Therapeutic Reviews

Series Co-Editors: Andrew Wilcock, DM, FRCP, and Paul Howard, BMedSci MRCP

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Prescribing Non-Opioid Drugs in End-Stage Kidney Disease

Andrew Wilcock, DM, FRCP, Sarah Charlesworth, BPharm, PG Dip Clin Pharm, MRPharmS, Robert Twycross, DM, FRCP, Anne Waddington, BPharm, PG Dip Clin Pharm, Olivia Worthington, MRCP, FFICM, Fliss E.M. Murtagh, PhD, FRCP, MRCGP, Jenny Beavis, PDACN, MPET, NP, Samuel King, MRCP, Mary Mihalyo, BS, PharmD, RPh, CGP, BCPS, CDE, and Aleksandra Kotlinska-Lemieszek, MD, PhD

University of Nottingham (A.W.), Nottingham, United Kingdom; Nottingham University Hospitals (S.C.), Nottingham, United Kingdom; Oxford University (R.T.), Oxford, United Kingdom; Aintree University Hospital NHS Foundation Trust (A.W.), Liverpool, United Kingdom; Aintree University Hospital NHS Foundation Trust (O.W.), Liverpool, United Kingdom; King's College London (F.E.M.M.), Cicely Saunders Institute, London, United Kingdom; Royal Melbourne Hospital (J.B.), Parkville, Australia; Saint Elizabeth Hospice (S.K.), Ipswich, United Kingdom; Mylan School of Pharmacy, Duquesne University (M.M.), Pittsburgh, Pennsylvania, USA; Karol Marcinkowski University of Medical Sciences and Hospice Palium, University Hospital of the Lord's Transfiguration (A.K.-L), Poznan, Poland

Introduction

Palliative care services are increasingly involved in the care of patients with chronic kidney disease, either alone or as a comorbid condition. Because renal impairment often changes the pharmacokinetic and/or pharmacodynamic effects of a drug, this presents a challenge for prescribers.

This article provides guidance for prescribing non-opioid drugs commonly used for palliative care symptom relief in patients with end-stage kidney disease (ESKD; i.e. Chronic Kidney Disease Stage 5, eGFR <15mL/min/1.73m^2) whether or not they are receiving dialysis. Opioids are not included, nor symptom relief in the last hours–days of life, because specific guidance is available elsewhere.[1–4]

Tables have been produced to highlight, when possible, the most, intermediate and least 'renally safe' drugs for *chronic use*. However, sometimes the cautious use of a familiar drug may be preferable to an unfamiliar (albeit 'renally safer') one. Similarly, we do *not* advocate the automatic switching of patients to a 'renally safer' drug when an alternative is proving satisfactory. Finally, this article aims to complement and not replace specialist renal unit guidance.

Safe prescribing in ESKD

Pharmacologically, the most important consequence of ESKD is increased toxicity as a result of accumulation of a renally excreted drug ± active metabolites. ESKD also has many other consequences which may alter the effect of a drug, whether or not accumulation occurs, e.g. an enhanced sedative effect of a centrally-acting drug (Box A).

Address correspondence to: Dr Andrew Wilcock, DM, FRCP, Hayward House Macmillan Specialist Palliative Care Unit, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, NG5 1PB. E-mail: andrew.wilcock@nottingham.ac.uk

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Box A. Drug-related consequences of ESKD[5]

Pharmacokinetic

Absorption

↑ gastric pH, ↑ gut wall oedema → ↓ PO absorption

Distribution

↑ oedema/ascites → ↑ volume of distribution → ↓ effect of water soluble drugs
↑ cachexia or dehydration → ↓ volume of distribution → ↑ effect of water soluble drugs
↓ drug removal transporters in the blood-brain barrier, e.g. p-glycoprotein → ↑ CNS effects
↓ albumin levels and binding capacity → ↑ unbound (active) fraction of highly protein-bound drugs → ↑ effect (and metabolism)
↓ tissue binding → ↓ volume of distribution → ↑ effect

Metabolism

↓ hepatic enzyme function, particularly CYP450 → ↓ metabolism → variable effect depending on drug, e.g. pro-drug, active metabolite

Elimination

↓ GFR and ↓ tubular secretion → ↓ elimination of parent drug/active metabolite → ↑ effect, ↑ risk of toxicity
↓ drug removal transporters, e.g. p-glycoprotein → ↓ biliary and GIT elimination → ↓ elimination of parent drug/active metabolite → ↑ effect, ↑ risk of toxicity

