Chronic Kidney Disease and commonly used medications in Palliative Care. Adaptation of Palliative Care drugs in Renal Failure by Yorkshire Palliative Medicine Guidelines Group (2006) and Broadbent et al (2003).

Waiver: All efforts have been made to ensure the accuracy of these guidelines. The best information available has been used. Readers should exercise clinical judgement in the use of all medications. The authors of this guideline do not accept responsibility for its use in practice.

DRUG	Action in end of life care	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure GFR	Adult Dose with Renal Failure	Dose/interval change in renal replacement Rx HF	HD PD	NEPHRO TOXIC? (Y/N)	OTHER COMMENTS
Amitriptyline (Endep)	Neuropathic Pain	Metabolised in the liver. Main active metabolite is nortriptyline.	D < 5% excreted unchanged in urine	No change to normal doses.	No change to usual dose. Starting dose 10mg nocte. Increase dose according to response and tolerability.	Not dialysed	Unknown / Not dialysed	No	"Although no dose reduction is required, a low starting dose is recommended given the likelihood of anticholinergic side effects." (Davison & Koncicki, 2014) Contraindicated in Glaucoma, recent AMIs, arrhythmias and any degree of heart block. Has multiple drug interactions (see *The Renal Drug Handbook* (4th ed) , *MIMS*). Note particularly the combination of TCAs and SSRIs causes an increase in plasma concentrations of TCAs by 20 % to 10 times (*Palliative Care Formulary* , 5th ed, 2014). Side effects - Antihistamine effect - sedation; Anticholinergic effect - dry mouth, blurred vision, constipation, urinary retention.
Atropine 1% Drops	Terminal secretions. Anticholinergic	Incompletely metabolised by the liver	Readily absorbed from mucous membranes. About 30-50 % excreted either as parent drug or metabolites in the urine		2 drops sublingual q 2-4hrly				May be used as first line as an anti-secretory agent in patients with terminal secretions. Atropine given by injection "should be administered with excessive care" in patients with renal impairment (MIMS, 2014).
Buprenorphine (Norspan) patches	Pain management	Buprenorphine -3-glucuronide (B3G) – inactive. Norbuprenorphine.	Approximately 70 % is excreted in the faeces as unchanged buprenorphine. Metabolites are principally excreted in the bilary system. Some urinary excretion of metabolites occurs.	10-50 ml/min No change <10 ml/min Patches 5mg minimum dose changed every 7 days Injection & S/L: Reduce dose by 25-50%. Avoid large single doses	Starting dose - 5mg patch changed every 7 days	Dialysed – dose as for GFR< 10mls/min	Dialysed – dose as for GFR< 10mls/min / Dialysed – dose as for GFR< 10mls/min	No	"Buprenorphine may be given in standard doses to patients with CKD. Generally considered safe for use in CKD if monitored carefully." (Davison & Koncicki 2014). Buprenorphine patches are not suitable for acute pain. *The Renal Drugs Handbook (4th ed)* states that "it may take up to 30 hours for plasma buprenorphine concentration to decrease by 50 % after the …patch has been removed" and advises against giving another opioid for 24 hours after the removal of the patch.
Buscopan (see Hyoscine Butylbromide)									
Clonazepam (Rivotril)	Benzodiazepine. Uraemic jerks, Restless Legs Syndrome, intractable hiccups, terminal agitation.	7-amino-clonazepam (I) 7-acetylamino-clonazepam (I) 3-hydroxy-clonazepam (A)	Renal (D) <1% unchanged	No dose adjustment required *INCREASED RISK OF SEDATION IN RENAL FAILURE	Commence 0.25 - 0.5 mg nocte SL/sci and increase according to response.	Dose as normal renal function Unknown dialysability	No data / Not dialysed	No	Can be used as a sublingual drops. In the terminal phase could use Clonazepam drops sublingually or Midazalom subcutaneously.
Codeine	Pain, cough, diarrhoea.	C6G (A), Norcodeine 20-50 10-20 <10 (?),Morphine (A) M3G (I)M6G (A)	0-16 % excreted in the urine. Note active metabolites.	20-50 - normal dose 10-20 - 75% normal dose <10 - 50% dose	Not recommended in CKD	Unlikely to be dialysed	Unknown dialysability. / Not dialysed.	No	"Metabolized to morphine derivatives and known to cause profound hypotension and CNS and respiratory depression. Not recommended in CKD". Davison & Koncicki et al (2014). Note Renal Drugs Handbook (4th ed) permits doses commencing 30mg qid in patients on dialysis and those with an eGFR < 10.
Cyclizine	Centrally acting antiemetic (antihistaminic, antimuscarinic)	The inactive metabolite is norcyclizine.	<1% excreted unchanged in urine	No change to normal doses.	50mg tds po/sci/ivi	Unknown	Unknown / Unknown	No	Increased central sensitivity in patients with renal failure. "Elderly patients are more susceptible to sedative and central antimuscarinic effects eg. postural hypotension, memory impairment, extrapyramidal reactions." (Palliative Care Formulary, 5th ed, 2014). Not recommended in the terminal phase.
Dexamethasone	Breathlessness Appetite	65% (I)	8% unchanged eliminated in urine Renal (D,M)	GFR <10ml/min Normal dose tapered to minimum effective dose	Dosing according to indication. Typical commencing dose - 4mg mane. If using more than one daily dose use mane and midi dosings only.	Not dialysed	No data / Not dialysed	No	"Does not require dose adjustment, but may be complicated by fluid retention" (Yorkshire Group, 2006. p.9) For anorexia should consult Renal Dietician. Be aware of the significant side effects of Dexamethasone in intermediate to long term use, including an increased susceptibility to infections, proximal myopathy, impaired glucose tolerance, hypertension and osteoporosis.
Duloxetine	Serotonin and noradrenaline reuptake inhibitor (SNRI). Painful peripheral neuropathy; anti-depressant.	Extensively metabolised into inactive metabolites.	Less than 1% excreted unchanged in the urine.	Normal interval dosing (daily), but reduced dose.	Commencing dose 30mg daily. See Other Comments section.	Not dialysed	Unlikely to be dialysed / Not dialysed		"Reduced starting dose in CKD (30mg daily) with a maximum dose of 60mg per day. Some sources …Contraindicated in uncontrolled HT due to the potential risk of hypertensive crisis (The Renal Drug Handbook.) "Reduced starting dose in CKD (30mg) with a maximum dose of 60mg per day. Some sources recommend avoiding in patients with a Cr/Cl of < 30 ml/minute. Others suggest start at a very low dose and increase according to response, with a maximum dose of 30mg daily." (Davison & Knocicki et al, 2014).

