Clinical Guidelines for the use of **Palliative Care Drugs in Renal Failure**

2006

Yorkshire Palliative Medicine Guidelines Group

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INTRODUCTION

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Primary objectives

1. To provide a compact form of advice for prescribing palliative care drugs in patients with renal failure
2. To suggest which drugs from a given class – eg opioids - might be most appropriate for a patient with renal failure

Secondary objectives

1. To suggest the use of calculated glomerular filtration rate **(GFR)** as a measure of renal function, in preference to serum creatinine (**Cr**)
2. To highlight the pros and cons of using different methods for estimating GFR in palliative care patients

If in doubt, or if further information is required, please consult a renal pharmacist.

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Competing interests: None declared

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RESOURCES

Literature searches (Medline) provided few examples of similar guidelines. Those that were identified contained advice for adjusting doses, but often, this advice did not appear to be in keeping with the pharmacokinetic information provided.

This document condenses existing resources in order to make the information more accessible at the patient's bedside.

We used the following resources (in order of authority):

1. Specification of Product Characteristics (**SPC** or **data sheet**)
   (available from www.emc.medicines.org.uk)
2. The Renal Drug Handbook, Second Edition
3. Palliative Care Formulary, Second Edition
4. British National Formulary 50
5. Micromedex (available from www.micromedex.com – password required)
6. dialog datastar
   Medline & Embase
   search by – drug & renal failure (with thesaurus mapping)
7. NSF for renal services – Part two: chronic kidney disease, acute renal failure and end of life care

Full references for the above resources can be found in appendix II

In general, once information was obtained from a given resource, we did not go on to search resources of lower authority for the same information. Where other sources gave more conservative advice than the SPC, we have included and highlighted the conflicting information in yellow in the table.

Abbreviations

CAV/VVHD…Continuous arterio-venous/ veno-venous haemodiafiltration
CG……..Cockcroft Gault
Cr……serum Creatinine
Cr Cl……...Creatinine Clearance
eGFR……..estimated Glomerular Filtration Rate
GFR……Glomerular Filtration Rate
HD……...Haemodialysis
HF……...Haemofiltration
Max……Maximum
MDRD…….....Modification of Diet in Renal Disease
NSF……National Service Framework
PD……..Peritoneal Dialysis
Rx……Treatment
SPC……Specification of Product Characteristics
Other abbreviations are standard, or are defined in the A-Z drug list tables.

MEASURES OF RENAL FUNCTION

Traditionally, serum creatinine has been used by many health professionals as a measure of renal function. This is inaccurate as patients may have a clinically significant deterioration in renal function while still having a serum creatinine within the normal reference range. (Lamb et al 2005)

Historically, some branches of medicine have recognised the need for more accurate measures of renal function, and creatinine clearance (**CrCl**) has been used.
Increasingly, it is recognised that glomerular filtration rate (**GFR**) is a preferable measure of renal function (NSF for renal services – Part two, 2005). While this can be measured with invasive techniques (inulin clearance), there are two generally accepted ways of estimating GFR.

These are:
1. The Cockcroft & Gault equation (CG)
2. 4 variant Modification of Diet in Renal Disease equation (4vMDRD)

Appendix 1 gives details of these equations and how they have been derived.

- Both methods are inaccurate, especially at extremes of age and body habitus, but the **Cockcroft Gault** formula is recommended when modifying prescribing in renal failure.

- **Normal GFR is between 100 and 130 ml/min in an adult. (Relying on serum creatinine will fail to identify 50% of patients with a GFR of 15 – 30ml/min/1.73m^2).**
- **Renal function can deteriorate from day to day, so the latest blood results must be used when calculating GFR**

The relative merits of the two methods are as follows:

	4v MDRD	**COCKCROFT & GAULT**
Track Record	Only recently developed	**The majority of data sheets issued by drug companies suggest dosing changes based on GFRs calculated by Cockroft and Gault.**
In patients with normal or mildly impaired renal function	Accuracy poor Accuracy improves as GFR falls UNDERestimates GFR	Accuracy poor Accuracy improves as GFR falls
In patients with moderately to severely impaired renal function	More accurate than CG	OVERestimates GFR
Body weight	Not required NB when modifying drug doses, GFR calculated using 4vMDRD must be adjusted for patient's total surface area	**Required**
Cachexia (BMI<18.5)	Less accurate	More accurate
Oedema		May overestimate GFR (The equation assumes that weight is a reflection of lean body mass, and weight is in the numerator).

(Lamb et al 2005)

There are plans to include an eGFR on U&E results sent to general practitioners from this year in the UK. This will be based on a 4vMDRD calculation. It will not have been adjusted for body total surface area. If racial origin has not been adjusted for, the eGFR should be multiplied by 1.2 for Afro-Caribbean patients.

PHARMACOLOGICAL CONSIDERATIONS IN RENAL FAILURE AND RENAL REPLACEMENT THERAPY

DRUG CLEARANCE

In general, drugs are cleared by:

- excretion (most often via the urine, but can also be excreted via bile or faeces)
- metabolism to an active or inactive form (usually in the liver)
- a combination of metabolism and excretion

When metabolism and/or excretion are impaired, the dose or frequency of administration of drugs may need to be altered to prevent accumulation of drugs. It is important to remember that some metabolites are active (ie have a similar effect to the original drug). Active metabolites can be cleared either by further metabolism, or by excretion in the urine.

HOW THE KIDNEYS REMOVE DRUGS

Drugs are delivered to the kidney via circulating blood. The blood is filtered, and the filtrate will eventually become urine after modification in the kidney tubule.

