugs above specified plasma concentrations.
https://www.legislation.gov.uk/uksi/2014/2868/regulation/2/made

4.2. Renal or hepatic impairment

Opioids differ in their potential to cause toxicity when renal or hepatic function is impaired and this may influence the choice of opioid used. When there is an acute deterioration in renal or hepatic function, an opioid may rapidly accumulate because of reduced excretion or metabolism. Consider a dose reduction pre-emptively and where there is already evidence of toxicity the doses must be reduced or the opioid switched. See UHL guidelines: *Opioid Analgesics in Adult Patients with Renal Impairment from all causes* or section 9.0 in this guideline. The Specialist Palliative Care team can advise further on this.

4.2.1 Dialysis

For patients on peritoneal (PD) or haemodialysis (HD), recommendations generally follow those for End Stage Renal Failure (ESRF) in the UHL guidelines: *Opioid Analgesics in Adult Patients with Renal Impairment from all causes*. Although it is possible that some opioids may be removed by PD or HD, this is generally not to a level sufficient to require a change in drug regime. Close monitoring is recommended however and if loss of analgesia occurs soon after dialysis, a rescue dose of the usual IR opioid may be required.

4.3. Opioid toxicity

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

- 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).
- respiratory depression
    - When titrated against the patient's pain, strong opioids do not usually cause clinically important respiratory depression. Strong opioids also relieve moderately severe breathlessness at rest using doses which do not cause respiratory depression.
    - Naloxone, a specific opioid antagonist, is rarely needed in palliative care. Its use is generally reserved for ***respiratory depression*** (respiratory rate <8/minute). Doses of naloxone in palliative care are commonly less that the traditional doses eg starting with 50-100micrograms rather than 400micrograms. The exception to this is buprenorphine as due to its high receptor affinity and prolonged receptor binding, much higher doses of naloxone are required to reverse respiratory depression. See UHL guidance: *Guidelines for the use of Naloxone in the management of opioid-induced respiratory depression in Adults receiving Palliative Care*.

4.4. Tolerance and dependence

Generally in the palliative care setting, tolerance to strong opioids is not a practical problem and addiction is rare.
Caution should be reserved for those with a present or past history of substance abuse but even then strong opioids should be used where there is a clinical need. It is recommended to involve the Specialist Palliative Care team in these situations.
For the use of strong opioids for chronic non-cancer pain, specialist advice should be sought from the Chronic Pain team.

5. Choice of opioid

This depends on the individual patient, but as a general rule in the palliative care setting:

5.1 Pethidine

This should not be used**.** It is a weak opioid with a short duration of action and toxic metabolites which accumulate when given regularly.

5.2 Oral weak opioids

There is no pharmacological need for weak opioids in cancer pain. Low doses of morphine (or alternative strong opioid) generally provide a quicker and better relief from cancer pain than weak opioids. All weak opioids are considered equipotent in terms of efficacy and are generally considered 10 times less potent than morphine. Weak opioids differ in their potential to cause toxicity when renal function is impaired. All weak opioids should be avoided in severe hepatic impairment.

- **Codeine**. Codeine has little or no analgesic effect until it is metabolised to morphine. In poor metabolisers it is therefore essentially ineffective and in ultra-metabolisers is potentially toxic.
- **Dihydrocodeine**. A semisynthetic analogue of codeine which is an active substance not a pro-drug like codeine. Twice as potent as codeine by injection but due to low oral bioavailability the two drugs are essentially equipotent by mouth.
- **Tramadol.** Is derived from codeine. Less constipating than codeine but causes more vomiting, dizziness and anorexia. Structurally similar to venlafaxine, it can lead to serotonin toxicity if combined with another drug that affects serotonin metabolism, particularly in the elderly. It lowers seizure threshold. As for codeine, tramadol needs to be metabolised to an active compound so can be ineffective or potentially toxic depending on individual speed of metabolism.

5.3 Strong opioids

5.3.1 First line opioids

- **Morphine** is used first line (oral and/or subcutaneous). It has renally-excreted active metabolites so need to be titrated slowly and monitored carefully in stage 1 to 2 Chronic Kidney Disease (CKD). Use alternative opioids in stage 3, 4 and 5 CKD and patients undergoing dialysis to avoid toxicity. However, if a patient with renal impairment is already established on morphine with no adverse effects and no rapid deterioration of their renal function, they may remain on morphine with careful monitoring. In liver failure use low doses of morphine and titrate slowly.