Note: Non-steriodals not recommended in renal failure

Waiver: All efforts have been made to ensure the accuracy of these guidelines. The best information available has been used. Readers should exercise clinical judgement in the use of all medications. The authors of this guideline do not accept responsibility for its use in practice.

DRUG	Action in end of life care	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure GFR	Adult Dose with Renal Failure	Dose/interval change in renal replacement Rx PD	HF	HD	NEPHRO TOXIC? (Y/N)	OTHER COMMENTS
Fentanyl (Durogesic) patch	Opioid	Norfentalyl (I)	D – 9% faecal D,M - 75% renal	20-50 - normal dose 10-20 - 75% normal dose <10 - 50% dose	Minimal commencing dose - 12mcg/hour patch changed every 3 days.	Not dialysed	Not dialysed	Not dialysed	No	"Inactive metabolites. Most pharmacokinetic studies in CKD use parenteral rather than transdermal fentanyl. Generally considered safe for use in CKD if monitored carefully". Davison & Koncicki et al (2014). If converting from other opioids to transdermal Fentanyl and vice versa be aware of the time (approximately 16 hours) for the Fentanyl to reach steady state when commencing a patch and to remain active after the removal of the patch.
Gabapentin (Neurontin)	Neuropathic pain Uraemic Pruritus Restless Legs Syndrome		Renal (D) eliminated unchanged in urine	In dialysis patients a single dose after each dialysis. In patients on a conservative pathway with eGFR < 15 a dose every second night.	Minimum commencing dose - If on dialysis - 100mg post dialysis. Titrate does by 100mg increments. If on a conservative non-dialysis pathway - (a) If eGFR >50 commence 100mg tds and titrate up by 100mg increments according to tolerability and response. See 'Other Comments' column. (b) If eGFR 30-49 commence 100mg nocte – 100mg bd and titrate up by 100mg increments according to tolerability and response. See Other Comments column. (c) If eGFR 15-29 commence 100mg nocte and titrate up by 100mg increments according to tolerability and response. See Other Comments column. (d) If eGFR < 15 commence 100mg every second night and titrate up by 100mg increments according to tolerability and response. See Other Comments column.	Probably dialysed	Dialysed	Dialysed	Yes	Note the efficacy of Gabapentinoids (Gabapentin and Pregabalin) in the management of several symptoms experienced by patient with ESKD (uraemic pruritus, Restless Legs Syndrome and painful peripheral neuropathy). Main side effects of gabapentinoids are drowsiness, blurred vision and ataxia. Note the dosing schedule in this chart are more conservative than other formularies and guidelines including the *Palliative Care Formulary* (5th ed, 2014, p 272). Also see the commentary on Gabapentin dosing on pages 5 and 9 and Table 5 of Davison SN, Koncicki H, Brennan FP. Pain in Chronic Kidney Disease : A Scoping Review. *Seminars in Dialysis* 2014;27(2): 188-204. Also note that both Gabapentin and Pregabalin should be used with caution on patients with severe congestive cardiac failure. The Renal Drugs Handbook (4th ed) recommends giving dialysis patients an initial loading dose of Gabapentin 300-400mg.
Glycopyrrolate (Robinul)	Respiratory secretions (Terminal)	No data	D = 48.5% renal remainder unchanged in bile	No data	200-400mcg q 2 - 4 hrs sci	No data	No data	No data	No	Recommended for terminal secretions in renal Dose is titrated against effect. Accumulation possible