Pharmacodynamic

Uraemia can alter the clinical response to certain drugs:
↑ sensitivity to drugs acting on the CNS
↑ risk of hyperkalaemia with potassium-sparing-drugs
↑ risk of GI bleeding or oedema with NSAIDs
↓ efficacy or ↑ toxicity of drugs such as warfarin or statins (due to altered physiological or pathological processes involved in other conditions)
Electrolyte imbalance can increase the risk of cardiac arrhythmia with QT prolonging drugs

Aims and development of the tables

The tables and accompanying text were developed for the Palliative Care Formulary (see www.palliativedrugs.com) to provide user-friendly summaries to guide rational and safe prescribing in patients with ESKD (± dialysis), by raising awareness of:

- suitable drugs and their starting doses
- suitable alternatives when patients experience undesirable effects
- the potential risks of using a less renally safe drug.

The tables cover the most common symptom relief drug classes. Because it is generally good practice to become experienced in using relatively few drugs well, the list is purposely limited.

Although ESKD is defined as an eGFR <15mL/min/1.73m^2, most sources of *prescribing* information use creatinine clearance to guide drug dosing, with slight variation in the values reflecting ESKD. Thus, for the *prescribing* recommendations in Tables 1–6, a creatinine clearance of <10mL/min has been adopted.

Initially, for each drug within each class, a full data table was produced summarizing the key pharmacokinetic data available from several established sources (Box B); see supplementary Appendix 1 online. In turn, the full data were used to inform Tables 1–6. Drugs were categorized as 'generally safe', 'use cautiously' and 'avoid if possible' from a *purely renal perspective*, according to their risk of accumulation with chronic use in ESKD.

The pharmacokinetic information derived from the established sources sometimes varied and was occasionally contradictory. Generally, information within Tables 1–6 reflects either the best evidenced and/or the majority view of the established sources. Where there was a lack of data, information was sought from the wider literature (Box B).

In the established sources, because specific prescribing advice was also noted to vary, additional sources of information were consulted (Box B). The prescribing advice was summarised separately (see supplementary Appendix 2 online) and circulated among the contributing authors to achieve a consensus view which is reflected in Tables 1–6. It is important to note that the consensus view may include off-label use. However, it is impractical to highlight all cases of off-label use because this can vary according to country, brand, indication, formulation, dose, route of administration or patient population. Prescribers should be aware of the implications of off-label use.[6]

Box B. Sources of information used

Established sources
American Hospital Formulary Service Drug Information[7]
Martindale: The Complete Drug Reference[8]
Oxford Specialist Handbook: Kidney disease from advanced disease to bereavement[9]
Package Inserts (USA)
Renal Drug Database[10]
Summary of Product Characteristics (UK)
Additional sources
Antidepressants[11-16]
Anti-emetics[17,18]
Anti-epileptics[19-23]
Benzodiazepines[24-26]
Miscellaneous drugs[27,28]
Prescribing advice[1,12,29-33]

Use of the tables

The tables should be used in conjunction with the accompanying text which highlights any general considerations for that class of drug and provides a commentary to help inform choice. As far as possible, specific prescribing advice is given. Even when a drug appears to be 'renally safe', because of the other effects of renal impairment (Box A), smaller starting doses and a slower titration than usual is generally advisable, particularly in the elderly and/or frail patient. Thus, the adage 'start low, go slow' will generally apply to the use of *any* drug, and particularly those with CNS effects.

In addition to the impact of ESKD and familiarity, the selection of the most appropriate symptom relief drug in ESKD also requires the prescriber to consider any relevant additional factors such as the presence of concurrent symptoms, co-morbidities (e.g. cardiovascular disease, liver impairment), other drugs (e.g. in relation to risk of a drug–drug interaction, QT prolongation) and patient preference.

Drug dosing in dialysis

For patients on dialysis, the tables provide information on whether the effect of dialysis is sufficient to require a change in the dosing regimen of the drug. Unless specified otherwise, the information is relevant for both peritoneal dialysis (PD; continuous ambulatory or automated) and thrice weekly conventional haemodialysis (HD). However, because information is often limited and HD regimens are variable, some renal units adjust drug regimens for HD patients so that administration is timed to occur after the dialysis procedure.

