Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Mid-Western Regional Hospitals Complex
St. Camillus and St. Ita's Hospitals

ANALGESIC POLICY

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Pain is what the patient says it is

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INTRODUCTION

ANALGESIC POLICY

'Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [IASP Definition].

Tolerance to pain varies between individuals and can be affected by a number of factors. Factors that lower pain tolerance include insomnia, anxiety, fear, isolation, depression and boredom. Treatment of pain is dependent on its cause, type (musculoskeletal, visceral or neuropathic), duration (acute or chronic) and severity.

Acute pain which is poorly managed initially can degenerate into chronic pain which is often more difficult to manage.

Pragmatic and practical approaches to pain management have been developed for different settings (*e.g.* acute pain, chronic benign pain and cancer pain). Realistic aims are to recognize pain, to minimize moderate to severe pain, to prevent pain where predictable, to bring pain rapidly under control and to continue pain control after discharge from hospital.

The following information is for guidance when prescribing or checking analgesia. This guide is divided into the following sections:

- ANALGESIA AND ADULT ACUTE AND CHRONIC PAIN
- ANALGESIA AND PAEDIATRIC PAIN
- ANALGESIA AND CANCER PAIN
- ANALGESIA AND THE ELDERLY
- ANALGESIA AND RENAL FAILURE
- ANALGESIA AND LIVER FAILURE

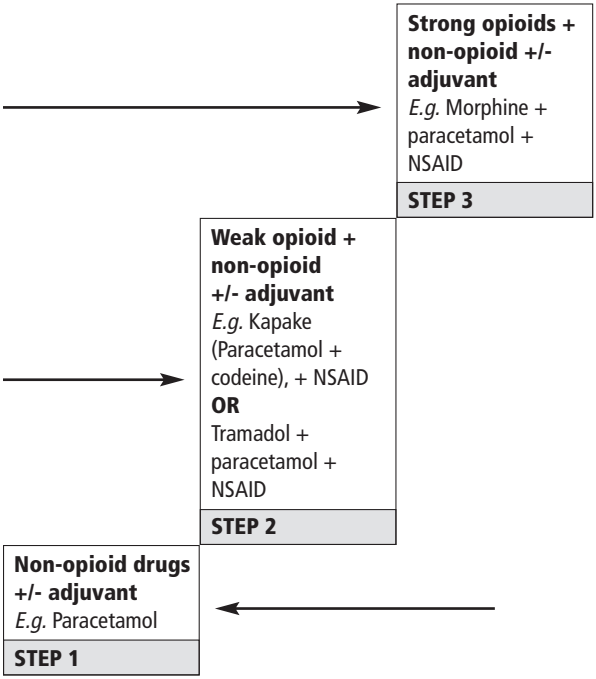
Expert advice is available through Pain Medicine and Palliative Medicine teams. Pharmacy is an invaluable resource for advice. Other Hospital specialists can also provide valuable assistance in the management of patient's pain.

1 ANALGESIA AND ADULT ACUTE AND CHRONIC PAIN

1.1 PRINCIPLES OF PAIN MANAGEMENT

- Pain is what the patient says it is and measures should be instigated to manage it as soon as possible.
- Aim to accurately diagnose the source of the pain (use verbal and non-verbal cues from patient).
- Consider any previous analgesic requirements when selecting an initial preparation and dose.
- Set realistic goals inclusive of the patient's needs.
- Prescribe according to the WHO analgesic ladder (note step down approach for acute pain).
- Use REGULAR analgesia.
- Give analgesics REGULARLY before consideration is given to moving up the analgesic ladder.
- Stop prescriptions for preparations containing weak opioids if stronger opioids are prescribed as they can potentially block opioid receptors reducing the efficacy of the stronger opioid (*e.g.* tramadol and morphine).
- Use the ORAL ROUTE at all times unless the patient's status precludes it.
- Re-assess frequently.
- Consider non-drug treatments (*e.g.* TENS, exercise, relaxation training etc.)
- Anticipate unwanted side effects of medication (*e.g.* nausea/vomiting, constipation).

1.2 WHO ANALGESIC LADDER



Adjuvant:
Non-steroidal anti-inflammatory drugs (NSAID) if no contra-indications.
Analgesics for neuropathic pain *e.g.* amitriptyline, gabapentin, pregabalin.
Other means of pain relief *e.g.* nerve blocks, TENS.

In postoperative pain management a step-down approach is used. Anticipate severity of pain. Start at highest rung of ladder necessary and then use a step-down approach.

First Three Rules of Analgesia:
BY THE CLOCK,
BY THE MOUTH
AND
BY THE LADDER

1.3 MILD PAIN – STEP 1

Simple analgesics

- Non-opioid analgesics given regularly for mild pain.
- **Prescribe on regular section of prescription chart**.
- Drugs of choice are paracetamol and an NSAID if no contra-indications.
- Move to step 2 if correctly used non-opioids are ineffective.

1.3.1 PARACETAMOL

- Paracetamol has analgesic and antipyretic properties.
- It is the drug of first choice in mild or mild-to-moderate pain.
- Give in conjunction with opioids for more severe pain.
- Caution in hepatic impairment.
- Paracetamol IV 1g/100ml (Perfalgan). **Administration by the intravenous route on the ward is justified only when other routes of administration (orally or rectally) are not possible.**

Dose

- Oral or rectal route dose is 0.5g–1g QDS
  Most effective if given REGULARLY 1g QDS.
  (Maximum dose 4g/day)
- Intravenous route dose (see notes above):
  - Adults weighing more than 50 kg = 1g QDS
    (Maximum dose 4g/day)
  - Adults weighing less than 50 kg = 15 mg/kg QDS
    (Maximum dose 60 mg/kg/day but do not to exceed 2 g/day)

1.3.2 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

- These have an analgesic effect when given on an 'as required' basis and an anti-inflammatory effect when a regular full dose is given.
- Start at a low dose and titrate up if necessary. A minimum trial of 2 weeks is recommended.
- **Use of NSAIDs is associated with an increased risk of GI bleeding.**
- **Risk of GI bleeding is increased in the elderly (> 65 years).**

- Use only one agent at a time (except with low dose aspirin used for its antiplatelet action). Concomitant use with aspirin and/or corticosteroids substantially increases GI risk.
- Consider proton pump inhibitor in those at risk (*e.g.* Omeprazole 20mgs PO daily).
- NSAIDS may enhance the effects of warfarin.
- **Risk in older patients of renal impairment particularly if also on diuretics or dehydrated due to illness.**
- **There is a class effect of increased thrombotic risk with NSAIDs. NSAIDs should thus be avoided in those at cardiac risk (Hypertension/Cardiac failure/Diabetes) and otherwise used at lowest effective dose and for the shortest possible duration.**
- Ibuprofen at doses less than 1200mgs daily is not associated with increased thrombotic risk.

Contra-indications to NSAIDs

- Patients with a history of previous or active peptic ulcer disease.
- Hypersensitivity to NSAIDs.
- Anyone in whom asthma, angioedema, urticaria or rhinitis has been precipitated by NSAIDs.

A history of asthma is a relative not absolute contraindication to NSAIDs. Check previous consumption of NSAIDs in asthmatics. If no history of asthma exacerbation by NSAIDs can administer. Monitor closely (consider peak flows- 20% decrease after dosing is considered significant). COX2 inhibitors have been used safely in asthma.

Cautions

Elderly, renal, hepatic or cardiac impairment, pregnancy, coagulation defects, Inflammatory bowel disease.

NSAIDs may remove the cardioprotective effect of aspirin. This is particularly true for Ibuprofen. If these are taken together advise patients to; take Ibuprofen at least 30 minutes after aspirin or more than 8 hours before aspirin (this is true for aspirin (not enteric coated).

Preparations and dose

DRUG	DOSE	NOTES
Ibuprofen	200mg, 400mg tds po	Increase if necessary to max 2.4g daily
Diclofenac	25–50mg tds po 100mg every 16 hours pr **IM route not recommended***	Max daily dose by any route 150mg
Difene	75 mgs iv (diluted in 300mls 0.9% NaCL over 30 mins)	Max two infusions in 24 hours. Second dose can be given after 8 hours. Max 2 days
Difene gel (Diclac)	Apply 3–4 times daily	Review therapy after 14 days (or 28 days for OA)

***Important Note**: IM Diclofenac is not recommended in MWRH. It is a viscous preparation that is painful to administer and can cause nerve and tissue damage at administration site.

1.3.3 COX-2 SELECTIVE NSAIDS

Cyclo-oxygenase 2 selective (COX2) inhibitors such as celecoxib and parecoxib are available. These drugs have a **lower risk** of serious upper gastro-intestinal adverse effects than the non-selective NSAIDs. However, they have also been associated with serious and fatal GI adverse reactions.

Co-prescription of aspirin for cardiovascular prophylaxis means that this advantage of reduced gastro-intestinal adverse events is lost. All other adverse effects of the traditional NSAIDs also apply to the COX-2 selective NSAIDs. Cautions are as for conventional NSAIDs.

WARNING:
In the light of emerging concerns about cardiovascular safety, cyclo-oxygenase -2 selective inhibitors should be used in preference to non-selective NSAIDS **only** when specifically indicated (*i.e.* for patients who are particularly high risk of developing gastroduodenal ulcer, perforation, or bleeding) **and** after an assessment of cardiovascular risk. Furthermore the CSM has advised (August 2005) that patients who have ischaemic heart disease or cerebrovascular disease should not receive a cyclo-oxygenase-2 selective inhibitor.

- COX-2 selective NSAIDs are associated with fewer endoscopically visible gastroduodenal ulcers or erosions than non-selective NSAIDs.
- No advantage in patients' already taking aspirin prophylaxis.
- The risk of thrombotic event with Diclofenac 150mg OD is similar to Etoricxoxib.
- Naproxen is associated with lower thrombotic risk and low dose Ibuprofen (<1.2G daily) is not associated with increased risk of Myocardial Infacrction.

COX-2 selective NSAIDs are for use in preference to conventional NSAIDs **only when specifically indicated *i.e.* for patients who are at a particular high risk of developing gastroduodenal ulcer, perforation or bleeding** (*e.g.* over 65 years, patients taking other medicines which increase the risk of gastrointestinal effects, a serious co-morbidity or those receiving long-term treatment with maximal doses of standard NSAIDs) **and after an assessment of cardiovascular risk.**

COX-2 Selective NSAIDs

Contra-indications

- Active peptic ulceration or GI bleeding,
- Inflammatory bowel disease,
- Ischaemic heart disease and/or cerebrovascular disease,
- Severe congestive cardiac failure,
- Severe hepatic or renal disease,
- Pregnancy,
- Patients with allergies to NSAIDs,

Preparations and dose

DRUG	DOSE	NOTES
Celecoxib Celebrex®	100–200mg daily or in 2 divided doses po	Max daily dose recommended = 400mg. Max in elderly 200mg. **Only** licensed for osteoarthritis/ rheumatoid arthritis/ Ankylosing Spondylitis.

continued overleaf

DRUG	DOSE	NOTES
Etoricoxib (COX-2 selective) Arcoxia®	60mg daily OA, 90mg daily in RA, 120mg Gout for max of 8 days	ETORICOXIB is on MWRH preferred list
Parecoxib Dynastat®	40mg IV/IM followed by 20–40mg at 6 to 12 hour intervals, Licensed for not more than 3 days post operatively at a maximum daily dose of 80mg	Max dose recommended = 80mg daily. Discontinue if rash develops. **Max 3 days**

Reference

1. Taking stock of coxibs. Drugs and therapeutics Bulletin Jan 2005 Vol 43 No 1.

1.3.4 NSAIDS IN THE PERIOPERATIVE PERIOD

GENERAL CONSIDERATIONS

- These guidelines are for short-term use only.
  The continuing requirement for NSAIDs should be reviewed after 5 days.
- Patients requiring low-dose aspirin should be co-prescribed omeprazole or lansoprazole.
- Only one NSAID should be prescribed at any 1 time (excluding low-dose aspirin).
- Avoid pre-operative administration in those situations where increased blood loss would be a problem.
- Upper gastro-intestinal bleeding and ulceration occurs irrespective of the route used for administration. The first indication of damage may be life-threatening complications. The risk of bleeding markedly increases after 5 days of treatment, especially in the elderly. Stop NSAID if patient develops dyspepsia in the postoperative period.

ABSOLUTE CONTRA-INDICATIONS

- Known sensitivity to aspirin or other NSAID.
- Recent history of peptic ulcer disease.
- Poorly controlled asthma (including patients requiring oral steroids).
- Moderate to severe renal impairment (creatinine >200 micromol/litre).
- Renal transplant patients.

- After major surgery the urine output must be >0·5 ml/kg/hour, without the aid of dopamine or furosemide.
- Severe congestive cardiac failure requiring high-dose diuretics.
- Poorly controlled hypertension.
- Bleeding problems *e.g.* low platelets, known coagulopathy, on heparin infusion or high dose enoxaparin.
- Severe liver dysfunction.
- Poorly controlled diabetes.
- Severe pregnancy-induced hypertension with proteinuria.
- Patients taking certain drugs *e.g.* mifepristone, ACE inhibitors.