At the kidney, drugs may undergo any of the following:

- Filtration
  - A given drug may or may not be filtered.
  - The larger the drug molecule, the less likely it is to be filtered. If a drug is bound to protein, it effectively becomes a larger molecule.
- Secretion
  - This occurs when the kidney actively pumps a substance from the blood into the fluid that will become urine. (This is in contrast to filtration which is a passive process.)
- Reabsorption
  - This occurs when a substance is actively pumped back into the blood from the fluid that will become urine, regardless of whether the drug entered the fluid by filtration or excretion.

When renal function is impaired, the rate of filtration at the kidney (GFR) is reduced. Therefore, drugs which rely on renal clearance will take longer to clear.

OTHER CONSIDERATIONS

Renal failure can make patients more susceptible to adverse effects of drugs.
In particular it causes:

- an increased bleeding tendency, therefore the risks of NSAIDs and anticoagulants are increased
- increased blood brain barrier permeability, and therefore increased sensitivity to CNS side effects of drugs (eg sedation).

RENAL REPLACEMENT THERAPY

This comprises haemodialysis, peritoneal dialysis and haemofiltration.

Haemofiltration (HF) involves passing the patient's blood through an external machine with a synthetic membrane. Fluids and other substances (including some drugs) cross the membrane by convection. This is used in acute rather than chronic renal failure and is usually run continuously for a number of days.

Haemodialysis (HD) involves passing the patient's blood through an external machine with a synthetic membrane. However, fluids and other substances (including some drugs) cross the membrane along a concentration gradient. This is used intermittently (often for ~ 4 hours, 2 or 3 times/week) in chronic renal failure.

Peritoneal dialysis (PD) involves passing fluid into the peritoneal cavity, and allowing fluid and some substances to cross the peritoneal membrane along a concentration gradient. The fluid is then drained back out of the peritoneal cavity. It is used in chronic renal failure, and has the advantage that patients can do it at home.

DRUG CLEARANCE IN RENAL REPLACEMENT THERAPY

Drug clearance in renal replacement therapy is affected by the following factors:

Properties of the drug
Delivery of drug to the filter
Properties of the filter

If the drug molecule is larger than the pore size of the membrane, then it will not be cleared by dialysis. If the drug has a large volume of distribution throughout the body (and therefore only a small percentage of it is in the circulation) it will be poorly cleared by dialysis.

In general:

- If a drug is **avidly cleared** by a particular type of dialysis, it would have to be administered after dialysis in order for it to have the desired effect.
- If a drug is **poorly cleared** by a particular type of dialysis, dosing and frequency of medication should be altered in keeping with the underlying renal function. GFR should be assumed to be less than 15 ml/min. Serum creatinine levels are reduced immediately after dialysis and therefore do not reflect GFR.

SUGGESTED FIRST LINE DRUGS IN RENAL FAILURE

- The suggestions below only apply when renal failure is the main factor in deciding which drug (in a given class) to use.
- The reasons for suggesting these drugs may include:
    1. Clearance (and therefore dosing) is relatively unaffected by renal impairment;
    2. The drug's mechanism of action has specific benefit in renal impairment and/or
    3. The drug is relatively less nephrotoxic (NB not important once a patient becomes anuric)
- There will be occasions where other considerations become more important than renal failure. For example, a particular drug may be preferable because of a beneficial side effect profile, even though it would require significant dose adjustment. In such circumstances, please refer to the alphabetical list of drugs (pages 11-22) for prescribing advice.
- *It should be remembered that the central nervous system effects of any drug can be increased in renal failure, even if drug clearance is not affected.*

ANTICOAGULANTS

For GFR <30:

Prophylaxis of venous thrombo-embolism:
Low molecular weight heparin in PROPHYLACTIC doses
(MAXIMUM dose of enoxaparin is 20mg per day)

Treatment of venous thrombo-embolism:
***Treatment dose LMWH can cause severe/fatal bleeding*.**
Acutely, dialysis patients should receive unfractionated heparin, but this requires frequent blood tests. Therefore, for patients with GFR<30 discuss individual cases with local haematologist.

ANTI-EMETICS

Patients with renal failure often have a "chemical" cause for nausea or vomiting.
For GFR >10, altered pharmacokinetics do not warrant adjustment of starting dose for the following: Haloperidol, Levomepromazine, Cyclizine, Ondansetron, Granisetron

However, haloperidol, levomepromazine and cyclizine can have increased sedative effects in renal failure, so doses should be reduced if sedation is undesirable.

For GFR <10, haloperidol and levomepromazine should be started cautiously, at low doses, and titrated according to response and side effects.

If a prokinetic anti-emetic is required, metoclopramide dose needs to be reduced when GFR <20.

ANTIDEPRESSANTS

Altered pharmacokinetics do not warrant adjustment of **amitriptyline** dose. However, it can have increased sedative effects in renal failure, so doses should be reduced if sedation is undesirable. (Some side-effects may be useful; others may preclude its use.)

In palliative care patients without renal impairment, citalopram and mirtazapine are first line anti-depressants. Doses need to be reduced in severe renal impairment (see A-Z drug list).

BISPHOSPHONATES

First choice is debatable because the information from different sources is conflicting.
There is evidence to suggest that pamidronate and zoledronate can be nephrotoxic. There is no evidence to suggest ibandronic acid (Ibandronate) is nephrotoxic, but, it is a newer drug. For individual patients, potential harm from underlying conditions (hypercalcaemia or prevention of skeletal related events) must be weighed against potential harm from the drug. Ibandronate **may** be the drug of choice when it is unacceptable to risk any worsening of a patient's renal function.

If GFR 10-30
Zoledronate: should **not** be used.
Ibandronate: The data sheet suggests that Ibandronate can be used in reduced doses. However, Micromedex advises against its use.
Pamidronate: This can be used in normal doses for GFRs above 10, but with a prolonged infusion time.

