University Hospitals of Leicester NHS Trust

# A Guide to Prescribing for Patients with Advanced Malignancy

**Dr Nicky Rudd & Dr Caroline Cooke**

**Consultants in Palliative Medicine**
**University Hospitals of Leicester NHS Trust**
**Leicestershire Hospice**
**LNR Cancer Network**

**Leicestershire Cancer Centre**

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## INTRODUCTION

This booklet is a guide to common problems encountered in patients with advanced cancer. If further advice is required, specialist help can be obtained from:-

**Leicestershire & Rutland**

| | | | |
|---|---|---|---|
| LRI | Palliative Care Team | Mon-Fri 9am - 5pm | 0116 2585414 |
| LGH | Palliative Care Team | Mon-Fri 9am - 5pm | 0116 2584680 |
| GH | Palliative Care Team | Mon-Fri 9am - 5pm | 0116 2563540 |
| UHL | Palliative Care Team | Saturday 9am - 5pm | Page 07659 514742 |
| Leicestershire Hospice | | Clinical Line 24 hrs | 0116 2318401 |

**Northamptonshire**

| | | | |
|---|---|---|---|
| NGH | Palliative Care Team | Mon-Fri 9am - 5pm | 01604 544484/545218 |
| KGH | Palliative Care Team | Mon-Fri 9am - 5pm | 01536 492565 |
| Cynthia Spencer Hospice | | Mon-Fri 9am - 5pm | 01604 678030 |
| Cransley Hospice | | Mon-Fri 9am - 5pm | 01536 493041 |


## ACKNOWLEDGMENTS

I would like to acknowledge help and input from palliative care colleagues, pain teams, oncologists, GPs and pharmacists whose comments and suggestions have been incorporated into this booklet. The help from Karen Mann has been invaluable.


*This guide conforms to the Leicestershire Prescribing Guide. It will be updated regularly. Please contact Dr Nicky Rudd if you have any comments for the next edition.*

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## PAIN

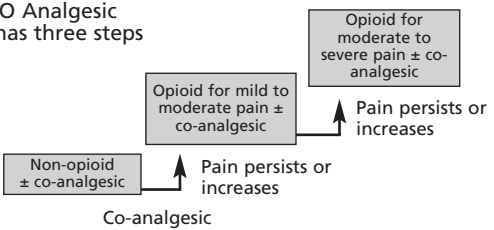
80% of cancer patients will experience pain some time in their last year of life. Successful treatment relies on the careful diagnosis of the aetiology of the pain and recognition that several types and sites of pain may co-exist.
Pain may, in part, be a reflection of emotional distress, underlining the need for obtaining a good history which includes psychosocial as well as physical details.

## ANALGESICS

- Continuous pain requires regular analgesics to prevent re-occurrence
- Give drugs by mouth unless patients are unable to tolerate this route, ie. vomiting, dysphagia
- Start simply and follow analgesic ladder
- Consider co-analgesics
- Be patient and give each drug a therapeutic trial at the appropriate dose
- Anticipate and treat side-effects
- Refer difficult cases to specialist teams

## ANALGESIC LADDER

The WHO Analgesic Ladder has three steps




Step 1 - simple non-opioids, eg. paracetamol, NSAIDs
Step 2 - opioids for mild to moderate pain, eg co-codamol, codeine, dihydrocodeine
Step 3 - opioids for moderate to severe pain, eg morphine

Move up the ladder if the current step is ineffective. Give all medication regularly and by mouth unless unable to take oral medication. It may be appropriate to add a co-analgesic before moving up the analgesic ladder (see section on Co-analgesics). See Table 4 for equivalent doses of opioids.

## THE PRESCRIPTION OF OPIOIDS

This is an extremely useful class of drugs which give good pain relief in the majority of patients. They need to be used carefully, the dose titrated and side-effects anticipated. The opioid of choice is oral morphine. Not all pains are opioid-responsive. However, it is important to give adequate doses before labelling a pain as unresponsive to opioids. If oral morphine is ineffective, there is no logic in trying a parenteral route.

## TITRATION OF MORPHINE

The initial dose depends on previous analgesia, age and co-existing medical problems, ie. renal failure. Ideally, patients should be titrated (see below) with short-acting morphine before conversion on to slow release preparations. Depending on preference, prescribe liquid morphine sulphate (oramorph) or morphine sulphate tablets (sevredol) [these become effective after approximately 20 minutes and last for 4 hours].

When starting morphine, write up a 4 hourly dose regularly, ie. 5 or 10 mg po 4 hourly and also the same dose in the "as required" section as required 20 minutes prn. The patient should be encouraged to ask for breakthrough medication as required and the nurses alerted to the regular 4 hourly dosing. There are times on acute wards when nursing levels preclude even this type of titration - a far from ideal alternative is to start on long-acting opioids, ie. MST. This is not ideal as the patient may be considerably under or overdosed and reaching the optimum dose may take longer. If the patient is on 4 hourly morphine, a double dose at night may get them through the night. However, if they do wake in pain, a 02.00 dose should be prescribed regularly and the patient woken to take it before waking in pain.

Once a patient's requirements are steady, they can be converted to a longer-acting opioid

- ***It is imperative that all patients should be prescribed prn analgesia - this is 1/6 the daily dose and is prescribed 20 minutes prn. It should be given if necessary every 30 minutes until pain is controlled.***

## OPIOIDS

### ZOMORPH

This is a modified release 12 hourly preparation of morphine. It is cheaper than MST.
(12 hourly preparations 10mg, 30mg, 60mg, 100mg, 200mg).
**THESE ARE ALL CAPSULES & NEED TO BE WRITTEN AS SUCH ON YOUR PRESCRIPTION.**

To calculate dose required for breakthrough pain:

**24 hour dose of immediate release morphine = 180 mg**
**→ zomorph 90 mg bd**
**+ 1/6 dose as breakthrough = 30 mg po prn oramorph or sevredol**

### MORPHINE SULPHATE CONTINUOUS (MST)

**Expensive - Not on formulary in Leicestershire**
12 hourly preparations (5 mg, 10 mg, 15 mg, 30 mg, 60 mg, 100 mg, 200 mg) tablets

Granules (20 mg, 30 mg, 60 mg, 100 mg, 200 mg) which can be reconstituted into a suspension for those who have difficulty in swallowing or have tubes, eg. RIGs

To calculate dose required for breakthrough pain:

**24 hour dose of immediate release morphine = 180 mg**
**→ MST 90 mg bd**
**+ 1/6 dose as breakthrough = 30 mg po prn oramorph or sevredol**

### MXL

A once-daily preparation has been manufactured and although not available in local hospitals, patients may be admitted on it (MXL CAPSULES 30 mg , 60 mg, 90 mg, 150 mg. These can be opened and contents sprinkled on food).

**24 hour dose of immediate release = 180 mg**
**→ MXL 180 mg od**
**+ 1/6 dose as breakthrough = 30 mg oramorph or sevredol po prn**

If a patient is admitted on MXL, it is important to ascertain the time of taking to avoid either under or overdosing on the day of admission.

## OXYCODONE

This is an alternative to morphine and can be tried in patients experiencing side-effects from morphine or in those whose pain is not fully controlled on morphine.
Oxycodone is available as long-acting (oxycontin) and short-acting (oxynorm) oral preparations.
5 mg oxycodone = 10 mg oral morphine.
Oxynorm is available in liquid 5 mg in 5 ml and capsules 5, 10 and 20 mg.
The long-acting oxycontin is given bd and is available in 10, 20, 40 and 80 mg tablets.

## FENTANYL

This is a synthetic opioid which is given by the transdermal route. Patches are made in 12 micrograms/hr, 25 micrograms/hr, 50 micrograms/hr, 75 micrograms/hr and 100 micrograms/hr. Fentanyl patches should be applied to a non-irritated and non-irradiated area of flat, non-hairy skin. The area should not be shaved prior to application. As the dose increases, more than one patch can be used

The patches last for 72 hours, but pharmokinetics are variable and some patients need to change them every 48 hours. The initial analgesic effect takes 12-24 hours and lasts for 12-18 hours after the patch is removed. Oral morphine should therefore be given regularly for the first 12 hours of starting a patch and thereafter prn. Long-acting opioids should not be started for at least 12 hours after removing a patch.

Fentanyl is considerably more expensive than morphine, particularly in the hospital setting. It does however have a less constipating effect and in some patients causes less sedation and nausea. It is a good choice in patients with:-

- Dysphagia or incipient dysphagia
- Constipation not particularly responsive to regular aperients
- Other side-effects of oral opioids ie. persistent drowsiness, nausea
- Dislike of tablets / non-compliance
- It is also useful in institutions where opioid use is difficult, ie. prisons

Fentanyl patches should not be used ***until the opioid dose is stable***. A 4 hourly breakthrough dose of short-acting morphine should be prescribed as previously described.