5.3.2 Second line opioids

- **Oxycodone** is used second line (oral and/or subcutaneous) when an opioid rotation is required for reasons of lack of efficacy or intolerable side effects from morphine (such as drowsiness, nausea or hallucinations) or first line for renal impairment eGFR <60. Avoid in moderate to severe liver impairment, where clearance is much reduced. In mild to moderate renal impairment, drug clearance is reduced so titrate slowly and monitor carefully. Avoid modified release preparations in stage 4 and 5 CKD.

- **Fentanyl and buprenorphine transdermal patches** may be used when patients have controlled pain but require an alternative route of opioid administration. They are contraindicated in acute or short term pain eg post operative, recent fracture etc or when there is need for rapid opioid titration due to severe uncontrolled pain.

5.3.3 Third line opioids

- **Alfentanil** (subcutaneous) is the opioid of choice for patients with significant renal impairment (eGFR<30) who require a continuous subcutaneous infusion (via syringe driver). This is a potent opioid so discussion with the Specialist Palliative Care team is recommended when switching to and from alfentanil.

- **Diamorphine** (subcutaneous). Converted to morphine to create the analgesic effect. Same indications and cautions as for morphine. Use in UHL is generally limited to situations where there are volume issues with high doses of morphine in a syringe driver. The conversion ratios are different to morphine so discussion with the Specialist Palliative Care team is recommended.

- **Tapentadol** (oral). Synthetic centrally acting mixed opioid agonist and noradrenaline reuptake inhibitor. Approximatively one third as potent as oral morphine but there is insufficient evidence at present to recommend it for routine practice in acute, chronic, cancer or neuropathic pain.

5.3.4 Fourth line opioids

- **Hydromorphone.** Potent opioid for specialist use only. Frail or elderly patients need smaller doses, less frequently with slower titration. Liver impairment reduces clearance and renal impairment reduces excretion. In these situations titrate slowly and closely monitor. Avoid in stage 4 and 5 CKD. At higher doses due to the low strength of the IR capsules, medication burden may need to be considered.

- **Methadone.** Potent opioid for specialist use only for complex pain where other opioids have inadequate efficacy. Dosing is difficult due to the potentially long and unpredictable half-life. Metabolism is modified to a clinically important extent by other medications which may be used in palliative care and it is associated with QT prolongation requiring caution in those pre-disposed to arrhythmias. Partial renal and biliary excretion occurs therefore dose reduction may not be required in CKD. Half-life is prolonged in severe liver disease. Methadone comes in both oral (tablet, liquid) and injectable formulations for subcutaneous delivery. Conversion from other opioids to methadone is complex and inpatient admission to a specialist palliative care unit is advised. Any palliative care patient who is admitted to UHL and takes methadone for pain control or who takes methadone as part of a drug rehabilitation programme and now requires support with pain management in a palliative care context, must be referred to the Specialist Palliative Care team for support with their analgesia during admission.

5.4 T34 McKinley syringe drivers

5.4.1 When using high doses of opioids, the volume of medication may become an issue. A 20mL syringe supports a 17mL volume. A 30mL syringe supports a 22mL volume. If a 30mL syringe cannot be sourced it may be necessary to either change the opioid or to divide the medication into two separate syringe drivers. The Specialist Palliative Care team can advise in these situations.

5.4.2 It is critical that a syringe driver should be set up as soon as is possible after the prescription in made. For prescriptions using ward stock drugs this should be within 2 hours and for non-stock drugs should be within 4 hours.

5.4.3 Syringe drivers should not be stopped without instruction from the medical team with the exception of significant side effect or life-threatening toxicity.

5.4.4 Syringe drivers should be changed at or before the time of completion. They must not be allowed to run out. Some of the drugs used in syringe drivers have very short half-lives so will wear off quickly, risking uncontrolled symptoms. See UHL policy *Ambulatory Syringe Pump (T34) in UHL* and UHL guideline *T34 pump – Patients attending on Syringe Driver UHL Emergency Department Guideline*

5.5 Breakthrough (PRN) dosing using IR opioids (oral /sublingual/buccal/ intranasal/subcutaneous)

Breakthrough pain describes a transient episode of increased pain which occurs despite relatively stable and adequately controlled background pain. It is common in cancer patients (<80%).

