1. Scope

Opioid prescribing guideline for use by healthcare professionals looking after adult patients at UHL

2. Purpose

To guide prescribers in the safe use of opioids in patients with altered renal function, ensuring good analgesia whilst minimising toxicity

3. Introduction

Great care is required when prescribing opioids to patients with impaired renal function. Many opioids (and/or their active/toxic metabolites) are renally excreted e.g. morphine. Injudicious use of opioids in renal failure can cause toxicity and dangerous side effects e.g. respiratory depression. There are some opioids with more favourable safety profiles in renal failure but it is recommended that specialist advice should be sought for guidance on selecting or switching opioids in this situation.

Decreased renal clearance of any drug/metabolite closely follows renal function as measured by creatinine clearance. In consequence, drug toxicity in renal disease depends on the extent to which renal clearance contributes to total drug/metabolite clearance and how critical a drug/metabolite concentration is. Where practicable, renal function should be checked prior to prescribing any drug which requires dose modification.

Potential pharmacokinetic and pharmacodynamic problems in renal failure are not only related to altered renal excretion and can occur even if elimination is unimpaired. All opioids are affected variably by one or more of these consequences of renal impairment:

- Reduced hepatic clearance (reduced CYP450 activity)
- Altered drug distribution (affected by changes in hydration [dehydration - reduced volume of distribution, ascites – increased volume of distribution])
- Hypoproteinaemia/ Reduced protein binding (increased unbound [active] fraction of drugs)
- Increased permeability of blood brain barrier (increased CNS drug levels)
- Increased sensitivity of CNS to opioid side effects e.g. drowsiness

Many of these problems can be avoided by reducing the prescribed doses or by using alternative drugs.

4. Definition of renal failure

The glomerular filtration rate (GFR) is the best overall measure of renal function but the most accurate ways of calculating this are impractical for routine use. Proxy measures include ***eGFR*** (estimated Glomerular Filtration Rate) and ***creatinine clearance*** (CrCl). The BNF generally now advises dose adjustments based on eGFR.

❖ eGFR (CKD EPI)

Is the more accurate measure with 90% of estimates being within 30% of the true value.

Changes in eGFR are more accurate than a single reading with a decrease of ≥15% likely to represent a true change in renal function.

Is expressed as a normalised value ie what that individuals eGFR would be if they had a body surface area of 1.73m^2. eGFR assumes the patient is of average size so may be less reliable in certain situations and needs to be interpreted with caution:

- acute kidney injury
- pregnancy
- oedematous states
- muscle wasting disorders
- adults who are malnourished e.g. cachexia in terminal illness
- amputees
- body builders
- eGFR is not well validated in certain ethnic groups e.g. in people of Asian family origin
- Is not validated for children under the age of 18

In palliative care with patients who are elderly, malnourished, cachexic and/or oedematous, renal impairment may exist even when the serum creatinine or eGFR are in normal limits. Additionally, even when eGFR is abnormal, the degree of impairment may be underestimated.

5. Classification of renal impairment

Chronic kidney disease is classified by NICE[1] into 5 stages using a combination of eGFR and ACR (albumin:creatinine ratio). Adverse outcomes are associated with decreased eGFR and increased ACR. If both are present, the risk of adverse outcomes are multiplied.

Degree of impairment	eGFR (ml/min/1.73m^2)	CKD stage	ACR	ACR category
Normal	>90 (with other evidence of renal disease)*	1	<3mg/ mmol	A1
Mild	60-89 (with other evidence of renal disease)*	2		
Mild - moderate	45-59	3A	3-30mg/mmol	A2
Moderate – severe	30-44	3B		
Severe	15-29	4	>30mg/mmol	A3
Established renal failure or renal replacement therapy	<15	5		

[1]NICE Guideline for Chronic Kidney Disease 2021

*Markers of kidney disease may include: albuminuria (ACR > 3 mg/mmol), haematuria (of presumed or confirmed renal origin), electrolyte abnormalities due to tubular disorders, renal histological abnormalities, structural abnormalities detected by imaging (e.g. polycystic kidneys, reflux nephropathy) or a history of kidney transplantation.

6. Monitoring drugs in renal impairment

When drug modification has been necessary or when using drugs known to cause renal impairment, a clinical review and repeat renal function testing should be carried out after 2 weeks of treatment or at any time a new rash, oedema, arthralgia or other sign of drug-induced nephrotoxicity occurs.

7. Evidence base for recommendations

The evidence base for the management of pain in renal impairment is limited and the following recommendations are based on the best available evidence and consensus 'best practice' guidelines.

There are a number of available resources including BNF (British National Formulary), PCF (Palliative Care Formulary), manufacturers SPC, *The Renal drug Handbook/ Database* and *Drug Prescribing in Renal Failure.* It should be noted that advice will vary between these sources.