**Short-Acting Oral Fentanyl Preparations for Breakthrough Pain**

***Sublingual tablets (abstral)***
100 microgram & 200 microgram tablets.
Initially 100 microgram repeated if necessary after 15-30 minutes.
Adjust dose according to response no more than two doses 15-30 minutes apart for each pain episode.
Maximum 800 microgram per episode of breakthrough pain.
Useful for patients with incident pain or prior to painful procedures as quicker onset of action than oramorph.
Approved for use in UHL, specialist use only.
***Buccal fentanyl (effentora)***
100 microgram, 200 microgram, 400 microgram, 600 microgram & 800 microgram – regime as above.
Not approved for use in UHL.
***Actiq***
Buccal lozenges with lollipop.
200 microgram, 400 microgram, 600 microgram & 800 microgram.
Not recommended, not approved for use in UHL.

## ALFENTANIL

It has a faster onset and shorter half-life than fentanyl, with the analgesic effect lasting 5-10 minutes when given sublingually. It is useful for incident pain and short painful procedures. Also available via an intranasal spray or subcutaneously. (Specialist use only).

**TABLE 1**

| Oral 24 hour morphine dose | prn morphine dose, ie. 4hrly dose | Fentanyl micrograms/hr |
|---|---|---|
| Less than 70 mg | 5 - 10 mg | 12 |
| Less than 135 mg | 5 - 20 mg | 25 |
| 135-224 | 25 - 30 mg | 50 |
| 225-314 | 35 - 50 mg | 75 |
| 315-404 | 50 - 60 mg | 100 |
| 405-494 | 55 - 80 mg | 125 |
| 495-584 | 80 - 100 mg | 150 |
| 585-674 | 100 - 110 mg | 175 |
| 675-764 | 115 - 130 mg | 200 |
| 765-854 | 130 - 140 mg | 225 |
| 855-944 | 145 - 160 mg | 250 |
| 945-1034 | 165 - 170 mg | 275 |
| 1035-1124 | 175 - 190 mg | 300 |

### HYDROMORPHONE

This produces less metabolites of morphine and theoretically has less side-effects. Some patients with severe side-effects on conventional treatments have been much improved on hydromorphone.

1 mg hydromorphone is equivalent to approximately 7.5 mg oral morphine.

**TABLE 2 Short-Acting Preparations**

| Hydromorphone | Morphine Sulphate (Oramorph/Sevredol) |
|---|---|
| 1.3 mg | 10 mg |
| 2.6 mg | 20 mg |

**TABLE 3 Long-Acting Preparations (12hrly)**

| Hydromorphone SR | Morphine Sulphate(MST) |
|---|---|
| 2mg | 15 mg |
| 4mg | 30 mg |
| 8mg | 60 mg |
| 16mg | 120mg |
| 24mg | 180mg |

This drug is more expensive than MST and should therefore only be used for patients who cannot tolerate oral morphine.

## OTHER OPIOIDS

### BUPRENORPHINE

Buprenorphine patches can be used for moderate to severe pain. 7 day patches are available at low dose – 5 micrograms/hr, 10 micrograms/hr and 20 micrograms/hr. 3 day patches are 35 micrograms/hr, 52.5 micrograms/hr and 72 micrograms/hr.

Breakthrough medication can be problematic as buprenorphine is theoretically a partial agonist to morphine but in practice oral morphine is effective at clinically used doses.

S/L tablets. May cause dizziness/nausea. Ceiling effect of 2.4 mg / day. **Not Recommended**.

## METHADONE

Methadone can be effective for those patients with opioid-sensitive pain requiring consistently larger doses of other opiates and those with neuropathic pain. It can be used in patients with renal impairment. In view of the long and variable half-life, it should be started only with specialist supervision and usually as an inpatient. It can be given orally, intravenously or subcutaneously. Oral/subcutaneous ratio = 2/1.

Most patients are on a bd oral dose with $^1/_4$ of the total daily dose as a 3 hourly prn dose. Doses can be adjusted as for other opioids once the patient has been titrated.
Some patients are given a small bd dose (5-10 mg bd) in addition to other opioids. This sometimes works synergistically in patients with difficult pain.

## PETHIDINE

**Not recommended** as repetitive dosing can lead to accumulation of toxic metabolites, leading to CNS excitability. Duration of effect is also shorter than that of morphine.

## TRAMADOL / DIHYDROCODEINE

These can be useful in patients with moderate to severe pain but have all the side-effects of morphine combined with a ceiling dose and less flexibility for breakthrough dosing. It is often easier to start on a small dose of morphine rather than use these.

**TABLE 4 Equivalent Analgesic Doses**

| Drug | Dose | Equivalent 4 hourly morphine |
|---|---|---|
| Hydromorphone | 1.3 mg (4 hrly) | 10 mg 4 hrly |
| Codeine | 30 mg (4 hrly) | 3 mg 4 hrly |
| Dihydrocodeine | 30 mg (4 hrly) | 3 mg 4 hrly |
| Tramadol | 50 mg (4 hrly) | 10 mg 4 hrly |
| Oxycodone | 5 mg (4 hrly) | 10 mg 4 hrly |
| Buprenorphine | 35 micrograms patch | 10 mg 4 hrly |
| Methadone | 5 mg (12 hrly) | 5 - 15 mg 4 hrly |

## PARENTERAL OPIOIDS

Morphine is now the drug of choice as diamorphine has become prohibitively expensive.
Morphine is as effective as diamorphine but less soluble. Morphine can be given iv, sc, im, as well as by the intrathecal or epidural route. Other alternatives are oxycodone and diamorphine – both are expensive.

When a patient can no longer absorb oral medication (see Indications for Syringe Drivers), they should be converted to a syringe driver (see conversion chart). If a patient is opioid-naive and in need of pain control, give stat s/c morphine 5 mg, depending on age/size/renal function. If that dose is effective, calculate total 24 hour dose by observing length of time of pain relief and dose, ie. if 5 mg is effective for 2 hours → 60 mg s/c in syringe driver over 24 hours (see section on the Dying Patient).

Conversion from oral morphine to s/c morphine/diamorphine/oxycodone:-

**Patient on MST 90 mg bd po ∴ daily dose 180 mg:-**
- **morphine 90 mg s/c ($^1/_2$ morphine dose) + 15 mg prn**
- **diamorphine (1/3 of morphine dose) ∴ 60 mg s/c over 24 hrs via syringe driver + 10 mg prn s/c**
- **oxycodone 45 mg s/c ($^1/_2$ morphine dose) + 5-10 mg prn**

***NB - do not forget to chart up to 1/6 of 24 hour dose as breakthrough. Reassess your patient frequently. Watch for signs of under and overdosing.***

Oxycodone can be used but volume precludes doses greater than 130 mg / 24 hours in the Graseby syringe drivers.

**TABLE 5 Equivalent Doses for Different Routes of Administration**

| Drug | 24 hour dose equivalent to 30 mg oral morphine |
|---|---|
| Morphine s/c | 15 mg |
| Diamorphine s/c | 10-15 mg |
| Diamorphine im | 10-15 mg |
| Diamorphine iv | 5 mg |
| Oxycodone s/c | 7.5 mg |
| Morphine epidural | 1/10 of oral dose ie. 3 mg |
| Morphine intrathecal | 1/10 of epidural dose ie. 0.3 mg |

## TREATMENT OF CANCER PAIN IN PATIENTS WHO ARE OPIATE DEPENDENT

A small proportion of patients who are on maintenance methadone will develop cancer and require analgesics. Pain control can be difficult in this group. The following guidelines should be used. If opiates are needed:-

- **DO NOT CHANGE THE MAINTENANCE METHADONE DOSE**
- **IF YOU NEED HELP, CONTACT THE COMMUNITY DRUG TEAM: 0116 2256400**
- Add another opiate if needed for pain control, eg. morphine and expect to need a higher dose, eg. start at 20 mg prn instead of 10 mg prn if otherwise relatively well.
- If you have concerns about ongoing opiate abuse and there is the possibility that prescribed drugs may be abused, either by the patient or others with drug addiction, consider using fentanyl patches once opiate dose is established.
- Refer to Palliative Care Team as these patients are complex.

## SIDE-EFFECTS OF OPIOIDS

**Constipation**

Occurs in 100% of patients, unless malabsorption, ileostomy etc. All patients, excluding the above, should be prescribed regular laxatives on starting opioids. This should include a stimulant and a softener. A softener alone (ie. lactulose) is not sufficient.

**Laxido or sodium picosulphate** are the laxatives of choice in the acute hospitals.

**Nausea**

Affects 1/3 of patients but in the majority is self-limiting ~ one week. Regular antiemetics should be considered for one week for outpatients. Antiemetics on the "as required" section is sufficient for patients in hospitals as otherwise there is a tendency not to stop them after one week.

**Drowsiness**

This does generally remit after a few days; if persistent consider a different opioid.

**Dry mouth**

This is a common side-effect (see section on Mouth Problems).

**Hallucinations**

Uncommon side-effect, often visual and in peripheral field of vision. May often not be troublesome to the patient.

**Nightmares**

Can be very vivid and unpleasant but uncommon.

**Myoclonic jerks**

Occur particularly if overdosed, often confused with fits.

**Respiratory depression**

**This is not a problem in patients in pain**. However, caution is required if pain is abolished, eg. after a nerve block or radiotherapy for pain. Follow advice from Pain Management Team / Palliative Care Team.

*If patients are warned about the common side-effects and appropriate action taken, the majority of patients will tolerate opioids with few problems.*

## TREATMENT OF OPIOID OVERDOSE

Naloxone can be used to reverse opioid respiratory depression. It is best given iv but can also be given im or s/c. After iv injection, antagonism lasts 15-90 minutes. Total antagonism will cause a return of severe pain and possible opioid withdrawal.

