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CLINICAL PRACTICE ARTICLE

Management of acute and post-operative pain in chronic kidney disease [v1; ref status: approved 1, approved with reservations 1, http://f1000r.es/wp]

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Abstract

Chronic kidney disease is common and patients with many co-morbid conditions frequently have to undergo surgical procedures and, therefore, require effective pain management. The pharmacokinetics of various analgesic agents are not well studied in patients with chronic kidney disease and the risk of accumulation of the main drug or their metabolites, resulting in serious adverse events, is a common scenario on medical and surgical wards. It is common for these patients to be cared for by 'non-nephrologists' who often prescribe the standard dose of the commonly used analgesics, without taking into consideration the patient's kidney function. It is important to recognize the problems and complications associated with the use of standard doses of analgesics, and highlight the importance of adjusting analgesic dosage based on kidney function to avoid complications while still providing adequate pain relief.

Article Status Summary

Referee Responses

Referees	1	2
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1   **Howard S Smith**, Albany Medical College USA

2   **Paul E Carns**, Mayo Clinic in Rochester USA

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Illustrative clinical scenario:- an example to illustrate the problem. A 63-year-old man with diabetes and end stage renal disease on maintenance continuous ambulatory peritoneal dialysis was admitted to the hospital with gangrene of the left foot and underwent left below-knee amputation under spinal anesthesia. Postoperatively, he was given meperidine (Demerol) 50–75 mg intramuscularly every 3 hr, as required, by the orthopedic surgeon, but this was found to be ineffective in controlling pain. The anesthetist ordered morphine 10–15 mg intramuscularly or subcutaneously every 3 hr as required (pro re nata) in the evening. He received 325 mg of meperidine in the first 24 hr and additional 200 mg of meperidine next day (total 525 mg) and 55 mg of morphine within the first 48 hr after surgery. 48 hr after surgery, he was found to be confused and somnolent. On examination the patient was drowsy and somnolent, but arousable with twitching of arms, and complained of mild pain at the stump site when awakened. He had labored breathing with a respiratory rate of 8 breaths per minute. An arterial blood gas showed pH of 7.19, pCO$_2$ of 60, pO$_2$ of 86 and oxygen saturation of 95%. His mental state improved transiently with intravenous naloxone, confirming narcotic effect. How could this situation have been prevented while effectively providing pain relief?

Chronic kidney disease (CKD) is common[1] and is regularly accompanied with various co-morbidities. Often these patients with various co-morbidities undergo operative procedures and require analgesics. The most-responsible physician providing the care to these individuals during their hospitalization is often a non-nephrologist. Opioids are commonly used in the management of post-operative pain, and often a standard dose is used by the health-care providers without taking into consideration kidney function[2]. In North America, morphine and meperidine (Demerol) still remain the commonly used parenteral agents, and acetaminophen with codeine (Tylenol #3) a commonly used oral agent for management of post-operative pain in patients with[3] and without renal failure. Prolonged narcotic effects and ventilatory depression due to morphine and other opioids have been known for over a century in patients with kidney failure[4–10] and the various contributing factors are outlined in Table 1. Despite the increased potential for respiratory depression, especially in patients with CKD, life-threatening cases of opiate toxicity continue to occur not only in patients with kidney disease[11],

but also in patients without kidney disease[12,13]. It is important to highlight the issue of central nervous system (CNS) and respiratory depression with opioid analgesics in patients with CKD and formulate strategies to prevent these complications, while providing effective pain relief.

In addition to the post-operative pain, patients with CKD may have underlying chronic pain that is often multi-factorial[14] i.e., ischemic pain from peripheral vascular disease, neuropathic pain of polyneuropathy (diabetes), bone pain from osteoporosis or dialysis-associated amyloidosis, and musculoskeletal pain that may or may not be related to kidney disease. Post-operative pain is often nociceptive, whereas chronic pain may be nociceptive, neuropathic or mixed. It is also important to recognize that depression is common in CKD[15] and that it may complicate the management and patient's ability to cope with pain[16].

Assessment of pain
Assessment of pain requires detailed history to elucidate the cause of pain, its location, nature (acute, chronic or acute and chronic), intensity and its impact on physical, social and emotional functioning[17].

Spectrum of pain
Acute pain is a protective and an adaptive response to injury, whereas chronic pain or the persistence of pain beyond the healing phase is maladaptive[18]. Acute pain results from direct stimulation of sensory neurons, called nociceptors. Nociceptors have two types of axons, the rapidly conducting thinly myelinated Aδ fibers that mediate the initial phase of acute pain that is extremely sharp pain, and the more slowly conducting unmyelinated C fibers mediate the second phase of acute pain that is more prolonged and less intense following injury. Nociceptors can be stimulated by mechanical, thermal, chemical and inflammatory stimuli[18].