Specialist advice should be sought for those patients on more frequent conventional HD, high flux dialysis or haemodiafiltration; drug removal is more likely and closer monitoring is required.[10]

Antidepressants (Table 1)

Low starting doses and cautious titration are required for *all* antidepressants, regardless of whether they (± any active metabolites) are renally excreted. In ESKD there is an increased sensitivity to drugs acting on the CNS coupled with a risk of enhanced central depressant effects from the variable pharmacokinetic changes (Box A), e.g.:

- all the featured antidepressants (apart from venlafaxine) are highly protein bound
- all the featured antidepressants are dependent on one or more of CYP3A4, CYP2D6, CYP2C19 and CYP1A2
- metabolism will be further impaired in constitutionally poor metabolizers, e.g. amitriptyline, nortriptyline (CYP2D6), amitriptyline, citalopram and sertraline (CYP2C19), and the risk of toxicity increased from a pharmacokinetic drug–drug interaction involving an inhibitor of the CYP450 enzyme(s).

Concurrent use of other drugs with CNS depressant activity, e.g. opioids, increases the risk of toxicity.

Because of the time taken to accumulate, undesirable effects may become apparent only after days or weeks of regular use for those antidepressants with long halflives, e.g. amitriptyline, citalopram, mirtazapine, nortriptyline and sertraline.

Choice of antidepressant

From a renal perspective, the first-line antidepressant of choice for the treatment of depression in ESKD is sertraline. Citalopram can be used cautiously, but has a risk of prolongation of the QT interval (and increased risk of ventricular arrhythmia), e.g. as a result of possible accumulation, electrolyte imbalance, drug-drug interaction or concurrent use of other QT prolonging drugs.

If an SSRI is not suitable, some renal units favour the cautious use of mirtazapine for depression, despite it being extensively excreted unchanged by the kidney and known to accumulate in ESKD.

Amitriptyline and nortriptyline may be used with caution for neuropathic pain, but starting doses in ESKD should be low. The presence of cardiac co-morbidity may limit their use.

For patients on PD or HD, none of the drugs in Table 1 require any additional changes to the ESKD dosing regimen.

Table 1

Antidepressants and ESKD. Before use, see introductory and class specific text

Antidepressant[a]	Halflife in normal renal function (h)	Active metabolite(s)[b]	Accumulation in renal impairment[c]	Removed by dialysis[d]	Dose and comment
Generally safe					
Sertraline[e]	26	No	No	No	Dose unchanged PO: start with 25mg each morning
Use cautiously					
Amitriptyline[e]	9–25	Yes	Possible	No	Lower doses may be sufficient PO: start with 10mg at night *Not a first-line treatment for depression*
Citalopram[e]	36	Yes	Possible	No	Dose unchanged; lower doses may be sufficient PO: start with 10mg each morning;
Nortriptyline[e]	15–39	Yes	Possible	No	Lower doses may be sufficient PO: start with 10mg at night *Not a first-line treatment for depression*
Trazodone	5–13	Yes	Possible	No	Lower doses may be sufficient PO: start with 25–50mg at night *Not a first-line treatment for depression*
Avoid if possible					
Duloxetine	8–17	No	Yes	No	If unavoidable, use lower doses PO: start with ≤30mg at night
Mirtazapine[e]	20–40	Yes	Yes	No	If unavoidable PO: start with 15mg at night
Venlafaxine	5 (11[f])	Yes	Yes	No	If unavoidable PO: start with 37.5mg daily, maximum 112.5mg/24h in divided doses *For HD patients* PO: dose after HD session to minimise undesirable effects

[a]whichever antidepressant is used, because ESKD can have general effects on the pharmacokinetics and/or pharmacodynamics of a drug (see text), a slower than usual titration and close monitoring of the patient is required
[b]of actual or potential clinical relevance in ESKD
[c]of drug and/or active metabolite(s); 'possible' has been used when definitive data are lacking, but accumulation likely on clinical or theoretical grounds
[d]sufficient to require a change in dosing regimen with PD or HD; for other forms of dialysis seek specialist advice
[e]because of a long half-life and time taken to reach steady state, undesirable effects with these antidepressants may only become apparent after several days or weeks of regular use
[f]active metabolite.