Haloperidol (Serenace)	Agitation, confusion, nausea, intractable hiccups.	Hepatic metabolism Hydroxyl-haliperidol (A)	(M) mainly eliminated via bile, faeces and urine	GFR <10ml/min or dialysis. Begin with low end of dose range and titrate according to response	Minimal commencing dose - 0.5 mg. Typical commencing doses for: * Nausea - 0.5 mg bd * Delirium - 1mg bd	Not dialysed Dose as for GFR <10	Not dialysed. Dose as for eGFR < 10.	Not dialysed Dose as for GFR <10	No	Elderly should use low doses to avoid extrapyramidal reactions. In CKD there is an increased CNS sensitivity and risk of sedation. Exacerbates Parkinson's Disease. Can cause fatal prolongation in QT interval if given intravenously and in higher than recommended doses.
Hydromorphone (Dilaudid)	Opioid	H-3-G is inactive as an analgesic but can cause neuroexcitation.	Renal(D,M) Metabolites renally excreted but inactive	20-50 Normal dose 10-20 Reduce dose <10 Reduce dose	If opioid naïve typical commencement dose - 0.5 - 1mg mg q 6 hours orally (or 0.25 - 0.5 mg sci) Titrate according to pain / dyspnea.	Unknown so dose as for GFR<10	Unknown so dose as for GFR<10	Haemodialysis reduces plasma concentrations of hydromorphone by about one half. Dialysis removes 40-55 % of the pre-dialysis levels of the metabolite, hydromorphone-3-glucuronide.	No	Much better tolerated than morphine. Start at low doses in CKD. "Pharmacodynamic data have shown less neuroexcitation compared to morphine and a greater than 65 % reduction in pain over dosing intervals with no clinically significant opioid toxicity when given in low doses and monitored carefully [Davison & Koncicki et al (2014)]. Koncicki et al, 2015 concluded that "Given the changes in pharmacokinetics in ESRD, titration should start at low doses, with an increased dosing interval and with close monitoring for side effects." Note that Murtagh, 2015 expressed a more cautious approach: "It may be reasonable, given the available evidence, to use hydromorphone carefully in mild or even moderate renal impairment, provided doses are reduced and the dose interval increased, and with careful monitoring and titration. In severe renal impairment, its use cannot be recommended however, until there is more evidence available." If converting from other opioids to hydromorphone and vice versa consult opioid conversion charts or the Pain or Palliative Care team.
Hyoscine Butylbromide (Buscopan)	Colicky pain, terminal secretions, malignant bowel obstruction	Unknown	D - 50% renal excretion	Normal dose	Typical commencement dose 20mg tds - qid po/sci. Maximum daily dose - 240mg.	Dialysed – dose as for GFR< 15mls/min	No data	Dialysed – dose as for GFR< 15mls/min	No	May be used to manage terminal secretions in patients with CKD. No dose adjustment required.
Hyoscine Hydrobromide	Inhibit Excessive Secretions	Apohyoscine	Excreted in urine, metabolised in liver (s/c only 3.4% D excreted in urine in 72 hrs)	eGFR > 15 Normal dose **eGFR < 15 - Not recommended in ESKD (crosses blood/brain barrier)**	**Not recommended in the Terminal Phase with ESRD**	Dialysable Normal dose	Dialysed	Dialysable Normal dose	No	Anticholinergic - Can cause urinary retention **Not recommended in the terminal phase. Uraemia causes increased permeability of the blood brain barrier to centrally acting agents. This may result in Hyoscine hydrobromide causing paradoxical agitation.** (Douglas C, Murtagh FEM et al. Palliative Medicine 2009;23:103-110).