If the respiratory rate is above 8 per minute and the patient easily rousable and not cyanosed, a watch and wait policy can be adopted. Omit the next dose of opioid.

If respiratory rate is less than 8, the patient is barely rousable or unconscious or cyanosed:-

- Dilute an ampoule of naloxone 400 micrograms/ml in 10 ml of saline
- Give 2.5-5ml (100-200 micrograms) boluses IV every 2-3 minutes until the patient's respiratory status is satisfactory
- If unable to give IV, then the same dose can be given SC or IM undiluted eg. 0-5-1 ml
- Long-acting opioids last longer than naloxone and so an infusion may need to be set up
- Initial infusion rate may be set at 60% of the initial effective intravenous bolus dose and given over an hour. This may have to be titrated according to response

**Example:** Improved respiratory rate observed after 200 micrograms
An infusion rate can be set at 120 micrograms per hour

It is important to titrate against the respiratory rate and not consciousness level as total reversal may lead to pain and agitation.

It may be necessary to continue with naloxone infusion for up to 24 hours if the patient has been on long-acting opioids. This is mandatory for patients using **FENTANYL** and **METHADONE.**

# CO-ANALGESICS

## NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

This encompasses a group of widely differing chemical compounds which have similar pharmacological effects. They are useful drugs and are used frequently in palliative care. They are used in mild/moderate cancer pain and particularly for pain from bone secondaries.

If one is ineffective, it is worth trying another from a different group, ie. changing from diclofenac to naproxen or ibuprofen.

Side-effects can limit their use. It is worth using gastric protection in the elderly, infirm and those with a history of dyspepsia. Cox II inhibitors may be useful in those who have symptoms of dyspepsia and no cardiac problems.

All NSAIDs are contraindicated in patients with multiple myeloma unless they are in the terminal phase.

## DRUGS FOR NEUROPATHIC PAIN

Patients tend to describe neuropathic pain as "burning" or "stabbing". The pain may be opioid-sensitive but opioids may be ineffective or partially effective in a proportion of patients.

**Gabapentin**

This should be used for patients with difficult pain or those who have failed on other agents. Start with 300 mg od day 1, 300 mg bd day 2, 300 mg tds day 3. The dose can be increased to 2.4 g/day and beyond. Patients may feel dizzy and "high" for the first few days but this tends to disappear unless the dose is increased. Twitching and hallucinations may also be problems. Elderly patients should start at 100 mg od and gradually increase.

**Tricyclic Antidepressants (Such as amitriptyline or imipramine)**

Start at a low dose, ie. amitriptyline 25 mg po nocte (10 mg if very elderly). Explain to the patient that you are giving it for pain and not depression and warn them that they will be drowsy for 3-4 days, and it takes 3-4 days before there is an analgesic effect. Gradually, increase the dose depending on efficacy. Anticholinergic side-effects will be reduced if dose is gradually increased. There is no good evidence that the SSRIs have an analgesic effect.

**Pregabalin** This is related to gabapentin and can be used for patients who are unable to tolerate, or do not respond to gabapentin or amitriptyline. Doses 150–600 mg / day. Start at 75 mg bd.

**Carbamazepine** Initial drowsiness, but less with SR preparation. Start at carbamazepine R 200 mg nocte and increase after two days to carbamazepine R 200 mg bd. Maximum daily dose 1.2 g. Analgesic effect may take 3-4 days and is dose-related. Can cause acute confusion, dizziness and sedation. Check for drug interactions.

**Sodium valproate** 200 mg tds unless elderly. Generally well tolerated but can cause GI irritability, tremor or confusion.

**Antispasmodics** Muscle spasm may contribute to pain. Useful drugs include clonazepam, diazepam and baclofen. Start at low doses and gradually increase.

**Other drugs** These should be used only on specialist advice:
Ketorolac Ketamine
Flecainide Bisphosphonates

## OTHER MODALITIES OF PAIN CONTROL

- Epidural & intrathecal opioids
- Nerve blocks
- Radiotherapy
- Chemotherapy
- TENS
- Acupuncture
- Surgery, eg. to stabilise fracture of spine or long bone

# NAUSEA & VOMITING

Nausea and vomiting are common symptoms in patients with advanced cancer and have many causes. **See Directorate of Cancer Services and Clinical Haematology Antiemetic Protocols.**

The emetic pathway is a complex system with the involvement of many neuronal pathways. The vomiting centres can be stimulated directly (eg. radiotherapy), indirectly from higher centres (eg. anxiety) or indirectly through the vagus due to stimulation of the gastrointestinal and genito-urinary tracts. A concentration of histamine H1 antimuscarinic receptors in the vomiting centres is the logic for choosing an antihistamine with antimuscarinic receptors such as cyclizine. The area postrema contains the chemoreceptor trigger zone and is stimulated by chemicals such as drugs, biochemical abnormalities (eg. hypercalcaemia), or toxins. A concentration of dopamine D2 receptors in this area is the logic for choosing a potent dopamine antagonist such as haloperidol.

Gastric stasis usually results from delayed emptying due to reduced motility. Metoclopramide and domperidone antagonise peripheral dopamine D2 receptors, while metoclopramide stimulates 5-$HT_4$ receptors in the stomach and bowel, resulting in more normal gastric and upper small bowel motility. Levomepromazine blocks several receptors including $\alpha$1-adrenoreceptors and 5-HT2 receptors and has a role in treating persistent nausea and vomiting of unknown cause.

Choice of antiemetic depends on the aetiology; any added or changed antiemetic should have a different action. Obviously, treatable causes eg. constipation should be tackled before starting antiemetics.

## COMMONLY USED ANTIEMETICS

| | |
|---|---|
| **Gastrokinetic** | |
| Metoclopramide | 10-20 mg tds po / s/c im. Can be given via syringe driver 30-100 mg over 24 hours |
| Domperidone | 20-80 mg daily po / pr, bd or tds |
| **Antihistamines** | |
| Cyclizine | 50 mg tds po or 100-150 mg s/c over 24 hours, max dose 200 mg |
| **Phenothiazines** | |
| Levomepromazine | 6.25-12.5 mg po / s/c at night |
| Prochlorperazine | 5-10 mg tds po, also buccal preparation 3-6 mg bd, 12.5 mg 6 hrly im or iv (not given s/c) |
| **Butyrophenones** | |
| Haloperidol | 1.5-3 mg po stat, max dose 9 - 10 mg in 24 hours, po or s / c |
| **Atypical Antipsychotics** | |
| Olanzapine | Starting dose 1.25 – 2.5 mg stat every 2 hours prn & nocte. Increase to 5 mg nocte |
| **Anticholinergics** | |
| Hyoscine Hydro-bromide (Kwells) | 0.3 mg 8 hrly po, 0.2 mg s/c tds |
| **5HT Antagonists** | |
| Ondansetron | 4 mg bd po / iv / s / c / pr |
| **Corticosteroids** | Can be used alone or with antiemetics |
| Dexamethasone | 1-4 mg 6-8 hrly. (Avoid night-time doses) |
| **Benzodiazepines** | |
| Lorazepam | 0.5-2 mg 8-12 hrly po |
| **Neurokinin Receptor Antagonists** | 80 & 125 mg capsules<br>125 mg one hour before chemotherapy, then 80 mg daily as a single dose for two days. |
| Aprepitant | Approved in UHL for highly emetic chemotherapy regimes and very resistant nausea and vomiting (specialist use only). |

**TABLE 6 Antiemetics for Specific Syndromes**

| Drug | 1st choice | 2nd choice |
|---|---|---|
| Metabolic | Haloperidol | Metoclopramide, Levomepromazine |
| Drug-Induced | Haloperidol | Metoclopramide |
| Radiotherapy, Chemotherapy | See Chemotherapy Protocol | See Chemotherapy Protocol |
| Raised Intracranial Pressure | Cyclizine, Dexamethasone | Levomepromazine |
| Bowel Obstruction | Cyclizine, Dexamethasone | Haloperidol Octreotide |
| Delayed Gastric Emptying | Metoclopramide | Domperidone |
| Fear/Anxiety/Anticipatory | Haloperidol, Levomepromazine | Benzodiazepine |

**Note** - low dose Levomepromazine is an increasingly useful anti-emetic in resistant cases, 6 mg tablet is now available. Ondansetron is licensed for nausea and vomiting induced by chemotherapy and radiotherapy. It is very expensive and should not be used for other causes of vomiting until other anti-emetics have failed. **See Directorate Antiemetic Protocols.**

## BOWEL OBSTRUCTION

Symptoms and signs will differ depending on the site of the obstruction, as described in Table 7.

**TABLE 7**

| Site | Pain | Vomiting | Distension | Bowel Sounds |
|---|---|---|---|---|
| Duodenum | None | Severe; large amounts with undigested food | None | Succussion splash may be present |
| Small bowel | Upper to central abdominal colic | Moderate to severe | Moderate | Usually hyperactive with borborygmi |
| Large bowel | Central to lower abdominal colic | Develops late | Great | Borborygmi |

If the patient is fit enough a surgical opinion should be sought. Patients, particularly with ovarian cancer, may have multiple sites of obstruction.

