30. GUIDELINES FOR STRONG OPIOID SUBSTITUITION IN PALLIATIVE CARE

30.1 GENERAL PRINCIPLES

* Morphine is the strong opioid of choice in palliative care. [1,2]
* Options for opioid substitution include oxycodone, fentanyl, methadone, hydromorphone and alfentanil. [3]
* The intramuscular route for strong opioids is not recommended in palliative care patients. [1,2]
* It is good practice to specify the brand when prescribing opioids e.g. Durogesic D-Trans,® MXL.® [24]

30.2 GUIDELINES

* Before considering opioid substitution, consider simple measures e.g.
  - Reduction in dose of strong opioid.
  - Use of appropriate rehydration.
  - Use of adjuvant medications to limit side effects e.g. haloperidol for hallucinations.
  - Checking for potential drug interactions.
  - Use of co-analgesics / interventional pain techniques appropriate to the pain syndrome. [1,4,5,6,7,8] [Level 2+]
* Indications for choosing alternatives to morphine are as follows:
  - Intolerable neuropsychiatric side effects developing during continuous use (e.g. agitation, delirium, myoclonic jerks, hallucinations, hyperalgesia or allodynia), and which are unresponsive to simple measures such as dose reduction, or if the dose reduction leads to increased pain. [1,4,6,7,8] [Level 2+]
  - Dose-limiting side effects of morphine prohibit dose escalation, leading to inadequate pain relief. [1,4,5,6,9] [Level 2+]
  - In patients with malabsorption, dysphagia or poor compliance, substitution to a transdermal patch such as fentanyl should be considered, but **only** if analgesic requirements are **stable**. If pain is unstable, subcutaneous diamorphine / morphine are considered first line. [10,11] [Level 2+]
  - For patients on morphine with moderate to severe constipation, despite adequate laxatives, substitution to transdermal fentanyl may be indicated. [10,11] [Level 2+]
  - Patient acceptability. [10] [Level 4]
* Table 30.1A gives further details about possibilities for opioid substitution.

* Care should be taken when calculating conversion doses, as variation in bioavailability and genetically determined receptor affinities can influence drug effect. When switching opioids due to symptoms of opioid toxicity, even in the presence of uncontrolled pain, consider a dose reduction of 25-50% (to adjust for incomplete cross tolerance). [4, 6, 12, 13] [Level 3]

* Tables 30.2 A and 30.2 B feature equianalgesic tables for the strong opioids currently in common usage. Responsibility for prescribing the correct dose of a strong opioid remains with the prescriber.

30.3 STANDARDS

1. Morphine is the oral strong opioid of choice. [1, 2] [Grade C]
2. Morphine or diamorphine are the parenteral strong opioids of choice. [1, 2] [Grade C]
3. The reason for a change of opioid should be documented in the case notes. [27] [Grade D]
4. Transdermal fentanyl should only be used if analgesic requirements are stable. [1, 9] [Grade C]
5. The drug brand name should be used when prescribing strong opioids. [24] [Grade D]