Note: Non-steriodals not recommended in renal failure

Waiver: All efforts have been made to ensure the accuracy of these guidelines. The best information available has been used. Readers should exercise clinical judgement in the use of all medications. The authors of this guideline do not accept responsibility for its use in practice.

DRUG	Action in end of life care	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure GFR	Adult Dose with Renal Failure	Dose/interval change in renal replacement Rx PD	HF	HD	NEPHROTOXIC? (Y/N)	OTHER COMMENTS
Ketamine	Neuropathic pain	Nor-ketamine (A) dehydronor-ketamine (I)	About 90 % of a parenteral dose of ketamine is excreted in the urine, mostly as conjugates of hydroxylated metabolites. Less than 5 % is excreted unchanged via the faeces and urine.	No change	Best be used under the supervision of the Pain or Palliative Care teams. Usual practice is to give a test dose of 10mg sci. Monitor for any psychomimetic effects. After two hours, if tolerated, commence 100mg sci in a syringe driver over 24 hours and titrate up by 100mg/ day according to efficacy and side effects.	Unlikely to be dialysed dose as for normal renal function	Unknown	Unknown dialysability dose as for normal renal function	No	NMDA Receptor antagonist. Dose as per normal renal function. Can cause profound psychomimetic effects. To prevent psychomimetic side effects best to prescribe a regular dose of Haloperidol (0.5-1mg bd) concurrently. Contraindicated in patients with severe hypertension and patients prone to psychosis.
Levomepromazine (Nozinam)	Restlessness, confusion, agitation, nausea	a) sulphoxide metabolite b) glucuronides	Majority excreted in urine as M D- small amount excreted unchanged in urine and faeces	GFR 10-50 - No change GFR <10 ml/min - start with small dose.	Minimal dose - 6.25 mg. Typical commencement dose - 6.25 mg bd sci. Doses are best adjusted according to symptoms.	No data	No data	No data		Start cautiously and at low doses, and titrated according to response and side effects (Yorkshire Group 2006, p.8) Can be added after Midazolam for terminal agitation if symptoms persist (Douglas et al 2009, p.106). Increased CNS sensitivity in CKD. More likely to cause sedation.
Lignocaine	Difficult to manage Neuropathic pain	Active metabolites accumulate during prolonged infusions		No change	Should be used under the supervision of the Pain or Palliative Care teams.	Unlikely	No data	Not dialysed	No	Caution in prolonged infusion in renal failure-dose modification if adverse effects. The Renal Drug Handbook (4th ed), p 558
Lorazepam (Ativan)	Breathlessness, anxiety	70-75 % as inactive glucuronide metabolites.	Renal (88%) The rest is eliminated in faeces and bile.	GFR <10ml/min or dialysis. Begin with low end of dose range and titrate according to response	0.5-1mg bd-tds (sublingual or po)	Unlikely to be dialysed	Unknown	Not dialysed	No	Increased CNS sensitivity in patients with CKD.