Anti-emetics (Table 2)

In addition to any specific advice because of reduced elimination, for any individual anti-emetic, lower starting doses should be used, and then cautiously titrated to response. This is because patients are at risk of an enhanced central depressant effect as a result of reduced hepatic clearance (reduced CYP450 activity), reduced protein binding (increased unbound (active) fraction), and increased CNS levels and sensitivity (Box A). All of the featured anti-emetics are affected by one or more of these general consequences of renal impairment, albeit variably, e.g. domperidone does not cross the blood-brain barrier.

The risk of toxicity is also greater from a pharmacokinetic drug–drug interaction involving an inhibitor of the CYP450 enzyme. For example, CYP3A4 inhibitors will lead to reduced metabolism of domperidone.

The risk of prolongation of the QT interval (and the consequential increased risk of ventricular arrhythmia) is higher with domperidone, haloperidol, levomepromazine (methotrimeprazine) and ondansetron. The risk may be increased as a result of, e.g. drug accumulation, drug–drug interaction, concurrent use of other drugs that either prolong the QT interval or cause electrolyte imbalance.

Because of the time taken to accumulate, undesirable effects may become apparent only after days or weeks of regular use, for those anti-emetics with a long halflife, e.g. cyclizine, haloperidol and levomepromazine. Concurrent use of other drugs with CNS depressant activity, e.g. opioids, increases the risk of toxicity of anti-emetics with central effects.

Choice of anti-emetic

Generally, all the anti-emetics used commonly in palliative care can be used in ESKD. Even those listed as 'use cautiously' are regularly used, in reduced doses, on renal units. Thus, choice should be primarily guided by the likely cause of the nausea and vomiting along with co-morbid conditions.

For patients on PD or HD, none of the drugs in Table 2 require any additional changes to the ESKD dosing regimen.

Table 2

Anti-emetics and ESKD. Before use, see introductory and class specific text

Anti-emetics[a]	Halflife in normal renal function (h)	Active metabolite(s)[b]	Accumulation in renal impairment[c]	Removed by dialysis[d]	Dose and comment
Generally safe					
Cyclizine[e]	20	No	No	No	Dose unchanged; lower doses may be sufficient
Granisetron	4–11	No	No	No	Dose unchanged
Ondansetron	3–6	No	No	No	Dose unchanged
Prochlorperazine[e]	6–20	No	No	No	Lower doses may be sufficient
Use cautiously					
Domperidone[f]	7–9	No	Possible	No	PO: maximum 10mg daily–b.d.
Haloperidol	12–38	Yes	Possible	No	For occasional use, dose unchanged For regular use, halve the usual dose *Also see Antipsychotics Table*
Levomepromazine[e]	15–30	Yes	Possible	No	PO/SC: start with 6–6.25mg at night and p.r.n. up to q8h; lower doses may be sufficient, e.g. 2.5mg–3mg
Metoclopramide[f]	4–6	No	Yes	No	PO/SC: start with 5mg t.d.s., maximum 10mg t.d.s.
Promethazine hydrochloride	5–14	No	No	No	PO: start with 10mg b.d., maximum 25mg t.d.s.

[a]whichever anti-emetic is used, because ESKD can have general effects on the pharmacokinetics and/or pharmacodynamics of a drug (see text), a slower than usual titration and close monitoring of the patient is required

[b]of actual or potential clinical relevance in ESKD

[c]of drug and/or active metabolite(s); 'possible' has been used when definitive data are lacking, but accumulation likely on clinical or theoretical grounds

[d]sufficient to require a change in dosing regimen with PD or HD; for other forms of dialysis seek specialist advice

[e]because of a long half-life and time taken to reach steady state, undesirable effects with these anti-emetics may only become apparent after several days or weeks of regular use

[f]domperidone and metoclopramide should be used at the lowest effective dose for the shortest possible time because of concerns over prolonged QT interval or drug-induced movement disorders respectively.

