Symptom control in patients with chronic kidney disease/ renal impairment

Introduction
• This guideline covers modifications to standard symptom control that are recommended in patients with chronic kidney disease or acute renal impairment.
• Renal impairment is common in patients with diabetes, cardiovascular disease or cancer (from disease or treatment eg. chemotherapy, obstructive uropathy, myeloma).
• Symptom control is complicated by delayed drug clearance, dialysis effects and renal toxicity associated with commonly used medication (eg. NSAIDs).
• 50% of dialysis patients have pain. Depression and other symptoms are common.

Assessment

| CKD stage 1 | Normal renal function |
| CKD stage 2 | Mild impairment (eGFR 60-89 ml/min) | Asymptomatic |
| CKD stage 3a | Moderate impairment (eGFR 45-59 ml/min) |
| CKD stage 3b | Moderate impairment (eGFR 30-44 ml/min) | Asymptomatic |
| CKD stage 4 | Severe impairment (eGFR 15-29 ml/min) | In addition: anorexia, nausea, insomnia, neuropathy, gout |
| CKD stage 5 | End stage renal disease (eGFR < 15 ml/min) | In addition: itch, headache, cognitive impairment; death |

- Pain is common and associated with many of the complications of advanced CKD.
- Look for multiple types of pain and/or other symptoms due to:
  o renal disease (polycystic kidneys, liver cysts, amyloid).
  o co-morbidity (diabetes, vascular disease, angina).
  o dialysis (abdominal pain in peritoneal dialysis, headache, fistula problems).
  o other pathology (cancer, osteoarthritis).
- Pain in patients with chronic kidney disease:
  o Musculoskeletal pain.
    • Muscle spasm, cramps, restless leg syndrome.
    • Osteoporosis.
    • Renal osteodystrophy.
    • Osteomyelitis, disc infection.
    • Carpal tunnel syndrome.
  o Neuropathic pain – renal or diabetic peripheral neuropathy.
  o Ischaemic pain – peripheral vascular disease, vasculitis.
  o Calciphylaxis – complex pain caused by tissue ischaemia due to calcification of small vessels/ subcutaneous tissue.
- Identify chronic pain (needs regular analgesia) and any intermittent/ episodic pain as this often needs managed separately with short acting analgesics/ non-drug measures.
  (see: Pain management, Pain assessment)
- Some drugs will be cleared by dialysis; an extra dose during or after dialysis may be needed.
- Patients are often on multiple drugs with a high risk of interactions/side effects.

Management
• Much of the advice in the palliative care guidelines is applicable to patients with renal disease. See table for renal prescribing advice.
• There is another renal palliative care guideline: Last days of life (renal).
• Choice and dose of opioids depends on the degree of renal impairment.
• Mild renal impairment; use lower starting doses of renally excreted opioids (codeine, dihydromorphone, morphine, diamorphine, oxycodone) and slower titration.
• Stages 3-5 chronic kidney disease; use a modified WHO analgesic ladder (see page 2).
Pain management in renal disease

**STEP 1: Mild Pain**
Paracetamol +/- adjuvant analgesic
1g, qds

**STEP 2: Mild to moderate pain**
Paracetamol + low dose opioid +/- adjuvant analgesic
- Low dose oxycodone or tramadol can be used; if GFR > 30ml/min – reduce dose and frequency, monitor closely for side effects (drowsiness, hallucinations, confusion).

**STEP 3: Moderate to severe pain**
Paracetamol + selected opioid +/- adjuvant analgesic
- Fentanyl patch – opioid of choice for stable pain; well tolerated, not renally excreted or removed by dialysis. Can accumulate with longer term use; monitor and adjust dose. Treat breakthrough pain with an oral opioid as in Step 2.
- Alfentanil injection – used as a SC injection, sublingually, or as a subcutaneous infusion. (see: Fentanyl patches, Alfentanil)
- Methadone – titration complex so only use on specialist advice.