Methadone	Pain Intractable cough	(I) 2-ethylidine-1, 5-dimethyl- , 3-diphenylpyrrolidine, 2-ethyl-3, 3-diphenyl-5-methylpyrrolidine (liver) Both metabolites are inactive.	Primarily excreted in the feces.	eGFR 10-50 Normal dose eGFR <10 50-75% of normal dose. (Aronoff et al. Drug Prescribing in Renal Failure, 5th ed)	Should be used under the supervision of the Pain or Palliative Care teams. Only recommended to be used by knowledgeable physicians (Mid-Atlantic Renal Coalition and the Kidney End-of-Life Coalition. *Clinical Algorithms to Treat Pain in Dialysis Patients.* 2009.) If eGFR 10-50 – Normal dose. If eGFR is < 10 50-75 % of normal dose. There are several recommended dosing schedules. Given its metabolism - high oral bioavailability and accumulation with repeated dosing - it requires care and clinical experience to use safely. If converting from another opioid the commencement dose is calculated according to the current background opioid dose. Accordingly a commencement dose should be individualised.	Not dialysed Dose as for GFR <10	Dialysed	Not dialysed Dose as for GFR <10	No	"Primarily excreted in the faeces. Plasma concentrations are similar in CKD compared to those with normal renal function. Generally considered safe to uses in CKD if monitored carefully." (Davison & Koncicki, 2014). "Risk of QT interval prolongation especially with high doses and concomitant risk factors." (*The Renal Drug Handbook,* (4th ed).
Metoclopramide (Maxolon)	Nausea, Early satiety, Hiccups.	Metabolised in the liver. Conjugated metabolites are inactive.	Predominantly renal (D,M)	Dose as in normal renal function.	Minimal dose 5 - 10 mg. Typical commencement dose - 5-10mg tds half an hour prior to meals	Not dialysed Dose as for GFR <10	Dialysed	Dialysed	No	For GFR <20, start at low doses. Increased risk of extrapyramidal reactions in severe renal impairment. The risk of extrapyramidal side effects is dose-related.
Midazolam (Hypnovel)	Terminal agitation	Alpha-hydroxymidazolam glucuronide is an active metabolite and accumulates in ESKD.	Renal (D,M) 45-57% <1% as unchanged drug	GFR 10-50 Normal dose GFR <10 50% of normal dose	Typical commencement dose 2.5 mg - 5 mg q 4 hours. Titrate dose according to symptoms.	Unlikely to be dialysed Dose as for GFR <10	Unlikely to be dialysed Dose as for GFR <10	Unlikely to be dialysed Dose as for GFR <10	No	Increased CNS sensitivity in CKD causing sedation. Dose reduction and an increased dosing interval for midazolam recommended (Douglas et al 2009, p.106)
Morphine	Pain control, breathlessness	M3G (I) M6G (A)	Renal (D,M)	Not recommended in CKD	Not recommended in CKD.	Not dialysed	Not dialysed	Morphine and its metabolites are dialysed.	No	"Rapid accumulation of active metabolites in CKD resulting in clinically significant opioid toxicity including sedation, confusion, myoclonus, and respiratory depression. Not recommended in CKD." (Davison & Koncicki 2014)
Octreotide	Malignant bowel obstruction	Extensive hepatic metabolism.	Renal (32% unchanged)	Normal dose	Commence with 150 mcg tds sci. Consider introducing a syringe driver over 24 hours. Maximum dose 1500 mcg over 24 hours	Unknown	Dialysed	Normal dose Dialysed: plasma clearance increased by around 30%. Supplemental dosing may be required	No	"In renal failure requiring dialysis… reduced elimination … may necessitate a dose reduction." Palliative Care Formulary, 5th ed, 2014, p 532. Potentially hazardous interaction with cyclosporine.