- Predictable (incident) pain eg caused by activity – movement, swallowing, defaecation, coughing
- Unpredictable (spontaneous) pain – unrelated to movement or activity eg colic, neuropathic pain

Breakthrough pain may be functional eg headache, or pathological and may be nociceptive or neuropathic. More than one type of breakthrough pain may be experienced. Commonly used non-drug measures include rest, repositioning and local heat. Breakthrough cancer pain commonly requires a dose of the prescribed IR opioid.

The effective PRN dose of IR opioid can vary considerably. Traditional practice is to use one sixth of the total daily opioid dose although some centres now recommend one tenth. When patients are encouraged to optimise their 'rescue' dose it varies from 5%-20% of the total daily opioid dose. PRN doses should be available 4 hourly for stable pain and 1-2 hourly whilst titrating analgesic requirements or in the last days of life. Patients with renal impairment may need a reduction in the dose and/or frequency – see UHL guideline: *Opioid Analgesics in Adult patients with Renal Impairment from all causes* or section 4.2 in this guideline for more details.

6. Converting between opioids: Opioid switching ('rotation')

See section 3.0 for general recommendations

6.1 Weak opioids to strong opioids

All weak opioids are considered equipotent and one tenth the strength of oral morphine. See table below.

To find the equivalent dose of oral morphine, divide the 24 hour total dose of the weak opioid by 10. The exact dose then prescribed will be based on available formulations and whether, based on the individual patient situation, the prescriber wishes to increase or decrease the equivalent dose. If an alternative strong opioid is more desirable than oral morphine for the individual patient situation, first convert the weak opioid to the oral morphine equivalent than use the guidance in the following sections to convert to an alternative option.

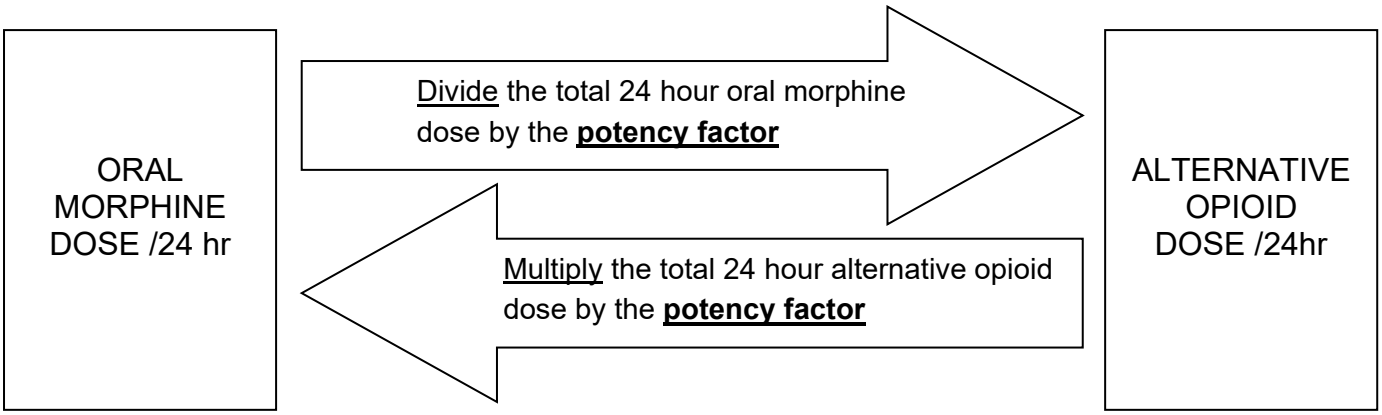
Drug/Preparation	Maximum Daily Dose	Approximate equivalent dose of *oral* Morphine/24hrs
Codeine Phosphate	240mg	24mg
Dihydrocodeine	240mg	24mg
Tramadol	400mg	40mg

Example:

A patient taking co-codamol 30/500, 8 tablets a day (total 240mg), will be taking an equivalent of 240/10 = 24mg morphine in 24 hours. If converting from co-codamol to oral morphine because the patient is still in pain, consider dose increase to 15mg BD of Modified Release oral morphine. In addition the paracetamol component of co-codamol will now need to be prescribed separately.

6.2 Switching between Strong Opioids

- Generally switching from morphine to an alternative strong opioid is done in an attempt to reduce side effects and improve analgesia. Before switching it is worth considering if other options may be more appropriate to manage pain eg prescribing adjuvant analgesics or modifying the management of the undesirable effects eg adjusting laxatives.
- When converting from morphine to an alternative strong opioid, or vice versa, the initial dose depends on the relative potency of the two drugs.