Anti-epileptics (Table 3)

In addition to any specific advice because of reduced elimination, for any anti-epileptic, lower starting doses should be used, and then cautiously titrated to response. This is because patients are at risk of an enhanced central depressant effect as a result of reduced hepatic clearance (reduced CYP450 activity), reduced protein-binding (increased unbound (active) fraction) and increased CNS levels and sensitivity (Box A). All the featured anti-epileptics are affected by one or more of these general consequences of renal impairment, albeit variably, e.g.:

- reduced protein-binding affects the most highly protein-bound, e.g. phenytoin and valproate (for monitoring purposes, or when toxicity is suspected, the free fraction plasma concentration should be measured)
- all but levetiracetam, oxcarbazepine and gabapentin/pregabalin are dependent on CYP450
- the risk of toxicity is also greater from a pharmacokinetic drug−drug interaction involving an inhibitor of CYP450 or other enzymes responsible for metabolism of the anti-epileptic. For example:
  - ➢ CYP3A4 inhibitors will lead to reduced metabolism of carbamazepine; CYP2C9 inhibitors, of phenobarbital and phenytoin; and CYP2C19 inhibitors, of phenytoin
  - ➢ valproate, by inhibiting epoxide hydrolase may reduce the metabolism of carbamazepine.

Concurrent use of other drugs with CNS depressant activity, e.g. opioids, increases the risk of toxicity.

Because of the time taken to accumulate, undesirable effects may become apparent only after days or weeks of regular use for those anti-epileptics with a long halflife, e.g. carbamazepine, clonazepam, phenobarbital and phenytoin.

Choice of anti-epileptic

From a renal perspective, the first-line anti-epileptic of choice in ESKD is valproate. Although carbamazepine is also 'renally clean', it is disadvantaged by drug−drug interactions. There does not appear to be any good evidence to support the commonly quoted advice to avoid modified-release formulations of anti-epileptics in ESKD.

Levetiracetam is increasingly used and the availability of a parenteral formulation is an advantage. It is primarily renally excreted, and thus accumulates in renal impairment. However, in reduced doses, it is authorized for use in ESKD (± dialysis), as are gabapentin and pregabalin. Gabapentin is used for pruritus and restless legs syndrome associated with ESKD,[34] and this may make its use for neuropathic pain a sensible multiple-purpose option.

There is an increased risk of toxicity from phenytoin; further, it is disadvantaged by drug−drug interactions. If it cannot be avoided, monitor plasma levels corrected for hypo-albuminaemia using the formula modified for ESKD.[35]

Phenobarbital is not generally used except in conjunction with specialist neurological advice.

For patients on PD or HD, specific changes to the dosing regimens are required for gabapentin, levetiracetam and pregabalin. The clinical effect should be monitored carefully for valproate, as the effect of dialysis may be variable.

Table 3
Anti-epileptics and ESKD. Before use, see introductory and class specific text

Antiepileptic[a]	Halflife in normal renal function (h)	Active metabolite(s)[b]	Accumulation in renal impairment[c]	Removed by dialysis[d]	Dose and comment
Generally safe					
Carbamazepine[e]	16–36	No	No	No	Dose unchanged
Valproate	6–20	No	Possible	No	Dose unchanged; lower doses may be sufficient
Use cautiously					
Clonazepam[e]	20–60	Yes	Possible	No	Lower doses may be sufficient PO: start with 500microgram/24h *Also see Benzodiazepines Table*
Gabapentin	5–7	No	Yes	Yes	*For non-dialysis or PD patients* PO: start with 100mg on alternate nights and titrate slowly *For HD patients with a urine output >100mL/24h* PO: start with 100mg at night; consider either a supplementary dose after each HD session or timing the daily dose post HD *For anuric HD patients* PO: start with 100mg stat and 100mg after every HD session; a regular maintenance dose is generally not required
Levetiracetam	6–8	No	Yes	Yes	*For non-dialysis patients* PO/IV: start with 250mg b.d., maximum dose 500mg b.d. If <50kg, dose on a mg/kg basis (see SPC) *For PD or HD patients* PO/IV: start with 750mg stat and give the maintenance dose (above) as a once daily dose, consider either a supplementary dose of 250–500mg after each HD session or timing the daily dose post HD
Oxcarbazepine	1–3 (9[f])	Yes	Yes	Unknown	PO: maximum starting dose 150mg b.d., lower doses may be sufficient, e.g. 75mg b.d., titrate by 75mg at weekly intervals
Pregabalin	5–9	No	Yes	Yes	*For non-dialysis or PD patients* PO: start with 25mg once daily, maximum dose 75mg once daily *For HD patients* PO: consider either a supplementary dose of 25–100mg after each HD session or timing the daily dose post HD
Avoid if possible					
Phenobarbital[d]	75–120	No	Possible	No	If unavoidable, use only under specialist neurological advice
Phenytoin[d]	20–60	No	An increase in the free (unbound fraction) can occur to a clinically significant degree; high risk of toxicity due to the narrow therapeutic range	No	If unavoidable, dose as in normal renal function. Monitor plasma levels adjusted for hypo-albuminaemia in ESKD, see text