USE WITH CAUTION

- Mild to moderate renal impairment (creatinine <150 micromol/litre).
- If creatinine is 150 to 200 micromol/litre use only after seeking senior medical advice.
- Elderly patients (over 65 years).
- Diabetes.
- Peripheral vascular disease or treated cardiac failure.
- After hepato-biliary, renal or major vascular surgery.
- Patients taking:
  - diuretics, especially potassium-sparing
  - ciclosporin
  - methotrexate
  - lithium

  (see BNF for other drug interactions)
- Dehydration, hypovolaemia and large blood losses need to be corrected prior to starting NSAID's.

In all of these patients, consider reducing the frequency of the NSAID *e.g.* diclofenac 50 mg twice daily, and monitor renal function regularly. Any increasing trend in plasma urea, creatinine or potassium is an indication for stopping the NSAID.

- The following patients are at risk of GI complications. If an NSAID is considered necessary they should be co-prescribed omeprazole or lansoprazole:
  - patients taking warfarin or oral steroids
  - patients with a previous history of peptic ulcer disease
  - patients with intermittent dyspepsia

1.4 MODERATE PAIN – STEP 2

1.4.1 WEAK OPIOIDS

- Weak opioids are used in addition to non-opioids for mild to moderate pain.
- Preparations of choice are Tramadol, Ixprim (Tramadol 37.5 mgs and Paracetamol 325mgs) and Kapake® (codeine 30mg with paracetamol 500mg).
- Consider prophylactic laxatives for patients receiving regular doses of opioids.

  e.g. Senna 2–4 tablets or 10–20 ml of syrup at night plus Movicol 1 sachet daily with 125 mls of water.

  Or Senna 2–4 tablets or 10–20 ml of syrup at night plus Milpar 10mls twice daily with 150mls of water.

  (Laxative therapy for patients on chronic opioid therapy. Non palliative care setting). Lactulose is associated with crampy abdominal pain.
- If weak opioids become ineffective, discontinue and move to step 3.

1.4.2 TRAMADOL

- Tramadol is indicated for moderate pain or weaning from strong opioids.
- *Do not prescribe with morphine or pure opioid receptor agonist. Due to its partial agonist activity it will limit analgesic effect of pure opioid agonist.* **Pure agonists; Morphine, Oxycodone, Fentanyl, Hydromorphone.**
- It produces analgesia by two mechanisms, an opioid effect and an enhancement of serotonergic and adrenergic pathways.
- It has fewer of the typical opioid side effects (less respiratory depression, constipation and addiction potential) but psychiatric reactions have been reported (hallucinations and confusion).
- High incidence of nausea and vomiting.
- Tramadol SR 50/100/150mgs (12 hourly).
- Tramadol XL 150mgs (24 hourly)

Contra-indications

Concomitant administration of tramadol with monoamine oxidase inhibitors or within two weeks of their withdrawal. Linezolid has significant reversible MAOI activity.

Cautions

Tramadol should be **avoided in patients with a history of epilepsy**. It should be used with caution in patients taking medication that can lower the seizure threshold particularly serotonin re-uptake inhibitors **(SSRIs**) and tricyclic antidepressants (**TCAs**).

1.4.3 COMPOUND ANALGESIC PREPARATIONS

Compound analgesic preparations contain paracetamol combined with an opioid. Sometimes the opioid content is at quite a low dose, which may not provide additional pain relief whilst adding side effects (*e.g.* **Maxilief®** containing only 8mg codeine). Compound analgesic preparations complicate treatment of overdose.

a. Kapake®

- Other brand names include Kapake®, Solpadol®.
- Each tablet contains paracetamol 500mg and codeine 30mg.
- Indicated for the relief of moderate to severe pain.
- Codeine can be very constipating – consider laxatives.

Cautions

Do not prescribe more than 8 tablets daily.

Do not prescribe with any other paracetamol containing preparation either regularly or on the prn side of the prescription chart (*e.g.* Maxilief®). Infants of breast feeding mothers prescribed codeine combination drugs need to be under medical supervision.

Preparations and dose

DRUG	DOSE	NOTES
Recommended Drug Kapake® – Each tablet contains Paracetamol 500mg and Codeine 30mg Ixprim® – Each tablet contains Paracetamol 325mg and Tramadol 37.5mg	2 Tablets qds po	Max 8 tablets/day
Recommended Drug Tramadol Tramadol SR	100mg qds po 100mg qds IM 50–100mg bd po Increased to 150–200 mg bd	Max 400mg/day Max 400mg/day

1.5 SEVERE PAIN – STEP 3

1.5.1 STRONG OPIOIDS

- Strong opioids are used in addition to non-opioids.
- Morphine and Oxycodone are the strong opioids of choice.
- Oral administration is the route of choice when available. Parenteral route should only be considered if the patient is nil by mouth, or if there is reduced consciousness, protracted vomiting or severe dysphagia.
- If drugs are to be given by via enteral feeding tubes then sustained release preparations like MST must not be crushed.
- Always prescribe regular laxatives for patients on strong opioids and anti-emetics as required.

  e.g. Senna 2–4 tablets or 10–20 ml of syrup at night plus Movicol 1 sachet daily with 125 mls of water.

  Or Senna 2–4 tablets or 10–20 ml of syrup at night plus Milpar 10mls twice daily with 150mls of water.

  (Laxative therapy for patients on chronic opioid therapy. Non palliative care setting). Lactulose is associated with crampy abdominal pain.
- The patient should be continuously assessed and treatment reviewed as appropriate.

1.5.2 MORPHINE

Oral **morphine** is the **first line strong opioid.** It is indicated for severe pain.

Initiation

- The starting dose should be dependent upon the patient's previous analgesic requirements, age and general condition. For dosing in the frail, the elderly, and those with renal or hepatic impairment smaller doses may be sufficient.
- Starting doses should be with a short acting preparation *e.g.* Sevredol® or Oramorph® orally every 4 hours.

Dose Titration

- Titrate the dose to the patient's pain. The aim is to prevent the pain returning before the next dose. After each dose monitor response and review.
- If the dose fails to provide analgesia for four hours the next dose should be increased by approximately 30%. Do not increase the frequency.

- Regular analgesic requirements can be assessed by calculating the total dose of morphine administered in the previous 24 hours.
- Once pain is controlled the short acting preparation can be converted to a 12-hour slow release preparation *e.g.* MST® (*e.g.* 10mg Sevredol® 4 hourly for 24 hours = 30mg MST® 12 hourly).

Breakthrough Doses for Strong Opioids

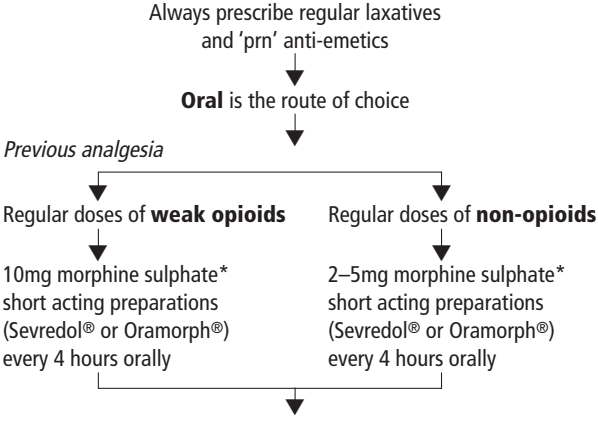
Morphine in a short acting preparation (Sevredol® or Oramorph®) should always be prescribed 'prn' in addition to the slow release preparation, to manage any breakthrough pain. Prescribe 1/6 (*i.e.* 4 hourly) of the total daily dose as the 'prn' dose.

Conversion between oral and IM or SC morphine

To switch from oral morphine to IM or SC morphine, use half the dose *e.g.* 10mg Sevredol® (oral) = 5mg morphine sulphate injection (IM/SC).
Intramuscular morphine is not recommended and not used in Palliative Medicine.

Oral opioid: peak effect, 45–60 min.
Subcutaneous opioid: peak effect, 45 min.
Intramuscular opioid: peak effect, 30 min.
Intravenous opioid: peak effect, 6 min.

1.5.3 SUMMARY GUIDELINE FOR USE OF STRONG OPIOIDS IN CHRONIC BENIGN PAIN



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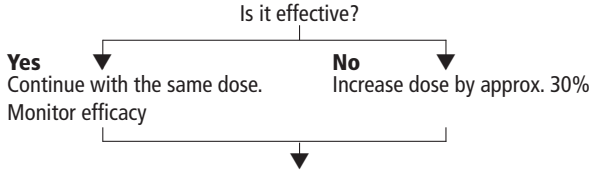


When stable convert to oral slow release preparation. Calculate total opioid requirement in 24 hours and divide by 2 (*e.g.* 4 x 10mg doses of Sevredol® in previous 24 hours = 20mg of MST® every 12 hours).

Maintain 'prn' dose of morphine short acting preparation (Sevredol® or Oramorph®) for breakthrough pain (1/6 (*i.e.* 4 hourly) of total daily morphine dose).

If regular MST® is not is providing incomplete pain relief, increase the dose. Increase the dose by approximately 30% of total 24-hour dose. If pain unresponsive to opioids do not increase MST® dose.

* *Dose reductions required in renal impairment and may be required in the elderly and in hepatic impairment. In end-stage renal impairment 'prn' dosing alone may be adequate.*

Contra-indications:

- Respiratory depression, Head injury,
- Paralytic ileus, 'acute abdomen', Delayed gastric emptying,
- Acute asthma attack,
- Known morphine sensitivity, Acute hepatic disease,
- Concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use,

Cautions:

- Chronic obstructive airways disease

Short-acting Oral Morphine Sulphate Preparations

Morphine Sulphate tablets 10mg, 20mg = Sevredol®
Morphine Sulphate oral unit dose vials 10mg/5ml = Oramorph®

Slow release Oral Morphine Sulphate Preparations

MST® tablets 5mg/10mg/30mg/60mg/100mg
MST® Continus® suspension sachets 20mg/30mg/100mg

Parenteral Morphine Preparations:

Morphine Sulphate Injection: 10mg/ml, 15mg/ml, 30mg/ml
Cyclimorph®: 5mg morphine + 50mg cyclizine/ ml,
10mg morphine + 50mg cyclizine/ ml,
15mg morphine + 50mg cyclizine/ ml
(Note: **Maximum dose of cyclizine 150mg/ 24 hours**)

Note: Cyclimorph cannot be given more than 8 hourly due to maximum daily dose of cyclizine. Respiratory depression and adverse cardiac effects are associated with cyclizine component of cyclimorph. Cyclimorph is not used in Palliative Medicine. Intramuscular opioids are not recommended. Oral route for opioids is preferred.

1.5.4 DOCUMENTATION OF OPIOID TREATMENT IN CHRONIC PAIN

All opioids have the potential to cause dependence.
Opioids should only be prescribed in chronic pain with appropriate documentation in the medical notes to define.

1) Object of therapy.
2) Record of the trial of therapy, its efficacy, conclusions and future plans.
3) Follow-up arrangements.
4) Prescribing responsibility.

1.5.5 OPIOID TOXICITY

Principal Signs and Symptoms:

- Respiratory depression Hypotension
- Hypotension
- Pinpoint pupils
- Hallucinations
- Vision changes
- Drowsiness
- Confusion
- Myoclonic jerking

If any of these symptoms is present in a patient receiving strong opioids, seek urgent expert advice.

1.5.6 APPROXIMATE EQUIVALENT DOSES OF ORAL/ TRANSDERMAL OPIOIDS

Morphine (mg po)	Morphine (mg sc)	Tramadol (mg po)	Codeine (mg po)	Oxycodone (mg po)	Oxycodone (mg sc)	Fentanyl (mcg/hr td)	Buprenorphine (mcg/hr td)	Hydromorphone (po mg)
10	5	50	60–120	5	2.5	0	5–10 Butrans - weekly	1.3
20	10	100	120–180	10	5	0	20 Butrans - weekly	2.6
30	15	150	180–300	15	7.5	12	35 Transtec - twice weekly	4
60	30	300		30	15	25	35 Transtec- twice weekly	8
90	45	450		45	22.5	37	52.5 Transtec - twice weekly	12
120	60			60	30	50	70 Transtec- twice weekly	16
150	75			75	37.5	50		20
180	90			90	45	62		24
210	105			105	52.5	75		28
240	120			120	60	75		32

All approximations to be used only as a guide.
60mg codeine is roughly equivalent to 6mg morphine. **po**=oral **sc**=subcutaneous **td**= Transdermal

1.5.7 OXYCODONE

- Oxycodone is indicated for severe pain.
- It is also used by the Acute Pain Team for step-down analgesia post-operatively.
- It has approximately **double the potency of morphine** *i.e.* 10mg oxycodone PO = 20mg morphine PO
- Seek specialist advice if there is renal or hepatic impairment

Preparations - Oxycodone

Slow release capsule – OxyContin® 5mg, 10mg, 20mg, 80mg.
Short acting capsule for immediate relief – OxyNorm® 5mg, 10mg

1.5.8 HYDROMORPHONE

Efficacy, side effects and titration method for hydromorphone are very similar to Oxycodone. It is 7 times as potent as morphine. Short acting capsules for immediate relief are only available in 1.3mg and 2.6mg.

Oral and Transdermal Opiod preparations should be prescribed and ordered by Brand Name.