Table 30.1A Options for Strong Opioid Substitution [1, 3, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 28] [Levels of evidence in brackets]			
Name of strong opioid	**Indication**	**Formulations available**	**Notes**
Alfentanil	First choice parenteral opioid in renal impairment. (see *Guidelines for Analgesic Prescribing in Renal Failure*).	Alfentanil injection: - 500microgams / ml: 2ml, 10ml ampoules - 5mg/ml: 1 ml ampoules	Alfentanil has a relatively quick onset and short duration of action making it suitable for pain of short duration e.g. incident pain. Rescue doses are independent of background opioid requirements, so initial doses should start low and be titrated e.g. 0.5-1mg PRN. [Level 3]
Diamorphine hydrochloride	First line opioid for parenteral use (if available). Morphine is an alternative.	Tablets: 10mg Injection: 5mg, 10mg, 30mg, 100mg, 500mg ampoules	Highly soluble. May be used to reduce the volume in a CSCI.
Fentanyl (transdermal)	Patient has **stable pain** but: − unable to swallow / malabsorption. − moderate to severe constipation despite laxatives. − intolerable side effects with morphine. − for consideration in renal failure. [Level 2+]	Patch strength(all micrograms/hour) 12mcg (matrix type only), 25mcg, 50mcg, 75mcg, 100mcg/hour	Patch should be changed every 72 hours. It should be continued in the dying phase even if additional additional analgesia is required vi a CSCI. There are reservoir and matrix patches available. Patches should not be cut or divided. 12microgram patch appears not to be licensed as a starting dose therefore suggest should start with 25microgram and use 12microgram patch as part of titration regimen.
Fentanyl (transmucosal)	For breakthrough pain when background pain control is achieved and titration of opioid complete.	Lozenges (Actiq®) 200mcg, 400mcg, 600mcg, 800 mcg, 1.2mg, 1.6mg Buccal tablet (Effentora®) 100mcg, 200mcg, 400mcg, 600mcg, 800mcg Sublingual tablet (Abstral®) 100mcg, 200mcg 300mcg, 400mcg, 600mcg, 800mcg tablets Intranasal spray (Instanyl®) 50mcg, 100mcg, 200mcg	Starting dose should be lowest available dose irrespective of background analgesic use and adjusted according to the intensity of breakthrough pain and dose response. Consult individual drug SPC for further details. Note that Abstral® Effentora ®and Actiq® can not be prescribed by non- medical prescribers Abstral®/ Effentora® / Instanyl® / Actiq® **only to be used for patients on 60mg oral morphine daily (or equivalent).** [25, 26]
Hydromorphone	Intolerable side effects limiting dose escalation of morphine. [Level 1-]. Possible benefit in pruritis. [Level 2-] For consideration in renal failure (see *Guidelines for Analgesic Prescribing in Renal Failure*).	Hydromorphone IR (immediate release) capsules: 1.3mg or 2.6mg Hydromorphone SR (slow release) capsules: 2mg, 4mg, 8mg, 16mg, 24mg	Capsule form only. Parenteral preparation available on an individual basis and is currently unlicensed in the UK.

30.1A Options for Strong Opioid Substitution [1, 3, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 28] [Levels of evidence in brackets]			
Name of strong opioid	**Indication**	**Formulations available**	**Notes**
Methadone	Partially opioid responsive pain especially neuropathic pain. Intolerable side effects limiting dose escalation of other strong opioids. Methadone should not be considered a first line alternative to morphine (see *Guidelines for Conversion from Strong Opioid to Methadone*).	Methadone tablets: 5mg Methadone solutions: 1mg/ml, 10mg/ml, 20mg/ml Methadone for injection 10mg/ml: 1ml, 2ml and 3.5ml ampoules NB: The 2mg/5ml linctus is only used for the management of intractable cough	Effects may be unpredictable. [Level 3] Dose titration should be carried out in a specialist unit following the established guidelines. [Level 4] No guidelines exist for conversion back to other strong opioids. [Level 3] Parenteral form should only be used with caution due to site reaction.
Morphine	First choice oral opioid. First choice parenteral opioid. Diamorphine is an alternative	Oramorph® solutions: 10mg/5ml or 20mg/ml or 100mg/5ml Sevredol® solutions 10mg/5ml or 100mg/5ml Sevredol® tablets: 10, 20, 50mg MXL® capsules: 30, 60, 90, 120, 150, 200mg MST® tablets: 5, 10, 15, 30, 60, 100, 200mg MST® sachets: 20, 30, 60, 100, 200mg Zomorph® capsules: 10, 30, 60, 100, 200mg Rectal preparations (immediate release) Morphine sulphate amps for injection:10mg/ml, 15mg/ml, 30mg/ml. 1ml or 2 ml ampoules	Avoid in patients with severe renal impairment i.e. (eGFR < 30ml/min). *See Guidelines for Analgesic Prescribing in Renal Failure*.
Oxycodone hydrochloride	Intolerable side effects limiting dose escalation of morphine. [Level 1+] For consideration in renal failure (see *Guidelines on Analgesic Prescribing in Renal Failure*).	Oxynorm® solutions: 5mg/5ml or 10mg/ml Oxynorm® capsules : 5, 10, 20mg Oxycontin® tablets: 5, 10, 20, 40, 80mg Oxycodone hydrochloride for injection: 10mg/ml: 1 ml or 2ml ampoules;50mg/ml ampoule	

Table 30.2A Equianalgesic Table for Strong Opioids [23] [Level 2]

These tables serve as a guide only. The prescriber is ultimately responsible for his/her own actions. Equianalgesic doses are difficult to ascertain due to wide inter-patient variations, drug interactions and non-interchangeability of products. Initial dose conversions should be conservative; it is preferable to under-dose the patient and use rescue medication for any shortfalls.