Note: Non-steriodals not recommended in renal failure

Waiver: All efforts have been made to ensure the accuracy of these guidelines. The best information available has been used. Readers should exercise clinical judgement in the use of all medications. The authors of this guideline do not accept responsibility for its use in practice.

DRUG	Action in end of life care	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure GFR	Adult Dose with Renal Failure	Dose/interval change in renal replacement Rx PD	HF	HD	NEPHRO TOXIC? (Y/N)	OTHER COMMENTS
Olanzapine	Management of delirium	Extensively metabolised in the liver. Major metabolites are olanzapine 10-N-glucuronide and 4'-N-desmethylolanzapine. Metabolites "appear to be inactive". (The Renal Drug Handbook)	Elimination of metabolites – renal (60 %); faecal (30 %).	Plasma half-life is unchanged in CKD.	In CKD initial dose - 5mg daily.	Not dialysed	Unknown dialysability	Not dialysed	No	Olanzapine has potentially hazardous interactions with many classes of medications. See The Renal Drug Handbook.
Ondansetron (Zofran)	Pruritus Nausea	Multiple metabolites (I)	Renal <5% unchanged in urine Hepatic	Normal dose	Commence 4mg prn, maximum tds. Regular dose – 4-8mg bd.	Unlikely to be dialysed	Unknown	Not dialysed	No	Ondansetron is very constipating. Consider an alternative anti-emetic. Best reserved for nausea secondary to chemotherapy and/or radiotherapy. Can cause a dose- dependent QT prolongation. Note – a systematic review found that Ondansetron was not efficacious in the management of uraemic pruritus. (To TH et al. J Pain Symptom Management 2012;44(5): 725-730).
Oxycodone (Endone, Oxycontin, Oxynorm)	Pain - strong Opioid	Noroxycodone (A) Oxymorphone (A)	Renal (D 19%,M 65%) Faecal (D,M)	In CKD oxycodone and its metabolites accumulate. If eGFR 15-50 give 75 % of normal dose. If eGFR < 15 give 50 % of normal dose. (The Renal Drug Handbook, 4th ed, 2014)	**Endone** - minimal dose 2.5mg. Typical commencement doses - 2.5 mg tds-qid. **Oxycontin** - minimal dose 5mg Typical commencement dose - 5 mg bd	Unknown dialysability	Dialysed	Unknown dialysability	No	The authorities express differing views. The Palliative Care Formulary, 5th ed, 2014 at p. 443 states that "Oxycodone is contraindicated in renal failure and is not recommended in severe renal impairment." A different view is expressed by two other authorities. Davison & Koncicki, 2014 state : "There are case reports of toxicity in association with CKD yet overall consensus from the literature is that oxycodone is reasonably safe to use in CKD if monitored carefully." The Renal Drug Handbook, 4th ed, 2014 recommends commencing with a reduced dose and gradually increasing according to response.
Paracetamol	Simple pain relief. Antipyretic.	Metabolised in the liver. More than 80 % is metabolised by conjugation to paracetamol glucuronide and paracetamol sulphate, 10 % is metabolised by oxidation to N-acetyl-p-benzoquinoneimine (NAPQI) and 5 % is not metabolised and excreted unchanged in the urine.	Renal elimination of parent drug and metabolites.	Normal dosing interval (q6hrly)	Typical dose 1g Q6H	Not dialysed	Dialysed	Dialysed	Yes in overdose	Note is dialysed by HD but not by PD. Normal doses may be used in patients with CKD. Note : The editors of The Renal Drug Handbook. 4th ed, 2014 recommend a maximum dose of 5g/day in smaller patients with CKD stage 5.
Pregabalin (Lyrica)	Neuropathic pain Uraemic Pruritus Restless Legs Syndrome	Undergoes negligible metabolism	Renally excreted as an unchanged drug	With normal renal function the dose schedule is bd With CKD need to adjust dose – see next column.	If on dialysis – commence 25 mg daily and titrate according to tolerability and response. (The Renal Drug Handbook, 4th ed). MIMS recommends giving an extra 25mg after each dialysis. If on a conservative pathway – (a) If eGFR 30-60 – commence 75 mg daily and titrate according to tolerability and response. (b) If eGFR 15-29 – commence 25-50mg daily and titrate according to tolerability and response. (c) If eGFR <15 – commence 25mg daily and titrate according to tolerability and response. (The Renal Drug Handbook, 3rd ed)	Dialysed	Dialysed	50% removal after 4 hours of HD	No	Note the efficacy of Gabapentinoids (Gabapentin and Pregabalin) in the management of several symptoms experienced by patient with ESKD (uraemic pruritus, Restless Legs Syndrome and painful peripheral neuropathy). Main side effects of gabapentinoids are drowsiness, blurred vision and ataxia. Note the dosing schedule in these guidelines are more conservative than other formularies and guidelines including the Palliative Care Formulary, 5th ed, 2014. Also see the commentary on Gabapentin dosing on pages 5 and 9 and Table 5 of Davison SN, Koncicki H, Brennan FP. Pain in Chronic Kidney Disease : A Scoping Review. Seminars in Dialysis 2014;27(2): 188-204. Also note that both Gabapentin and Pregabalin should be used with caution on patients with severe congestive cardiac failure.
Risperidone	Management of delirium	Metabolised in the liver. Major metabolite is 9-hydroxy-risperidone.	Elimination is mainly urine, some faecally.	In ESKD the clearance of parent drug and metabolites is deceased by 60 %.	The Palliative Care Formulary recommends, in normal renal function, a starting dose in delirium of 1mg nocte and prn. In the context of CKD, The Renal Drug Handbook recommends commencing with 50 % of the normal dose and slowly titrating up ie. commence with 0.5mg nocte and prn.	Unlikely to be dialysed	Dialysed	Dialysed	No	Can cause postural hypotension, deterioration in Parkinson's Disease and, in the case of epilepsy, lowering of the seizure threshold. Risperidone has potentially hazardous interactions with many classes of medications. See The Renal Drug Handbook.
Sertraline	SSRI medication. Uraemic Pruritus, antidepressant	Extensively metabolised in the liver.			"Can be used in renal failure at normal doses with caution." *The Renal Drug Handbook* (4th ed)	Unlikely to be dialysed.	No data	Not dialysed		Multiple drug interactions. See *The Renal Drug Handbook* (4th ed), p 665.