If GFR<10
Zoledronate: should **not** be used.
Ibandronate: as for GFR 10-30.
Pamidronate: The data sheet suggests that normal doses can be used, but that the infusion infusion time should be prolonged. However, the Renal Drug Handbook advises reduced doses if GFR < 10. In this instance, the risks when using a normal dose (ie possible nephrotoxicity and over-correction of calcium) must be weighed against the risks when reducing the dose (ie possible under-treatment) for the individual patient.

LAXATIVES

Generally, there is minimal absorption of laxatives, and therefore no alteration of doses is required.
Particular issues include:

- If a patient needs to be fluid restricted, avoid movicol (as large volumes of fluid must be consumed along with this drug).
- Senna can cause electrolyte imbalance, especially hypokalaemia.

NEUROPATHIC PAIN

- Amitriptyline starting dose needs no adjustment unless sedation is undesirable. Must be titrated carefully.
- If amitriptyline is inappropriate, gabapentin and pregabalin require significant dose adjustments.
- Dexamethasone does not require dose adjustment, but may be complicated by fluid retention.

NSAIDS

As a group, NSAIDs can be nephrotoxic and should be used with extreme caution, particularly in patients with moderate to severe renal impairment unless there are no alternatives and dependent upon the clinical situation (eg the last few days of life).
NSAIDs (with PPI cover) can still be used in dialysis patients if they have no significant residual renal function (eg anuric patients)

The most hazardous NSAID in renal failure is ketorolac. Otherwise, no NSAID is recommended over any other.
NB

- Damage to the kidneys from nephrotoxic drugs (including NSAIDs) is additive.
- Increased bleeding tendency in people with renal failure increases the risk of GI bleeding.
- Sulindac was once thought to be the most sparing of the NSAIDs on renal prostaglandin inhibition and hence least nephrotoxic. However, for doses >100mg BD there is no evidence to support this. (Brater 1999)

OPIOIDS

Morphine should be avoided as it accumulates in renal failure and can cause over-opiation.

If not using subcutaneous route, consider transdermal route for background analgesia, with oral PRN medication.

- Subcutaneous: Alfentanil (no dose adjustment required)
- Transdermal:
  - Buprenorphine (still a small risk of accumulating weakly active metabolite)
  - Fentanyl (especially if high dose opioid required, but greater risk of accumulation)
- Oral:
  - For GFR 10-50: Oxycodone
  - For GFR<10: Hydromorphone at reduced dose – small risk of accumulating drug/active metabolite

NB Methadone is well cleared in renal failure, but has a very long half life, even when renal function normal.

SECRETIONS

Hyoscine butylbromide or hyoscine hydrobromide.
(neither needs dose adjustment unless sedation is unacceptable in which case consider reducing dose of hyoscine hydrobromide)

SEDATIVES / ANXIOLYTICS

Subcutaneous: Midazolam – theoretical risk of accumulation for GFR<10, so start low and titrate dose.
Sublingual: Lorazepam – no need for dose adjustment, but sedative effect may be exaggerated.

Clinical Guidelines for
PALLIATIVE CARE DRUGS IN RENAL FAILURE

Information is from individual data sheets, except, in blue = Renal Drug Handbook 2nd Edition, in pink = Renal Drug Handbook – Draft 3rd edition and in green = Micromedex. All other references are specified.

DRUG	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure			Dose/interval change in renal replacement Rx			NEPHRO TOXIC? (Y/N)	OTHER
			GFR			HF	PD	HD		
Alfentanil	Several including Noralfentanil (?I), glucoronides(I) (liver)	Renal (D,M) only 1 % unchanged	Normal dose				Normal dose		N	Not removed by PD or HD T1/2 bolus injection = 90 minutes, but extended half life in obese, >65yrs, deranged liver function.
Amitriptyline	Nortriptyline (A) 10-hydroxyamitriptyline (A) 10-hydroxynortriptyline (A)	Renal D <10% M 90%	Normal dose BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE				Normal Dose			Introduce / withdraw treatment gradually in renal impairment.
Amoxicillin		Renal (D)	>30 Normal dose	10-30 500mg BD MAX	<10 500mg / day MAX	Dialysed. Dose as for normal GFR	Dialysed. Dose as for GFR<10		N	Care with electrolyte content of infusions
Baclofen	chlorophenyl-4-hydroxybutyric acid (I)	Renal (D, M) 75%	20-50 5mg **tds**	10-20 5mg **bd**	<10 5mg **od**	Unknown – dose as for GFR<10			N	Doses are starting doses and should be titrated according to response and side effects.
Buprenorphine (patches)	Norbuprenorphine (weakly A)	Renal M - 33% in urine D - 1% unchanged Faecal D - 66% unchanged	10-50 ml/min No change	<10 ml/min **Patches** No change **Injection & S/L** Reduce dose by 25-50%. Avoid large single doses		Dialysed – dose as for GFR< 10mls/min			N	Can cause urinary retention and oedema (non - renal) CAV/VVHD – not dialysed – dose as GFR 10-20ml/min
Carbamazepine	10,11 transdiol and glucuronide	Renal (72%)but only 2% of the drug is excreted unchanged Faeces (28%)	Normal dose BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE			Normal dose			Very rarely	Not dialysed in HD,PD or HF
Ciprofloxacin		Renal D - 45% M - 11% Faecal D - 25% M - 7%	20-50 Normal dose	<20 50%of normal dose		Dialysed **PO** 250-500mg/ 12hrs **IV** 200-400mg/ 12hrs	Not dialysed **PO** 250mg/8-12hrs **IV** 100mg/ 12hrs	Not dialysed **PO** 250mg/8-12hrs **IV**100-200mg/ 12hrs	N	