Alternative opioid	*Potency Factor* to oral Morphine	Alternative opioid dose equivalent to 30mg oral Morphine/ 24 hrs
Morphine (PO)	1	30mg
Morphine (SC)	2	15mg
Morphine (IV)	2 or 3	10-15mg *must be discussed with palliative care consultant
Diamorphine (SC)	3	10mg
Oxycodone (PO)	1.5 (2)*	20mg (15mg)
Oxycodone (SC)	3 (4)*	10mg (7.5mg)
Alfentanil (SC)	30	1mg
Hydromorphone (PO)	5 - 7.5	4mg – 6mg

*Ratio in brackets is the manufacturers preferred relative potencies

Examples:

1. *To convert oral Morphine modified release 30mg BD (total 60mg/24hr) to subcutaneous Morphine via syringe driver, divide by 2 = 30 mg/24hr.*
2. *To convert oral Morphine modified release 30mg BD (total 60mg/24hr) to oral Oxycodone Modified Release divide by 1.5 = 20mg BD (total 40mg/24hr)*

This new dose may then require adjusting based on individual circumstances as previously outlined.

6.3 Transdermal opioids

The conversion from patches to oral opioids is less precise due to individual variation in metabolism.

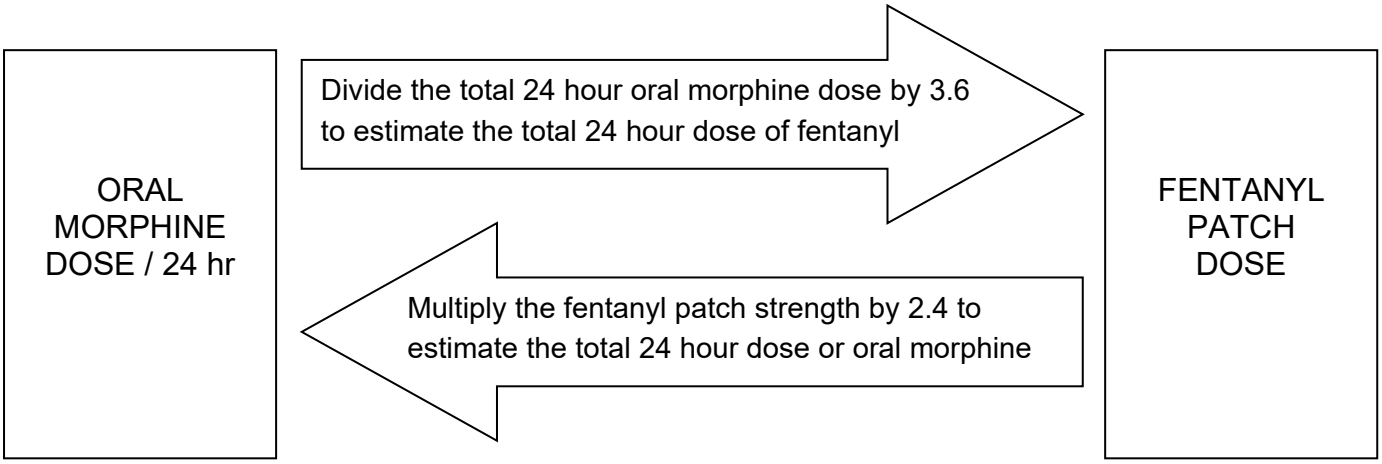
For patients who are not taking a dose of morphine that is an exact equivalent of a transdermal patch, it will be necessary to opt for a patch that is slightly more or slightly less than the morphine dose. In general, if the patient has pain, round up to a higher patch and if the patient is pain-controlled or frail then round down.

Systemic analgesic concentrations are generally reached within 12-24 hours. Fentanyl patches and buprenorphine patches <20mcg/hour will reach steady state in 36-48 hours. Buprenorphine patches >20micrograms/hr may take up to 9 days. When applying a patch therefore, the following general principles apply. If converting from:

- 4 hourly PO IR morphine / IR oxycodone – continue regular doses of the oral IR opioid for 12 hours after applying patch
- 12 hourly PO MR morphine/ MR oxycodone – apply the patch at the same time as the final MR dose
- Syringe driver – continue the syringe driver for 12 hours after applying the patch

This approach may be challenging to coordinate in a non-specialist environment. The Specialist Palliative Care team can advise further.

Fentanyl 25 micrograms/hour patch is approximately equivalent to 60-90mg /24hr PO morphine. For safety, a different calculation is made depending which way the conversion is required.