1.5.9 FENTANYL AND BUPRENORPHINE TRANSDERMAL PATCHES

- The fentanyl patch (Matrifen® or Durogesic®) and buprenorphine (Transtec® or BuTrans®) provide a transdermal strong opioid.
- They may be indicated in the management of chronic intractable pain in patients requiring opioid analgesia.
- The patches are only suitable when **pain is stable**, not if pain is rapidly changing.
- Transdermal opioids should **NOT** be started in end stage palliative patients.
- The recommendations given overleaf are approximate guidelines only. Owing to inter-individual variation, patients must be treated on an individual basis and carefully titrated to pain control.

1.5.10 DOSE CONVERSION: MATRIFEN/DUROGESIC® AND TRANSTEC® PATCHES

Morphine dose prior to conversion (mg/24 hours)	INITIAL PATCH STRENGTH	
Morphine PO	**Transtec® (micrograms/ hour)**	**Matrifen/Durogesic® (micrograms/hour)**
30–60mg	35	12 microgram patch
90mg	52.5	25 microgram patch (equivalent to approx. 90mg–135mg oral morphine)
120mg	70	50 microgram patch (equivalent to 135–224mg oral morphine)
240mg	2 x 70	

- **BuTrans®** is a once weekly buprenorphine patch, and is indicated for the treatment of moderate to severe pain which is not responding adequately to NON-OPIOID analgesics. It is less potent than other analgesic patches and is changed every 7 days.

Transdermal Opioid Patches may be indicated when:

- There is an absorption problem *e.g.* constant and intractable nausea/ vomiting.
- The oral route is compromised and more invasive routes of administration are considered inappropriate.
- If adverse effects have prevented adequate doses of an oral opioid from being given.

Cautions – Transdermal Opioid Patches

- In elderly, cachectic, debilitated, renal impairment & hepatic impairment: – monitor and may need to reduce dose and consider changing.
- Avoid exposing application site to external heat, and monitor for toxicity if patient develops fever due to rapid absorption.

Long Duration of Action

- In view of the long duration of action, patients who have had severe side-effects should be monitored for up to 72 hours after patch removal in the case of Durogesic D Trans® or 72 hours after patch removal in the case of Transtec® or BuTrans
- Patients using Fentanyl patches who are **scheduled for surgery** should be **reviewed by an anaesthetist before theatre** to allow assessment of analgesic requirements.
- Transtec® and fentanyl patches should be maintained in the Perioperative period. This makes analgesic requirements easier to manage and less risk of withdrawal.

SAFETY ALERT: Special Caution required in reversal of buprenorphine

- Naloxone is of limited usefulness in antagonising respiratory depression due to buprenorphine (*e.g.* Transtec®, BuTrans®, Temgesic®). High doses of naloxone (5–12 mg intravenously) are required and the onset of effect may be 30 minutes or more. Maintenance of adequate ventilation is more important than treatment with naloxone for these patients.

Initiation

- In patients who are previously untreated with strong opioids, start with the lowest strength patch (if unable to use an alternative opioid to titrate analgesia).
- **Onset is gradual**, so evaluate the initial effect only after the first 24 hours. Carry out dose adjustments only every 72-hours**.**
- **Phase out previous analgesic therapy gradually during first 24 hours** *e.g.* continue 4 hourly short acting morphine for about 6–12 hours, or apply patch at same time as the last 12 hourly slow release morphine dose.
- Matrifen® (fentanyl) and Transtec® (buprenorphine) are changed every 3–4 days (max 96 hours) (twice a week).
- BuTrans® (buprenorphine) is changed every 7 days.
- Apply patches to dry non-irritated, non-hairy skin on the upper torso, siting a replacement patch on a different area. If it is difficult to locate a non-hairy site, hair should be clipped with a scissors, not shaved. Matrifen® can also be applied to the upper arm.

Breakthrough Pain

Patients using these patches require a rapid onset oral morphine preparation for breakthrough pain prescribed 4 hourly *e.g.* Oramorph®, Sevredol®

Preparations:

Matrifen® 12, 25, 50, 75 and 100 (micrograms/hour).

Durogesic D Trans® 12, 25, 50, 75 and 100 (micrograms/hour).

Transtec® 35, 52.5 and 70 (micrograms/hour).

BuTrans® 5, 10 and 20 (micrograms/hour).

1.5.11 METHADONE

In patients on maintenance Methadone for history of opioid abuse:

- Prescribe analgesia **in addition** to baseline methadone dose.
- Patients may have a higher tolerance for opioids.
- Avoid injectable route of analgesia wherever possible.

Methadone should not be prescribed as an analgesic, except in consultation with Acute Pain Service or Palliative Medicine.

1.5.12 PETHIDINE – NOT TO BE USED

Pethidine has a short duration of action – only 3 hours.
It has a toxic metabolite (norpethidine), which can cause convulsions due to accumulation. Repeated administration may lead to dependency.

1.5.13 SIDE-EFFECTS OF OPIOID ANALGESICS

SIDE EFFECT	APPROX. FREQUENCY	TOLERANCE	NOTES
Constipation	100%	No	Prophylactic laxatives required *e.g.* Milpar and senna 2–4 tablets nocte.
Nausea & vomiting	30%	Yes (after 2–4 days)	Prophylactic anti-emetics may be required short-term *e.g.* ondansetron.

SIDE EFFECT	APPROX. FREQUENCY	TOLERANCE	NOTES
Sedation	30%	Yes (after 5–7 days)	Sedation usually mild & self-limiting. Reduce dose if necessary until tolerance to sedation develops. Dose may subsequently be increased.
Confusion & nightmares	1%	No	Reduce the dose or change the opioid.
Pruritus	–	–	Try chlorphenamine (caution increased risk of drowsiness).
Hallucinations	1%	No	Add haloperidol at night or change opioid/decrease dose (caution if antipsychotics contraindicated *e.g.* parkinsons).

Additional Side Effects of Opioid Analgesics

- Urinary retention.
- Bradycardia and hypotension.
- Respiratory depression – if guidelines are followed to titrate opioid dose up slowly as per pain requirements it should not be a problem. It can be reversed by naloxone.

Tolerance can be a problem in chronic pain (consult specialists) but is rarely seen in the palliative care setting. Physical dependence/ addiction is **not a problem** when opioids are used appropriately to **control severe pain**.

Consider gradual dose reduction by a third the total 24 hour dose every 3 days when stopping opioid therapy after treatment for one week or more.

1.5.14 USE OF NALOXONE FOR THE REVERSAL OF OPIOID INDUCED RESPIRATORY DEPRESSION

Doses for reversal of side effects due to therapeutic doses of opioids are lower than doses required for the treatment of acute opioid over dosage. If acute opioid over dosage is suspected, seek urgent medical advice.

It is important to titrate dose against respiratory function and not the level of consciousness because total antagonism will cause a return of severe pain with hyperalgesia and, if physically dependent, severe physical withdrawal symptoms and marked agitation.

Guidelines – American Pain Society 1992

If respiratory rate > 8 / min and the patient easily rousable and not cyanosed, adopt a policy of 'wait and see'; consider reducing or omitting the next regular dose of opioid.

If respiratory rate < 8 / min, patient barely rousable / unconscious and/or cyanosed:

- Dilute a standard 400 mcg ampoule of Naloxone to 10mls with saline for injection
- Administer a 0.5 mls (20 mcg) I.V. every 2 min until patient's respiratory status is satisfactory
- Further boluses may be necessary because Naloxone is shorter acting than morphine and other opioids (max dose 10mg)

Notes

- Naloxone is a specific opioid antagonist that is indicated for the reversal of opioid–induced respiratory depression.
- It has a short duration of action after parenteral administration (less than 1 hour) and repeat doses or an infusion of naloxone may be required to maintain effect, especially with longer acting opioids and those with active metabolites
- Naloxone is of limited usefulness in antagonising respiratory depression due to buprenorphine (*e.g.* Transtec®, BuTrans®, Temgesic®). High doses of naloxone (5–12mg intravenously) are required and the onset of effect may be 30 minutes or more. Maintenance of adequate ventilation is more important than treatment with naloxone for these patients.

Adverse Effects

Nausea and vomiting. Individual reports of hypotension, hypertension, cardiac arrhythmias and pulmonary oedema. Rarely seizures.

Cautions

- Cardiovascular disease or those requiring cardiotoxic drugs
- Dose should be titrated for each patient in order to obtain sufficient respiratory response while maintaining adequate analgesia

Preparation

Naloxone Hydrochloride 400 micrograms per 1 ml.

Dose

100–200 micrograms (1.5–3 micrograms/kg) **by intravenous injection.**
If response is inadequate, increments of 100 micrograms every 2 minutes; **further doses** by **intramuscular** injection after 1–2 hours if required.
When the IV route cannot be used, the drug may be administered by IM or SC injection but onset of action will be slower.

Patients who have responded to naloxone should be carefully monitored, since the duration of action of some opioids (*e.g.* methadone) may exceed that of naloxone.

1.6 POST-OPERATIVE ADULT ACUTE PAIN MANAGEMENT

Baseline analgesia for all patients

- Paracetamol 1g PO/PR 6 hourly **regularly**
- Diclofenac 50mg TDS PO or 100mg PR 16 hourly **regularly (if no contra-indications)**

Minor Surgery *e.g.* Removal of ingrown toenail

- Regular Kapake® orally (stop paracetamol)
- Regular NSAID (if no contra-indication)
- Peripheral nerve block or local anaesthetic infiltration

Intermediate Surgery *e.g.* Total hip replacement

- Regular paracetamol
- Regular NSAID (if no contra-indication)
- Regular opioids PO/IM (Morphine/Oxycodone- both sustained and immediate release) **OR** PCA
- Peripheral nerve block ± infusion or local anaesthetic infiltration

CONSIDER

- Epidural Analgesia
- Intrathecal morphine *(See hospital policy regarding analgesics in this setting)*

Major surgery *e.g.* Abdominal surgery

- Regular Paracetamol
- Regular NSAID (if no contra-indications)
- Peripheral nerve block ± infusion or local anaesthetic infiltration
- PCA
- Epidural Analgesia

CONSIDER

- Intrathecal morphine *(See hospital policy regarding analgesics in this setting)*

PCA = Patient Controlled Analgesia.

Oral opioids are preferred over intramuscular route if patient can take orally.

1.7 PRESCRIBING "STEP-DOWN" ANALGESIA

1.7.1 MINOR SURGERY

Review regular analgesia by the 3rd day post-operatively to change analgesia to 'as required'. Review analgesia on discharge if this occurs sooner.

1.7.2 INTERMEDIATE – MAJOR SURGERY

IM/PO Opioids – **step-down to REGULAR Kapake + NSAID** (if not contra-indicated).
Review by the 5th day post-operatively to change analgesia to 'as required'.

1.7.3 MAJOR SURGERY -MORPHINE PCA -STEP DOWN GUIDE

PCA can only be prescribed by an anaesthetist.
Prescription only valid for 48 hours.
Patients seen by Acute Pain Team Monday – Friday inclusive who manage step-down therapy.
Patients remain on PCA for only 48 hours usually. If patient remains NPO after 48 hours continue PCA until oral route available.
Do not step down to IM opioids.

1.7.4 CALCULATING MORPHINE USE USING THE PCA PUMP

PCA pump allows history to calculate total use.
Also check running balance in PCA chart in nursing notes.

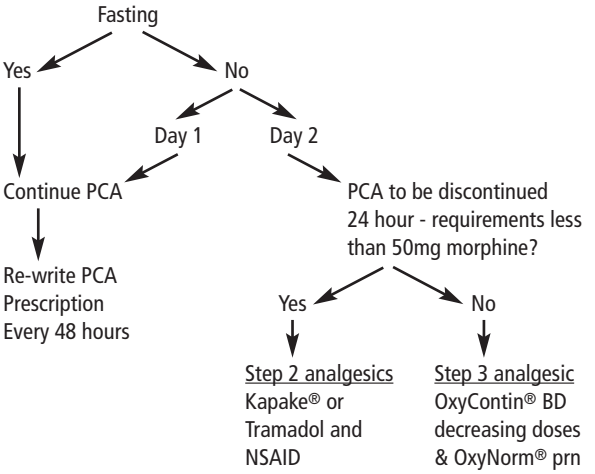
A. For patients using **less than 50mg of morphine (24hrs), step down to REGULAR Kapake® (stop paracetamol) & NSAID** (if not contra-indicated).
B. For patients using **more than 50mg of morphine (24hrs), step down to oxycodone, paracetamol & NSAID** (if not contra-indicated).

Conversion used: Morphine IV = Oxycodone PO

e.g. 60mg morphine via PCA in 24 hours = 15mg bd OxyContin® PO (12 hour slow release oxycodone tablets).
Oxycodone PO = Morphine PO x2.

STOP DATES for Oxycodone prescriptions should be CLEARLY SPECIFIED at the time of prescribing and also on discharge prescriptions. Discharge scripts should clearly specify whether immediate release or sustained release formulation is to be used, and the interval prescribed should match the release pattern of the formulation prescribed.

1.7.5 PCA STEP-DOWN FLOW-CHART



***E.g.* 1)** 72mg morphine used in PCA for 24 hours

- Switch to OxyContin® 20mg bd po then reduce to,
- OxyContin® 10mg bd po following day then,
- OxyContin® 5mg bd po following day and
- Stop prescription the next day
- Also prescribe OxyNorm 10mg 4–6 hourly po as required' on the PRN side of the prescription chart and stop prescription when Oxycontin® stopped.