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			GFR			HF	PD	HD		
Citalopram	Demethylcitalopram (A); Didemethylcitalopram (A); citalopram-N-oxide (A); deaminated propionic acid derivative (I)	Hepatic 85% Renal D - 12%	10-50 Normal dose	<10 Normal dose; with caution			Dose as for GFR <10			Use with caution in severe renal failure.
Clarithromycin	14 hydroxy metabolite (A)	Faecal70-80%(M) Urine 20-30% (D)	20-50 Normal dose **PO** 250-500mg /12 hrs **IV** 500 mg 12hrly	10-20 **PO** 250-500mg every 12-24hrs **IV** 250-500 mg/12hr	<10 **PO** 250mg every12-24 hrs **IV** 250mg/ 12hrs	Unknown Dose as for GFR 10-20	Unknown Dose as for GFR<10	Dialysed Dose as for GFR<10	N	Inhibits metabolism of Midazolam
Clonazepam	7-amino-clonazepam (I) 7-acetylamino-clonazepam (I) 3-hydroxy-clonazepam (A)	Renal (D) <1% unchanged	No dose adjustment required BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE			Dose as normal renal function			N	Not haemodialysed Unknown peritoneal dialysability
Co-danthramer	Dantron part metabolised by GI flora, both D and M adsorbed. Glucuronide and sulphate metabolites (Breimer et al 1976)	In rats – approx 20-30% only excreted in the urine and faeces as D and M. <9% in faeces as D and M (poor quality data) (Breimer et al 1976)	No information available			no information available			N	Dantron is partially adsorbed, poloxamer 188 is not adsorbed. May colour urine red Recommendation - Titrate dose as required (Breimer et al 1976)
Codeine	C6G (A), Norcodeine (?),Morphine (A) M3G (I)M6G (A)	Renal (D,M)	20-50 Normal dose	10-20 75% dose	<10 50% dose	Unknown so as <10			N	Unknown dialysability
Cyclizine	Hepatic metabolism n-demethylated to norcyclizine [I]		Normal dose BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE				Normal dose		N	Increased cerebral sensitivity in patients with renal failure.

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			GFR			HF	PD	HD		
Dalteparin		Renal	20-50 Normal dose	<20 For prophylaxis, normal dose can be used DO NOT USE for TREATMENT of PE / DVT – see "Other" column		Unknown dialysability	Not dialysed			LMWH is renally excreted and therefore accumulates in renal failure. Prophylactic doses are well tolerated but **treatment doses for DVT and PE have been associated with severe and sometimes fatal bleeding episodes**. Therefore use of **unfractionated** heparin is recommended in patients with severe renal impairment. Note: heparin can suppress adrenal secretion of aldosterone causing **hyperkalaemia,** particularly in patients with chronic renal impairment and diabetes.
Dexa-methasone	Various metabolites(I)	Renal (D,M)	Normal dose			Unlikely removal Normal dose	Not dialysed Normal dose		N	
Diamorphine	6MAM (?A), M6G (A)	Renal (D,M)	20-50 Normal 4hrly	<20 Small, 6hrly	<10 Small, 8hrly	As GFR <10			N	Not dialysed Start at low doses and titrate up
Diazepam	a. N-desmethyl diazepam (A) b. Temazepam (A) a & b both converted to Oxazepam (A)	Renal (75%)	20-50 Normal dose BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE	10-20 Use small doses & titrate to response	<10	Dose as GFR 10-20	Dose as GFR <10		*?	Not dialysed via HD or PD Unknown haemofiltration Case report: allergic interstitial nephritis and deteriorating pre-existing chronic renal failure.
Diclofenac	Hydroxylated into inactive metabolite (liver) (I)	Renal and Biliary (M)	20-50 Normal dose but avoid if possible	10-20	<10 Use only if patient on dialysis	Normal dose (not dialysed)			Y	SPC recommends use in advanced renal failure in **"exceptional circumstances" only**. ½ life 1-2 hrs (same in ESRF)
Docusate Sodium	Some adsorption	Biliary	No information available			No information available			N	Titrate dose against effect
Domperidone	Extensive first pass hepatic metabolism Metabolites [I]	Renal M ~ 1/3 D negligible Faecal M ~ 2/3	Normal dose				Normal dose		N	Elimination half life is increased in severe renal failure. Frequency of dosing should be reduced to once/twice daily

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			GFR			HF	PD	HD		
Enoxaparin			30-50	<30		Not dialysed Dose as for GFR<10			N	LMWH is renally excreted and therefore accumulates in renal failure. Prophylactic doses are well tolerated but **treatment** doses for DVT and PE have been associated with severe and sometimes fatal bleeding episodes. Therefore use of **unfractionated** heparin is recommended in patients with severe renal impairment. Note: heparin can suppress adrenal secretion of aldosterone causing **hyperkalaemia,** particularly in patients with chronic renal impairment and diabetes.
			Normal dose	PROPHYLAXIS 20mg/day maximum TREATMEMT Data sheet suggests reducing dose to 1mg/kg **daily** but Renal Drug Handbook **recommends against use** at treatment doses						
Erythromycin		Biliary(D)	10-50	<10		Unknown Dose as for normal renal function	Removal unlikely. Dose as for GFR<10	Not dialysed. Dose as for GFR<10	N	Increased risk of ototoxicity in renal impairment. Avoid peaks produced by twice-daily dosing – ie **dose four times/day**
			Normal dose	50-75% dose. Max 1.5g/day						
Fentanyl	Norfentalyl (I)	D – 9% faecal D,M - 75% renal	20-50	10-20	<10	Dose as for GFR <10			N	Not dialysed
			Normal dose	75% dose	50% dose					
Flucloxacillin		Renal (D)	10-50	<10		Not dialysed. Dose as in normal renal function	Not dialysed. Dose as for GFR<10		N	Care with electrolyte content of infusions
			Normal dose	Normal dose, up to 4g/24hrs						
Fluconazole	1,2,3-triazole and others (liver – poor metab)	Renal D,M (approx. 80% unchanged)	10-50		<10		Dose as for GFR<10	Dose as for GFR<10 Post dialysis	N	Known to be removed by PD Known to be removed by HD No dose adjustments required for single doses T1/2 = 30 hrs
			Normal dose		50% of normal dose					
Fluoxetine	Norfluoxetine (A) (and other unidentified M)	Urine <12% (D) 7% (M) Faecal15% (D)	20-50	10- 20	<10		Dose as for GFR <10			Accumulation can occur in severe renal failure during chronic treatment due to long half life. Usual maximum 20mg oral daily
			Normal dose	Normal dose or alternate days	Normal dose or alternate days					
Gabapentin		Renal (D)	30-60	15-30	< 15	Dose as for GFR 15-30	Dose as for GFR <15	Load 300-400mg then 200-300mg after each HD	Y	Can be removed by HD,HF and PD Can cause false positive reading with some urinary protein tests In practice start with 100mg ON and titrate slowly
			300mg twice daily MAXI-MUM	300mg once daily MAXI-MUM	300mg alternate days MAXI-MUM					

