NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

PALLIATIVE CARE

Pharmacological Management of Cancer Pain in Adults

NCEC guideline number 9

1. WHO ANALGESIC LADDER

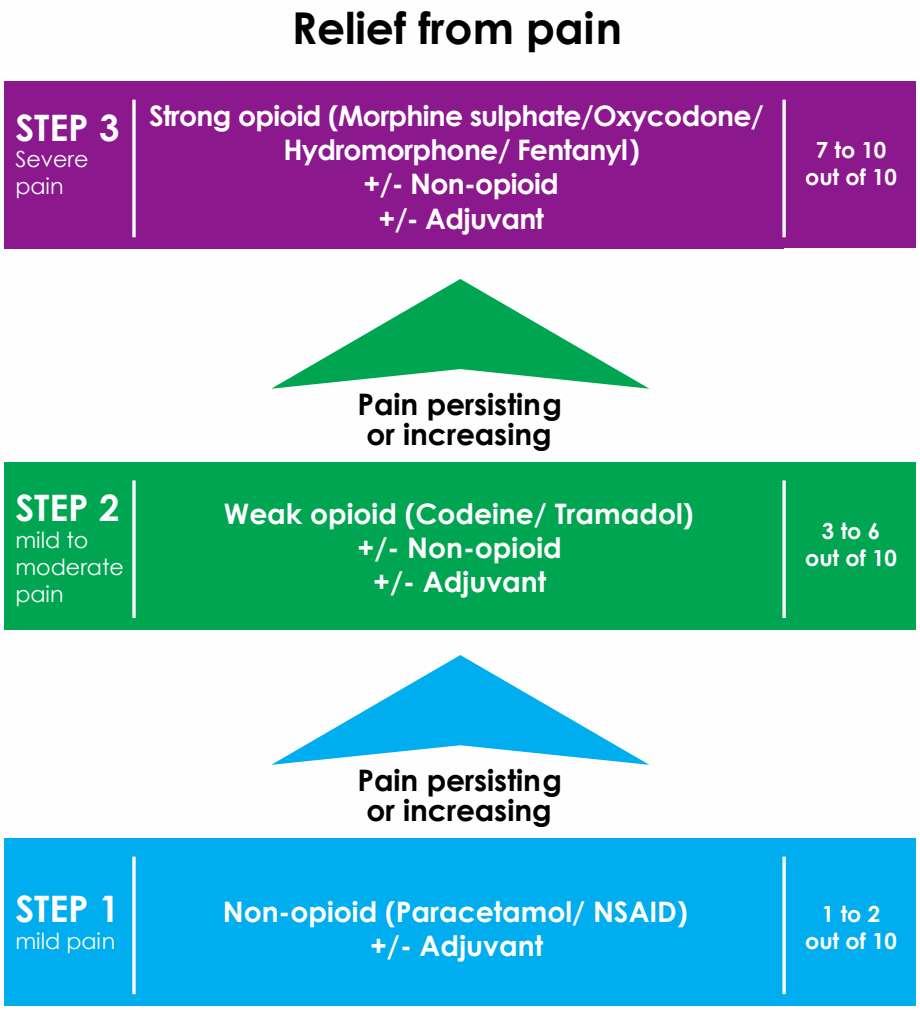

Figure 1 Adapted from World Health Organisation analgesic ladder from World Health Organisation. Cancer Pain Relief, 2nd ed. Geneva: WHO, 1996.

2. TYPES OF MEDICATIONS

Table 2 Opioids Routes of Administration

Opioid	Oral long acting	Oral short acting	Patch	Injection (SC/IV)
Morphine sulphate	MST	Oramorph (liquid Severedol (tab)	–	Morphine sulphate
Oxycodone	OxyContin Targin	OxyNorm (tablet or liquid)	–	Oxycodone
Hydromorphone	Palladone SR	Palladone IR	–	Hydromorphone
Fentanyl	–	Effentora (TB) Abstral (TB) Instanyl (TB) Pecfent (TB)	Durogesic Matrifen	Alfentanil Fentanyl
Buprenorphine	–	–	Transtec BuTrans	–

The average relative potency ratio of oral morphine sulphate to subcutaneous or intravenous morphine sulphate is between 2:1 and 3:1, with variability between patients.