Morphine PO 4 hourly	Morphine SR PO BD	Morphine SR PO 24 hourly	Oxycodone PO 4 hourly	Oxycodone SR PO BD	Hydromorphone PO 4 hourly	Hydromorphone SR PO BD	Transdermal Fentanyl 72 hrly
2.5mg	10mg	-	1.25mg	5-10mg	-	-	-
5mg	15mg	30mg	2.5mg	10mg	1.3mg	2mg	12mcg
10mg	30mg	60mg	5mg	20mg	1.3 mg	4 mg	25 mcg
20mg	60mg	120mg	10-15mg	40mg	2.6 mg	8 mg	50 mcg
30mg	90mg	180mg	20mg	60mg	3.9 mg	12 mg	75 mcg
40mg	120mg	240mg	25mg	80mg	5.2 mg	16 mg	100 mcg
50mg	150mg	300mg	30-35mg	100mg	6.5 mg	20 mg	125 mcg
60mg	180mg	360mg	40mg	120mg	7.8 mg	24 mg	150 mcg
65-70mg	200mg	400mg	40-45mg	130mg	9.1 mg	28 mg	162–175 mcg
80mg	240mg	480mg	50-55mg	160mg	10.4 mg	32 mg	200 mcg
85-90mg	260mg	520mg	55mg	170mg	11.7 mg	36 mg	225 mcg
100mg	300mg	600mg	65mg	200mg	13 mg	40 mg	250 mcg
110mg	330mg	660mg	70-75mg	220mg	14.3 mg	44 mg	275 mcg
120mg	360mg	720mg	80mg	240mg	15.6 mg	48 mg	300 mcg
140mg	420mg	840mg	90-95mg	280mg	18.2 mg	56 mg	¥
160mg	480mg	960mg	105mg	320mg	20.8 mg	64 mg	¥
180mg	540mg	1080mg	120mg	360mg	23.4 mg	72 mg	¥

¥ Manufacturer recommends that above doses of 300 microgram/hour, alternative or additional methods of analgesia should be used

Due to the non-uniformity with equianalgesic ratios in the literature with oxycodone, use the table below to convert between routes

Oxycodone SR PO BD	Oxycodone SC PRN	Oxycodone CSCI in 24 hrs
5mg	2.5mg	5-10mg
10mg	2.5-5mg	10-15mg
20mg	5mg	25-30mg
40mg	10mg	50-55mg
60mg	15mg	80mg
80mg	20mg	105-110mg
100mg	20-25mg	130-135mg
120mg	25-30mg	160mg
130mg	30mg	170-175mg
160mg	35mg	210-215mg
170mg	40mg	225-230mg
200mg	45mg	265-270mg
220mg	50mg	290-295mg
240mg	55mg	320mg
280mg	60mg	370-375mg
320mg	70mg	425-430mg
360mg	80mg	480mg

General Guidance

- **Prescribe *all* strong opioid preparations by brand where applicable to ensure continuity of therapy.**
- Leave transdermal patches *in situ* when the patient can no longer tolerate oral medication and use subcutaneous injections to deliver breakthrough medication and a syringe driver to deliver the increasing analgesia requirements.
- Doses shown here are approximated to the most practical, based on current formulations.
- The tables have been generated using values based on expert consensus which may differ from manufacturers' recommendations:-
  - Oral *morphine* 3mg = oral *oxycodone* 2mg (oxycodone is more potent than morphine when given by mouth; NB – manufacturer states 2:1).
  - Oral *morphine* 3mg = parenteral *morphine* 1.5mg = parenteral *diamorphine* 1mg.
  - Oral *oxycodone* 3mg = parenteral *oxycodone* 2mg (manufacturer states 2:1).
  - Parenteral *morphine* 1.5mg = parenteral *oxycodone* 1.5mg = parenteral *diamorphine* 1mg (morphine and oxycodone are considered equivalent when given parenterally).