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			GFR			HF	PD	HD		
Glycopyrrolate	No information	D = 48.5% renal remainder unchanged in bile	No information available			No information available			N	Anticholinergic – may cause urinary retention Dose is titrated against effect. Some accumulation possible
Granisetron	Hepatic metabolism (? Activity)	Renal 59% [D,M] Faecal remainder [M]	Normal dose				Normal dose	Normal dose *	N	*Manufacturer recommends timing of HD should be more than 2 hrs after granisetron.
Haloperidol	Hepatic metabolism Hydroxyl-haloperidol [A]	Renal and faecal	10-50 Normal dose	<10 Lower dose	BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE		Dose as in GFR < 10		N	For GFR<10 avoid repeated dosage because of accumulation. For single dose, use normal dose. Not dialysed
Hydromorphone	Dihydro-isomorphine (A), dihydromorphine (A), H3G (I)	Renal(D,M)	20-50 Normal dose	10-20 Reduce dose	<10 Reduce dose	Unknown so dose as for GFR<10			N	Start at low doses in renal failure
Hyoscine Butylbromide	?	a) D –50% renal excretion	No change			?	Dialysed – dose as for GFR <10 mls/min		N	Anticholinergic - Can cause urinary retention CAV/VVHD – not dialysed – dose as in GFR 10-20ml/min
Hyoscine Hydrobromide	Apohyoscine	metabolised in liver and then M renally excreted (S/C only 3.4% D excreted in urine in 72 hrs)	No change BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE			?	Dialysed – dose as for GFR <10 mls/min		N	Anticholinergic - Can cause urinary retention CAV/VVHD – not dialysed – dose as in GFR 10-20ml/min
Ibandronic acid	Not metabolised	Renal (D)	30-50 Normal dose	<30 The dose for prevention of skeletal events should be reduced to 2mg **iv** every 3-4 weeks infused over 1 hour. The **oral** dose should be reduced to 50mg weekly.		No information available			N**?**	Clinical studies have shown no evidence of deterioration in renal function with long term use but monitoring of renal function, serum calcium, phosphate and magnesium is recommended. **NB Although manufacturers recommend dose reduction for patients with GFR<30, Micromedex recommends against use in patients with CrCl<30ml/min** Patients should be administered an oral calcium supplement of 500mg and 400IU of vitamin D daily.

Clinical Guidelines for PALLIATIVE CARE DRUGS IN RENAL FAILURE

Information is from individual data sheets, except, in blue = Renal Drug Handbook 2nd Edition, in pink = Renal Drug Handbook – Draft 3rd edition and in green = Micromedex. All other references are specified.

DRUG	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure			Dose/interval change in renal replacement Rx			NEPHRO TOXIC? (Y/N)	OTHER
			GFR			HF	PD	HD		
Ibuprofen	Liver metabolism to inactive conjugates (I)	Renal D <10% Rest inactive metabolites	10-50		<10	Normal dose (not dialysed) but avoid if possible	Normal dose (not dialysed – highly protein bound)		Y	½ life 2-3 hrs (same in ESRF)
			Normal dose but avoid if possible		Use only if patient on dialysis					
Ketamine	Nor-ketamine (A) dehydronor-ketamine (I)	a) Ketamine and norketamine - Renal 5% in urine unchanged + 5% unchanged in faeces b) Inactive metabolites renally excreted	No change			Not dialysed - dose as for normal renal function	Unlikely to be dialysed - dose as for normal renal function	Unknown dialysability- dose as for normal renal function	N	Can cause urinary retention and oedema (non - renal) CAV/VVHD – not dialysed – dose as in GFR 10-20ml/min 20-50% protein bound
Ketorolac	Hydroxylated into inactive metabolite (I)	Unclear: reports of 10-65% excreted unchanged in urine. Remainder: faecal (D) and renal(M)	20-50	10-20	<10	Unknown dialysability – dose as for GFR 10-20	Unlikely dialysability – dose as for GFR<10		Y	Nephrotoxicity can occur after a single dose. Avoid use if Creatinine >160 and use 60mg below this level. ½ life 3.5-9 hrs (6-19 in ESRF)
			60mg max/day	Avoid (Small doses in exceptional circs)						
Lactulose	Lactic acid (A) Formic acid (A) Acetic acid (A)	Faecal (M) Not significantly absorbed	Normal dose			Not dialysed. Normal dose			N	
Lansoprazole	Metabolised in gastric parietal cell (A) Metabolised in the liver (A,I)	Renal (M) Biliary (M)	Normal dose			Unknown dialysability	Unlikely removal	Not dialysed	N	
						Dose as in normal renal function				
Levo-mepromazine	a) sulphoxide metabolite (?activity) b) glucuronides (?activity)	Majority excreted in urine as M - glucuronide and sulphoxide metabolites D – small amount unchanged in urine and faeces	10-50	<10 ml/min		?	Not Dialysed – dose as for GFR <10 mls/min			CAV/VVHD – unknown dialysability – dose as in GFR 10-20ml/min
			No change	Start with small dose						
			BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE							
Loperamide	Metabolised by the liver where it is conjugated and excreted via the bile	Biliary (M) Faecal (D)	Normal dose			Unlikely dialysability Dose as for normal renal function			N	
Lorazepam	3-0-phenolic glucuronide (I) = 75% of metabolites Other metabolites also inactive	Renal (88%) Faecal (7%)	Normal dose BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE			Normal dose			N	HD – Dialysed