[a]whichever antiepileptic is used, because ESKD can have general effects on the pharmacokinetics and/or pharmacodynamics of a drug (see text), a slower than usual titration and close monitoring of the patient is required
[b]of actual or potential clinical relevance in ESKD
[c]of drug and/or active metabolite(s); 'possible' has been used when definitive data are lacking, but accumulation likely on clinical or theoretical grounds
[d]sufficient to require a change in dosing regimen with PD or HD; for other forms of dialysis seek specialist advice
[e]because of a long half-life and time taken to reach steady state, undesirable effects with these anti-epileptics may only become apparent after several days or weeks of regular use
[f]active metabolite.

Antipsychotics (Table 4)

In addition to any specific advice because of reduced elimination, for any individual antipsychotic, lower starting doses should be used, and then cautiously titrated to response. This is because patients are at risk of an enhanced central depressant effect as a result of reduced hepatic clearance (reduced CYP450 activity), reduced protein-binding (increased unbound (active) fraction) and increased CNS levels and sensitivity (Box A). All of the featured antipsychotics are affected by one or more of these general consequences of renal impairment, albeit variably, e.g.:

- all the featured antipsychotics are highly protein bound
- all the featured antipsychotics are dependent on one or more of CYP3A4, CYP2D6, and CYP1A2; the risk of toxicity is greater from a pharmacokinetic drug-drug interaction with inhibitors of the relevant CYP450, e.g. haloperidol, quetiapine, risperidone (CYP3A4), haloperidol and risperidone (CYP2D6), and olanzapine (CYP1A2).

Undesirable effects may become apparent only after days or weeks of regular use for those antipsychotics with long halflives, e.g. haloperidol, olanzapine, risperidone. Concurrent use of other drugs with CNS depressant activity, e.g. opioids, increases the risk of toxicity.

The risk of prolongation of the QT interval (and increased risk of ventricular arrhythmia) may be higher with haloperidol and lowest for quetiapine. The risk may be increased as a result of, e.g. drug accumulation, drug–drug interaction, concurrent use of other drugs that either prolong the QT interval or cause electrolyte imbalance.

Choice of antipsychotic

From a renal perspective, olanzapine is a good first-line choice in ESKD; it is also least dependent on CYP450 for its metabolism. Haloperidol can also be used cautiously, halving the dose for chronic use. For the use of levomepromazine as an anti-emetic, see Table 2.

For patients on PD or HD, haloperidol, olanzapine and quetiapine do not require any additional changes to the ESKD dosing regimen. Risperidone should be avoided due to unpredictable drug removal.

Table 4

Antipsychotics and ESKD. Before use, see introductory and class specific text

Antipsychotic[a]	Halflife in normal renal function (h)	Active metabolite(s)[b]	Accumulation in renal impairment[c]	Removed by dialysis[d]	Dose and comment
Generally safe					
Olanzapine[e]	34 (52 elderly)	No	No	No	Lower doses may be sufficient PO: maximum starting dose 5mg/24h
Use cautiously					
Haloperidol[e]	12–8	Yes	Possible	No	For occasional use, dose unchanged. For regular use, halve the usual dose *Also see Anti-emetics Table*
Quetiapine	6–14	Yes	Possible	No	Lower doses may be sufficient PO: maximum starting dose 25mg/24h
Avoid if possible					
Risperidone[e]	20[f]	Yes	Yes	Yes	If unavoidable, use lower doses PO: start with 500microgram b.d. and titrate in steps of 500microgram b.d. every 3–4 days *For PD or HD patients* Avoid due to unpredictable drug removal

[a]whichever antipsychotic is used, because ESKD can have general effects on the pharmacokinetics and/or pharmacodynamics of a drug (see text), a slower than usual titration and close monitoring of the patient is required
[b]of actual or potential clinical relevance in ESKD
[c]of drug and/or active metabolite(s); 'possible' has been used when definitive data are lacking, but accumulation likely on clinical or theoretical grounds
[d]sufficient to require a change in dosing regimen with PD or HD; for other forms of dialysis seek specialist advice
[e]because of a long half-life and time taken to reach steady state, undesirable effects with these antipsychotics may only become apparent after several days or weeks of regular use
[f]total for the parent drug and active metabolite.