8. Recommendations for initiation of opioids

Always use lowest effective dose

Unstable/ acute pain		
Mild Pain STEP 1	**First choice: Paracetamol** (non-opioid)	1g qds PO/PR/IV **Use** For any stage renal disease **Dose adjustments** Stages 4-5 Reduce IV to tds if using for >48 hr
Moderate Pain STEP 2	**First choice: Tramadol** (weak opioid)	50-100mg qds (equivalent to 5-10mg PO morphine IR qds) **Use** Immediate release preparation For any stage renal disease Modified release preparation For stages 1-3 ONLY **Dose adjustments** Stages 1-3 No dose adjustment (max 400mg /24hr) Stage 4 50mg-100mg max 8 hourly (max 300mg/24hr) Stage 5/ RRT 50mg max 8 hourly (max 150mg/24hr)
Severe pain STEP 3	**First choice** **Stage 1-2 ONLY:** **Morphine** (strong opioid)	**Opioid naïve** – use low dose: 2.5mg-5mg PO morphine IR 6 hourly or 1.25-2.5mg SC morphine 6 hourly initially then increase dose as needed to achieve pain control **Already on regular opioids**: *Tramadol* – switch to morphine at appropriate doses (see above) and increase as needed to achieve pain control *Morphine* - increase current dose if well tolerated or switch to an alternative opioid if developing side effects (see below). If pain is not controlled either cautiously up titrate dose or reduce interval to 4 hourly ***If pain remains uncontrolled after 48 hrs:*** • ***For pain related to malignancy or if patient is in last days of life - refer to specialist palliative care team*** • ***For non-malignant pain – acute or chronic – refer to pain team*** **Use** Immediate release preparations For stages 1-2 Modified release preparation Avoid unless stable requirements **Syringe pump (CSCI)** For stages 1-2 *– consider using if patient is needing 2 or more breakthrough doses within 24hr* To convert PO morphine to CSCI morphine, add up total 24 hr dose and divide by 2. (e.g. 30mg PO morphine = 15mg morphine CSCI) To convert SC morphine to CSCI morphine, add up total 24 hr dose. (e.g. 30mg SC morphine = 30mg morphine CSCI)
	First choice Stage 3-5 or Second choice stage 1-2: **Oxycodone** (strong opioid)	For any stage renal disease (1.5-2x potency of PO morphine) • Use in stage 1-2 only if patient intolerant of morphine or on advice of pain/ specialist-level palliative care teams • May use in stages 3-5 /RRT as PO/ SC option (Alfentanil is preferred option for CSCI if eGFR<30 – see Alfentanil below) **Opioid naïve** – use low dose (see below) PO oxycodone IR 6 hourly or SC oxycodone 6 hourly **Already on regular opioids** – switch to oxycodone at appropriate doses. To convert PO morphine to PO oxycodone, add up total 24 hr dose and divide by 1.5 (e.g. 30mg PO morphine = 20mg PO oxycodone)

		If pain is not controlled either cautiously up titrate dose or reduce interval to 4 hourly If converting from high doses, discuss with specialist palliative care team ***If pain remains uncontrolled after 48 hrs:*** • ***For pain related to malignancy or if patient is in last days of life - refer to specialist palliative care team*** • ***For non-malignant pain – acute or chronic – refer to pain team*** **Use** Immediate release preparations — For any stage renal disease Modified release preparation — For stages 1-3 ONLY Avoid unless stable requirements **Dose adjustments** Stage 3-4 — 2.5mg-5mg PO or 1mg-2mg SC 4-6 hourly Stage 5/ RRT — 1mg-2mg PO / SC 6-8 hourly **Syringe pump (CSCI)** — For any stage renal disease *– consider using if patient is needing 2 or more breakthrough doses within 24hrs* • To convert PO oxycodone to CSCI oxycodone, add up total 24 hr oral dose and divide by 2 (e.g. 30mg PO oxycodone = 15mg oxycodone CSCI) • To convert SC oxycodone to CSCI oxycodone, add up 24 hr SC dose (e.g. 30mg SC oxycodone = 30mg oxycodone CSCI) Usually wait 72 hrs before increasing CSCI dose unless directed otherwise by specialist teams.
	Second choice: Alfentanil (strong opioid)	For any stage renal disease including RRT (30x potency of PO morphine) **For use following specialist palliative team / pain team advice only** **Use** SC PRN dosing — Short half life means duration of action is <30mins so unsuitable for most patients. **Syringe pump (CSCI)** — For any stage renal disease *– consider using if patient is needing 2 or more breakthrough doses within 24hrs* To convert PO morphine to CSCI alfentanil, add up total 24hr dose PO morphine and divide by 30 (e.g. 15mg PO morphine MR bd = 1mg CSCI alfentanil)
	Alternative oral analgesia: Tapentadol (strong opioid)	50mg bd-tds (equivalent to 15mg PO morphine IR bd-tds) **Use** Immediate release preparation — For any stage renal disease Modified release preparation — For stages 1-3a ONLY **Dose adjustments** Stages 1-3a — No dose adjustment (max 500mg/24hr) Stages 3b-5 — Avoid using