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DRUG	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure			Dose/interval change in renal replacement Rx			NEPHRO TOXIC? (Y/N)	OTHER
			GFR			HF	PD	HD		
Megestrol	M = glucuronide conjugates	D – mean 66.4% renal + mean 19.8% faecal M – 5-8% in urine	No information available. Reduced dose would seem most likely appropriate due to high renal clearance of drug.			Three small studies for cachexia in malnourished dialysis patients (non malignant) indicated that both high and low doses caused significant side effects			Y	Megestrol acetate can worsen its own clearance via the kidneys in patients with pre-existing renal insufficiency and thus precipitate the development of Cushing syndrome (Caution in renal dysfunction where, if Cushingoid, additional fluid retention/oedema may become an issue) Some reports of increased urinary frequency
Methadone	Several incl. EDDP (I) (liver)	Faecal Liver (50% each)	10-50		<10		Dose as for GFR<10		N	Not removed by PD or HD T1/2 = 12-18 hrs after single po dose, 13-47 after regular po doses
			Normal dose		50% of normal dose					
Methly-phenidate	ritalinic acid (PPAA) (I) + Hydroxymeth-lyphenidate (I) + hydroxyritalinic acid (I)	a) M - ritalinic acid - 80 % in urine b) D - less than 1% excreted unchanged in urine	No change					no specific info dose as for GFR <10ml/min	N	CAV/VVHD – no specific info dose as in GFR 10-20ml/min
Meto-clopramide	Hepatic Metabolites [I]	Predominantly renal [D,M]	20-50	10-20	< 10		Dose as for GFR <10		N	Increased risk of extrapyramidal reactions in severe renal impairment For GFR < 20, start at low doses
			Normal dose	75%-100% of normal dose	50%-100% of normal dose					
Metronidazole	2-hydroxymetronidazole (A)	Renal (D, M)	10-50	<10		Unknown – dose as normal	Not dialysed – dose as GFR <10	Dialysed – dose as normal **after dialysis**	No	Active metabolites accumulate in renal failure – clinical significance unknown
			Normal dose & frequency	Normal dose **bd**						
Midazolam	α-hydroxy midazolam (A)	Renal (D,M) 45-57% <1% as unchanged drug	10-50	<10		Normal dose	Dose as GFR <10		N	Not Haemodialysed Unlikely peritoneal dialysability Unknown haemofiltration
			Normal dose	50% of Normal dose						
			BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE							
Mirtazapine	8-hydroxy (I) N-demethyl (A) N-oxide (I)	Urine >75% (D) Faecal 15% (D)	10-50	<10			Dose as for GFR <10		?	
			Normal dose	Low dose Monitor clinically						

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			GFR			HF	PD	HD		
Morphine	M3G (I) M6G (A)	Renal (D,M)	20-50 25% dose	10-20 Small dose eg start with 2.5-5mg	<10 Small dose eg start with 1.25 - 2.5mg	Dose as for GFR <10			N	Dialysed in HD and CAV
Movicol	None	Faecal (D) Not significantly absorbed	Normal dose			Not dialysed. Normal dose			N	Lower risk of impaired electrolyte balance, as sachet contains salts
Octreotide	(?liver)	Renal (32% unchanged)	Normal dose				Normal dose		N	Unknown peritoneal dialysability Known to be haemodialysed LAR (sustained release) same as for normal release Elimination t1/2 sc = 100 minutes
Olanzapine	10-N-glucuronide (I) N-desmethyl and 2-hydroxymethyl (A) but < olanzapine	Renal (57%) Faecal(30%)	20-50 Initial dose 5mg daily & titrate as necessary	10-20	<10	Dose as for GFR 10-20	Dose as for GFR <10		N	Not dialysed via HD or PD Unknown haemofiltration
Omeprazole	Hepatic metabolism Metabolites in plasma = sulphone, sulphide & hydroxyl-omeprazole (I)	Renal 80% (M) Faecal 20% (M)	Normal dose			Unknown Dose as for normal renal function	Unlikely dialysability Dose as for normal renal function	Not dialysed. Dose as for normal renal function	N	As omeprazole is metabolised in the liver through cytochrome p450 it can prolong the elimination of phenytoin, diazepam and warfarin. Monitoring is recommended.
Ondansetron	Multiple metabolites [I]	Renal <5% unchanged in urine Hepatic	Normal dose				Normal dose		N	Can be used to treat uraemic pruritis
Oxycodone	Noroxycodone (A) Oxymorphone (A)	Renal (D 19%,M 65%) Faecal (D,M)	10-50 Normal dose BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE	<10 Avoid *		Unknown dialysability Dose as for GFR <10			N	*Used in ESRF – low doses of Oxynorm Metabolites may be more likely to accumulate and cause sedation, than hydromorphone metabolites at very low GFRs GFR<60 increased plasma concentration of active drug by 20-50%