OxyNorm® 'prn' dose should be approximately 1/6 of the starting OxyContin® 24-hour dose.

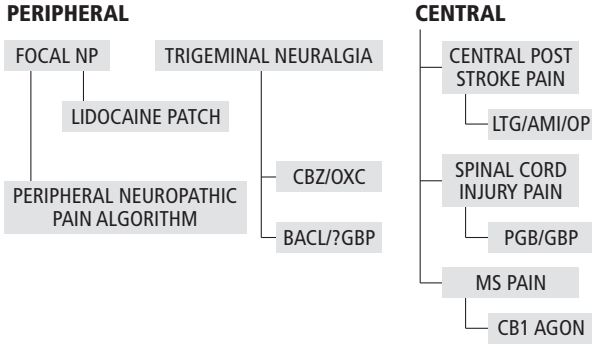
Step down to **Regular** Kapake + NSAID (if not contra-indicated) after oxycodone prescription finishes.

STOP DATES for Oxycodone prescriptions should be CLEARLY SPECIFIED at the time of prescribing and also on discharge prescriptions.

1.8 NEUROPATHIC PAIN

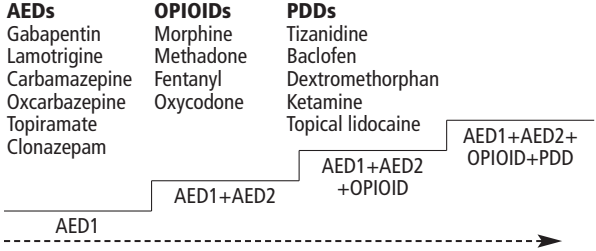
1.8.1 Neuropathic pain is due to dysfunction or damage of the peripheral or central nervous system. Symptoms classically include burning and shooting pain. It often requires combination therapy *e.g.* tricyclic antidepressants and/ or anticonvulsants. See peripheral neuropathic pain analgesic ladder. In neuropathic cancer pain opioids will be typically be used early. Pain may be mixed in origin (both nociceptive and neuropathic). Seek expert advice.

1.8.2 EFNS TASK FORCE ON THE MANAGEMENT OF NEUROPATHIC PAIN - *EUROPEAN JOURNAL OF NEUROLOGY 2006*



CBZ = Carbamazepine; OXC = Oxycarbazepine; GBP = Gabbapentin; BACL = Baclofen; LTG = Lamotrigine; AMI = Amitriptyline; OP = Opioids; PGB = Pregabalin; CB1 Agon = Canabinoid agonist (Sativex).

1.8.3 PERIPHERAL NEUROPATHIC PAIN ANALGESIC LADDER



Adjunct medication: Low dose tricylics, non-opioid analgesics prn

AED = antiepileptic drugs; PDD = precision diagnosis drugs.

1.8.4 ANALGESIC DRUGS IN NEUROPATHIC PAIN SUMMARY		
DRUG AND DOSE	**PAIN TYPE**	**NOTES**
Amitriptyline Start with 10mg at night. Increase gradually to 25mg if tolerated.	Neuropathic pain	10mg tablets are unlicensed in Ireland for commercial reasons. (Must be sourced from the UK by hospital/ community pharmacy). 25mg tablets available (Very difficult to halve) Response takes 3–7 days. See BNF for cautions/ contraindications/interactions.
Gabapentin 300mg at night increased by 300mg every 2–3 days based on response, to a usual maximum dose of 1800mg daily in 3 divided doses.	Neuropathic pain	Most patients respond at 1.2g daily or more. Response often seen within a few days but peak effect after a few weeks. Dosage reduction required in renal impairment.
Pregabalin Initially 25–75mg BD. Dose may be increased gradually to 150mg BD after an interval of 3–7 days between increases and further increased to 300mg BD.	Neuropathic pain	No published evidence that pregabalin is more effective than gabapentin. Dosage reduction required in renal impairment
Capsaicin cream 0.025% & (Zacin) 0.075% (Axsain) Apply a small amount 4 times daily.	Axsain-Diabetic neuropathy and Post-herpetic neuralgia Zacin-Osteoarthritis	Avoid contact with eyes, inflamed or broken skin. Burning sensation on application is worse at start of treatment and if applied less than 3 times daily.
5% Lidocaine patch	Postherpetic neuralgia or nerve injury	Apply 12 hourly. Expensive in Ireland until licensed (July 2008)
Carbamazepine	Trigeminal Neuralgia	Starting dose 100mg bd. Associated with blood, hepatic and skin disorders
Oxcarbazepine	Trigeminal Neuralgia	Alternative to Carbamazepine. Starting dose 150mg bd.
Baclofen	Muscle spasm and neuropathic pain	5–10mgs tid. Not first line for neuropathic pain. Used in combination.

2. ANALGESIA AND PAEDIATRIC PAIN

2.1 PRINCIPLES OF PAIN MANAGEMENT IN CHILDREN

The following information is for guidance when prescribing or checking analgesia in children.

1. Most doses are **weight based** therefore accurate weighing of the child is essential.

2. The rounding up and down of doses is appropriate to make administration easier, provided the child receives sufficient analgesia and the maximum daily dose is not exceeded.

3. **Regular multimodal** *i.e.* combination of drugs, is recommended; local anaesthetics, paracetamol, NSAID's and opioids.

4. Ascertain at which point the patient would choose treatment or if the patient is too young or sick to tell you, consider an intervention when pain is ≥ 4/10. Reassess the pain level within one hour of the administration of the analgesic. If pain is severe or changes in severity or character, a full diagnostic work-up is warranted.

5. Pain management strategies should be aimed at well being, avoid nausea and vomiting, sedation and motor block where possible.

6. Information should be provided for parents, and also in a form understandable to young children.

7. Always assume child's pain report is valid. Pain assessment scales are available and should be appropriate for the child's age. For younger children (less than 4 years), behaviour scales and/or physiological stress parameters are used (**FLACC scale**). Older children (4–7) who can self report, use the **Faces pain scale**. A **Numeric Rating Scale** (NRS 0–10) can be used from 7 years.

8. Good nursing and supportive care for the child in pain cannot be underestimated.

9. Psychology, distraction, other non-pharmacological techniques are helpful and should be used where possible.

2.2 LOCAL ANAESTHETICS

NERVE BLOCKS	MAXIMUM DOSE	COMMENTS
Caudal	0.25 % bupivicaine to avoid motor block (2.5mg/kg). 0.25% Levobupivicaine (2.5mg/kg). Clonidine 1 microgram/kg. Fentanyl 1 microgram/kg. Or Morphine (preservative free) 33 microgram/kg.	**Neonates and infants less than 3 months** • Decreased hepatic metabolism. • Reduced albumin and alpha-1 acid glycoprotein. • Higher peak plasma levels. • Greater free unbound free fraction. • Maximum amide dose decreased by 50%. **Test dose** • Routine use of adrenaline is controversial due to lack of reliability. • Used to decrease rapid vascular uptake important in the anaesthetised child. • Meticolous attention to the ECG for ST-T changes and slow incremental doses. • Negative aspiration test not very valuable in children.
Epidural	0.25% bupivicaine 0.1 ml/year/segment Fentanyl 1 microgram/kg. Morphine (preservative free) 33 microgram/kg.	
Epidural Infusion	0.1% bupivicaine (+/- fentanyl 2 micrograms/ml) At 0.05–0.2 ml/kg/hour.	
Spinal	0.1 ml + 0.06 ml/kg heavy bupivicaine 0.5% N.B. Do not tilt head down after spinal	
Penile Block	0.25 ml/kg of 0.5% bupivicaine (plain). Max 4 mls.	

NERVE BLOCKS	MAXIMUM DOSE	COMMENTS
Ilioinguinal	1 mg/kg/side 0.25–0.5% Bupivicaine	**Cuadal opioids** • Not to be used in day-case surgery. • Not to be used in children < 6 months. **Armitage formula for caudal Anaesthesia** • 0.5 ml/kg sacral. • 1.0 ml/kg lower thoracic. • 1.25 ml/kg mid thoracic. **Epidural** • Distance from skin to epidural space much smaller (1 mm/kg- 6 months to 10 years). • Mean depth in neonates is 1 cm. **Ultrasound** • Has many advantages for paediatric regional anaesthesia.
Plexus Block	0.75 ml/kg to 20 kg (0.25% bupivicaine or Levobupivicaine) 20 ml 20–30kg 25 ml 30–55kg	
Peripheral Nerve Block Infusion	<1 year 0.2 mg/kg/hr >1 year 0.4 mg/kg/hr Bupivicaine 0.125% or Levobupivicaine 0.1% +/- clonidine 3 micrograms/kg/hr	
Maximum dose	Lidocaine 7mg/kg with adrenaline / 4mg/kg without adrenaline. Bupivicaine 2–3 mg/kg (in any 4 hour period). Adrenalaline 5 microgram/kg	

2.3 PARACETAMOL

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME AND DURATION
PARACETAMOL Calpol® Calpol 6 Plus® Panadol® Paralink®	**Oral** Sugar free suspension available in 120mg/5ml and 250mg/5ml liquid Tablets available in 500mgs preparations	From 32 weeks gestation – 3 months: 10–15mg/kg 6–8 hourly 3 months – 12 years: 15–20mg/kg 4–6 hourly Over 12 yrs: 0.5–1g 4–6 hourly	60mg/kg for children under 3 months 90mg/kg for child 3 months – 12 years: do not exceed 4g in 24 hours Over 12 yrs: do not exceed 4g in 24 hours	*Onset:* 10–60 minutes *Duration:* 4 hours
Paralink®	**Rectal** Preparations available in 30mg, 60mg, 180mg and 500mg suppositories	From 32 weeks gestation – 3 months: 20mg/kg 8 hourly 3 months – 12 years: Loading dose 40mg/kg then 15–20mg/kg 4–6 hourly Over 12 years: 0.5–1g 4–6 hourly	60mg/kg for children under 3 months 90mg/kg for child 3 months – 2 years: do not exceed 4g in 24 hours Over 12 yrs: do not exceed 4g in 24 hours	*Onset:* 10–60 minutes *Duration:* 4 hours

2.3 PARACETAMOL – continued

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION
Perfalgan®	**Intravenous** 10mg/ml available in 50ml and 100 ml vials	Term infants – Infants under 10kg: 7.5mg/kg 4–6 hourly Child body-weight 10kgs–50kgs: 15mg/kg 4–6 hourly Adolescents weighing more than 50kgs: 1g 4–6 hourly	Not exceeding 30mg/kg in 24 hrs for infants under 10kgs Not exceeding 60mg/kg in 24 hrs for children between 10kgs–50kgs. Not more than 2g in children 10–33kg and not more than 3g in children 33–50kg Not exceeding 4g in 24 hrs for children over 50kg	*Onset:* 5–10 minutes *Duration:* 4 hours NOTE: Paracetamol 30mg and 60mg suppositories are not licensed in Ireland

2.4 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION	COMMON SIDE EFFECTS	COMMENTS
IBUPROFEN Brufen® Fenopine® Melfen® Nurofen® for children Provin® Nurofen®	**Oral** Tablets available in 200mg and 400mg preparations Suspension available in 100mg/5ml syrup **Rectal** Suppositories available in 60mgs	3 months – 12 years: 10mg/kg 6–8 hourly Over 12 years: 200–400mg 6–8 hourly	30mg/kg for child over 3 months Do not exceed 2.4g in 24 hours	*Onset:* 45–70 minutes *Duration:* 4–6 hours	Dyspepsia Nausea Vomiting Hypersensitivity reactions Fluid retention Rash Prolonged bleeding time	Not licensed for children less than 3 months. **Give after food or milk.** Use cautiously in children with: – Dehydration – Liver disease **Asthma is not a contraindication to NSAIDs a previous reaction in asthmatics to aspirin or NSAIDs is** – Renal impairment – Cardiac failure – Peptic ulceration Do not use in those with known sensitivity to NSAID's.

2.4 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS – continued

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION	COMMON SIDE EFFECTS	COMMENTS
DICLOFENAC Difene® Diclac® Cataflam® Diclomel® Voltarol®	**Oral** Available in 25mgs tablets and 50mgs capsules preparations **Rectal** Suppositories available in 12.5mgs, 50mgs and 100mgs	Over 6 months: 1mg/kg 8 hourly 1mg/kg 8 hourly	3mg/kg not exceeding 150mgs in 24 hours	*Onset:* 1–2 hours *Duration:* 6–8 hours	Dyspepsia Nausea Vomiting Hypersensitivity reactions Fluid retention Rash Prolonged bleeding time	Not licensed for children under 6 months. **Give after food or milk.** Use cautiously in children with: – Liver disease **Asthma is not a contraindication to NSAIDs a previous reaction in asthmatics to aspirin or NSAIDs is as is** – Renal impairment – Cardiac failure – Dehydration – Peptic ulceration Do not use in those with known sensitivity to NSAID's

NOTES: Aspirin is not used in children because of the potential to cause Reye's syndrome.
Ibuprofen has the fewest side effects and the greatest evidence to support its use in children.
NSAIDs not currently recommended in neonates due to concerns that may adversely effect cerebral renal and pulmonary blood flow regulation.

2.5 PROTOCOL FOR THE USE OF NSAID'S IN CHILDREN WITH ASTHMA

Caution is indicated in any child with a history of wheezing due to the difficulty of diagnosing asthma in children.