Stable pain : For any stage renal disease including RRT		
Severe pain with stable opioid requirements *(as alternative to MR morphine & MR oxycodone)* STEP 3	**Fentanyl transdermal patch** (strong opioid)	**For use following specialist palliative team / pain team advice only** Safest pharmacological/ pharmacokinetic profile in renal impairment however – use is contraindicated in unstable pain or opioid naïve patients: • Takes 48-72 hrs to reach steady state • 25micrograms/hr fentanyl = 60-90 mg PO morphine/ 24hr **If a patient is dying and has a patch in situ DO NOT REMOVE IT. Continue to change as per usual schedule. Additional analgesia can be given via CSCI if needed.**
	Buprenorphine transdermal patch (strong opioid)	**For use following specialist palliative team / pain team advice only** Safest pharmacological/ pharmacokinetic profile in renal impairment however – use is contraindicated in unstable pain or opioid naïve patients: • Takes 48-72 hrs to reach steady state • 5 micrograms/hr buprenorphine = 12mg PO morphine/ 24hr **If a patient is dying and has a patch in situ DO NOT REMOVE IT. Continue to change as per usual schedule. Additional analgesia can be given via CSCI if needed.**

LAST DAYS OF LIFE
- USE OF OPIOID ANALGESICS IN ADULT PATIENTS WITH RENAL IMPAIRMENT FROM ALL CAUSES

Is patient already prescribed regular opioids?

No – patient is opioid naïve

ANTICIPATORY SC (PRN) PRESCRIBING IS REQUIRED

If the patient is still be able to manage oral analgesia at this time they may continue to receive analgesia in this way if that is their preference but SC options will also need prescribing

- Prescribe PRN oxycodone SC 1mg-2mg 6 hourly.

If oxycodone is not available on the ward and patient requires analgesia, prescribe morphine SC 1-2mg as an alternative to be used until oxycodone is available. Ask ward nurses to order SC oxycodone as a priority.

- If pain does not respond or >2 doses are given in 24 hours, start regular opioids as per guidelines above

IMPORTANT CONSIDERATIONS FOR ALL DYING PATIENTS

1. *Do not forget to assess for reversible causes of pain even in last days of life e.g:*
   - *Urinary retention/ blocked catheter*
   - *Constipation/ faecal impaction*
   - *Pain requiring alternative approach e.g. anti inflammatory analgesia*

2. ***Dose of oxycodone or frequency of administration may be increased following discussion with a senior doctor (StR or consultant) if patient is in a pain crisis.***

3. ***Contact Specialist Palliative Care team if pain remains uncontrolled after 24 hrs <u>or</u> for advice on dose conversions***

Yes – patient is currently receiving either opioids either as modified release tablets, transdermal patch or syringe pump (CSCI)

REGULAR OPIOIDS NEED REVIEWING

If patient is receiving a fentanyl or buprenorphine transdermal patch then <u>DO NOT REMOVE</u>. Additional opioids can be given via syringe pump (CSCI) if necessary.
In this instance, you will need to take both patch and CSCI into account when calculating PRN doses

If patient has been on stable dose of oral MR morphine/ oxycodone and no side effects have been experienced or observed, this can be converted to CSCI to ensure ongoing administration of pain relief.

- Add up total 24 hour dose of PO morphine and divide by 2 = CSCI morphine dose
- Add up total 24 hour dose of PO oxycodone and divide by 2 = CSCI oxycodone dose

If morphine/ oxycodone are/ may be causing side effects esp if renal failure is now stage 3-5, convert background opioids to alfentanil via CSCI and use SC oxycodone as PRN opioid. **If converting from high doses, discuss with the specialist palliative care team.**

- Add up 24 hour dose of PO morphine and divide by 30 = CSCI alfentanil
- Add up 24 hour dose of PO oxycodone and divide by 20 = CSCI alfentanil

- PRN SC oxycodone = Total CSCI alfentanil dose multiplied by 10 and divided by 6 e.g. Alfentanil 2mg CSCI = 2x10/6 = approx. 3mg SC oxycodone. Round down to nearest 2.5mg dose for ease of administration. I.e 2.5mg SC oxycodone in this example.

If oxycodone is not available on the ward and patient requires analgesia, prescribe SC morphine at 2/3 of the SC oxycodone dose as an alternative to be used until oxycodone is available. Ask ward nurses to order SC oxycodone as a priority.