Pain lasting longer than 3 months or beyond the duration required for complete tissue healing is called chronic pain. It may be nociceptive, resulting from prolonged tissue injury with persistent activation of nociceptors, neuropathic resulting from a lesion or a process affecting the somatosensory system or mixed processes.

Table 1. Factors contributing to opioid toxicity in CKD.

Factors contributing to opioid toxicity in chronic kidney disease		
Patient factors		**Exogenous factors**
Independent of kidney function	Dependent on kidney function	Drug-drug interactions
• Age – extremes of age, increases sensitivity • Gender – women more sensitive • Genetic – absence of A118G SNP* • Route of administration§ • Enterohepatic circulation • Hypoalbuminemia • Concomitant illness(es) – Sepsis, liver disease	• Decreased clearance – accumulation of parent drug and active metabolites • Decreased threshold • Change in volume of distribution (V_d) • Change in protein binding • Impaired ventilatory response to carbon dioxide in CKD	• Cytochrome P450 2D6 system@ • P-glycoprotein inhibitors¶ • Concomitant antibiotic use°

* A118G polymorphism protects against M6G-related opioid toxicity[28].
§ Routes that use first pass metabolism results in higher production of metabolites than those that bypass it.
¶ P-glycoprotein inhibitors increase uptake of M6G across blood brain barrier[16,17].
° Concomitant antibiotics by altering bacterial flora reduces bacterial glucuronidase, resulting in reabsorption of M6G.
@ Extensive 2D6 metabolism may occur in up to 1/3rd of patients of east African heritage – increasing the risk of opioid overdose from codeine.

Intensity of pain

Pain intensity may be measured by one of the major pain rating scales including verbal, numerical and visual analogue scales. However, a numerical rating scale comprising of a range of numbers from 0 to 10, is the most widely used system in clinical practice and is generally based on a subjective 10-point scoring system, where 0 denotes the absence of pain and 10 the worst pain imaginable[19].

Pain management

Effective pain management requires a multifaceted approach with an understanding of the type (nociceptive, neuropathic or mixed), underlying cause, assessment of intensity and duration of pain[17]. In addition, assessment of concomitant medications and co-morbidities is important when selecting analgesic agent(s). Adjuvant analgesics and non-pharmacological methods of pain control are important to consider in such circumstances[17]. We review the strategies to manage acute pain in CKD with main focus on the use of opioids since most of the challenges occur in the use of opioids in CKD.

In 2005, a modified World Health Organization (WHO) step-wise approach was proposed for pain management in patients with CKD[20] (Figure 1) and this approach was found to be effective in acute pain control in >90% of hemodialysis patients, at least short-term, in a 4-week study[21]. This approach is important to follow to achieve 'balanced analgesia' by effectively utilizing 'co-analgesics' (Box 1).

Figure 1. Modified WHO analgesic ladder in patients with chronic kidney disease [adapted from references[17,18]], with relative potency compared to morphine (1) of commonly used opioids in parenthesis. *Non-steroidal anti-inflammatory agents, including cyclo-oxygenase-2 inhibitors should be avoided, except for acute pain with close clinical observation.

Box 1. Glossary.

Opiate: Naturally occurring alkaloid i.e., morphine or codeine.

Opioid: Any natural or synthetic compound that has morphine-like properties.

Balanced analgesia: Principle of combining different classes of analgesics to optimize efficacy while minimizing side-effects.

Co-analgesic: A drug administered alongside opioids enabling a reduction in opioid dose.

Adjuvant: A substance that helps and enhances the pharmacologic effects of an agent (analgesic).

Non-opioid analgesics

Acetaminophen: Has potent analgesic and antipyretic properties and is effective in various acute and chronic painful syndromes. It is the analgesic of choice in the elderly and in patients with kidney disease[22] and should be considered in all patients (except in patients with hepatic insufficiency) experiencing pain, regardless of pain level, until pain is relieved or up to a maximum dose of 3,000 mg a day[23] or 2.6 g/d in high-risk patients[24] (malnourished or alcoholic). It often does not require dose adjustment in CKD but some authors recommend increasing dosing interval from every six to eight hours when GFR is <10 mL per minute[25]. Acetaminophen is underutilized in the peri-operative period and when prescribed it is often in an "on demand" basis rather than "by the clock". It's important to prescribe at least half of total daily dose "by the clock"[17] e.g., Acetaminophen 500 mg four times a day and remaining dose could be given "on demand" or in combination with other agents.

Anti-inflammatory agents: Nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclo-oxygenase (COX-2) inhibitors block prostaglandin synthesis and, when used as co-analgesic, reduce opioid need by 30–50%. However, because of their gastro-intestinal and cardio-renal side effects, they should be avoided for prolonged use in CKD, as these agents may decrease renal blood flow and may precipitate acute renal failure and can cause life-threatening hyperkalemia. However, if used, it should be for short term management (3 to 7 days) of acute pain and consider short-acting agents[26] with careful monitoring of renal function and serum potassium.