## MEDICAL TREATMENT

- **Trial of high dose steroids** - ie. dexamethasone 12 mg s/c / iv per day. Give for 7 days and then stop if no improvement or reduce down if has been beneficial. May need maintenance dose. May act by reducing inflammation /oedema around tumour.

- **Octreotide** - 250-750 micrograms over 24 hours via syringe driver or in divided s/c doses tds. Reduces intraluminal secretions in bowel obstruction. May help with large volume vomiting. Expensive but some patients have been well maintained at home for several weeks. 28 day depot preparation now available. **For Specialist Use Only**

- **NG Tube** - avoid if possible but may give symptomatic relief in high obstruction with profuse vomiting.

## SYMPTOM CONTROL

- Use enemas and osmotic laxatives as appropriate as it can be difficult, at times, to distinguish between severe constipation and obstruction

- **Intestinal colic** - stop stimulant, laxatives. Stop metoclopramide and domperidone.
  - antispasmodics if required, ie. hyoscine butylbromide 60 80 mg / day
  - subcutaneous opiates

- **Nausea** - cyclizine, haloperidol or levomepromazine.

- Bowel obstruction can be managed at home, patients will usually tolerate 1-2 vomits per day as long as nausea is controlled. If obstruction is in the large bowel, most patients absorb enough fluid from the SI to avoid dehydration. In some cases when fluids are needed, dermoclysis (s/c fluids) can be given at home.

## CONSTIPATION

63% of elderly people in hospital are constipated. Causes include debility; immobility; inadequate fluid intake; drugs particularly opioids, tricyclic antidepressants, diuretics, ferrous sulphate; tumour effects ie. spinal cord compression; compression of bowel by tumour; depression. Other concurrent problems ie. diabetes, local anal pathology.

Constipation can cause:-

- nausea and vomiting
- impaction with overflow causing spurious diarrhoea
- abdominal pain
- urinary incontinence or urinary retention
- confusion

If examination, including PR, is unhelpful, consider plain abdominal X-ray to distinguish constipation/overflow/bowel obstruction. Even if patients are anorexic, they should open bowels. Constipation may be a cause of agitation in the terminally ill.

Anticipate constipation before it becomes established. Try to ensure adequate fluid intake. All patients should start laxatives with weak and strong opioids. Titrate to ease of defaecation, not a set frequency. Laxative dose may need to be increased as opioids increase. Bulking agents or softeners used alone do not help constipation due to opioids. Preferred laxatives are laxido and sodium picosulphate.

### STIMULANT & SOFTENER

- Sodium picosulphate elixir (dulcolax) 5-15 ml nocte, occasionally higher or twice daily doses are needed.

Alternatives are the combination of senna and lactulose.

## OSMOTIC LAXATIVES

- Laxido 1-3 sachets daily, with fluid up to 8 per day can be useful.
- Use docusate (max 500 mg daily) if partial bowel obstruction.
- Lactulose (10 - 30ml) is expensive and often poorly tolerated, and can cause bowel distension in high doses. If used for opioid induced constipation, it should be combined with senna.

## OPIOID ANTAGONIST

Methylnaltrexone is approved for specialist use in patients with severe opioid-induced constipation resistant to maximum laxative therapy.

## SUPPOSITORIES

If suppositories are needed, the following can be used either together or alone:-

- Bisacodyl – stimulant.
- Glycerine – softener

## ENEMAS

- Microlax - softener
- High phosphate
- Arachis oil enema at night followed by phosphate enema next morning - for more resistant cases.

## DYSPNOEA

Dyspnoea is one of the most unpleasant symptoms which inevitably is associated with fear and panic. Conversely, panic attacks often present as dyspnoea and these need to be recognised and treated appropriately.

A multidisciplinary approach is often helpful, with some physiotherapists offering lung function assessment, breathlessness groups and rehabilitation facilities. Simple measures are often effective and as with other symptoms, it is important to determine the aetiology.

Many patients will develop carcinoma of the bronchus on a background of chronic obstructive pulmonary disease (COPD). It is important to optimise their treatment with bronchodilators and steroids if appropriate. Exclude and treat reversible causes, ie. chest infection, heart failure, pulmonary emboli, asthma, anaemia, pleural effusion, pneumothorax.

- Consider whether the patient has had maximum radiotherapy / chemotherapy / hormone treatment.
- Consider trial of bronchodilators, simple respiratory reversibility studies may be helpful.
- Steroids may be helpful, particularly in lymphangitis carcinomatosis, but response may be limited to weeks and prognosis should be considered when starting treatment.
- Treat anxiety/panic, address fears. Low dose lorazepam 0.5 mg - 1 mg tds may be of benefit.
- Low dose morphine can reduce sensation of breathlessness, ie. oramorph 2.5-5 mg 4 hourly. This rarely causes $CO_2$ retention even in patients with COPD.
- Consider a bronchial stent, discuss with radiologists if appropriate.
- Offer oxygen if it helps symptoms especially before exertion if this precipitates dyspnoea.

- Simple measures such as sucking a sweet
- Methadone linctus 2-4 mg nocte or bd - may accumulate as has long half-life
- Nebulised saline can be helpful in those with insipated sputum
- Nebulised lignocaine, 5 ml 2% may help - use maximum of tds. Contraindicated in asthmatics as can cause bronchospasm. Pharyngeal numbness occurs - therefore no food for 2 hours and no fluids for 1 hour after treatment.

## MOUTH PROBLEMS

These are common and distressing and include dry mouths, unpleasant taste in the mouth, altered taste sensation and intra-oral infections. Care should be taken to treat reversible causes and attempt to palliate those which are irreversible. **See Mouth Care Policy.**

### DRY MOUTH

- Commonest cause is drugs, eg. opioids, tricyclic antidepressants, diuretics, cyclizine, antipsychotics
- Candida may be manifested by dry mouth and presence of white plaques

### UNPLEASANT TASTE

- Drugs, eg. metronidazole
- Infections

### ALTERED TASTE SENSATION

Common in advanced cancer. Try spicier foods or addition of lemon juice. Whisky may be more palatable than other alcoholic drinks.

### COATED TONGUE

- Effervescent vitamin C 1/4 tab (200 mg) on tongue tds or qds
- Frozen pineapple chunks which contain a cleansing enzyme

### ORAL CANDIDIASIS

Common, particularly if also on corticosteroids. May present with dry sore mouth or angular stomatitis rather than white plaques. Treat with nystatin if mild or fluconazole 50 mg od for 7 days or 150 mg po stat. Dentures must be soaked in corsodyl to prevent re-infection.

### HERPES

Less common than candida but should be considered if patient has a painful mouth.
The mouth lesions may not be vesicular but can be ulcers.
Treat with oral aciclovir 200 mg x5/day.

### TRAUMATIC ULCERS

May be due to ill-fitting dentures or areas of paraesthesia. Use difflam mouthwash and refer to dentist if appropriate.

## GENERAL TREATMENTS

Artificial saliva is a poor substitute for natural saliva. Saliva can be stimulated by chewing sugar-free gum. If this is ineffective, pilocarpine or bethanechol may help. Of the artificial saliva, BioXtra is available in UHL.

## ANOREXIA

This is a common symptom in advanced cancer. Exclude reversible or treatable causes, eg. intra-oral infections, hypercalcaemia, nausea, constipation, drugs (eg. digoxin, metronidazole), depression and anxiety.

### TREATMENT

***ALCOHOL (Try first)***
Alcohol stimulates gastric secretions and can act as an effective appetite stimulant. It may also have a beneficial mood-enhancing effect. It is not contraindicated in patients on opiates unless they are using any large machinery.

***DIETARY ADVICE***
Reassure the family that the low intake is due to the disease and is unlikely to worsen outcome. Small and frequent meals may be easier to manage and patients should be encouraged to eat anything they like at any time. Dietary supplements can be helpful, particularly if the patient has dysphagia. They also help to defuse the distress felt by the family, watching the patient's diminishing oral intake. Disadvantages include filling up with supplements and therefore not eating proper food, unpalatability and expense.

***MEGESTROL ACETATE***
- Takes approximately 2 weeks to work
- Some evidence that larger dose is more effective - therefore can increase to 480 mg daily
- Large pills but dispersible in water
- Increased risk of thrombosis

***CORTICOSTEROIDS***
- Useful in short-term
- Length of response is approximately 6 weeks
- Multiplicity of side-effects
- Start at dexamethasone 4 mg po od for one week and then reduce to lowest effective dose 0.5-2 mg od (see section on Steroids)

## SWEATING

Sweating not associated with fever may be a paraneoplastic or opiate effect.

**NSAI (naproxen has been recommended by some authors); or if no effect:**

- amitriptyline 25-50 mg nocte
- propantheline 15-30 mg bd or tds
- propranolol 10-20 mg bd or tds
- thioridazine 10-50 mg od (note: restricted use as may prolong QT interval)
- thalidomide 100-200 mg is effective but now very expensive and can be complicated to prescribe. Start at 50 mg and gradually increase

## HICCOUGH

This may be due to irritation of the vagus nerve, eg. gastric distension, peritonitis, laryngeal, pharyngeal, meningeal irritation, diaphragmatic irritation, eg. by tumour or abscess.