EXCLUSION CRITERIA:

Children should not receive any Non-Steroidal Anti-inflammatory Drugs (NSAIDs) if they fulfil any of the following criteria;

1. A history of bronchspasm, urticaria or angio-oedema after exposure to any NSAID.
2. A definite history of nasal polyps in association with wheezing, or cough.
3. Children with definite aspirin sensitivity (this is rare in children).
4. Proven or suspected impairment of renal function or dehydration.
5. Impaired platelet function or impaired haemostasis.
6. Diclofenac is not advised in children less than six months of age (64 weeks post conceptual age).
7. Ibuprofen is not advised in children less than three months of age (52 weeks post conceptual age).

GUIDELINES FOR USE OF NSAIDS:

1. Any child who has asthma should have the choice of postoperative analgesia discussed with the consultant anaesthetist.
2. The child's bronchodilators should be prescribed and easily available on the ward before the NSAID is given.
3. The NSAID should be given on the ward, A&E or OPD. The child should be observed for 2 hours after administration of the NSAID before being deemed fit to go home.
4. Parents should be advised as to the nature of possible Aspirin induced Asthma/hypersensitivity before the drug is prescribed. Should a parent request an alternative to an NSAID, an alternative should be prescribed if clinically suitable.
5. Other analgesics (Paracetamol or Codeine) should always be considered in children with asthma.

NOTES: 2% of asthmatic children are sensitive to aspirin. 5% of these are sensitive to NSAIDs (1:1000).
The safety of short-term NSAID use in asthmatics has been established.
Lesko S, Louik C, Vezina R et al. Asthma morbidity after the short-term use of ibuprofen in children. Pediatrics 2002; 109:E20.
Short J, Barr C, Palmer C et al. Use of diclofenac in children with asthma. Anaesthesia 2000; 55: 334–337.

2.6 WEAK OPIOIDS

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION	COMMON SIDE EFFECTS	COMMENTS
PARACETAMOL 500MG, CODEINE 8MG & CAFFEINE 30MG Solpadeine® Maxilief® (efferecant form)	Available in soluble tablets and non-soluble capsules	6–12 yrs: 1 tablet 4–6 hourly Older than 12 yrs: 1–2 tablets 4–6 hourly	Less than 12 yrs do not exceed 4 tablets in 24 hours Older than 12 yrs do not exceed 8 tablets in 24 hours	Soluble tablets: *Onset:* 30–60 minutes *Duration:* 2–4 hours Capsules *Onset:* 1–2 hours *Duration:* 2–4 hours	See individual drugs *i.e.* Paracetamol and Codeine	Do not use for children under 6 yrs. Do not give if child has received paracetamol or codeine within previous 4 hours. Has addictive properties.
PARACETAMOL 500MG, CODEINE 30MG Kapake® solpadol®	Available in soluble tablets and non-soluble capsules	6–12yrs: 1 tablet 6–8 hourly Older than 12 yrs: 1–2 tablets 6–8 hourly	Less than 12 yrs do not exceed 4 tablets in 24 hours Older than 12 yrs do not exceed 8 tablets in 24 hours	Soluble tablets: *Onset:* 30–60 minutes *Duration:* 2–4 hours Capsules *Onset:* 1–2 hours *Duration:* 2–4 hours	See individual drugs *i.e.* Paracetamol and Codeine	Do not use for children under 6 yrs. Do not give if child has received paracetamol or codeine within previous 4 hours. Has addictive properties.

continued overleaf

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION	COMMON SIDE EFFECTS	COMMENTS
CODEINE	**Oral** Tablets available in 30mgs preparation. Suspension available in 15mg/5ml linctus Supp **Rectal** Suppositories available in 10mgs	Neonate–12 yrs: 0.5–1mg/kg 4–6 hourly Over 12 yrs: 30–60mg 4–6 hourly	6mg/kg not exceeding 240mgs in 24 hours	*Onset:* 30–60 minutes *Duration:* 4 hours	Respiratory depression Constipation Nausea Drowsiness	As codeine is derived from morphine salts it should not be given with other opioids. Has addictive properties. In the control of pain in terminal illness, these cautions should not be a deterrent to use of opioids. Analgesic effect does not increase if larger dose given, however, side effects do.

NOTES: Codeine is a weak opioid and should not be used in conjunction with another opioid.
Codeine phosphate is now the analgesic of choice for mild/moderate pain in children who are currently undergoing chemotherapy and who are likely to be neutropenic. Age restriction in above table does not apply here.
Children on active chemotherapy treatment should not receive paracetamol or Ibuprofen (NSAID) unless directed by their Haematologist or Oncologist.

2.7 STRONG OPIOIDS (ORAL)

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION	COMMON SIDE EFFECTS	COMMENTS
MORPHINE Oramorph®	**Oral** Available in oral solution 10mg/5ml and oramorph concentrate 20mg/ml	1–12 months: 0.08mg (80 micrograms)/kg 4 hourly 1–12 years: 0.2–0.4mg (200–400 micrograms) /kg 4 hourly	Do not exceed 6 doses in 24 hours	*Onset:* 30–60 minutes *Duration:* 3–4 hours	Nausea and vomiting Constipation Pruritus/Urticaria Urinary retention Flushing Dry mouth Mood and behavioural changes Respiratory depression	Not recommended in children less than 1 month. **Contra-indicated in children with:** – Acute respiratory depression – Paralytic ileus – Raised intracranial pressure – Head injury – Known morphine sensitivity **Caution in children with**: – Hepatic Impairment – Renal Impairment – Convulsive disorders – Decreased respiratory depression Has addictive properties. In the control of pain in terminal illness, these cautions should not be a deterrent to use of opioids.
Sevredol®	5mg, 10mg, 20mg and 50mg tablets	Over 12 years: 5–20mg 4 hourly				
MST®	Oral tablets 10, 30, 60, 100mg Granules 5, 20, 15, 30, 60, 100 and 200mg	Once child's pain is stable, consider converting to twice daily MST and prescribe oramorph/sevredol as breakthrough 1/6th of total 24hr dose	Maximum dose determined by pain control or side effects	*Onset:* 1–2 hours Peak 4 hours *Duration:* 12 hours		

continued overleaf

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION	COMMON SIDE EFFECTS	COMMENTS
OXYCODONE Oxynorm®	Available in oral liquid 5mg/5ml suspension in unit dose vials. 5, 10 and 20mg tablets. Also available in concentrate 10mg/ml.	1 month–12years: 0.2mg (200 micrograms)/kg 4 hourly) Over 12 years: 5–10 mg/kg 4 hourly	Do not exceed 6 doses in 24 hours	*Onset:* 30–60 minutes *Duration:* 3–4 hours		Associated with less nausea compared to morphine.
Oxycontin®	Oral tablets 5, 10, 20, 40, 80mg	Once child's pain is stable, consider converting to twice daily Oxycontin and prescribe Oxynorm as breakthrough 1/6th of total 24hr dose				

2.8 PATIENT CONTROLLED ANALGESIA (PCA)

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	COMMON SIDE EFFECTS	MONITORING	COMMENTS
Morphine	Available in Morphine 10mg/ml, 15mg/ml, 20mg/ml and 30mg/ml ampoules	**Morphine** 2 milligram per kilogram mixed to make up a total of 50ml with normal saline. Maximum dose in any bag = 100 milligrams **Bolus dose 0.5ml (20 micrograms per kilogram)** Lockout interval = 6 minutes Changes to the above protocols can only be made at the discretion of the Consultant Anaesthetist	Nausea and vomiting- regular antiemetic required. Pruritus/Urticaria Urinary retention Flushing	**All children must in addition to the normal ward observations be managed with a PCA observation chart and continuous pulse oximetry.** If a dedicated iv line is not used an anti-reflux valve must be used to prevent back flow of morphine	**Contra-indicated in children with:** – Acute respiratory depression – Paralytic ileus – Raised intracranial pressure – Head injury – Known morphine sensitivity **Caution in children with**: – Hepatic Impairment – Convulsive disorders – Decreased respiratory depression – Renal Impairment In the control of pain in terminal illness, these cautions should not be a deterrent to the use of opioids. Inform on call anaesthetist If; PAIN SCORE greater than 6 on a scale of 0–10 while the child is on the maximum dose of morphine. SEDATION SCORE = 4. RESPIRATORY RATE below rate set by anaesthetist (see observation form). OXYGEN SATURATION below rate set by anaesthetist. Whilst on morphine PCA regular paracetamol should be encouraged.

2.9 INTRAVENOUS OPIOID INFUSION (MORPHINE)

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	COMMON SIDE EFFECTS	MONITORING	COMMENTS
Morphine iv infusion	Available in Morphine 10mg/ml, 30mg/ml and 60mg/ml ampoules	**Under 6 months:** 100 microgram/kg in 40 ml of saline 0.9% or glucose 5% Rate 0–5ml/hour 0–12.5 microgram/kg/hour **Over 6 months:** 200 microgram/kg in 40 ml of saline 0.9% or glucose 5% Rate 0–5ml/hour 0–25 microgram/kg/hour	Nausea and vomiting- regular antiemetic required. Constipation Pruritus/Urticaria Urinary retention Flushing Dry mouth Mood and behavioural changes	Rate and dosage is adjusted according to child's pain and sedation scores. **All children must in addition to the normal ward observations be managed with a Mophine infusion observation chart and continuous pulse oximetry.** **Children under six months must have additional apnea monitoring.**	**Contra-indicated in children with:** – Acute respiratory depression – Paralytic ileus – Raised intracranial pressure – Head injury – Known morphine sensitivity **Caution in children with**: – Hepatic Impairment – Convulsive disorders – Decreased respiratory depression – Renal Impairment In the control of pain in terminal illness, these cautions should not be a deterrent to the use of opioids.

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	COMMON SIDE EFFECTS	MONITORING	COMMENTS
		Doses above 25 microgram/kg/hour may be prescribed at consultant anaesthetists discretion. **If fluid restricted:** 500 microgram/kg in 40 ml of saline 0.9% or glucose 5% Rate 0–2ml/hour 0–25 microgram/kg/hour		If a dedicated iv line is not used an anti-reflux valve must be used to prevent back flow of morphine.	Inform on call anaesthetist If; PAIN SCORE greater than 6 on a scale of 0–10 while the child is on the maximum dose of morphine. SEDATION SCORE = 4. RESPIRATORY RATE below rate set by anaesthetist (see observation form). OXYGEN SATURATION below rate set by anaesthetist. Whilst on morphine infusion regular paracetamol should be encouraged.

NOTES: In Palliative Medicine iv morphine is rarely prescribed in children. If iv morphine is used 1/3 of 24hr oral dose of morphine over 24 hours is given iv and ½ of 24hr oral total dose as subcutaneous dose.
Pain control in the setting of terminal/advanced illnesses in children the cautions/requirements for intensive monitoring do not apply (pulse oximetry monitoring etc).

2.10 SUBCUTANEOUS OPIOIDS

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	COMMON SIDE EFFECTS	MONITORING	COMMENTS
Morphine sc infusion	Available in Morphine 10mg/ml, 30mg/ml, 60mg/ml ampoules	**Under 12 months:** < 50 microgram/kg 4 hourly Subcutaneous stat injection **Over 12 months:** 100–250 microgram/kg 4 hourly Subcutaneous stat injection **Subcutaneous infusion** Calculate 24 hour dose required, draw up medication in luer lock syringe and add diluent (water for injn) to make up to 48mm on syringe.	Nausea and vomiting- regular antiemetic may be required. Constipation Pruritus/Urticaria Urinary retention Flushing Dry mouth Mood and behavioural changes	Rate and dosage is adjusted according to child's pain and sedation scores.	**Contra-indicated in children with:** – Acute respiratory depression – Paralytic ileus – Raised intracranial pressure – Head injury – Known morphine sensitivity **Caution in children with**: – Hepatic Impairment – Convulsive disorders – Decreased respiratory depression – Renal Impairment In the control of pain in terminal illness, these cautions should not be a deterrent to use of opioids. Whilst on morphine infusion regular paracetamol should be encouraged.

2.10 SUBCUTANEOUS OPIOIDS – continued

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	COMMON SIDE EFFECTS	MONITORING	COMMENTS
Morphine sc intermittent injection Apply ametop to deltoid region 45 minutes before injection or cannula insertion.		Intermittent injection via 25 G hypodermic needle. Morphine 0.1–0.2 mg/kg subcutaneously 4–6 hourly. Intermittent injection via subcutaneous cannula. Morphine 0.1–0.2 mg/kg subcutaneously 4–6 hourly.			Secure the cannula with an IV 3000 dressing and marked clearly **"For subcut Morphine use only" time and dated.** A Microclave bung (C11–C3300) is used. The subcutaneous cannula can be left in situ for 72 hours. No child should be considered for subcutaneous cannula insertion unless they have IV access. Do not use in infants less than 6 months or 10kg weight. Other contraindications above apply. Consider antiemetic administration.