2. TYPES OF MEDICATIONS – *CONTINUED*

HOW TO AVOID predictable opioid side effects:

Constipation: PRESCRIBE regular laxatives, the combination of softener and stimulant is recommended.

Nausea: ENSURE availability of an antiemetic (e.g. cyclizine 50mg, metoclopramide 10mg, or haloperidol 0.5-1.5mg either regularly or PRN.)

Sedation: WARN patients that mild sedation may occur for the first few days, and advise of the risks of driving or using machinery.

Dry Mouth: ADVISE on simple mouthcare regimens.

2. TYPES OF MEDICATIONS – *CONTINUED*

Breakthrough (PRN) analgesia

In addition to regular strong opioids patients should have access to breakthrough analgesia. This 'rescue' dose is typically prescribed as 1/6th of the total daily dose of opioid.

For management of breakthrough pain use either oral immediate release opioids OR short acting fentanyl preparations (only for patients on background opiate of 60mg PO morphine equivalent -*seek specialist advice) given before or soon after breakthrough pain has started.

More than four episodes of breakthrough pain a day generally indicates that the current management of the baseline/ persistent pain should be reviewed.

2. TYPES OF MEDICATIONS – *CONTINUED*

Adjuvants

These medications can be used throughout all steps of the WHO analgesic ladder where appropriate. Some common examples are provided in table 3. *Note they may have an opioid sparing effect and reduction of opioid may be required.*

Table 3 Adjuvant medications and treatments for relief of cancer pain

Adjuvant medications and treatments	Examples	Specific use for relief of pain
Corticosteroids	Dexamethasone	To alleviate inflammatory component of pain where present e.g. liver capsule pain; nerve root/ trunk compression
Anti-spasmodics	Hyoscine butylbromide (buscopan) Baclofen	To relieve pain due to visceral spasm To relieve pain due to muscle spasm
Anti-depressants	Tricyclics (amitryptiline)	For neuropathic pain
Anti-epileptics	Gabapentin, pregabalin Clonazepam	For neuropathic pain
Muscle relaxants	Diazepam Local anaesthetic or steroid injections	To relieve pain due to muscle spasm For trigger point pain
Bisphosphonates	Zoledronic acid	For metastatic bone pain

3. HOW TO START STRONG OPIOIDS

HOW TO START STRONG OPIOIDS FOR MODERATE TO SEVERE CANCER PAIN (Using oral morphine sulphate as an example)

The starting dose of analgesia is dependent on a number of factors, including severity of pain, current or prior use of analgesia, renal and hepatic function, age and BMI. Stop the regular weak opioid and consult opioid equivalence table for appropriate starting dose. Seek specialist advice where needed.

Method 1: Starting Opioids Using Immediate Release Oral Preparations
(Using oral morphine sulphate as an example)

- Use immediate release morphine sulphate (e.g. Oramorph or Sevredol), given every 4 hours, and the same dose for breakthrough pain. This rescue dose may be given as often as required and the total daily dose of the morphine sulphate should be reviewed daily.
  e.g. Oramorph 2.5mg 4hourly PO regularly, with access to PRN doses
  - Lower doses e.g. 1-2.5mg may be required in the opioid-naïve, elderly or frail and those with renal impairment.
  - Higher doses may be required in those who have been taking step 2 analgesics prior to commencement of opioid.
- If pain returns consistently before the next regular dose is due, titrate the regular 4-hourly dose accordingly, either through calculation of the number of breakthrough doses taken, or by a percentage increase of 30-50%. Re-assess analgesic effect in 24-48hrs. Patients require continued access to a rescue dose to treat breakthrough pain.
- Continue to titrate up the regular and PRN dose until 4 hourly pain relief is achieved: once controlled with immediate release morphine sulphate, the 24 hour dose can be converted into modified 12 hour release preparation (e.g. MST®).