### TREATMENT

- pharyngeal stimulation, e.g. hold iced water in oropharynx
- defoaming antiflatulent pre and post meals e.g. asilone
- metoclopramide 10 mg tds
- nifedipine tablets 10 - 20 mg bd - tds
- baclofen 5 - 10 mg bd
- chlorpromazine 25 mg po nocte
- gabapentin 300 mg tds
- sodium valproate (for central origin)

## PRURITUS

Correct reversible causes e.g. drugs, obstructive jaundice. Drug treatment has variable success. The following can be tried:

- Corticosteroids
- NSAIDs
- Antihistamine
- Paroxetine
- Ondansetron
- Androgens e.g. stanazolol

**ANXIETY**

Take a good history - much can be done with listening and reassurance

- Consider relaxation therapy
- Counselling
- Referral to psychologist

If symptoms are severe with panic attacks, fear of sleeping or poor concentration, lorazepam 0.5-1 mg po or s/l prn or tds, half-life 8-25 hours (diazepam half-life 21-46 hours 2-10 mg in divided doses / day).

**DEPRESSION**

Common in patients with cancer (~ 25-40%). Think about the diagnosis in those with persistent low mood, loss of concentration, low self-esteem, early morning wakening, anhedonia, persistent thoughts of death and suicide, anxiety, fixed facial expression.

A trial of antidepressants should be given sooner rather than later. SSRIs are better tolerated than tricyclics.

1st choice - citalopram 20 mg initially
2nd choice - sertraline 50-100 mg depending on age
- Fluoxetine 20 mg od
- Mirtazepine

***In patients with nausea, SSRIs may worsen symptoms.***

**Other antidepressants:-**

- lofepramine 70 mg bd
- dothiepin 75-150 mg od
  - 80% improvement in mood after 3 weeks if appropriate doses are used
  - Consider counselling if appropriate
  - Refer severe or refractory cases to the psycho-oncology service

## CONFUSION

Confirm this has been a recent onset and not long-standing dementia. Consider treatable causes, ie. infections, drugs, hypoxia, hypercalcaemia, uraemia, subdural, severe constipation, urinary retention, alcohol withdrawal, brain metastases (rare presentation), hyponatraemia.

Opioids can occasionally be a cause of confusion but **not** in a patient on a stable dose with unchanged renal and hepatic function.

It may be necessary to sedate the psychotic patient:-

- haloperidol 2-5 mg od - tds po / s/c
- levomepromazine po/s/c stat dose 12.5–25 mg and titrate according to response

### ATYPICAL ANTIPSYCHOTICS

These have less propensity to cause drug-induced movement disorders.

- Olanzapine – starting dose 2.5 mg po stat and od. Increase if necessary to 5-10 mg od
- Risperidone 500 micrograms po bd and prn. Increase if necessary by 500 micrograms bd alternate days. Median dose 1 mg/ day, rare to need >3 mg / day

## EMERGENCIES IN ONCOLOGY/PALLIATIVE CARE

When patients present with an oncological emergency, eg. spinal cord compression, stridor and SVCO, the oncology team should be contacted as rapidly as possible so they may advise on appropriate management.

### SPINAL CORD COMPRESSION

**See Spinal Cord Policy**

This should be suspected in patients with metastatic cancer. There may be only subtle neurological changes in early stages. It is therefore important to listen to the patient and investigate appropriately. Once spinal cord compression is established, there is a window of reversibility of 24 hours. Metastatic disease does not preclude active treatment as the alternative will be life confined to bed or wheelchair. If there is a clinical picture of spinal cord compression:-

- Dexamethasone 16 mg / day po/iv (some centres give more)
  [see Use of Steroids]
- Consider urgent MRI but referral to oncologist should not be delayed until scan done
- Refer urgently to oncologist
- Consider neurosurgical opinion if appropriate

### SUPERIOR VENA CAVAL OBSTRUCTION

No longer considered as an immediate emergency

- Give dexamethasone 16 mg / day
- Refer to oncologist
- Consider referral for stenting

### MAJOR HAEMORRHAGE

This fortunately is uncommon and if it occurs, leads to rapid loss of consciousness of the patient. Many patients will have experienced warning bleeds. It is usually unhelpful to warn patients about major haemorrhage, although it may at times be appropriate to discuss the possibility with the carers.

**If clearly a terminal event, the patient should be given a sedative:-**

- midazolam 10 mg iv/im **or**
- diazepam 10 mg iv **or**
- diamorphine or morphine iv/im at dose, ie. x2/3 of prn dose can be used, if those above are not available
- pr diazepam (stesolid) 30 mg may be easier to administer and can be kept at home in case of need

## HAEMOPTYSIS

The same principles apply for catastrophic haemoptysis. Diamorphine, morphine and midazolam iv/im may be helpful. Diazepam pr is also used.

## SUDDEN INCREASE IN PAIN

**PATHOLOGICAL FRACTURE**
Suspect if sudden increase in pain, particularly in patients known to have bone metastases.
Treat with analgesics, X-ray and refer to:-

- Orthopaedic surgeon
- Clinical oncologist

## HYPERCALCAEMIA

Occurs in 20% of patients with advanced cancer, particularly with cancers of breast, lung and myeloma. It is relatively common and should be suspected in patients who are or have:-

- vomiting
- confused
- constipated
- dehydrated
- polydipsia/polyuria

## TREATMENT

- Rehydrate with N saline
- Treat with iv bisphosphonate

Disodium pamidronate 30-90 mg over 90 minutes depending on serum calcium.
The calcium level may take 2-7 days to return to normal. Unless indicated do not recheck level for 3 days. Rarely patients have resistant hypercalcaemia and will require a further dose of bisphosphonate. Bisphosphonates are usually well-tolerated. However, some patients will experience pyrexia and drowsiness for 24 hours.

**Calcitonin** - (may be used if calcium unresponsive to bisphosphonates). Up to 200 units tds s/c. Less painful if mixed with lignocaine and warmed. Effect lasts only 2-3 days.

**Oral Bisphosphonates** - may help to maintain normocalcaemia, variable absorption, can be poorly tolerated. Ibandronate has now been approved for patients with carcinoma of the breast. Patients with myeloma may be on oral clodronate.

**Corticosteroids** - are not indicated for the treatment of hypercalcaemia due to solid tumours. May be helpful for myeloma and other lymphoproliferative malignancies.

Calcium levels should be re-checked two weekly as most patients will require re-treatment, which ideally should be done before they become symptomatic.

## STRIDOR

Due to tracheal compression. Give 100% oxygen and dexamethasone 16 mg iv. Refer as an emergency to either oncologists for radiotherapy or head and neck surgeons for tracheostomy if there is a treatable cause of the compression.

If the patient is dying, follow the guidelines in the section on "The Dying Patient" and consider sedation.

## THE USE OF CORTICOSTEROIDS

Steroids are used for a multiplicity of reasons in advanced cancer. They are a useful group of drugs but need to be prescribed with caution.

Uses:-

- Spinal cord compression
- Superior vena caval obstruction
- Lymphangitis/breathlessness due to tumour
- Raised intracranial pressure
- Nerve root compression / stridor
- Liver capsular pain
- Co-analgesic
- Persistent nausea and vomiting
- Intestinal obstruction
- Appetite stimulant

Dexamethasone is commonly used as fewer tablets need to be given. As with any patients, doses should be decreased and if appropriate, either stopped altogether or maintained on a minimal dose. The usual guidelines should be followed when stopping steroids. Life expectancy should be considered when starting steroids for symptom control, as young patients particularly tend to manifest severe side-effects. See conversion charts for dosing.

### EQUIVALENT ANTI-INFLAMMATORY DOSES OF CORTICOSTEROIDS

**TABLE 8**

| Prednisolone 5 mg |
|---|
| ≡ Dexamethasone 750 micrograms |
| ≡ Hydrocortisone 20 mg |
| ≡ Betamethasone 750 micrograms |
| ≡ Cortisone acetate 25 mg |
| ≡ Methylprednisolone 4 mg |
| ≡ Triamcinolone 4 mg |

This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action.

## THE DYING PATIENT

Careful management of the symptoms of dying patients is important. Both pain and distress may be manifested by agitation and difficult to distinguish. Comments from nursing staff about reactions to procedures and observations from relatives may help differentiate between the two.

Principles of management of symptoms are no different to those described previously:-

- Treat pain and other symptoms adequately but do not overdose
- Prescribe breakthrough medication
- Review symptoms regularly
- Anticipate problems and chart drugs on the "as required" section with their indication
- Look at route of prescription - do they need s/c drugs or a syringe driver?
- Consider stopping invasive treatments, ie. ivi and unnecessary treatments
- Refer to palliative care teams for advice if necessary

The Integrated Care Pathway (ICP) for Dying Patients is in use in all the wards in UHL, KGH & NGH. Further information can be obtained from:-

| | | |
|---|---|---|
| UHL | Jane Lee | Tel: 0116 2047951<br>Mobile: 0794 9743660 |
| NGH | Vicky Howard | Tel: 01604 544484 |
| KGH | Palliative Care Team | Tel: 01536 492565 |

## TERMINAL AGITATION & RESTLESSNESS

Exclude reversible causes, ie. urinary retention, constipation, pain.
Midazolam or levomepromazine are the most commonly used drugs.