2.11 ANTI-EMETICS

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION	COMMON SIDE EFFECTS	COMMENTS
CYCLIZINE Valoid®	Preparations available in INJECTION: 50mg/ml TABLET: 50mg	1 month–6yrs: 0.5 (500 micrograms)mg –1mg/kg 8 hourly 6–18yrs: 0.5mg–1mg (500–1000 micrograms)/kg 8 hourly	Maximum single dose 25mgs Maximum single dose 50mgs	*Onset:* Within 2 hours *Duration:* 4 hours	Drowsiness Dry mouth Tachycardia Blurred vision Restlessness	Use with caution in children with renal or hepatic impairment. Administer by slow IV bolus injection.
ONDANSETRON Generic injections and Ondran tablets	Preparations available in INJECTION: 2mgs/ml in 2ml and 4 ml ampoules TABLET: 4 mgs, 8mg SYRUP: 4mg/5ml	2–12 yrs: 0.1mg (100micrograms)/kg as a single dose before, during, or after induction of anaesthesia 12–18 yrs: 4mg, as a single dose before, during, or after induction of anaesthesia	Maximum single dose 4mg	*Onset of IV preparation:* 15–30 minutes *Duration:* 6–8 hours	Constipation Headache Flushing Injection site reaction	Does not produce drowsiness. Can be given as a slow injection over 2–5 minutes. The IV preparation can be administered by infusion over 15 minutes.

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION	COMMON SIDE EFFECTS	COMMENTS
DOMPERIDONE Motilium®	Preparations available in oral TABLET: 10mg SUPPOS: 10,30 and 60mg SUSP: 5mg/5ml	Up to 34kg child 250–500 micrograms/kg 3–4 times/day 15–34kg child 30mg suppos BD Greater than 34kg and 12 yrs 20mgs 3–4 times/day or 60mg suppos BD Palliative medicine 800 micrograms /kg/day orally in 4 divided doses	Maximum 2.4mg/kg in 24 hours	*Onset:* 30 mins *Peak:* 0.5–2 hrs PO; 1 hr PR *Duration:* 12–24 hours	Cramps Rashes Extra-pyramidal effects	Use with caution in children with hepatic impairment Bowel obstruction.

2.12 REVERSAL OF OPIOID INDUCED RESPIRATORY DEPRESSION

DRUG	PREPARATIONS AVAILABLE	RECOMMENDED DOSE	MAXIMUM DAILY DOSE	ONSET TIME and DURATION	COMMON SIDE EFFECTS	COMMENTS
NALOXONE Narcan®	Preparations available in INJECTION: 400mcg/ml, 1ml	**BY IV INJECTION** **Neonate:** 0.01mg/kg (10 micrograms/kg) increased and repeated every 2–3 minutes if required. **Child 1mth–12yrs:** 0.01mg/kg (10 micrograms/kg) if no response subsequent dose of 0.1mg/kg (100micrograms/kg) **Child 12–18yrs:** 100–200 micrograms bolus, if response is inadequate increments of 100 micrograms at intervals of 2 minutes to a max of 10mg if respiratory function does not improve.		*Onset:* 1–2 minutes *Duration:* 45 minutes	*Large doses can cause:* Reversal of pain relief over stimulation and hypertension *Too rapid reversal can cause:* Nausea, Vomiting, Sweating and Tachycardia.	Following response continue to monitor for respiratory depression as the duration of action of some opioids may exceed that of naloxone.

2.13 NEUROPATHIC PAIN IN CHILDREN

See neuropathic pain ladder 1.8.3. Seek expert advice.

DRUG	PREPARATIONS AVAILABLE	TOTAL DAILY DOSE (T.D.D) 1 MONTH TO 12 YEARS	TOTAL DAILY DOSE OVER 12 YEARS	TIMES DAILY (Divide T.D.D by this figure)	COMMENT
Imipramine	Preparation available in ORAL TABLET 10mg	200–400 microgram/kg increasing by 50% every 2–3 days to 2mg/kg	200–400 microgram/kg increasing by 50% every 2–3 days to 2mg/kg	2. Start at lower dose at night and titrate against pain/side effects	Not first line. Risk of cardiac arrhythmias a concern
Amitriptyline	Preparations available in ORAL TABLETS: 10, 25 and 50 mgs SUSP: 25mg/5ml and 50mg/5ml	200–400 microgram/kg increasing by 50% every 2–3 days to 2mg/kg	0.1mg/kg at bedtime. Increase by doubling dose every 3–5 days to a maximum of 2mg/kg	2. Start at lower dose at night and titrate against pain/side effects	Not first line. Risk of cardiac arrhythmias a concern
Carbamazepine	Preparations available in ORAL TABLETS: 100, 200 and 400mgs SUSP: 100mg/5ml SUPPOSITORIES: 125mg MODIFIED RELEASE: 200 and 400mgs	5mg/kg at night. Increase by 2.5–5mg/kg every 3–7 days. Usual dose 5mg/kg 2–3 times daily	800–1200mg	2–3. Start at lower dose and titrate against pain/side effects	

continued overleaf

DRUG	PREPARATIONS AVAILABLE	TOTAL DAILY DOSE (T.D.D) 1 MONTH TO 12 YEARS	TOTAL DAILY DOSE OVER 12 YEARS	TIMES DAILY (Divide T.D.D by this figure)	COMMENT
Phenytoin	Preparations available in ORAL TABLETS: 100mgs CAPSULES: 25, 50 and 100 mgs SUSP: 30mg/5ml	5mg/kg than 5–15mg/kg (Maximum 300mg/kg)	150–300mg then 300–400mg (Maximum 600mg)	2	Narrow therapeutic index. TDM required
Gabapentin	Preparations available in ORAL CAPSULES: 100 and 400 mgs TABLETS: 600 and 800mgs	**6 to 12 years** 5mg/kg per day divided TID (<50kg). Increase dose gradually to a maximum of 70mg/kg	900–1800mgs 1.2 grams (37–50kg)	3	First line

TDM – therapeutic drug monitoring.

Reference: Ingelmo PM, Fumagalli R. Neuropathic Pain in Children. Minerva Anestesiol 2004; 70:393–8.

2.14 POST-OPERATIVE PAEDIATRIC ACUTE PAIN MANAGEMENT

Baseline analgesia for all paediatric patients

- Paracetamol **regularly**
- Ibuprofen or Diclofenac **regularly (if no contra-indication)**

Minor Surgery *e.g.* Circumcision;

- Regular paracetamol
- Regular NSAID (if no contra-indication)
- Local anaesthetic infiltration / block

Intermediate Surgery *e.g.* Appendectomy; Tonsillectomy;

- Regular paracetamol
- Regular NSAID (if no contra-indication)
- Peripheral nerve block ± infusion or local anaesthetic infiltration

Consider

- Regular/prn opioids PO (Morphine/Oxycodone)
- PCA

Major Surgery *e.g.* Limb amputation; Abdominal surgery;

- Regular Paracetamol. (Consider IV route as no absorption issues)
- Regular NSAID (if no contra-indications)
- Peripheral nerve block ± infusion or local anaesthetic infiltration
- Regular opioids PO (Morphine/Oxycodone) Consider
- PCA **OR** intravenous infusion
- Epidural Analgesia

PCA = Patient Controlled Analgesia.

Oral opioids are preferred over intramuscular route if child can take orally.

International guidelines suggest that intramuscular opioids are contraindicated if other routes are available.

2.15 PROCEDURAL PAIN MANAGEMENT IN INFANTS AND OLDER CHILDREN

Painful procedures are often identified as the most feared and distressing component of medical care for children and their families. When managing procedural pain in infants, older children and adolescents special emphasis should be given not only to proven analgesic strategies but also to reduction in anticipatory and procedural anxiety by suitable preparatory measures. Families, play therapists, nursing staff and other team members play key roles in reducing anxiety by suitable preparation. The personality, previous experience and analgesic preferences of the child will influence management strategies.

Analgesia-sedation with ENTONOX (Nitrous oxide/oxygen), by supervised self administration should be considered where indicated, especially in children older than 6 years who can cooperate or general anaesthesia may be needed for complex, invasive or multiple procedures.

Good Practice points

Children and their parents/ carers benefit from psychological preparation prior to painful procedures.

Pain management for procedures should include both pharmacological and non-pharmacological strategies where possible.

Entonox should be considered for painful procedures in children who are able to cooperate with self-administration.

Sedation or general anaesthesia should be considered, particularly for invasive, multiple and repeated procedures.

2.16 PROTOCOL FOR THE USE OF ENTONOX IN CHILDREN

Introduction

Entonox is a gaseous mixture of 50% Nitrous Oxide and 50% Oxygen, which acts as an analgesic agent when inhaled.

Uses of Entonox

The use of Entonox is indicated prior to and during a number of painful procedures:

- Change of dressing, removal of packs, drains or sutures.
- Re-dressing burns.
- Changing position of limbs, manipulation or splinting.

Contraindications

A. Entonox should not be used with any condition where air is trapped within the body and where expansion might be dangerous *i.e.* pneumothorax, abdominal distention.

B. Patients with partial airway obstruction or history of airway obstruction.

C. Reduced level of consciousness *i.e.* head injury.

D. Use with caution in presence of IV sedation.

E. Entonox should be sued with caution in children who suffer from "Glue Ear". Discontinue immediately if child complains of ear ache.

Method of Administration

Self Administration. This should be explained to child and parent. Self administration is an important safety feature.

By use of face mask or mouth piece connected through a demand valve to the Entonox cylinder.

For use in any child over 5 years fulfilling the above criteria.

Safety actions

A. The Entonox cyclinder is coloured blue and has a white quartered collar.

B. Cylinders should be stored above –6°. If not the cylinder must be brought inside for 24 hours before use. Horizontal/vertical mixing of the cylinder takes place before use.

C. Entonox must be prescribed on the patients drug prescription chart.

D. Entonox must only be administered by staff that have undertaken appropriate training and have been assessed as competent.

E. An Entonox patient assessment form must be completed.

F. Suction equipment, oxygen and resuscitation equipment must be available. Oxygen saturation monitoring must take place.

G. Patients do not need to be starved if Entonox alone is being used.

H. Patients on IV opioids or other sedative drugs will need to be fasted from food for 2 hours prior to the use of Entonox. Use observation form on reverse of Entonox Patient Assessment form to record respiration, level of sedation and oxygen saturation levels.

I. Child must remain in bed for a minimum of 10 minutes following cessation of the Entonox with the nurse in attendance.

2.17 A GUIDELINE FOR ORAL SUCROSE IN NEONATES IS AVAILABLE ON THE RELEVANT WARDS

2.18 PSYCHOLOGICAL AND BEHAVIOURAL THERAPY

Children with chronic pain also report chronic disability and emotional distress due to recurrent or persistent pain, distress that is also reported by family members.

Psychological therapies have been promoted as potentially effective interventions for the management of severe pain and its disabling consequences.

There is strong evidence that psychological treatment principally relaxation and Cognitive Behavioural Therapy, are highly effective in reducing the severity and frequency of chronic pain in children and adolescents.

For these therapies there is a number needed to treat of 2.3 producing more than 50% relief of pain. This is comparable with other therapeutic profiles in chronic pain.

3 ANALGESIA AND CANCER PAIN

Adapted from *Pain Control in Palliative Medication* by the Scottish Intercollegiate Guidelines Network.

Opioids should be used for control of pain in patients with cancer as indicated in the WHO analgesic ladder. This section considers dosage, formulations, side effects, and methods of administration of opioids.

3.1 OPIOID DOSE

The opioid dose required to control an individual's pain will depend on many factors and is not related to any one parameter. Patients require a wide range of opioid doses. For these reasons, it is necessary to titrate the dose of opioid against each patient's pain. Opioid side effects can be predicted and failure to minimise side effects, particularly sedation, will limit titration and therefore the level of analgesia which can be achieved.

3.2 ORAL MORPHINE FORMULATIONS

The time to onset of effect of the different morphine formulations varies, as does the time to peak drug levels.

3.2.1 NORMAL RELEASE PREPARATIONS

Normal release morphine preparations have an onset of action of about 20 minutes and reach peak drug levels on average at 60 minutes. The rapid onset of analgesia makes these preparations more suitable for use in initiating therapy for severe pain and for treating breakthrough pain. Normal release preparations must be given every four hours to maintain constant analgesic levels. When given every four hours these preparations will reach a steady plasma concentration and hence full effect within 12–15 hours. Thus the full effect of any dose change can be assessed at this time. In practice, during titration, dose adjustments are usually made every 24 hours unless the pain is more severe when adjustments may be made sooner.

3.2.2 CONTROLLED RELEASE PREPARATIONS

Controlled release morphine preparations have a slower onset and later peak effect. Many of the twice daily preparations have an onset of action of 1–2 hours and reach peak drug levels at four hours. Controlled release preparations generally do not allow rapid titration for patients in severe pain, due to slow onset and the long dosing intervals.

3.3 INITIATING AND TITRATING ORAL MORPHINE

Pain severity, age, and previous use of opioids for moderate pain will be considered when choosing the initial dose of opioid for moderate to severe pain. Extra care should be taken in patients with renal impairment.

The active metabolites of morphine are cleared through the renal system. Therefore in patients with renal impairment, morphine metabolites may accumulate and lead to toxicity. In patients with renal dysfunction, smaller doses of morphine and longer dosing intervals are required. It is good clinical practice to avoid controlled release morphine preparations in patients with renal dysfunction. Normal release morphine preparations are safer in the presence of renal impairment.

When moving up from step 2 of the analgesic ladder, start the patient on normal release formulation of morphine sulphate 5–10mg orally, every four hours.