**Adjuvant analgesics (for prescribing advice see table below)**

**Antidepressant or anticonvulsant:** for nerve pain
Start at a low dose; titrate slowly. No clear difference in efficacy.
- amitriptyline (side effects: confusion, hypotension, dry mouth)
- gabapentin (side effects: sedation, tremor); adjust dose for renal function
- sodium valproate
- carbamazepine
- clonazepam

**Ketamine:** complex neuropathic pain including calciphylaxis
(see: Ketamine on website; use is unlicensed)

**Symptom control in renal disease (see prescribing advice tables)**
- Depression – common and underdiagnosed. (see: Depression)
- SSRI antidepressant (eg sertraline) is often used.
- Dialysis associated symptoms (hypotension, nausea, cramps, fatigue) – review dialysis prescription.
- Hiccups – (see: Hiccup)
  - Treat any other underlying cause eg gastro-oesophageal reflux.
  - Prokinetic antiemetic (metoclopramide or domperidone).
  - Baclofen – adjust dose for renal function.
- Itch – common and distressing. (see: Itch)
  - Good skin care with regular use of emollients +/- antihistamine.
  - Ondansetron has been used for intractable uraemic itch; 4-8mg twice daily.
- Nausea/ vomiting – assess likely cause (see: Nausea/ vomiting).
  - Gastric stasis is common – treat with metoclopramide (short term) or domperidone
  - Levomepromazine is a useful broad spectrum antiemetic; use low doses and monitor for hypotension.
  - Cyclizine worsens dry mouth in patients on fluid restriction.
- Restless leg syndrome – affects 20-40% of uraemic patients.
  - Clonazepam orally starting at 0.5mg nocte.
  - Gabapentin 100-300mg nocte (adjust dose for renal function).
- Other common symptoms include anorexia, constipation and fatigue – see relevant palliative care guidelines.
### Palliative Care Guidelines: Renal Palliative Care

Prescribing advice for palliative care patients with chronic kidney disease/renal impairment - Part 1

For further information see: other Palliative Care Guidelines & Last days of life (renal) guideline

<table>
<thead>
<tr>
<th>Drug</th>
<th>GFR &gt; 20ml/min</th>
<th>GFR 10-20ml/min</th>
<th>GFR 5-10ml/min</th>
<th>GFR 1-5ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td></td>
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</tr>
<tr>
<td>Paracetamol (oral)</td>
<td>Normal starting dose</td>
<td>Normal starting dose</td>
<td>Normal starting dose</td>
<td>Normal starting dose</td>
</tr>
<tr>
<td>CAUTION</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
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<tr>
<td>Tramadol</td>
<td>Normal starting dose</td>
<td>Normal starting dose</td>
<td>Normal starting dose</td>
<td>Normal starting dose</td>
</tr>
<tr>
<td>CAUTION</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Morphine/diamorphine</td>
<td>Normal starting dose</td>
<td>Normal starting dose</td>
<td>Normal starting dose</td>
<td>Normal starting dose</td>
</tr>
<tr>
<td>CAUTION</td>
<td></td>
<td></td>
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<tr>
<td><strong>Antiemetics</strong></td>
<td></td>
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</tr>
<tr>
<td>Domperidone</td>
<td>Oral starting dose</td>
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</tr>
<tr>
<td>Ondansetron/Granisetron</td>
<td>Oral starting dose</td>
<td>Oral starting dose</td>
<td>Oral starting dose</td>
<td>Oral starting dose</td>
</tr>
</tbody>
</table>

### Drug Clearances

- **HD**: Hemodialysis
- **PD**: Peritoneal dialysis
- **CAUTION**: Use with caution. Only use when patient is dying.
- **AVOID**: Avoid use. Use with extreme caution.

### Comments

- **Nephrotic**: Risk of GI bleed (platelet dysfunction).
- **Metabolites accumulate**: Reports of severe toxicity in CKD stage 4.
- **CNS**: Central nervous system.
- **Gl**: Glomerular.
- **PD**: Peritoneal dialysis.
- **HD**: Hemodialysis.
- **AVOID**: Avoid use. Use with extreme caution.
- **CAUTION**: Use with caution. Only use when patient is dying.
- **Unknown**: Information not available.
- **Short acting**: Do not exceed maximum dose.
- **Reduced clearance**: More risk of extrapyramidal side effects.
- **Urine output**: More CNS side effects.
- **Increased half life**: More risk of extrapyramidal side effects.
- **↓ excretion**: Lower seizure threshold.
- **May help**: Constipation.
- **May help**: Dry mouth.
- **May help**: May help with dry mouth.
- **May help**: May help with nausea.
- **May help**: May help with itching.