### MIDAZOLAM

Give 2.5-5 mg s/c stat and assess response and duration, which usually lasts no more than 2 hours. May be given in a syringe driver 10-60 mg over 24 hours, starting with about x8 the effective dose given as a stat subcutaneous dose.

### LEVOMEPROMAZINE

25 mg po s/c and assess response and duration. Maximum dose 200 mg over 24 hours via syringe driver. Start with x4 effective stat dose. If agitation is not controlled, combination of midazolam and levomepromazine can be used.

### DIAZEPAM

5 - 10 mg pr as required.

## TERMINAL SECRETIONS

These are secretions accumulating in patients who are too weak to cough. They can be a cause of distress to relatives.

### HYOSCINE HYDROBROMIDE

Sedative, not to be used in the conscious patient. 400 micrograms every 4-6 hours or 400 micrograms - 2.4 mg over 24 hours via syringe driver.

### GLYCOPYRRONIUM BROMIDE

Antimuscarinic and alternative to hyoscine. Fewer side-effects and less sedating. 200 micrograms 6 hourly, maximum 800 micrograms/ 24 hours via syringe driver. Maximum dose 1.2 mg.

### HYOSCINE BUTYLBROMIDE (BUSCOPAN)

20 mg stat 60 - 180 mg / 24 hours. Cheaper than the alternatives.

## THE USE OF SYRINGE DRIVERS

This is an extremely useful route of drug administration for patients who are unable to take oral medication. However, it is no more than a different method and is no more efficacious than the oral route. It is therefore not to be used for patients with poor pain control although is useful temporarily for those with persistent vomiting until symptoms are under control.

### INDICATIONS

- Dysphagia
- Persistent nausea / vomiting
- Bowel obstruction
- Reduced level of consciousness
- Poor absorption

Drugs used in the syringe driver include diamorphine, morphine, oxycodone *(see Pain Control)*, antiemetics *(see Nausea and Vomiting)*, sedatives *(see Agitation)*, hyoscine, dexamethasone *(see Steroids)* and octreotide *(see Nausea & Vomiting)*.

A patient without nausea on oral opioids **does not** require an antiemetic in the syringe driver.

Most pharmacies will be loathe to mix more than two drugs in the syringe. Drugs should be mixed with water for injection. Dexamethasone is given alone either as stat subcutaneous injections or via syringe driver.

Some patients may experience local inflammation at the site, requiring changes in placement or the use of hyaluronidase to help drug dispersal. A teflon cannula may be less irritant. Dexamethasone 0.5 mg can be added to the syringe driver.

**TABLE 9 Summarising the use of Syringe Drivers**

| ANALGESICS |
|---|
| **Diamorphine** - calculate the initial dose to be given (1/3 of the total 24 hr oral morphine intake), but be prepared to increase at regular intervals and prescribe a s/c prn dose. |
| **Morphine** ½ of total oral dose |
| **Oxycodone** ½ of oral dose |

| ANTI-EMETICS | |
|---|---|
| Metoclopramide | Dose of 30-60 mg / 24 hrs |
| Haloperidol | Dose of 2.5-10 mg / 24 hrs (may be sedating) |
| Cyclizine | Dose of up to 150 mg / 24 hrs |
| Levomepromazine | Dose of 6.25–12.5 mg / 24 hrs |

| SEDATION | |
|---|---|
| Levomepromazine | Dose of 12.5 - 200 mg / 24 hrs |
| Midazolam | Dose of 10-60 mg terminal restlessness<br>Dose of 10-90 mg myoclonic jerks, anti-convulsant |

| SECRETIONS |
|---|
| For excess respiratory secretions, consider the use of hyoscine hydrobromide in doses of 0.4-2.4 mg / 24 hrs (this can also sedate) or glycopyrronium bromide max. 1.2 mg / 24 hrs |

| ANTISPASMODICS |
|---|
| Hyoscine butylbromide may be effective in bowel colic given in a dose of 60-180 mg / 24 hrs |

## Drugs should be diluted with water for injections

**NP** = No problems in usual clinical dose
**ND** = No data
**OI** = Occasional incompatibility
**CHD** = Caution at higher doses
**MNR** = Mixture not recommended clinically or incompatibility
**CU** = Commonly used. Compatible at therapeutic concentrations. No published data

| | Hyoscine Butylbromide (bucospan) | Cyclizine (Cyc) | Diamorphine (D) | Glycopyrronium (Gly) | Halperidol (Hal) | Hyoscine Hydrobromide (HHbr) | Levomepromazine (Lpz) | Metoclopramide (Met) |
|---|---|---|---|---|---|---|---|---|
| Cyclizine | OI | | | | | | | |
| Diamorphine | NP | | | | | | | |
| Glycopyrronium | MNR | ND | D 200 mg Gly 0.6 mg | | | | | |
| Haloperidol | CU | NP | NP | ND | | | | |
| Hyoscine Hydrobromide | MNR | CHD | NP | MNR | CU | | | |
| Levomepromazine | CHD | MNR | NP | ND | MNR | CHD | | |
| Metoclopramide | MNR | MNR | NP | MNR | MNR | MNR | MNR | |
| Midazolam | CU | CHD | NP | CHD Gly 1.6 mg Mid 40 mg | NP | CU | CU | CU |

**SEEK SPECIALIST ADVICE FOR COMBINING MORE UNUSUAL DRUGS OR MORE THAN TWO DRUG COMBINATIONS OR MORPHINE OR OXYCODONE**

## PRESCRIBING FOR PATIENTS WITH RENAL IMPAIRMENT

The aim of this section is to give guidelines on the use of medication described in the first part of this booklet with suggested dose adjustments in renal impairment. They are listed in symptom order. Appropriate doses of medication should be given and the efficacy and side-effects closely monitored. In the absence of troublesome side-effects, higher than recommended doses may be given to achieve the desired therapeutic goal.

(For information of other drugs or more detailed information, please refer to the current British National Formulary (BNF) or The Renal Drug Handbook (C. Ashley, A. Currie)).

### GENERAL CONSIDERATIONS

- Renal impairment is common in patients with advanced cancer
- While the urea level is heavily dependent on dietary intake and catabolism, the creatinine is more on age and muscle mass. The measurement of serum creatinine will often underestimate the degree of renal impairment in frail, cachectic patients. There can be multiple predisposing factors including:
  - Urinary tract obstruction eg. due to tumour infiltration or external pressure on the renal tract
  - Electrolyte imbalance, eg. hypercalcaemia and hyperuricaemia
  - Iatrogenic – including NSAIDs, chemotherapy and radiotherapy
  - Paraneoplastic glomerulonephritis
- It is important to review and, if appropriate discontinue any medication that could precipitate renal failure, eg. diuretics, antihypertensives, NSAIDs
- Patients with renal failure are particularly susceptible to developing side-effects due to the accumulation of the parent drug and/or metabolites that are renally excreted.
- There is no routinely available laboratory means of measuring drugs/metabolite levels – the diagnosis of toxicity must be based on clinical awareness and a high index of suspicion

- The major determinant of dosage alteration in renal impairment is drug clearance which can be estimated from the glomerular filtration rate (GFR) that is calculated using the serum creatinine. The laboratory estimate of GFR (eGFR) should be used with caution as it does not take the patient's weight into account. Discuss with ward pharmacist if the value needs adjusting for patient size

For the purpose of drug prescribing, renal impairment can be divided into three grades:-

| Grade | Serum creatinine micromol/L | Glomerular Filtration Rate (GFR) ml/min/1.73m$^2$ |
|---|---|---|
| Mild | 150 – 300 | 20 – 50 |
| Moderate | 300 - 700 | 10 – 20 |
| Severe | > 700 | < 10 |

- Other aspects of pharmokinetics (absorption, metabolism, distribution, including protein binding and renal haemodynamics) may be affected in renal failure.
- Intermittent haemodialysis can produce a significant reduction in drug levels resulting in development of symptoms during or shortly after haemodialysis, eg. pain

# ANALGESICS

## PARACETAMOL

Paracetamol is metabolised in the liver but the metabolites accumulate in patients with renal impairment and on renal replacement therapy (RRT). There is however no need to reduce the maximum daily dose of up to 4 g/day.

## WEAK OPIOIDS

- **Codeine, dihydrocodeine**
  The half-life of codeine is prolonged in patients with renal failure and those on RRT. Codeine is principally metabolised in the liver. Approximately 10% of codeine is metabolised to morphine. These drugs should therefore be used with caution and doses reduced in patients with moderate / severe renal disease as they can cause drowsiness.

- **Tramadol**
  Tramadol is metabolised in the liver to its active metabolite which is then excreted by the kidneys. Tramadol may be epileptogenic in conditions associated with a lowered seizure threshold, eg. uraemia. It should therefore be used with caution, the maximum prescribed dose not exceeding 50 mg qds in patients with severe renal impairment.