Adjuvant analgesics

Adjuvant analgesics are medications with a primary indication other than pain that may possess analgesic activity or modify pain response. These are often helpful for management of chronic neuropathic pain. Examples include cabamezapine, gabapentin, and pregabalin. These agents are not required for management of acute pain. However, CKD patients may have associated underlying chronic neuropathic pain that could affect acute pain response or management. Therefore, some patients may already be taking these agents for control of their 'chronic pain' and these agents may be stopped inadvertently in the peri-operative period. If this is the case, adjuvant analgesics should be resumed when possible, with considerations being taken for the possible drug-drug interactions when prescribing opioid analgesics for acute pain.

Opioids

The relative potency of commonly used opioids is shown in Figure 1. As most opioids or their metabolites are excreted by the

kidneys, dosage adjustment is often required when estimated glomerular filtration rate (eGFR) falls below 50 ml/min or during stages 3b, 4 and 5 of CKD, and for patients on dialysis (Table 2)[27,28]. In addition to CNS and respiratory depression, constipation is a common side effect that is important to identify and manage, especially in patients on peritoneal dialysis, as constipation is the common cause of catheter malfunction[29], and appropriate laxatives should be used in conjunction with treatment.

Morphine: Morphine is the most studied opiate in kidney disease. It is primarily an agonist at the μ-receptors with pain relief at μ_1-receptors, and causes respiratory depression and constipation through its agonist action at μ_2-receptors[14]. Morphine is metabolized in the liver to several metabolites[30]. Of these diamorphine and morphine-3-glucuronide (M3G) do not bind to opiate receptors, whereas normorphine and morphine-6-glucuronide (M6G) do, with M6G being approximately 10-fold more potent than morphine[31]. All metabolites are excreted in the urine along with about 10% of the parent compound. M6G accumulates in kidney failure and causes CNS and respiratory depression[32]. M6G crosses the blood brain barrier (BBB) slowly, and once it crosses the BBB, the CNS effects may be prolonged and may persist after stopping morphine or after hemodialysis, as the M6G slowly re-equilibrates across the BBB back into systemic circulation[6]. Transport of M6G across the BBB is an active process mediated by 170-kd P-glycoprotein. P-glycoprotein is an ATP-dependent carrier system that acts as an efflux pump to transport chemicals or metabolites from endothelial cells to vascular compartment and inhibition of this results in an increase of M6G in the brain[33,34]. The analgesic and respiratory depressant effects are related to serum concentrations of both morphine and M6G[31]. A dosage reduction of 25%, 50% and 75% is recommended in patients with mild (stage 3), moderate (stage 4) and severe kidney failure (stage 5) respectively. However, 20–25% of patients may tolerate the full dose of morphine without ill-effects because of *A118G* polymorphism[35,36].

Meperidine: Normeperidine, an active metabolite of meperidine, is neurotoxic and accumulates in renal failure and may cause a range of neuroexcitatory effects ranging from irritability to agitation to seizures[37]. Although normeperidine is removed by hemodialysis[38], its regular administration is ***contraindicated*** in patients with any degree of renal failure[39].

(Dextro)Propoxyphene: It is no longer available in North America and its metabolite norpropoxyphene is excreted by the kidneys and accumulates in renal failure[39]. This results in CNS and respiratory depression, cardiac conduction disturbances and hypoglycemia. Both the parent drug and its metabolite are not removed by hemodialysis and is ***contraindicated*** in patients with renal failure[39].

Hydromorphone: Hydromorphone is an analogue of morphine with shorter duration of action and with excellent efficacy in moderate to severe pain. It is five to seven times potent than morphine. It is eliminated by both hepatic (60%) and renal routes[40]. Hydromorphone doesn't accumulate in renal failure because of its rapid conversion to its less-potent metabolite hydromorphone-3-glucuronide (H3G) that accumulates in renal failure but is effectively removed by hemodialysis[41]. However, typical opioid adverse effects have been reported in patients with renal failure[42], but experience suggests efficacy without excess toxicity, if monitored carefully[43].

Codeine/Dihydrocodeine: Codeine is metabolized by the liver to a variety of active metabolites that are renally excreted[44]. The half-life of codeine is prolonged 5-fold in hemodialysis patients[45]. Codeine and its metabolites accumulate in renal failure and can cause hypotension and CNS and respiratory depression[46,47]. A similar elimination pathway is proposed for elimination of dihydrocodeine, although this has not been fully evaluated[39]. Dihydrocodeine can cause prolonged narcosis after therapeutic doses in patients with acute[48] or chronic renal failure[49]. Therefore, these agents should be used with caution in patients with renal failure. A reduction in dose by 50% is suggested for codeine in renal failure[39,45] and chronic use should be avoided.