Fentanyl Patch (micrograms/hour)	Approximate 24hour total oral Morphine dose (mg)	Breakthrough oral Morphine dose (mg) (divide 24 hour dose by 6)
12	30-45	5 - 7.5
25	60-90	10 - 15
37	90-130	15 - 25
50	120-180	20 - 30
75	180-270	30 - 45
100	240-360	40 - 60

Buprenorphine 5 micrograms/hour is approximately equivalent to 12mg/24hr oral morphine.

Buprenorphine Patch (micrograms/hour)	Approximate 24hour total oral Morphine dose (mg)	Breakthrough oral Morphine dose (mg) (divide 24 hour dose by 6)
5	12	2.5
10	24	2.5 - 5
15	36	5 - 7.5
20	48	7.5 - 10
35	84	12.5 - 15
52.5	126	15 - 20
70	168	25 - 30

6.4 Breakthrough/ PRN doses when using an analgesic patch as background pain relief.

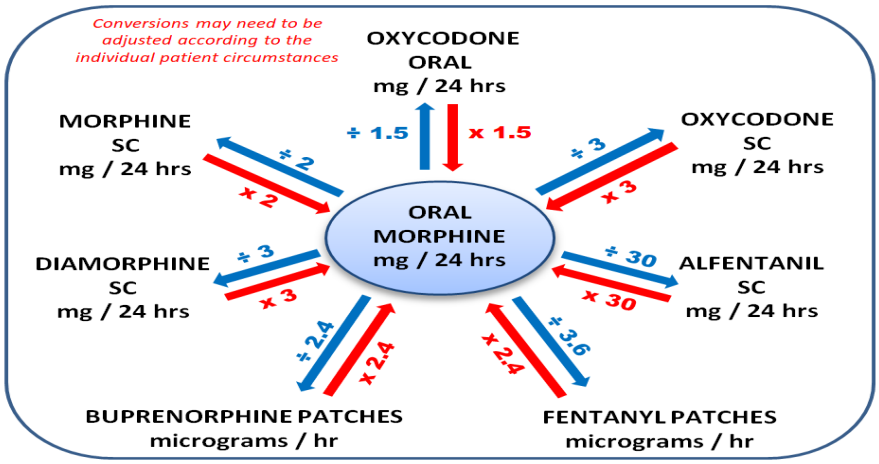
- Several sublingual or nasal fentanyl products are available but tend to have a short lived action and can take time to titrate to effective doses. They can however be useful for incident pain if longer acting immediate release opioids are causing side effects. The Specialist Palliative Care team will be able to advise if this approach is appropriate.
- Sublingual buprenorphine 200micrograms approximates to 15mg oral morphine and often provokes nausea so is not recommended for routine use in palliative care.
- In general either morphine or oxycodone immediate release (oral or subcutaneous), depending on the patients individual situation, are used for PRN medication when transdermal patches provide background pain relief.

7. Combining opioids

In an imminently dying patient or in a situation of acute pain where a transdermal patch is already in situ, it is recommended to continue the patch at the same dose and to give any additional regular analgesia either orally or using a continuous subcutaneous infusion via a syringe driver if the patient cannot swallow or absorb oral medication. This is due to the time taken to achieve steady state with an increased patch dose. It is important to remember that when calculating the PRN doses in this situation that both patches and syringe driver are taken into consideration. It is recommended that the prescriber contacts the Specialist Palliative Care team directly in hours or via UHL switchboard out of hours if uncertain how to do this.

8. Opioid conversion visual representation

Some people find calculating conversions easier using this figure:



9. Prescribing in renal impairment

Refer to UHL Guidelines: *Opioid Analgesics in Adult patients with Renal Impairment from all causes* and *Symptom management of Adult patients in their Last days of life* for more details.

Transdermal patches are a reasonably safe option for patients with renal impairment and stable pain. Low dose buprenorphine can be used in opioid naïve patients, fentanyl patches should not be used unless the patient is already receiving regular opioids at a dose equivalent to 30-45mg oral morphine/24hours.

Alfentanil is the safest opioid to use as a continuous subcutaneous infusion in patients with significant renal impairment (consider if eGFR < 30 or is rapidly deteriorating).