**Caution – Tramadol should not be used with SSRI's or tricyclic antidepressants**

| | Degree of renal failure | | |
|---|---|---|---|
| **Drug** | **Mild** | **Moderate** | **Severe** |
| Paracetamol | ND | ND | ND |
| Codeine | ND | 75% of ND | 50% of ND |
| Codeine 8/500 or 30/500 | ND | 6 tablets in 24 hrs | 4 tablets in 24 hrs |
| Dihydrocodeine 30 mg | ND | Avoid or use small doses and titrate to response | |
| Tramadol | ND | 50 – 100 mg bd starting dose can increase up to qds | 50 mg 12 hrly up to a maximum of qds |

ND = *Normal dose*

## STRONG OPIOIDS

**General considerations:**

- Many opioids and/or their metabolites are renally excreted. There is no "safe" opioid in renal impairment. Some are better tolerated than others.
- Use opioids with caution and avoid slow release oral preparations, particularly in opioid naïve patients and those with worsening function, as any side-effects will be further prolonged.
- It is important that **naloxone** is readily available as a response to even a small dose of an opioid can be unpredictable. Prolonged usage or an infusion may be required due to the long lasting side-effects especially for those who have been on opioid patches.

## SAFER OPIOIDS

Fentanyl, alfentanil and methadone have inactive metabolites and are therefore considered to be safer in patients with renal failure.

- **Fentanyl**
  Fentanyl has a number of advantages in patients with renal failure in that it is mainly metabolised in the liver to inactive metabolites and has a short half-life. A fentanyl patch should only be applied to patients with stable, well controlled pain. When using patches evaluate the analgesic effect after 24 hours. When withdrawing it, it can take up to 17 hours for the concentration to decrease by 50%. Replacement opioid therapy should therefore be short acting only, started at a low dose and gradually increased.
- **Alfentanil**
  Alfentanil is a derivative of fentanyl and well tolerated in patients with renal impairment as it does not have active metabolites. It has a faster onset of action and a shorter half-life than fentanyl. Its analgesic effect probably lasts 5–10 minutes when used sublingually. It is therefore useful for incident pain and prior to dressing changes. It is only available in the injectable form and can be given intranasally using a metered aerosol spray, buccally, or subcutaneously in a syringe driver for persistent pain use only (specialist use only. Not yet widely available).

- **Methadone**
  There is little information on the recommended dose of methadone in renal failure. Whilst it has no known significant active metabolites it is characterised by marked inter-individual variability in its pharmacokinetics. A long and unpredictable half-life can occur in normal as well as in sick patients with resulting accumulation. It should therefore only be started with specialist supervision and usually as an inpatient.
  There is huge variability between individuals and their response to even a small dose of an opioid. The table below gives guidance on prescribing strong opioids.

**Suggested starting doses in patients with renal failure**

| Drug | Degree of Renal Failure | | | Comment |
|---|---|---|---|---|
| | Mild | Moderate | Severe | |
| Morphine | 75% ND | 2.5 (- 5 mg) 6–8 hrly prn then titrate | 1.25 mg 6–8 hrly prn then titrate | Familiar drug. Well documented issues. |
| Diamorphine | 75% ND | 2.5 mg sc 6 hrly then titrate | 2.5 mg sc 8 hrly then titrate | Familiar drug. Well documented issues. |
| Fentanyl | ND | 75% ND | 50% ND | Continuous administration. Potentially problematic – consider alternative. |
| Alfentanil | ND | ND | ND | Useful for incident pain Can be used in a syringe driver for more continuous analgesia |
| Hydromorphone | ND | 1.3 mg 6–8 hrly | 1.3 mg 6–8 hrly | Limited evidence of better tolerance than morphine. |
| Methadone | ND | ND | 50% ND | Inactive metabolites and faecal excretion –but marked variability. |
| Buprenorphine | - | - | - | No evidence. |

SC = *subcutaneous* ND = *normal dose*

### OPIOIDS AND DIALYSIS

If drugs and/or metabolites are renally excreted then intermittent haemodialysis can cause marked fluctuations in drug levels with dips during/just after dialysis and "rebound" peaks as drugs and/or metabolites re-equilibrate between the CNS and plasma. Use prn medication as usual. If the patient develops pain with or after dialysis, a further dose may be required. The safety of a drug will relate to how dialysable it is.

| Avoid (most dialysable) | Use with caution (limited data) | Safe (not dialysable) |
|---|---|---|
| Codeine | Hydromorphone | Fentanyl |
| Morphine | Oxycodone | Alfentanil |
| Diamorphine | | Methadone |

## CO-ANALGESICS

### NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

NSAIDs are potent inhibitors of prostaglandin (PG) synthesis. This can cause gastrointestinal toxicity by impairing platelet aggregation and by inhibiting the secretion of cytoprotective mucus. Reduced renal blood flow and GFR may also occur due to PG inhibition, in addition to salt, water and potassium retention in patients with decreased renal function. Adverse effects of NSAIDs are more clinically apparent in patients with decreased effective circulating fluid volume eg. congestive heart failure, dehydration and haemorrhage.

Direct hypersensitivity occasionally occurs as an idiosyncratic reaction with NSAIDs. A history of intolerance to aspirin is a contraindication to their use. Renal function should return to normal in these cases if the NSAID is stopped.

**NSAIDs should be avoided in patients with multiple myeloma as they are at risk of developing renal failure.**

NSAIDs could be considered for patients with no renal function eg. on dialysis.

## KETOROLAC

**SPECIALIST USE ONLY. Ketorolac** is a potent analgesic NSAID which is particularly likely to precipitate gastrointestinal bleeding if used in the elderly for more than seven days. However, in palliative care it has been used parentally for extended periods but **always** with a gastroprotective drug. As with other NSAIDs, ketorolac can precipitate acute renal failure. Avoid use with ACE inhibitors.

## DRUGS FOR NEUROPATHIC PAIN

### Tricyclic Antidepressants (Such as amitriptyline or imipramine)

Dosage adjustment in renal impairment is unnecessary with amitriptyline and imipramine. However, treatment should be introduced at a lower dose ie. 10 mg nocte and increased gradually due to dizziness and postural hypotension. They may also be poorly tolerated owing to excessive sedation, confusion and extrapyramidal symptoms.

### Gabapentin

Gabapentin accumulates in renal failure. Start with lowest possible dose and titrate upwards according to response. Suggested maximal doses are:-

| | | |
|---|---|---|
| GFR | 60 – 90 | 400 mg tds |
| | 30 – 60 | 300 mg bd |
| | 15 – 30 | 300 mg od |
| | <15 | 300 mg on alternate days |

When on haemodialysis give 200-300 mg after each dialysis session only ie. three times weekly. For peritoneal dialysis give 100-300 mg daily. Exceeding these doses leads to toxic effects including agitation and aggression.

## Pregabalin

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug and therefore accumulates in renal failure. As pregabalin clearance is directly proportional to creatinine clearance, dosage reduction in patients with renal impairment must be adjusted according to their GFR as shown below:-

| GFR | Starting Dose | Max. Dose | Frequency |
|---|---|---|---|
| ≥=60 | 150 mg | 600 mg | bd or tds |
| ≥=30 - ≤=60 | 75 mg | 300 mg | bd or tds |
| ≥=15 - ≤=30 | 25-50 mg | 150 mg | od or bd |
| ≤15 | 25 mg | 75 mg | od |
| Supplementary dose after haemodialysis | 25 mg | 100 mg | Single dose |

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every four hour haemodialysis treatment.

## Anticonvulsants

Dosage adjustment in renal impairment is not necessary with sodium valproate and carbamazepine. Sodium valproate has fewer drug interactions than carbamazepine and therefore it should be used first-line.

## Antispasmodics

| | Degree of Renal Failure | | | |
|---|---|---|---|---|
| **Drug** | **Mild** | **Moderate** | **Severe** | **Comment** |
| Diazepam | ND | Use small dose and titrate to response | Use small dose and titrate to response | Cerebral sensitivity is increased possibly resulting in excessive sedation and encephalopathy. Flumazenil should be available to reverse the effects. |
| Clonazepam | ND | ND | ND | |
| Baclofen | 5 mg tds and titrate to response | 5 mg bd and titrate to response | 5 mg od | Withdraw treatment gradually over 1 – 2 weeks to avoid anxiety and confusional state. |

## OTHER DRUGS

These should only be used on specialist advice.

| | Degree of Renal Failure | | |
|---|---|---|---|
| **Drug** | **Mild** | **Moderate** | **Severe** |
| Ketamine | ND | ND | ND |
| Flecainide | Caution required - consider using an alternative | | |
| Mexiletine | ND | ND | 50% ND |
| Clonidine | ND | ND | ND |
| Bisphosphonates | Alendronate and Risedronate used if GFR <35, manufacturers advise to avoid | | |
| Pamidronate disodium | ND | ND | 60 mg if serum calcium >4.0<br>30 mg if serum calcium <4.0<br>Reduce infusion rate<br>Maximum infusion rate 20 mg/hr |
| Zoledronic acid | Increased risk of renal deterioration if GFR is less than 10 ml/min so renal function should be monitored. Increased risk of renal failure if 8 mg used. | | |

ND = *Normal dose*

## NAUSEA AND VOMITING

There are numerous possible causes of nausea and vomiting in patients with renal failure. Drugs should be prescribed according to probable cause. Uraemia and some drugs, eg. opioids, may stimulate the chemoreceptor trigger zone in which case a dopamine receptor antagonist such as haloperidol may be effective.