Table 30.2B Equianalgesic Table for Strong Opioids [23] [Level 2]

These tables serve as a guide only. The prescriber is ultimately responsible for his/her own actions. Equianalgesic doses are difficult to ascertain due to wide inter-patient variations, drug interactions and non-interchangeability of products. Initial dose conversions should be conservative; it is preferable to under-dose the patient and use rescue medication for any shortfalls.

Morphine SC PRN	Morphine CSCI in 24hrs	Diamorphine SC 4hrly	Diamorphine CSCI in 24hrs	Alfentanil SC PRN	Alfentanil CSCI in 24hrs	Oxycodone SC PRN	Oxycodone CSCI in 24 hrs
2.5mg	10mg	2.5mg	5-10 mg	0.25mg	0.5-1mg	2.5mg	10mg
2.5mg	15mg	2.5mg	10 mg	0.25mg	1mg	2.5mg	15mg
5mg	30mg	5mg	20 mg	0.5mg	2mg	5mg	30mg
10mg	60mg	5-10mg	40 mg	0.5-1mg	4mg	10mg	60mg
15mg	90mg	10mg	60 mg	1mg	6mg	15mg	90mg
20mg	120mg	15mg	80 mg	1.5mg	8mg	20mg	120mg
25mg	150mg	15-20mg	100 mg	1.5-2mg	10mg	25mg	150mg
30mg	180mg	20mg	120 mg	2mg	12mg	30mg	180mg
30-35mg	200mg	20mg	130 mg	2mg	13mg	30-35mg	200mg
40mg	240mg	25-30mg	160 mg	2-3mg	16mg	40mg	240mg
40-45mg	260mg	25-30mg	170 mg	3mg	17mg	40-45mg	260mg
50mg	300mg	30-35mg	200 mg	3-3.5mg	20mg	50mg	300mg
55mg	330mg	35-40mg	220 mg	3.5-4mg	22mg	55mg	330mg
60mg	360mg	40mg	240 mg	4mg	24mg	60mg	360mg
70mg	420mg	45-50mg	280 mg	4.5-5mg	28mg	70mg	420mg
80mg	480mg	50-55mg	320 mg	5.5mg	32mg	80mg	480mg
90mg	540mg	60mg	360mg	6mg	36mg	90mg	540mg

Transtec® Patch 96 hourly	Morphine PO 4 hourly	Morphine SR PO BD	BuTrans® Patch weekly
-	2.5-5mg	10-20mg	10 mcg
-	5-10mg	20-30mg	20mcg
35 mcg	10-15mg	30-50mg	-
52.5 mcg	15-25mg	50-75mg	-
70 mcg	20-30mg	60-100mg	-
105 mcg	30-50mg	100-150mg	-
140 mcg (max)	40-60mg	120-190mg	-
Buprenorphine equianalgesia with PO morphine varies in the literature from 75:1 to 115:1. The values in the table reflect this.			

General Guidance

- **Prescribe *all* strong opioid preparations by brand where applicable to ensure continuity of therapy.**
- Leave transdermal patches *in situ* when the patient can no longer tolerate oral medication and use subcutaneous injections to deliver breakthrough medication and a syringe driver to deliver the increasing analgesia requirements.
- Doses shown here are approximated to the most practical, based on current formulations.
- The tables have been generated using values based on expert consensus which may differ from manufacturers' recommendations:-
  - Oral *morphine* 3mg = oral *oxycodone* 2mg (oxycodone is more potent than morphine when given by mouth; NB – manufacturer states 2:1).
  - Oral *morphine* 3mg = parenteral *morphine* 1.5mg = parenteral *diamorphine* 1mg.
  - Oral *oxycodone* 3mg = parenteral *oxycodone* 2mg (manufacturer states 2:1).
  - Parenteral *morphine* 1.5mg = parenteral *oxycodone* 1.5mg = parenteral *diamorphine* 1mg (morphine and oxycodone are considered equivalent when given parenterally).

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