Clinical Guidelines for PALLIATIVE CARE DRUGS IN RENAL FAILURE

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			GFR			HF	PD	HD		
Pamidronate	Not metabolised	Renal 20-55% (D)	10-50 Normal dose	<10 Serum Ca>4: give 60mg Serum Ca<4: give 30mg		No informat[n] available	Unknown dialysability Dose as for GFR <10ml/min	Dialysed Dose as for GFR <10ml/ min	Y at high doses	Pharmacokinetic studies indicate that **no dose adjustmen**t is needed in any degree of renal impairment. However, until further experience is gained a **maximum infusion rate of 20mg/hr** is recommended in patients with impaired renal function. AS PER DATA SHEET Patients receiving frequent infusions of disodium pamidronate concentrate over a prolonged period of time, especially those with pre-existing renal disease or a predisposition to renal impairment (e.g. patients with multiple myeloma and/or tumour-induced hypercalcaemia), **should have periodic evaluations of standard laboratory and clinical parameters of renal function**, as deterioration of renal function (including renal failure) has been reported following long-term treatment with disodium pamidronate concentrate in patients with multiple myeloma. Patients should be administered an oral calcium supplement of 500mg and 400IU of vitamin D daily.
Paracetamol	Glucuronide, sulphate and glutathione conjugates (I)	Renal (D and M, only 3% unchanged)	10-50 Normal dose	<10 500mg-1g 6-8hrs			Dose as GFR<10		Y in overdose	Not removed by PD Known to be removed by HD Normal doses are very often used in ESRD
Paroxetine	Oxidation (I) & methylation (I)	Urine 2% (D) Faecal 36% (D)	Normal dose			Normal dose				Lower end of dose range in Cr_{CL} <30 ml/min In practice, usual max 20mg OD in GFR <10
Phenobarbital		Renal (20-25%) Metabolised by liver	20-50 Normal dose	10-20 Normal dose, but avoid large doses	<10 Reduce by 25-50% and avoid large doses	Dose as for GFR 10-20	Dose as for GFR <10		N	Dialysed in PD and HD Not dialysed in HF
			BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE							
Phenytoin	None	Liver (D)	<50			Dialysability unknown	Not dialysed		N	Where protein binding decreased in uraemia total phenytoin levels may decrease but active free drug unaltered. Therefore total phenytoin levels may be need to be below normal range 10-20mg/l
			Normal dose BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE							

Clinical Guidelines for PALLIATIVE CARE DRUGS IN RENAL FAILURE

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DRUG	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure			Dose/interval change in renal replacement Rx			NEPHRO TOXIC? (Y/N)	OTHER
			GFR			HF	PD	HD		
Piroxicam	Hydroxylation then glucuronic acid conjugation (I)	5-10% excreted in urine unchanged – rest renal excretion of metabolite	20-50 Normal dose but **avoid** if possible	10-20	<10 Use only if patient **on dialysis**	Not dialysed – dose as GFR 10-20	Normal dose (not dialysed – highly protein bound)		Y	Note concomitant use of aspirin reduces plasma concentrations of piroxicam by 20%. ½ life 41-50 hrs (same in ESRF)
Prednisolone	Glucuronide (I) Sulphate (I) Conjugated (I)	Renal (D,M)	Normal dose			Unknown Normal dose	Not dialysed Normal dose	Not dialysed Normal dose **after** HD	N	Interacts with ciclosporin (levels of both increased)
Pregabalin	N-methylated derivative (major)	Renal D 90% M 0.9%	30-60 Starting 75mg /d Max 300mg/d (in 2-3 divided doses)	15- < 30 Starting 25-50mg/d Max 150mg/d (in 1-2 divided doses)	<15 Starting 25mg/ d Max 75mg/ (once a day)	? Dose as for GFR <15mls/min		Dose as for GFR < 15mls/min **Extra dose post dialysis** 25-100mg (single dose)	Y	Side effects include: Urinary incontinence, dysuria (uncommon) Renal failure, oliguria (rare) Can cause peripheral oedema SPC recommends calculating GFR using Cockcroft and Gault equation
Risperidone	9-hydroxy-risperidone (A) (liver –CYP2D6)	Renal 15% Faecal 70% (D+M)	0.5mg bd, increase by 0.5mg bd to 1-2mg bd			?	Dose as GFR<10		N	Unlikely peritoneal dialysability Known to be haemodialysed Elimination t1/2 = 24hrs
Senna	Anthraquinones (A)	Faecal (D,M) Not significantly absorbed	Normal dose			Unknown - Normal dose			N	Can result in impaired electrolyte balance, particularly hypokalaemia, if taken excessively
Sulindac	Reversible reduction to sulphide metabolite (A) then irreversible oxidation to inactive sulphone i.e it is actually a pro-drug	Renal (M) PO admin → 25% unchanged in faeces	20-50 Normal dose but try to avoid	<20 50-100% of dose but try to avoid		Unknown dialysability – dose as GFR 10-20	Unknown dialysability – dose as GFR<10	Not dialysed – dose as GFR<10	Y	Normal dose 200mg BD. NSAID of choice in some centres due to reports of renal sparing – however effect lost at doses>100mg BD. Subsequent studies have not corroborated this effect (PCF2). Data sheet treats it like other NSAIDs. ½ life 8 hrs (17 in ESRF)
Temazepam	Glucuronides (I)	Renal (D,M) 80-90% <2% as unchanged drug	20-50 Normal dose BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE	10-20 Start with low dose - 20mg daily maximum	<10 Start with low dose - 10mg daily maximum	Dose as GFR 10-20	Dose as GFR <10		N	Not haemodialysed. Unknown dialysability for PD and HF.