Note: Non-steriodals not recommended in renal failure

Waiver: All efforts have been made to ensure the accuracy of these guidelines. The best information available has been used. Readers should exercise clinical judgement in the use of all medications. The authors of this guideline do not accept responsibility for its use in practice.

DRUG	Action in end of life care	METABOLITES (A=active, I=inactive)	ELIMINATION (D=drug, M=metabolites)	Dose/interval change in renal failure GFR	Adult Dose with Renal Failure	Dose/interval change in renal replacement Rx PD	HF	HD	NEPHRO TOXIC? (Y/N)	OTHER COMMENTS
Sodium Valproate (Epilim)	Epilepsy. Neuropathic pain	Extensively metabolised in the liver, up to 60 % by glucuronidation. The glucuronide metabolites are inactive.	Liver (D) 5% excreted unchanged in urine	eGFR <10ml/min Normal dose tapered to minimum effective dose (and blood conc)	Commence - 200mg bd	Unknown dialysability Normal dose	Dialysed	Not dialysed Normal dose	No	Alter doses according to *free* serum levels Increased CNS sensitivity in CKD, including greater risk of sedation. Palliative Care Formulary, 5th ed, 2014, at p 280 recommends "lower initial doses and slower titration may be required in renal impairment.".
Tapendatol	Analgesic. Has a dual action – mu receptor agonist and noradrenaline re-uptake inhibitor.	Approximately 97 % of the parent drug is metabolised in the liver to inactive glucuronides.	Mostly renally excreted in the glucuronide form. 3% is excreted unchanged in the urine.	If eGFR > 15 – normal dose. If eGFR < 15 – not recommended.	If eGFR > 15 – normal dose; if eGFR < 15 – not recommended.	Probably dialysed.	Probably dialysed.	Probably dialysed.	No	Not recommended due to limited information regarding use in severe renal insufficiency. (Koncicki & Brennan et al, 2015). The editors of The Renal Drug Handbook (4th ed) state : "Not recommended by manufacturer in severe renal impairment due to lack of studies."
Tramadol (Tramal)	Analgesia. Weak opioid; also acts to enhance the inhibitory pathway.	O-desmethyl-tramadol (A) N-desmethyl-tramadol (A)	Renal (D,M) 90% Faecal(D) 10%. In CKD there is a two-fold increase in the elimination half-life	If eGFR < 30 reduce dose frequency from qid to bd.	If on dialysis commence 50mg bd; maximum 100bd. If on a conservative pathway : (a) If eGFR >30 – dose as in normal renal function. (b) If eGFR 15-30 – commence 50mg bd; maximum 100mg bd (c) If eGFR <15 – 50mg bd (maximum).	Unknown dialysability	Dialysed	Slowly dialysed	No	Note that the authorities recommend differing dosing regimens. Davison & Koncicki, 2014, Davison, Chambers, Ferro et al, 2010, King et al, 2011, Murtagh, 2015 and the Palliative Care Formulary, 5th ed, 2014 recommend a bd dosing schedule. The Renal Drug Handbook, 4th ed, 2014 recommends a tds dosing regimen. The extended release formulation of Tramadol is not recommended if the Cr/Cl is < 30mls/min. Note: uraemia lowers the seizure threshold and Tramadol may be epileptogenic in ESKD patients.
Thalidomide	Uraemic Pruritus resistant to other medications. Also used in the management of Multiple Myeloma in certain clinical situations.	Metabolised almost exclusively by non-enzymatic hydrolysis.				Unlikely to be dialysed	Not dialysed	Unlikely to be dialysed	No	"Major route of elimination is non-renal therefore normal doses may be given in renal failure." (The Renal Drug Handbook, 4th ed, 2014). May cause unexplained hyperkalaemia. May cause peripheral neuropathy. Use with caution with other medications that may cause peripheral neuropathy.
Tranexamic acid	Haemostatic agent.	None	Excreted mainly unchanged in the urine.	eGFR < 30, once daily dosing.	If eGFR is 15-30 – 15 mg/kg once daily. If eGFR is < 15 – not recommended. See Other Comments column.	Unknown dialysability Dose as for GFR <10	Unknown dialysability Dose as for GFR <10	Unknown dialysability Dose as for GFR <10	No	Contraindicated if history of DVT/Pulmonary Emboli. One UK manufacturer recommends against its use in ESKD due to accumulation and increased risk of thrombus formation.