Benzodiazepines (Table 5)

In addition to any specific advice because of reduced elimination, for any individual benzodiazepine, lower starting doses should be used, and then cautiously titrated to response. This is because patients are at risk of an enhanced central depressant effect as a result of reduced hepatic clearance (reduced CYP450 activity), reduced protein-binding (increased unbound (active) fraction) and increased CNS levels and sensitivity (Box A). All of the featured benzodiazepines are affected by one or more of these general consequences of renal impairment, albeit variably, e.g. lorazepam elimination is not dependent on CYP450.

The risk of toxicity is also greater from a pharmacokinetic drug–drug interaction involving an inhibitor of the CYP450 enzyme mostly responsible for metabolism of the benzodiazepine, e.g. clonazepam and diazepam (CYP3A4), and diazepam (CYP2C19).

All the featured benzodiazepines have a long halflife and thus take time to accumulate. Undesirable effects may become apparent only after days or weeks of regular use. Concurrent use of other drugs with CNS depressant activity, e.g. opioids, increases the risk of toxicity.

Choice of benzodiazepine

From a renal point of view, lorazepam is a good first-line choice. Clonazepam can also be used cautiously and is used by some renal units for restless legs syndrome associated with ESKD. Diazepam should be avoided if possible due to the risks of accumulation from an active metabolite with a very long half-life. Even so, some patients with ESKD tolerate it.

For patients on PD or HD, none of the drugs in Table 5 require any additional changes to the ESKD dosing regimen.

Table 5

Benzodiazepines and ESKD. Before use, see introductory and class specific text

Benzodiazepine[a]	Halflife in normal renal function (h)	Active metabolite(s)[b]	Accumulation in renal impairment[c]	Removed by dialysis[d]	Dose and comment
Generally safe					
Lorazepam[e]	10–20	No	No	No	Lower doses may be sufficient SL/PO: start with 500microgram/24h
Use cautiously					
Clonazepam[e]	20–60	Yes	Possible	No	Lower doses may be sufficient PO: start with 500microgram/24h *Also see Anti-epileptics Table*
Avoid if possible					
Diazepam[e]	25–50 (≤200[f])	Yes	Yes	No	If unavoidable, use half the usual dose

[a]whichever benzodiazepine is used, because ESKD can have general effects on the pharmacokinetics and/or pharmacodynamics of a drug (see text), a slower than usual titration and close monitoring of the patient is required
[b]of actual or potential clinical relevance in ESKD
[c]of drug and/or active metabolite(s); 'possible' has been used when definitive data are lacking, but accumulation likely on clinical or theoretical grounds
[d]sufficient to require a change in dosing regimen with PD or HD; for other forms of dialysis seek specialist advice
[e]because of a long half-life and time taken to reach steady state, undesirable effects with these benzodiazepines may only become apparent after several days or weeks of regular use
[f]active metabolite.

Table 6

Miscellaneous drugs and ESKD. Before use, see introductory and class specific text

Drug[a]	Halflife in normal renal function (h)	Active metabolite(s)[b]	Accumulation in renal impairment[c]	Removed by dialysis[d]	Relative safety	Dose and comments
Antidiarrhoeals						
Loperamide	9–14	No	No	No	**Use cautiously**	Dose unchanged; lower doses may be sufficient
Antimuscarinics						
Glycopyrronium	1–1.5	Yes	Yes	Unknown	**Use cautiously**	SC: Start with 200micorgram p.r.n.; lower doses may be sufficient PO: dose unchanged
Hyoscine butylbromide	5–10	No	No	No	**Generally safe**	CSCI or PO: dose unchanged
Bisphosphonates and denosumab						
Denosumab	624	No	No	No	**Generally safe**	Dose unchanged; see text
Ibandronic acid	10–72	No	Yes	No	**Use cautiously**	For prevention of skeletal-related events in patients with bone metastases in breast cancer: PO: 50mg once weekly IVI : 2mg in 500mL 0.9% saline or 5% glucose over 1h every 3–4 weeks For tumour-induced hypercalcaemia, seek specialist renal unit advice
Pamidronate disodium	1–27	No	Yes	No	**Avoid if possible**	For tumour-induced hypercalcaemia, seek specialist renal unit advice
Zoledronic acid	146	No	Yes	No	**Avoid if possible**	See text
Corticosteroids					**Generally safe**	See text
Laxatives					**Generally safe**	See text
Non-opioids						
Paracetamol	1–4	Yes	Possible	No	**Use cautiously**	PO: start with 500mg q6–q8h; maximum 3g/24h IV: see SPC; minimum interval 6h
Nefopam	4 (10–15)[e]	Yes	Possible	No	**Use cautiously**	PO: maximum 30mg t.d.s.
NSAIDS				No	**Avoid if possible**	See text
Skeletal muscle relaxants						
Baclofen	3–4	No	Yes	Yes	**Avoid if possible**	If unavoidable PO: maximum 5mg once daily *For HD patients* Dose after HD session
Tizanidine	3	No	Yes	No	**Use cautiously**	PO: start with 2mg once daily; if necessary, slowly titrate in 2mg steps. Only increase the frequency of administration if a single daily dose is inadequate