3. HOW TO START STRONG OPIOIDS – *CONTINUED*

Method 2: Starting Opioids Using Modified Release Oral Preparations

(using oral morphine sulphate as an example)

- Use a 12 hourly modified release preparation(e.g. MST®) prescribed twice daily. In generalist clinical practice, a typical starting dose for an opioid-naïve, elderly or frail patient would be MST® 5mg bd PO.
- Co-prescribe an immediate release oral morphine sulphate preparation, (e.g. Oramorph or Sevredol) to be taken as often as required as a breakthrough dose e.g. oramorph 1-1.25mg PO 2-4hourly.
- After 24 hours, assess the effectiveness of the regimen based on clinical assessment of the patient. Titrate the modified release formulation accordingly (either through calculation of number of breakthrough doses taken, or by a percentage increase of 30-50%)

4. OPIOID TOXICITY

Opioid toxicity
Opioid toxicity may present as subtle agitation, drowsiness, seeing shadows at the periphery of the visual field, vivid dreams, hallucinations, confusion and myoclonic jerks. If untreated, this may progress towards respiratory depression.

Management:

- If opioid toxicity is present and pain control is **adequate**
  - a reduction in opioid dose is indicated (as well as treating any possible precipitants such as infection and dehydration, or deteriorating renal function).
- If opioid toxicity is present but pain control is inadequate,
  - rotation to an alternative opioid may allow titration to adequate analgesia without the same disabling effects (see below).

Management of opioid toxicity, where pain control is adequate:
Renal and hepatic function should be checked where appropriate and other causes of systemic deterioration excluded e.g. infection, hypercalcaemia. Any reversible precipitating cause should be treated.

Mild opioid toxicity
In mild opioid toxicity:

- Reduce the dose of opioid (percentage reduction is dependent on clinical presentation)
- Ensure adequate hydration and treat any underlying cause
- If agitation/confusion are problematic despite use of non-pharmacological strategies, consider a neuroleptic such as haloperidol.

Moderate opioid toxicity
If respiratory rate ≥ 8/min, oxygen saturations are normal and the patient is not cyanosed and is easily rousable, omit the next dose (or stop infusion/remove patch) of regular opioid immediately, and adopt a 'wait and see' approach. When the situation is more stable, either omit or reduce further doses and re-assess pain before re-introducing regular opioid therapy.

Severe opioid toxicity
If respiratory rate is 8/min or less, oxygen saturations are abnormal or the patient is cyanosed, urgent admission is indicated. Consider reversal of respiratory depression using naloxone; use reversing agents cautiously. The aim is to reverse respiratory depression without compromising pain control. This may not fully reverse sedation. The patient's background analgesia will subsequently need to be reviewed. **Seek specialist palliative medical advice**, particularly if transdermal patches have been used.

5. OPIOID ROTATION

Opioid rotation

When prescribed opioids for cancer pain, a number of patients will experience inadequate pain relief, persistent unacceptable side-effects, or a combination of the two, despite dose titration and management of predictable side-effects. Opioid rotation is the term given to the clinical practice of substituting one opioid – the 'initial opioid' - with another, in order to obtain a satisfactory balance between pain relief and side-effects.

When converting from an 'initial' opioid to a new opioid, the dose of the new opioid should depend on the relative potency ratio of the two drugs. Clinicians must remember that opioid dose conversion ratios are not fixed but are affected by the clinical context of the switch and the setting of care.

Opioid equivalence summary table

Guidelines for use:

- Relative potency ratios should only be used as an approximate guide and individual and clinical factors should be taken into account
- **When rotating opioids, particularly at high doses, a dose reduction of 25 – 50% should be considered to account for incomplete cross-tolerance** (specialist advice should be sought when rotating at high doses).
- Pain control should be assessed regularly, and doses titrated according to the assessment findings.