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### Prescribing advice for palliative care patients with chronic kidney disease/renal impairment - Part 2

**For further information see other Palliative Care Guidelines & Last days of life (renal) guideline**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Dialysis Clearance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Normal starting dose (GR 0-29ml/min)</td>
<td>0.5mg, orally, 6 hourly or nocte</td>
<td>Used for insomnia, anxiety and muscle spasm/myoclonus. Start lower and titrate dose for all benzodiazepines. Metabolites excreted renally and protein binding is reduced. Check BNF for drug interactions.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Normal starting dose (GR 30-59ml/min)</td>
<td>2.5mg, orally, 1-2 hourly</td>
<td>Max dose 10mg, orally</td>
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<tr>
<td>Midazolam</td>
<td>Normal starting dose (GR 60-89ml/min)</td>
<td>0.5mg, orally, nocte</td>
<td>Lower dose &amp; titrate</td>
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<tr>
<td>Temazepam</td>
<td>Normal starting dose (GR 15-29ml/min)</td>
<td>300mg, orally, alternate days</td>
<td>Yes; 300mg post HD</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Normal starting dose (GR 15-29ml/min)</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Adjuvants</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gabapentin</td>
<td>Oral starting dose (GR 0-29ml/min)</td>
<td>300mg, orally, 12 hourly</td>
<td>Yes; 300mg post HD</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Oral starting dose (GR 30-59ml/min)</td>
<td>50-100mg, orally</td>
<td>Normal starting dose</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Oral starting dose (GR 60-89ml/min)</td>
<td>100-200mg, orally</td>
<td>Normal starting dose</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Oral starting dose (GR 15-29ml/min)</td>
<td>10mg, nocte</td>
<td>Normal starting dose</td>
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<tr>
<td>Citalopram</td>
<td>Normal starting dose (GR 15-29ml/min)</td>
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<tr>
<td>Sertraline</td>
<td>Normal starting dose (GR 15-29ml/min)</td>
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<td>No</td>
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<tr>
<td>Mirtazapine</td>
<td>Normal starting dose (GR 15-29ml/min)</td>
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<td>Normal starting dose</td>
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<tr>
<td>Baclofen</td>
<td>Oral starting dose (GR 15-29ml/min)</td>
<td>5mg, orally, 8 hourly</td>
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<tr>
<td>Ketamine</td>
<td>Oral starting dose (GR 15-29ml/min)</td>
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<td><strong>Anti-depressants</strong></td>
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<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Normal starting dose (GR 0-29ml/min)</td>
<td>50-100% dose</td>
<td>Yes</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Normal starting dose (GR 30-59ml/min)</td>
<td>50% dose</td>
<td>Yes</td>
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<tr>
<td>Hyoscine butylbromide</td>
<td>(Buscopan) SC</td>
<td>20mg SC, orally</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**SIGN 103 recommends that creatinine clearance estimated by the Cockcroft-Gault formula be used for drug dosing as published recommendations are based on this prediction equation for GFR. The tables are a guide to dose adjustments. Each patient should be assessed and monitored individually.**
Measuring renal function

- Prediction equations are more accurate than serum creatinine or 24-hour urine creatinine clearance.
- The equations are affected by age, sex and weight so are less reliable in older people and those with cachexia, obesity or oedema.
- eGFR is reported in routine laboratory results but is less accurate at values of > 60ml/ min.
- Cockcroft-Gault formula is recommended in drug manufacturer’s information.
  \[
  \text{GFR (ml/min)} = \frac{(140- \text{Age}) \times \text{IBW (kg)} \times 1.23 \text{ if male} \times (1.04 \text{ if female})}{\text{serum creatinine (micromoles/l)}}
  \]
  Ideal Body Weight (IBW) is recommended for the calculation particularly if the patient is oedematous or obese.
  - = male 50 + 2.3kg per inch over 5 feet
  - = female 45.5 + 2.3kg per inch over 5 feet

Key references