Bibliography

Ashley C, Dunleavy A (eds). The Renal Drug Handbook. 4th ed, 2014, Radcliffe Publishing, Oxford.

Broadbent, A. Khor, K. Heaney, A. 2003. Palliation and Chronic Renal Failure: Opioid and Other Palliative Medications - Dosage Guidelines. 2003. Progress in Palliative Care 11(4), pp 183-190

Brown E et al (eds) End of Life Care in Nephrology. 2007, p.99.

Cervelli, M. The Renal Drug Reference Guide, 1st edition, 2007. Nexus Printing, Adelaide

Chambers, J. Brown, E. Germain, M. 2005. Supportive Care for the Renal Patient. Oxford University Press, UK

Chambers, J. Brown, E. Germain, M. eds 2010. Supportive Care for the Renal Patient, 2nd edition. Oxford University Press, UK

Davison S. Chambers, EJ. Ferro, CJ. Management of pain in renal failure. Chambers, J. Brown, E. Germain, M. eds 2010. *Supportive Care for the Renal Patient, 2nd edition*. Oxford University Press, UK

Davison S, Ferro CJ. Management of Pain in CKD. *Progress in Palliative Care* 2009; 17:186-195.

Davison SN, Koncicki H, Brennan FP. Pain in Chronic Kidney Disease : A Scoping Review. Seminars in Dialysis 2014;27(2): 188-204.

Department of Health. Renal NSF Team and Marie Curie Palliative Care Institute. National LCP Renal Steering Group. 2008. Guidelines for LCP Prescribing in Advanced Chronic Kidney Disease. Downloaded 4.5.09 http://www.mcpcil.org.uk/files/NationalLCPRenalsymptomcontrolguidelinesJuneprintablepdf_0.pdf

Douglas, C. Murtagh, F. Chambers, E. Howse, M. & Ellershaw, J. 2009. Symptom management for the adult patient dying with advanced chronic kidney disease: A review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group. Palliative Medicine, 23, pp 103-110

Edwards, A, Yorkshire Palliative Medicine Guidelines Group. 2006. Clinical Guidelines for the use of Palliative Care Drugs in Renal Failure.

Johnson, C. 2009, *Dialysis of Drugs 2009* , CKD Insights USA and Amgen Australia Pty Ltd.

King S, Forbes K, Hanks GW et al. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment : A European Palliative Care Research Collaborative opioid guidelines project. *Palliative Medicine* 2011; 25(5): 525-552.

Koncicki, H, Brennan F, Vinen K, Davison SN. An Approach to Pain Management in ESKD : considerations for General Management and Intradialytic Symptoms. Sem Dial 2015, Epub April 2015.

Mid-Atlantic Renal Coalition (MARC) and the Kidney End-of-Life Coalition. *Clinical Algorithms to Treat Pain in Dialysis Patients* . 2009

Murtagh, FEM. End-stage kidney disease. In; Cherney, NI et al. (Eds) *Oxford textbook of Palliative Medicine*, 5th Edition, 2015, OUP, Oxford, PP1004-1012.

Twycross R, Wilcock A, Howard P (eds) *Palliative Care Formulary* , 5th ed. Palliativedrugs.com, Nottingham, 2014.

Note: Non-steriodals not recommended in renal failure