[a]whichever drug is used, because ESKD can have general effects on the pharmacokinetics and/or pharmacodynamics of a drug (see text), a slower than usual titration and close monitoring of the patient is required
[b]of actual or potential clinical relevance in ESKD
[c]of drug and/or active metabolite(s); 'possible' has been used when definitive data are lacking, but accumulation likely on clinical or theoretical grounds
[d]sufficient to require a change in dosing regimen with PD or HD; for other forms of dialysis seek specialist advice
[e]for active metabolite.

Miscellaneous drugs (Table 6)

The relative safety and dose adjustments for other common palliative care drugs in ESKD are shown in Table 6.

Full data have not been included for corticosteroids or laxatives. Corticosteroids, e.g. dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, can be used in normal doses. Similarly, commonly used laxatives, e.g. bisacodyl, docusate, lactulose, macrogols (polyethylene glycols), senna, are also generally safe in ESKD with doses unchanged. However, because of the amount of water required for their administration, macrogols should be used with caution and bulking agents, e.g. ispaghula (psyllium) husk, avoided completely.

Loperamide is highly protein bound, extensively metabolised by CYP3A4 and is a substrate for p-glycoprotein. In ESKD, lower doses may be sufficient, particularly in the presence of CYP3A4 and p-glycoprotein inhibitors, the latter potentially increasing the amount of loperamide within the CNS and the risk of central opioid effects.

Hyoscine butylbromide is generally safe in ESKD, and glycopyrronium can be used cautiously. However, for both, there is potential for greater CNS penetration due to the changes to the blood brain barrier.

Of the bisphosphonates, pamidronate disodium and zoledronic acid are both nephrotoxic, whereas the risk of renal toxicity with ibandronic acid is no greater than placebo.[36] Thus, for the reduction of skeletal-related events in cancer, the risk-benefit balance favours the use of ibandronic acid over other bisphosphonates. An alternative in this setting is denosumab, which is authorized for use in renal impairment and does not require dose adjustment.

The management of tumour-induced hypercalcaemia can be complex in ESKD, because of the need for caution with fluid administration and presence of other potentially contributing factors, e.g. tertiary hyperparathyroidism, use of vitamin D analogues, calcium-based phosphate binders. Thus, specialist renal unit advice should be sought.

For non-opioid analgesics, a reduced dose of paracetamol (acetaminophen) or nefopam is preferable to NSAIDS which should be avoided due to their nephrotoxicity. However, in anuric patients on dialysis, NSAIDS can be used in normal doses.

The choice of skeletal muscle relaxant in ESKD is not straightforward; for all, changes in the integrity of the blood brain barrier may result in increased penetration into the CNS. Baclofen and diazepam (also see Table 5) are best avoided because of the risks of accumulation. Even so, many renal units report that patients can tolerate low doses of diazepam. However, the better long-term option may be the cautious use of tizanidine in reduced doses. CYP1A2 inhibitors can significantly reduce the metabolism of tizanidine, and the concurrent use of ciprofloxacin and fluvoxamine is contra-indicated.

For patients on PD or HD, apart from baclofen for which dosing is recommended after HD, none of the featured drugs requires any additional changes to the ESKD dosing regimen.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpainsymman.2017.08.014.

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