5. OPIOID ROTATION – *CONTINUED*

Table 4 Opioid Equivalence Summary Table (see Table 12 National Guideline No.9 Pharmacological Management of Cancer Pain in Adults) (all recommendations Grade C)

Morphine		Codeine	Tramadol	Oxycodone		Hydromorphone		Buprenorphine		Fentanyl	Morphine	
(mg / 24 hrs)		*(mg / 24 hrs)*	*(mg / 24 hrs)*	*(mg / 24 hrs)*		*(mg / 24 hrs)*		*(mcg / hour) Butrans®*	*(mcg / hour) Transtec®*	*(mcg / hour)*	*(mg / 24 hrs)*	
Oral	**S/C**	**Oral**	**Oral**	**Oral**	**S/C**	**Oral**	**S/C**	**Transdermal**		**Transdermal**	**Oral**	**S/C**
5	2.5	60	50	-	-	-	-	-		-	5	2.5
10	5	120	100	-	-	-	-	5	See Butrans®		10	5
20	10	240	200	-	-	4	2	10		12	20	10
30	15	Titrate to strong opioid		20	10	6	3				30	15
40	20		400			8	4	20		18	40	20
50	25			-	-	10	5				50	25
60	30			40	20	12	6	See Transtec®	35	25	60	30
70	35					14	7				70	35
80	40					16	8			37	80	40
90	45		Titrate to strong opioid	60	30	18	9		52.5		90	45
100	50					20	10				100	50
110	55					-	-			50	110	55
120	60					24	12				120	60
130	65			80	40	-	-		70		130	65
140	70					28	14			62	140	70
150	75					-	-				150	75
160	80			100	50	32	16				160	80
170	85					-	-	Consider the use of an alternative opioid		75	170	85
180	90					36	18				180	90
190	95					-	-				190	95
200	100					-	-			-	200	100

5. OPIOID ROTATION – *CONTINUED*

Table 5 Process for converting opioid doses (see Table 11 National Guideline No.9 Pharmacological Management of Cancer Pain in Adults)

Converting From	Converting To	Process
Oral (mg)	**Oral (mg)**	
Codeine	Morphine sulphate	Divide by 10
Tramadol	Morphine sulphate	Divide by 5 – 10
Morphine sulphate	Oxycodone	Divide by 1.5 -2
Morphine sulphate	Hydromorphone	Divide by 5
Oral (mg) / 24 hours	**Subcutaneous / 24 hours**	
Morphine sulphate	Fentanyl (mcg)	Divide by 100 to obtain equivalent fentanyl dose in mg. Multiply by 1000 to obtain dose in mcg / 24 hrs.
Morphine sulphate	Alfentanil (mg)	Divide by 32
Oral (mg) / 24h hours	**Transdermal (mcg / hour)**	
Morphine sulphate	Buprenorphine	Divide by 75 to obtain equivalent buprenorphine dose in mg. Multiply by 1000 to obtain dose in mcg / 24 hrs. Divide this by 24 to obtain equivalent transdermal dose in mcg / hour, and use closest available patch strength.
Morphine sulphate	Fentanyl	Divide by 100 to obtain equivalent fentanyl dose in mg. Multiply by 1000 to obtain dose in mcg / 24hrs. Divide this by 24 to obtain equivalent transdermal dose in mcg / hour, and use closest available patch strength.
	Alternatively, use Table 4 to obtain closest appropriate patch strength	

REMEMBER

- Holistic assessment and regular review are the cornerstones of good pain management
- The patient is the prime assessor of their pain
- Start at the level of the WHO analgesic ladder appropriate for the severity of the pain
- If pain uncontrolled prescribe medication from the next step of the ladder rather than alternative analgesic from the same step
- Don't treat a pain you don't understand – seek expert advice when needed
- Remember that disease modifying treatment may help pain control
- Involve patient and carer as partners in management plan

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This summary guideline applies to healthcare professionals involved in the management of cancer pain. This includes Palliative Care staff, Physicians, Surgeons, General Practitioners, Pharmacists and Nursing staff in hospital, hospice and community-based settings. They may also be of interest to patients with cancer pain and their carers. This summary guideline does not apply to cancer survivors, to patients who do not have a cancer diagnosis or to other forms of acute or chronic non-malignant pain. This guideline does not apply to children.

Disclaimer

The Guideline Development Group's expectation is that healthcare staff will use clinical judgement, medical, nursing and clinical knowledge in applying the general principles and recommendations contained in this document. Recommendations may not be appropriate in all circumstances and the decision to adopt specific recommendations should be made by the practitioner taking into account the individual circumstances presented by each patient/ resident and available resources. Therapeutic options should be discussed with the responsible physician on a case-by-case basis as necessary.