3.3.1 BREAKTHROUGH ANALGESIA

It is established practice when using morphine to prescribe one sixth of the total daily morphine dose to be taken at any time for breakthrough pain. Breakthrough pain is defined as an unexpected increase in pain to greater than moderate intensity, occurring on a baseline pain of moderate intensity or less.

- **Breakthrough analgesia should be administered at any time in addition to regular analgesia if the patient is in pain.**
- **Following the delivery of oral breakthrough analgesia wait 30 minutes to assess the response. If pain persists, repeat analgesia and reassess in a further 30 minutes. If pain still persists, full reassessment of the patient is required.**
- **Normal release morphine can be used for predictable, movement related pain. Where possible it should be used 30 minutes before movement.**

3.3.2 DOSE TITRATION

Each day assess the pain control, degree of side effects and total amount of morphine required, including breakthrough doses, in the

previous 24 hours. Divide the total amount required in the previous 24 hours by six. Prescribe this dose every four hours and alter the breakthrough analgesia dose accordingly (this is the same as the four hourly dose) ie. one sixth of the total daily regular morphine dose.

If a patient is unable or unwilling to use breakthrough doses but is still in pain the dose of normal release morphine prescribed four hourly should be increased. The increase depends on the individual but is usually in 30–50% increments.

The rate of titration of morphine may be limited by drowsiness and in some patients longer is required to become tolerant to this effect before escalation of dose can be continued. Opioid responsiveness is a continuum and while a trial of opioids is required in all cases of moderate to severe cancer pain, some pains (*e.g.* neuropathic) do predictably require larger doses of opioids. However, the side effect profile associated with larger doses can restrict dose titration and hence limit analgesia. Careful titration with opioids is necessary and in such situations allow time for tolerance to develop to side-effects, prior to increasing the dose.

Care should be taken when calculating a new regular dose for patients who are pain free at rest but have pain on movement. If all the analgesia for this incident pain is incorporated into the new regular morphine dose, such patients could be rendered opioid toxic. In particular, they will be rendered excessively sleepy at rest. This is because pain is a physiological antagonist to the sedative and respiratory depressant side effects of opioids. In such cases, optimum analgesia is achieved by maximising background analgesia, anticipatory analgesia for movement related pain, maximum use of non-opioid and adjuvant analgesics and consideration of other treatment modalities such as radiotherapy, anaesthetic nerve blocks, and stabilising surgery.

3.3.3 CONVERTING TO CONTROLLED RELEASE PREPARATIONS

The same level of analgesia can be achieved by giving the total daily amount of normal release morphine as controlled release morphine. When pain is controlled, add up the total daily dose of normal release morphine the patient is receiving, divide the total dose by two and give this dose as a twice daily controlled release preparation.

In addition to the controlled release morphine preparation continue to prescribe the appropriate dose of normal release morphine preparation as breakthrough analgesia.

When transferring a patient from four hourly normal release morphine to a controlled release preparation start the controlled release preparation at the time the next normal release morphine formulation dose is due and discontinue the regular normal release morphine.

3.4 PREDICTABLE SIDE EFFECTS OF MORPHINE AND OTHER STRONG OPIOID ANALGESICS

Opioids have predictable side effects. If these are not prevented or minimised, titration of analgesics will be limited. Sedation is the common limiting side effect to opioid analgesia and can cause a 'pseudo'-pharmacological ceiling dose. There may be some differences in side effect profiles between different opioids. The following are the most common side effects.

3.4.1 CONSTIPATION

The majority of patients taking opioids for either mild or moderate to severe pain will develop constipation. Little or no tolerance develops. The best prophylactic treatment for preventing opioid induced constipation is a combination of stimulant and softening laxatives.

3.4.2 NAUSEA AND VOMITING

In clinical practice it appears that in opioid naïve patients, 30–60% will develop nausea and/or vomiting. Tolerance in the majority of patients usually occurs within 5–10 days. Patients commencing opioids should have access to antiemetics. A dopamine antagonist such as metoclopramide 10mg tds (which is also prokinetic) or low dose haloperidol 1.5mg nocte will be effective.

If a patient remains nauseated and/or continues to vomit, and if gastroparesis is excluded, the parenteral (most commonly subcutaneous or rarely intravenous) or transdermal route should be used for drug delivery until the patient stabilises.

3.4.3 SEDATION

This can occur in the first few days of regular opioids for moderate to severe pain and subsequently if the dose is increased. This effect is augmented by concomitant use of other medication with central nervous system depressant effects.

The use of other sedative drugs or drugs with sedative side effects should be rationalised.

3.4.4 DRY MOUTH

This usually occurs and the effect is augmented by concurrent medication with a similar side effect. Patients should be encouraged to take regular sips of cool water. All patients should be educated on the need for, and methods to achieve, good oral hygiene. The use of other drugs which can cause dry mouth, especially those with anti-cholinergic side effects, should be rationalised.

3.4.5 LESS COMMON SIDE EFFECTS OF OPIOIDS

Health professionals should be alert to the possibility of less common side effects developing, such as hypotension, respiratory depression, confusion, poor concentration, gastroparesis, urinary hesitancy or retention and itch.

3.5 OPIOID TOXICITY

There is wide individual variation in the dose of opioid that causes toxicity. The ability to tolerate a particular dose depends on the degree of opioid responsiveness of the pain, prior exposure to opioids, rate of titration of the dose, concomitant medication and renal and hepatic function.

Opioid toxicity can present as subtle agitation, seeing shadows at the periphery of the visual field, vivid dreams, nightmares, visual and auditory hallucinations, confusion and myoclonic jerks. Agitated confusion may be misinterpreted as uncontrolled pain and further opioids given. The sedated patient may then become dehydrated with resultant renal impairment. For opioids with significant active metabolites which are excreted via the kidney, metabolites will accumulate and may cause further toxicity in patients with renal impairment. The presence of opioid toxicity is an indication that the opioid dose is too high for the patient at this particular time, and it may warn of developing renal dysfunction or other co-morbidity such as sepsis.

Opioid toxicity should be managed by reducing the dose of opioid,* ensuring adequate hydration and treating the agitation/confusion with haloperidol 1.5–3mg orally or subcutaneously. This dose can be repeated hourly in the acute situation.

** The degree of dose reduction depends on the clinical strategy, renal function, and responsiveness of the patient to opioids.*

3.6 PHARMACOLOGICAL TOLERANCE

Clinically relevant pharmacological tolerance to opioid analgesia does not occur in chronic cancer pain management. Increases in analgesia usually coincide with disease progression.

3.7 PHYSICAL AND PSYCHOLOGICAL DEPENDENCE

Psychological dependence on opioids (addiction) generally does not occur in cancer patients experiencing pain.

Patients should be reassured that they will not become psychologically dependent on their opioid analgesia.

Physical dependence on chronically administered opioids may occur in cancer pain patients. Sudden discontinuation of opioid therapy may lead to a physical withdrawal syndrome, which can be treated by administering a small dose of the opioid in question. However, abrupt discontinuation of opioids does not always produce this syndrome.

3.7.1 OPIOIDS AND DRUG ABUSERS

Some drug abusers will develop malignancies. The prescription of analgesia in such cases nearly always results in anxiety and tension on all sides. Inadequate prescription of opioids in such cases will result in drug-seeking behaviour for pain relief, commonly referred to as pseudoaddiction. A common sense approach is to accept background drug maintenance therapy, *e.g.* a methadone maintenance programme, and to titrate the most appropriate opioid analgesic along with NSAIDs and adjuvant analgesics as appropriate.

Knowledge of the pharmacokinetic/pharmacodynamic effects of the therapeutic opioid used (most commonly morphine) will usually guide the prescriber on the question of opioid titration. If the pain is opioid responsive, prescription of opioid should lead to improved function and less pseudoaddiction. Less opioid-responsive pains should be dealt with in the same way as in the non-drug abuser.

3.8 PARENTERAL ADMINISTRATION

When patients with moderate to severe pain are unable to take opioids by mouth, delivery by subcutaneous continuous infusion is effective. This avoids the need for repeated injections which may be painful. In addition the subcutaneous route can be used for prolonged periods of time. Indications for using the parenteral route are inability to swallow nausea and/or vomiting, gastrointestinal

obstruction and any pathology limiting gastrointestinal absorption. In situations where pain control has been stable, Fentanyl may be administered transdermally. Uncontrolled pain is not an indication for using the parenteral route if further titration by the oral route is possible. If a breakthrough injection is needed, the subcutaneous route is less painful than the intramuscular route.

The infusion devices most often used to deliver subcutaneous infusions are portable syringe drivers.

Patients requiring parenteral opioids should receive the appropriate dose of morphine via the subcutaneous route.

Transdermal fentanyl is an effective analgesic for severe pain and can be used in patients with stable pain who are unable to take oral medication.

3.8.1 CONVERTING FROM ORAL MORPHINE TO SUBCUTANEOUS MORPHINE

From clinical practice, subcutaneous Morphine is approximately twice as potent as oral morphine. To convert from the oral to the subcutaneous route, add up the oral morphine requirements, both regular and amount of breakthrough used in the previous 24 hours. Divide this dose by two. This dose may need to be adjusted prior to administration according to the clinical situation.

When converting from oral to subcutaneous morphine remember to prescribe a subcutaneous breakthrough dose which should be one sixth of the total daily dose of regular subcutaneous morphine.

If the patient's pain is controlled, start the continuous infusion when the next dose of oral morphine is due.

If pain is uncontrolled, start the infusion as soon as possible and give a breakthrough dose of morphine immediately.

Prescribe breakthrough analgesia (to be given at anytime by subcutaneous bolus injection) at a dose of one sixth of the total daily dose of subcutaneous morphine. Alternatively, patients able to continue taking small amounts orally can continue to take their oral equivalent morphine breakthrough dose.

To adjust the dose of morphine required, assess the pain control, prevalence of side effects and total amount of morphine required in the previous 24 hours (continuous infusion and breakthrough

doses). This is the new dose of morphine required over 24 hours. Remember to adjust the dose of breakthrough morphine to one sixth of the new total daily dose of morphine.

Care should be taken when calculating a new regular dose for patients who are pain-free at rest but have pain on movement. If all the 'breakthrough' analgesia is incorporated into the new 24-hour morphine dose, such patients could be rendered opioid-toxic. Maximize background analgesia, anticipatory analgesia for movement related pain, use of non-opioid and adjuvant analgesics, and consider other treatment modalities such as radiotherapy, anaesthetic nerve blocks.

3.9 ALTERNATIVE OPIOIDS SUITABLE FOR THE TREATMENT OF MODERATE TO SEVERE CHRONIC PAIN

The alternative opioids for moderate to severe pain in patients with cancer have all been shown to be effective analgesics. However there is no evidence at present of any superior clinical analgesic effect for these agents over morphine. These alternative opioids can be tried in patients with opioid sensitive pain who are unable to tolerate morphine side effects.

Equi-analgesic doses of alternative opioids can vary between individuals and within individuals over time. This is because the potency of an opioid in an individual will vary with a number of factors *e.g.* the type of pain, renal function, and previous opioid exposure. Therefore theoretical equianalgesic doses can only be taken as an approximate guide when transferring patients from one opioid to another. Careful clinical observation is required during such transfers.

3.9.1 OXYCODONE

Oxycodone is a powerful mu opioid receptor agonist and in equivalent doses is as effective as morphine in achieving pain control in patients with cancer. Oxycodone is available in both normal release and controlled release formulations.
The Oxycodone:Morphine ratio is 1:2. Oxycodone has a more predictable bioavailability than morphine (15–65% for morphine vs. 60–87% for Oxycodone). Controlled release Oxycodone has a biphasic pharmacokinetic release profile showing two peaks after oral administration. This allows onset of analgesia within an hour of oral ingestion and an analgesic duration of 12 hours. This release pattern may be clinically useful.

3.9.2 HYDROMORPHONE

Hydromorphone is a powerful mu opioid receptor -agonist and is effective in achieving pain control in patients with cancer. It may be useful where patients have persistent drowsiness and cognitive impairment despite careful titration with morphine. Hydromorphone is available as both normal release and controlled release capsules, allowing titration as described for oral morphine. Hydromorphone is approximately 7.5 times as potent as morphine and has similar pharmacokinetic properties.

3.9.3 TRANSDERMAL FENTANYL

Fentanyl is a powerful -receptor agonist. It is indicated in patients with stable pain who have difficulty or pain when swallowing, in patients who have unacceptable toxicity from morphine, in patients with persistent nausea or vomiting, and in gastrointestinal obstruction.

Transdermal Fentanyl has been shown to have similar clinical efficacy in pain relief as morphine. It is formulated in a patch delivery system. The patch is generally replaced every 72 hours. It has a lag time of 6–12 hours to onset of action and after initiation of patch usage, any subsequent increase in dose takes 36–48 hours before steady state drug levels are achieved. Drug plasma levels show little fluctuation at a regular dose. Patch size should not be increased for at least 48 hours until peak blood levels are reached. Therefore titration is slow and for unstable pain states the patch will not be appropriate. It is suitable for the control of stable pain.

There is growing evidence that in some patients, Fentanyl causes less constipation than morphine.