Alfentanil has a very short duration of action so is not usually suitable as a breakthrough medication. The prn opioid in renal impairment should usually be oxycodone. When eGFR<30, it may be prudent to reduce the usual PRN dose and/or extend the PRN dose interval. The approach should be individualised; appropriate options may include halving the usual PRN dose and/or extending the dose interval to 6 hourly taking the severity of symptoms and analgesic requirements into account. Discussion with the Specialist Palliative Care team may be necessary.

Example 1:*A patient is established on oral Morphine MR 60mg bd (total 120mg/24hrs):*

- *120mg oral Morphine/24hrs ÷ 30 = Alfentanil 4mg/24hrs via subcutaneous syringe driver.*
- *Breakthrough dose **oral** morphine:*
  - *120mg ÷ 6 = 20mg orally PRN (minimum dose interval 6 hours)*
  - ***Or** 120mg ÷ 12 = 10mg orally PRN (minimum dose interval 2-4 hours)*
- *Breakthrough dose **subcutaneous** Morphine (halve the PRN oral Morphine dose):*
  - *20mg ÷ 2 = 10mg subcutaneously PRN (minimum dose interval 6 hours)*
  - ***Or** 10mg ÷ 2 = 5mg subcutaneously PRN (minimum dose interval 2-4 hours)*

Example 2: *A patient is already using oral Oxycodone MR 30mg BD (total 60mg/24hrs)*

- *60mg oral Oxycodone x1.5 = 90mg oral Morphine/24hrs.*
- *90mg oral Morphine ÷ 30 = Alfentanil 3mg/24hrs via subcutaneous syringe driver.*
- *Breakthrough dose **oral** Oxycodone:*
    - *60mg ÷ 6 = 10mg orally PRN (minimum dose interval 6 hours)*
    - ***Or** 60mg ÷ 12 = 5mg orally PRN (minimum dose interval 2-4 hours)*
- *Breakthrough dose **subcutaneous** Oxycodone (halve the PRN oral Oxycodone dose):*
    - *10mg ÷ 2 = 5mg subcutaneously PRN (minimum dose interval 6 hours)*
    - ***Or** 5mg ÷ 2 = 2.5mg subcutaneously PRN (minimum dose interval 2-4 hours).*

10. Education and Training

The Specialist Palliative Care Team deliver education and training on symptom control and end of life care. This guidance aims to raise awareness and help structure normal clinical activity rather than develop new skills. Further advice on this guidance is available from the Specialist Palliative Care Team on ext. 15414 (LRI), 13540 (GH) and 14680 (LGH).

11. Monitoring and Audit Criteria

Key Performance Indicator	Method of Assessment	Frequency	Lead
Appropriate opiate conversion or clinically appropriate reasoned and documented individualised decision	Audit	Annual	Sarah Bell

12. Legal Liability Guideline Statement

Guidelines or Procedures issued and approved by the Trust are considered to represent best practice. Staff may only exceptionally depart from any relevant Trust guidelines or Procedures and always only providing that such departure is confined to the specific needs of individual circumstances. In healthcare delivery such departure shall only be undertaken where, in the judgement of the responsible healthcare professional it is fully appropriate and justifiable - such decision to be fully recorded in the patient's notes.

13. Supporting Documents and Key References

The dosage conversions in this document align with those recommended by the Palliative Care Formulary and the WM Cares Guidelines for the Use of Drugs in Symptom Control.

https://www.medicinescomplete.com

https://www.westmidspallcare.co.uk/wmpcp/guide/pain/relative-doses-of-opioids/

NG46 Controlled drugs: safe use and management
https://www.nice.org.uk/guidance/ng46/chapter/Recommendations#prescribing-controlled-drugs

14. Key Words

Opiate, Opioid, Analgesia, Conversion, Conversions, Switching, Morphine, Oxycodone, Alfentanil, Buprenorphine, Fentanyl, Hydromorphone, Methadone, Codeine, Dihydrocodeine, Tramadol, Tapentadol, Pain control, Palliative, Last Days of Life, End of Life, Dying, Renal, Syringe driver, Syringe pump, pain patches, analgesic patches, Transdermal, subcutaneous

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This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Dr Sarah Bell/ Dr Rosie Bronnert Executive Lead: Medical Director	**Job Title:** Consultant in Palliative Medicine/ Consultant in Palliative Medicine
Reviewed by:	End of Life Steering Group, CHUGGS Quality and Safety Board, Medicines Optimisation Committee, Palliative Care Consultants	
Approved by:	**Policy and Guideline Committee**	**Date Approved: 19.8.22 v2 - 16.2.24**

REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**

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