## NAUSEA AND VOMITING - SUGGESTED DOSES OF COMMONLY USED ANTIEMETIICS

Dose adjustment is not necessary with cyclizine, promethazine, levomepromazine (palliative care doses are small), domperidone, hyoscine hydrobromide, ondansetron, dexamethasone and octreotide.

| | Degree of Renal Failure | | |
|---|---|---|---|
| **Drug** | **Mild** | **Moderate** | **Severe** |
| Prochlorperazine | ND | ND | Start with a small dose, ie. 6.25 mg im or 5 mg orally |
| Haloperidol (palliative care doses are small) | ND | ND | Start with a small dose, ie. 0.5 mg od |
| Metoclopramide | ND | 75% ND | 50% ND up to 10mg tds |

## GASTRITIS

| | Degree of Renal Failure | | |
|---|---|---|---|
| **Drug** | **Mild** | **Moderate** | **Severe** |
| Antacids | Caution advised as aluminium and magnesium are absorbed and may accumulate | | |
| **Peptic ulcer healing drugs** | | | |
| Lansoprazole | ND | ND | ND |
| Omeprazole | ND | ND | ND |
| Esomeprazole | ND | ND | ND |
| Ranitidine | ND | ND | 50% of maximum dose ie. 150 mg bd |
| Sucralfate | ND | ND | Avoid – aluminium is absorbed and may accumulate |



ND = *Normal dose*

## BOWEL OBSTRUCTION

Dose adjustment is not necessary with hysocine butylbromide (buscopan). Other drugs used in bowel obstruction are mentioned under nausea and vomiting.

## CONSTIPATION

Laxatives can be used at a normal dose in patients with renal impairment. Avoid picolax if possible due to high sodium content and risk of hypermagnesaemia. Sodium picosulphate (dulcolax), senna and lactulose can be used at the normal dose. Use laxido with caution due to sodium and potassium content although manufacturers advise it is safe to use and does not secrete or absorb any sodium or potassium.

## BREATHLESSNESS AND COUGH

Use low doses of oramorph and codeine and increase dose intervals (see section on Analgesics)

## ANOREXIA

| | Degree of Renal Failure | | |
|---|---|---|---|
| **Drug** | **Mild** | **Moderate** | **Severe** |
| Alcohol | Not contraindicated in moderation | | |
| Corticosteroids | ND | ND | ND |
| Megestrol acetate/megace | ND | ND | ND |

## SWEATING

Not associated with infection.

| | Degree of Renal Failure | | |
|---|---|---|---|
| Drug | Mild | Moderate | Severe |
| NSAIDs | Use lowest effective dose and monitor renal function | Avoid if possible | Avoid if possible unless patient is dialysis dependent |
| Amitriptyline | ND | Start with low dose and gradually increase due to side-effects | |
| Propantheline | Manufacturer advises caution | | |
| Propranolol | ND | Start with a small dose | |
| Thioridazine | ND | ND | ND |
| Thalidomide | ND | ND | ND |

ND = *Normal dose*

**1. Uraemic Pruritis**

Pruritis is very common in renal failure. Emollient creams and ointments can be very helpful especially if the skin is dry. Paraffin-based products are preferable if the skin is cut or broken to avoid stinging. Sometimes pruritis can be worse during dialysis and enhancing dialysis can help. Drug treatments should be tested sequentially. The following can be tried:

- Oral antihistamines – inexpensive and safe although little evidence they work.
- Phototherapy with UVB light three times a week – quite effective but inconvenient.
- Naltrexone 50 – 100 mg od – benefit disputed. Contra indicated if patients need opioids.
- Eurax Cream tds – Crotamiton content eases localised itch.
- Capsaicin cream 0.025% or 0.075% 2–4 times daily – for localised itch in uraemia. It causes a local burning sensation for the first few days that is poorly tolerated.
- Ketotifen 2 mg bd – mast cell stabiliser.
- Ondansetron 4 mg bd – 5-hydroxytryptamine antagonist.
- Cholestyramine 5 mg bd.
- Activated charcoal 6 g per day in 4 – 6 divided doses – can be effective but can interfere with absorption of other medication.
- Mirtazapine 7.5 mg – 15 mg od.

**2. Pruritis due to Obstructive Jaundice**

| | Degree of Renal Failure | | |
|---|---|---|---|
| Drug | Mild | Moderate | Severe |
| Chlorphenamine | ND | ND | ND |
| Cholestyramine | ND | ND | ND |
| Ondansetron | ND | ND | ND |

ND = *Normal dose*

## HICCOUGH

| | Degree of Renal Failure | | |
|---|---|---|---|
| Drug | Mild | Moderate | Severe |
| Asilone | ND | ND | Avoid |
| Metoclopramide | ND | 75% ND tds | 50% ND up to 10 mg tds |
| Nifedipine | ND | ND | ND |
| Baclofen | 5 – 10 mg bd and titrate to response | 5 mg bd and titrate to response | 5 mg od |
| Chlorpromazine | ND | ND | Start with small dose 25 mg tds. Increased cerebral sensitivity |
| Sodium valproate | 200 mg bd | 100 mg bd | 100 mg od |

## CONFUSION

Exclude treatable or iatrogenic cause. If sedation is required: -

| | Degree of Renal Failure | | |
|---|---|---|---|
| Drug | Mild | Moderate | Severe |
| Haloperidol | ND | ND | Start with small dose 0.5 mg od |
| Levomepromazine (palliative care doses are small) | ND | ND | ND |

Caution: Patients may already be on opioids, benzodiazepines and sedating antihistamines and so start with small doses.

***Hypercalcaemia*** – see section on bisphosphonates under Co-analgesics.

| | Degree of Renal Failure | | |
|---|---|---|---|
| Drug | Mild | Moderate | Severe |
| Amitriptyline | ND | Start with a low dose and gradually increase due to side-effects | |
| Citalopram | ND | ND | 10mg to start |
| Clonazepam | ND | ND | ND |
| Diazepam | ND | Use small dose and titrate to response | Use small dose and titrate to response |
| Dothiepin | ND | Start with small dose eg. 25 mg nocte | Start with small dose eg. 25 mg nocte |
| Fluoxetine | ND | ND | 20 mg alternate days |
| Imipramine | ND | Start with a low dose and gradually increase due to side effects | |
| Lorazepam | ND | ND | ND |
| Midazolam | ND | ND | Use with caution especially when with opiates |
| Mirtazapine | Manufacturer advises caution | | |
| Paroxetine | Usual initial dose. Small increase if necessary. | Maximum dose 20 mg/day | Maximum dose 20 mg/day |
| Sertraline | ND | ND | ND |

**Caution:**

- Do not use SSRIs or TCADs with tramadol.
- Use SSRI with caution on epileptic patients as convulsion threshold lowered.
- Citalopram is the SSRI with fewest drug interactions in this class.

## ANTICONVULSANTS

Dosage adjustment is not necessary with sodium valproate and carbamazepine. Check drug interactions. Sodium valproate should be used first-line. Benzodiazepines are shown in the table on Anxiety and Depression.

## PHENYTOIN

Avoid as it is difficult to interpret phenytoin levels and low albumin levels in patients with renal failure.

## TERMINAL SECRETIONS

| | Degree of Renal Failure | | |
|---|---|---|---|
| **Drug** | **Mild** | **Moderate** | **Severe** |
| Hyoscine hydrobromide | Manufacturer advises caution | | |
| Glycopyrronium bromide | ND | ND | ND |

## ANTIBIOTICS AND ANTIFUNGALS

Common ones used are:-

| | Degree of Renal Failure | | |
|---|---|---|---|
| **Drug** | **Mild** | **Moderate** | **Severe** |
| Amoxicillin | ND | ND | 250 mg 8 hourly |
| Co-Amoxiclav | ND | 375 – 625 mg<br>2 – 3 times a day | 375 mg 3 times a day |
| Flucloxacillin | ND | ND | ND up to a total daily dose of 4 g |
| Fluconazole | ND | ND | Up to maximum daily dose of 200 mg |
| Metronidazole | ND | ND | ND |
| Trimethoprim | ND | ND for 3 days then 50% ND every 18 hours | 50% ND every 24 hrs |

The principles of end of life prescribing in patients with renal failure are similar to those with patients in normal renal function and the Liverpool Care Pathway (LCP) can be followed. The patient's comfort is paramount and it is important that drugs should not be withheld because of renal impairment, eg. NSAIDs. All drugs should be prescribed at an appropriate dose for comfort. For further details of the LCP see section on The Dying Patient.

## BREAKING BAD NEWS GUIDELINES

- Try to ensure that relative/friend is present
- Ensure that you have privacy
- No interruptions (bleep, telephone)
- Set the scene, eg. "I have come to discuss some of your results" or "I wanted to talk to you about how things are at present"
- Ask permission - "I have your results, would you like me to let you know what they show?"
- Warning shot - "I'm afraid that it is not very good news, would you like me to go on?"
- Give bad news - "I am afraid that ...." or "I am very sorry ...."
- Acknowledge distress
- Elicit concerns - "I know that this is very bad news but is there anything that is particularly distressing or in your mind?"
- Do not be trapped into the advice and reassurance path
- Give details of management plan if able to absorb
- Give follow up appointment soon
- Written or taped information may be of help

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