When the transdermal Fentanyl patch is removed, a subcutaneous depot remains. Serum Fentanyl concentrations decline gradually, falling by 50% in 16 hours (range 13–22 hours). This means extra care must be taken if transferring to other opioids. Particular care should be taken when patients already on transdermal Fentanyl are commenced on a subcutaneous morphine infusion. This may be required when the pain state becomes unstable. Small amounts of subcutaneous morphine will be required until the Fentanyl clears from the system and this can take up to 24 hours. In patients close to death, the patch should be left in situ and additional analgesia given by normal release oral morphine or intermittent or continuous subcutaneous morphine as dictated by the clinical situation.

3.9.4 METHADONE

Methadone is an effective analgesic. Variation in half life between patients and also for each patient with time makes titration difficult. Advice from specialists in palliative care should be sought concerning dose conversion and titration.

4 ANALGESIA IN THE ELDERLY

4.1 PRINCIPLES OF PAIN MANAGEMENT IN THE ELDERLY

- Consider topical agents that have little risk of systemic side effects or drug-drug interactions.
- Consider age-related alterations of drug metabolism resulting in increased drug sensitivity and adverse reactions in the elderly (Typically decrease dose and longer dosing interval).
- Keep in mind that pain is often unrecognized and under-treated in the elderly.
- Start with the lowest possible dose and proceed slowly.
- Consider Paracetamol as the drug of choice for mild to moderate musculoskeletal pain.
- Use NSAIDs with caution because of the limitations of the ceiling effect and its renal and gastrointestinal adverse reactions.
- Avoid NSAIDs in older patients with renal dysfunction, a history of peptic ulcer disease, or bleeding disorders.
- Consider opioid analgesics for moderate to severe nociceptive pain in the elderly.
- Use sustained-release opioids for continuous pain and short-acting preparations for breakthrough or episodic pain.
- Titrate opioid dosage based on the use of medications for breakthrough pain.
- Prevent constipation with opioid use by recommending a prophylactic bowel regimen.
- Anticipate and manage opioid side effects such as sedation, confusion, and nausea until tolerance develops.
- Avoid the use of opioids that have frequent adverse reactions in the elderly, such as Propoxyphene (Dystalgesic) and Pethidine.
- Monitor patients on long-term analgesic therapy closely for side effects, drug-drug interactions, and drug-disease interactions.
- Consider adjuvant analgesics such as anticonvulsants, topical lidocaine patch, and antidepressants for neuropathic pain, using agents with the lowest side effect profile.

- Realize the importance of non-pharmacologic approaches to pain management, both alone or in combination with analgesics, as a means of avoiding the high incidence of adverse drug reactions in the elderly.
- Recognize the importance and efficacy of patient and caregiver education in the management of pain to enable the patient and caregiver to understand:
  - Goals of therapy
  - Method of pain assessment
  - Appropriate use of analgesics
  - Self-help techniques.
- Incorporate the appropriate use of osteopathic manipulative treatment to decrease pain and enhance function.
- Consider the role of cognitive-behavioural therapy in the elderly as a means of
  - Education
  - Enhancement of coping skills
  - Prevention of pain.
- Recognize the role of exercise targeted to the individual as a means of pain management to maintain and enhance functioning and avoid de-conditioning.
- Consider the role of physical and occupational therapy to:
  - Avoid dysfunction
  - Improve muscle strength
  - Aid in identifying the appropriate use of heat, cold, and massage therapy.
- Recognize that some older patients may be helped by other non-pharmacologic modes of therapy such as acupuncture and transcutaneous electric nerve stimulation (TENS).
- Appreciate the spiritual aspects of pain in the elderly, and provide counselling and refer to a clergy person if appropriate.

5 ANALGESIA AND RENAL FAILURE

SEEK SPECIALIST ADVICE

Serum creatinine is not the best measure of renal function as many elderly patients with reduced muscle mass have only marginally elevated creatinine values. Glomerular filtration rate (GFR) is the preferable measure of renal clearance. It was formerly estimated by the Cockcroft & Gault equation (CG), but is now more easily ascertained by ordering an estimated GFR (eGFR) with a standard U& E sample. The laboratory in Limerick will currently only report eGFR values when requested specifically with the U&E request.

Estimated GFR (4 variable MDRD formula)

$=186 \times (SCr)^{-(1.154)} \times (age)^{-(0.203)} \times 0.742$ [if female] $\times 1.210$ [if black]

Normal GFR is between 100 and 130ml/min in an adult. Estimated GFR measurements should only be calculated when serum creatinine is stable (*i.e.* eGFR or any other estimated measure of GFR should not be used in cases of acute renal failure).

Pharmacological considerations in renal failure and renal replacement therapy

DRUG CLEARANCE

Drugs are cleared by excretion (urine, bile or faeces), metabolism (to active or inactive form) or a combination of both. If either is impaired the dose or frequency of administration of drugs may need to be altered to prevent accumulation of drugs.

When renal function is impaired, the rate of GFR is reduced. Therefore, drugs which rely on renal clearance will take longer to clear and frequency of administration should be reduced. It is imperative not to underdose critical medications in renal failure and to remember that loading doses of medications are not affected by renal or liver clearance. It is the frequency of administration of drugs that is affected by the reduced clearance.

Renal failure makes patients more susceptible to adverse effects of drugs. Since there is an inherent bleeding tendency with uraemia, NSAIDs and anticoagulants can potentiate bleeding in a patient with kidney failure. There is an increased blood brain barrier permeability, and therefore increased sensitivity to CNS side-effects of drugs (*e.g.* sedation).

Drug clearance in renal replacement therapy is affected by properties of the drug, delivery of drug to filter and properties of the filter. If drug is avidly cleared by dialysis, it should be administered after dialysis for desired effect. If it is poorly cleared, dosing and frequency should be altered in keeping with the underlying function.

Non-steroidal anti-inflammatory agents are generally avoided in chronic renal failure except in specific situations where short courses of treatment are possible. This class of agent should be discontinued in any patient with acute renal failure.

Opioids are effective analgesic drugs. Change from sustained release to immediate release in renal failure. Reduce dose and increase interval of opioid dosing in renal failure. Careful continued monitoring of patient is fundamental. Signs of opioid toxicity include subtle agitation, vivid dreams, pseudo-hallucinations usually at the periphery of the visual field and myoclonus. **Fentanyl is the recommended opioid. It does accumulate over time in renal failure so careful monitoring is warranted. Buprenorphine is also a recommended opioid. Methadone is considered safe but long unpredictable t1/2 makes it more difficult to use.**

Commonly laxatives need to be also prescribed. There is minimal absorption of laxatives, and therefore no alteration of doses required. If a patient needs to be fluid restricted, avoid movicol as large volumes of fluid required. Senna can cause electrolyte imbalance especially hypokalaemia. Avoidance of constipation is important in patients on peritoneal dialysis.

If renal failure is the only factor in deciding prescription practice, the following are important attributes of an ideal medication;

1. Clearance is relatively unaffected by renal impairment.
2. The drugs mechanism of action has specific benefit in renal impairment.
3. The drug is relatively non nephrotoxic.

Analgesic medications and renal failure (a)

DRUGS	ELIMINATION D=DRUG M=METABOLITE	DOSE/INTERVAL CHANGE	NEPHROTOXIC (Y/N)	COMMENTS
OPIOIDS				
Fentanyl patch	Renal 75% Faecal 9%	GFR 10–50 normal dose GFR<10 50% of dose		Not dialysed
Buprenorphine patch	Renal 33% Faecal 66%	No change		Not dialysed
Methadone	Faecal 50% Liver 50%	GFR 20–50 normal dose GFR<10 50% of dose		Well cleared but long t1/2. Not dialysed
Hydromorphone	Renal (D, M)	GFR 20–50 normal dose GFR<10 50% of dose		Start at low doses
Morphine	Renal (D,M)	25% dose		Accumulates. **Avoid.** If used start with 2.5–5mg
Oxycodone	Renal (D, M) Faecal (D, M)	GFR 20–50 normal dose GFR<10 avoid		Unknown dialysability. At low GFR metabolites more likely to accumulate than hydromorphone

continued overleaf

ANALGESIC MEDICATIONS AND RENAL FAILURE (A) – continued

DRUGS	ELIMINATION D=DRUG M=METABOLITE	DOSE/INTERVAL CHANGE	NEPHROTOXIC (Y/N)	COMMENTS
OPIOIDS				
Codeine	Renal (D,M)	GFR 10–50 normal dose GFR<10 50% of dose		Unknown dialysability. **Avoid.**
NON-OPIOID ANALGESICS				
Paracetamol	Renal	GFR 10–50 normal dose GFR<10 50% of dose		Removed by HD. Normal dose in ESRF.
Tramadol	Renal 90% Faecal 10%	GFR 20–50 normal dose GFR10–20 50–100mg 12hourly		
Diclofenac (no particular NSAID recommended)	Renal and Billary	Normal dose but avoid		Can be used in dialysis patients with no residual function

Analgesic medications and renal failure (b)

DRUGS	ELIMINATION D=DRUG M=METABOLITE	DOSE/INTERVAL CHANGE	NEPHROTOXIC (Y/N)	COMMENTS
Anticonvulsants				
Carbamazepine	Renal 72%	Normal dose GFR< 25 use with caution		Not dialysed
Gabapentin	Renal	300mg max daily. If GFR< 15 300mg alternate days	Y	Effectively removed by dialysis. Start with 100mg daily and increase slowly based on efficacy, tolerability and renal function. Give a supplementary dose immediately after dialysis.
Pregabalin	Renal	See below	Y	Effectively removed by dialysis. Start with low dose (see below). Give a supplementary dose immediately after dialysis.
Antidepressants				
Amitriptyline	Renal D<10% M 90%	Normal dose. Increased risk of sedation	N	Introduce and withdraw gradually

Table. Pregabalin dosage adjustment based on renal function

CREATININE CLEARANCE (CL_{cr}) (ml/min)	TOTAL PREGABALIN DAILY DOSE*		DOSE REGIMEN
	STARTING DOSE (mg/day)	MAXIMUM DOSE (mg/day)	
≥ 60	150	600	BID or TID
≥ 30 – <60	75	300	BID or TID
≥ 15 – <30	25–50	150	Once Daily or BID
<15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

\+ Supplementary dose is a single additional dose.

Table. Gabapentin dosage adjustment based on renal function

CREATININE CLEARANCE (ml/min)	TOTAL DAILY DOSE (mg/day)	DOSE REGIMEN
≥ 80	900–3600	TID
50–79	600–1800	TID
30–49	300–900	TID
15–29	150b–600	To be administered as 300 mg every other day
<15c	150b–300	Daily dose should be reduced in proportion to creatinine clearance

Use in patients undergoing haemodialysis

For **anuric patients** undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400 mg, then 200 to

300 mg of gabapentin following each 4 hours of haemodialysis, is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For **renally impaired** patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table. In addition to the maintenance dose, an additional 200 to 300 mg dose following each 4-hour haemodialysis treatment is recommended.

6 ANALGESIA AND LIVER FAILURE

SEEK SPECIALIST ADVICE

Most analgesic drugs are metabolized in the liver. Liver disease may result in the accumulation of drugs or toxic metabolites with increased risk of adverse effects. Decreased hepatic blood flow and the process of shunting of blood means that drugs will be metabolized more slowly, and hence have a higher bioavailability. Also decreased serum albumin and changes in body water, will change the volume of distribution of many drugs.

In liver failure, sedating drugs such as midazolam and opioids, may have a greater effect, due to the presence of un-metabolised toxins, cerebral oedema, increased sensitivity to the drugs and disruption of the blood brain barrier.

Care needs to be taken to avoid constipation with opioids, as an increased bowel transit time may result in increased ammonia absorption and precipitate encephalopathy.

Suggested alterations in analgesic medication dosages should be used in conjunction with other factors that are clinically important *e.g.* the patients renal function, life expectancy, mental status, and individual response to current medications.

Analgesic medications and liver failure

DRUGS	NORMAL t1/2	CIRRHOSIS t1/2	COMMENTS
OPIOIDS			May precipitate coma
Fentanyl	263 min	304 min	Opioid of choice
Morphine iv	1.7 hrs	4.2 hrs	Reduce dose
Morphine oral	3.3 hrs	5.5 hrs	Reduce dose
Morphine SR	4 hrs	7.6 hrs	Reduce dose and frequency
Oxycodone	4 hrs	13.9 hrs	Reduce dose and frequency
Pethidine	6.4 hrs	10.9 hrs	Avoid
Remifentanil	10.49 min	9.96 min	No change
Codeine			Avoid or reduce dose

ANALGESIC MEDICATIONS AND LIVER FAILURE – continued

DRUGS	NORMAL t1/2	CIRRHOSIS t1/2	COMMENTS
NON-OPIOID ANALGESICS			
Aspirin	7.9 hrs	7.3 hrs	No change, increased risk of GI bleeding
Paracetamol	2.43 hrs	3.42 hrs	No change. Avoid large doses
Naproxen	14.14 hrs	20.36 hrs	Avoid in failure. Reduce dose if impairment. Associated with fluid retention and GI bleeding
Tramadol	5.1 hrs	13.3 hrs	Reduce dose and avoid if possible
Anticonvulsants			
Carbamazepine	12-17 hrs	No data	Avoid
Gabapentin	5.7 hrs	No data	
Antidepressants			
Amitriptyline	21 hrs	Unchanged	No change

Notes

Notes

Notes

Review analgesics daily

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