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			GFR			HF	PD	HD		
Tinzaparin	Inactive	Renal (D)	30-50	<30		Dose as for GFR <30			N	LMWH is renally excreted and therefore accumulates in renal failure. Prophylactic doses are well tolerated but **treatment** doses for DVT and PE have been associated with severe and sometimes fatal bleeding episodes. Therefore use of **unfractionated** heparin is recommended in patients with severe renal impairment. Note: heparin can suppress adrenal secretion of aldosterone causing **hyperkalaemia,** particularly in patients with chronic renal impairment and diabetes.
			Normal dose	*see "OTHER" column						
Tramadol	O-desmethyl-tramadol (A) N-desmethyl-tramadol (A)	Renal (D,M) 90% Faecal(D) 10%	20-50	10-20	<10	Unknown dialysability		Slowly dialysed	N	Although data sheet advises against use in PD, HD & GFR <10, Renal Drug Handbook suggests using doses of 50mg 12 hourly.
			Normal dose	50 -100mg **12hourly**	Data sheet advises against use	Data sheet advises against use				
Tranexamic acid	None	Renal (D)	20-50	10-20	<10	Unknown – dose as GFR<10			N	Accumulates in renal failure.
			PO: 25mg/kg ***12 hourly*** **IV**: 10mg/kg ***12 hourly***	**PO**: 25mg/kg ***24 hourly*** **IV**: 10mg/kg ***24 hourly***	**PO**: 12.5 mg/kg ***24 hourly*** **IV**: 5mg/kg ***24 hourly***					
Trimethoprim		Renal (D,M)	>30	15-30	<15	Probably dialysed Dose as for GFR 15-25	Not dialysed Dose as for GFR 10-15	Dialysed. Dose as for GFR 10-15	N	Short courses (3-5 days) may be given at full dose For long term prophylaxis with trimethoprim use 50% normal dose. For high dose Septrin regimes consult renal physician IV trimethoprim lowers ciclosporin blood levels. Increased risk of nephrotoxicity. Serum creatinine may rise due to competition for renal secretion
			Normal dose	50% of normal dose	Avoid					
Valproate sodium	None	Liver (D) (5% excreted unchanged in urine)	Start with normal dose, but titrate against clinical effects and side effects BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE			Normal dose			N	Unknown dialysability in CAPD and HF Not dialysed in HD In severe renal insufficiency may need to alter doses according to FREE serum levels – but therapeutic effects may not be clearly correlated with the total or free (unbound) levels

Clinical Guidelines for PALLIATIVE CARE DRUGS IN RENAL FAILURE

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Venlafaxine	O-desmethylvenlafaxine (A) N-desmethylvenlafaxine (A) N,O-didesmethylvenlafaxine(A)	Hepatic (D) extensive 1st pass metabolism by CP450 [CYP2D6] Renal (D) 1-10% unchanged 30% as O-desmethylv. 6-19% as N,O-desmethylv. 1% as N-desmethylv.	>30 Normal dose	10-30 Halve dose Give once daily	<10 Do not use	Not dialysed Do not use			N	Reduced frequency of dosing necessary due to longer half lives of parent drug and O-metabolite
Warfarin	Diastereoisomeric alcohols (A) 7-hydroxywarfarin (I)	Renal (M) Bile (M)	Titrate vs INR as normal			Titrate vs INR as normal			N	Active metabolites are renally excreted and therefore may accumulate in renal failure.
Zoledronic acid	Not metabolised	Renal (D)	*Doses are for prevention of skeletal related events* 50-60 3.5mg	40-49 3.3mg	30-39 3.0mg	<30 Do not use	Unknown dialysability. Dose as for GFR 10-20ml/min	Unknown dialysability. Dose as for GFR <10ml/min	Unknown dialysability. Dose as for GFR <10ml/min	Y (9-15%)	Use with caution in combination with other nephrotoxic drugs as can enhance nephrotoxicity. Measure creatinine prior to each dose and withhold if renal function deteriorates Patients with hypercalcaemia and severe renal impairment should be considered only after evaluating the risks and benefits of treatment. Patients with bone metastases and deterioration of renal function should have treatment withheld until serum creatinine values return to within 10% of baseline Doses >4mg and infusion times<15min are associated with increased risk of renal toxicity. Patients should be administered an oral calcium supplement of 500mg and 400IU of vitamin D daily
Zopiclone	N-desmethylzopiclone (I) Zopiclone N-oxide (A) Other inactive metabolites.	Renal 4-5% (D) 80% (M) Faecal (16%)	10-50 Normal dose BUT BEWARE INCREASED RISK OF SEDATION IN RENAL FAILURE		<10 3.75 – 7.5mg on	Normal dose	Dose as GFR <10		N	Unknown peritoneal dialysability. HD – Dialyzable No adverse renal effects reported in over 1000 treated with 7.5mg daily for at least 1 week.

APPENDIX I:

Formulae for calculating eGFR

Cockcroft Gault (Cockcroft & Gault 1976)

- Equation derived from a study of 236 inpatients
- The mean of 2 serum creatinine measurements and the mean of two 24hr urine collections for Cr Clearance were compared with measured GFR
- Found that age, weight and creatinine could be used to estimate the measured creatinine clearance

$$\text{Estimated GFR (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{wt (kg)}}{\text{serum creatinine (µmol/litre)} \times 0.814} \times 0.85 \text{ if female}$$

4-variable MDRD (Levy et al 1999)

- Equation derived from another study: "Modification of Diet in Renal Disease" (originally designed to assess the effect of protein intake and treatment of hypertension on progression of renal disease)
- 1070 (of 1628 patients in original study) used for modeling equation
- Six main factors were identified. Of these, serum urea and albumin were excluded due to minimal effect on accuracy.
- An estimated GFR reported by a laboratory must be adjusted to take account of the patient's body surface area.

$$\text{Estimated GFR (ml/min/1.73m}^2\text{)} = 186 \times [\text{Cr (µmol/litre)} \times 0.011312]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if Afro-Caribbean}]$$

4-variable MDRD tables are available for quick reference at
http://www.renal.org/CKDguide/full/Conciseguid141205.pdf (pages 15-18)

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