Oxycodone: Oxycodone is a strong opioid with a higher oral bio-availability. It is metabolized by the liver to active metabolites – noroxycodone and oxymorphone[50]. Approximately 19% of the drug is excreted unchanged in the urine. The clearance of oxycodone and its metabolites is reduced in renal failure[50] and results in an increase in plasma concentration by 50% and prolongation of its half-life by an hour[50]. There is lack of consensus of its use in CKD because of varied case reports of toxicity and good tolerance. When required, use cautiously and start with a lower dose[51].

Buprenorphine: Buprenorphine is a long-acting semi-synthetic partial agonist with the advantage of having less respiratory depression and hypotension[52,53] but has a ceiling effect[54,55]. There is no significant difference in the clearance of the drug in patients with normal or impaired renal function. It has limited oral bioavailability because of an extensive first-pass metabolism. Sublingual, transdermal or parenteral administration is required. It is extensively metabolized by the liver with less than 30% renal excretion. The metabolite norbuprenorphine may accumulate in renal failure that has minor analgesic activity. Buprenorphine is 96% protein bound so is not dialyzable[56].

Fentanyl, Alfentanil, and Sufentanil: Fentanyl, Alfentanil and Sufentanil are potent opioid receptor agonists, with a rapid onset of action and shorter duration of action. Fentanyl is rapidly metabolized in liver to inactive metabolites. Less than 10% of the parent drug is excreted in urine with no significant accumulation in CKD, but there is considerable inter-patient variability in fentanyl pharmacokinetics when given as a continuous infusion or via transdermal route. However, no dosage modification is necessary in patients with renal failure when fentanyl is given as a bolus. However, prolonged sedation is observed in critically ill patients when fentanyl is given as a continuous infusion, as its half-life increases to 25 hr[39] due to saturation of its distribution sites, independent of renal function. Accumulation of fentanyl may occur when given by infusion[39] or transdermal patch. Its clearance may be altered in advanced kidney disease[57] and prolonged sedation and ventilatory depression have been observed in patients with end stage renal disease following fentanyl infusion[39]. Fentanyl is highly protein bound (80–86%), has a high volume of distribution, and removal by hemodialysis is negligible[58,59]. Opioid-naïve patients should not be initiated on transdermal fentanyl because of its variable absorption.

Table 2. Recommendations for commonly used opioids in CKD.

IN CKD	Opioid	Comments	Dialyzability	Dosing Normal	CKD (eGFR/ml) >50	CKD (eGFR/ml) 10–50	CKD (eGFR/ml) <10/RRT	Recommendation(s)
PARENT COMPOUND	Morphine	Metabolites accumulate in renal failure, CNS and Respiratory depression, 20–25% of patients may tolerate well	Yes, but M6G slowly re-equilibrates across the blood brain barrier, delaying the response to hemodialysis; Very small amount removed by CVVH or CVVHD		75–100% 2.5–5 mg q6h	50–75% 2.5–5 mg q6–8h	25–50% small dose 1.25–2.5 mg q 8–12h	Short-term use Avoid standing order Reassess dose q24–48h Not recommended for long-term use
RECOMMENDED/USE WITH CAUTION	Hydromorphone	Metabolite H3G accumulates in renal failure, has no analgesic activity but possibly neuro-excitatory	Yes	1.3 mg q6h	100%	75% Start with 0.5 mg q6–8h	50% Start with 0.5 mg q6–8h	**RECOMMENDED, Use carefully**
	Fentanyl	Inactive metabolite, highly protein bound, large volume of distribution (V_d). CNS & Respiratory depression reported with infusion and Transdermal patch	No	25–100 mcg q4–6h SC	100%	75%	25–50%	**RECOMMENDED,** starting dose 25–50 mcg q4–6h SC. Transdermal patch takes 3 days to reach steady state Do NOT use patch in opioid naïve patients
	Tramadol	20% protein bound	Slowly removed, 50% clearance by HD	50–100 mg q6h	100%	50% q12h	50% q12h	Use with caution, dose after hemodialysis on dialysis days
	Oxycodone	50% protein bound	To some extent	5–10 mg q6h	100% q6h	50–75% q8h	25–50% 18–12h	Limited evidence, use with caution
	Buprenorphine	Partial opioid agonist, ceiling analgesic effect, 96% protein bound	unlikely	0.3 mg IM/IV 8–16 mg S/L		Reduce dose and increase interval	Reduce dose and increase interval	Use with caution
NOT RECOMMENDED	Codeine	Both codeine and its metabolites accumulate in renal failure			100% q 6h	75% q 8h	50% q 12h	**Not recommended in dialysis patients**
	Dihydrocodeine		NA	NA	NA	NA	NA	**Not recommended**
	Meperidine	Toxic metabolite, normeperidine accumulates in renal failure and can cause seizures	Yes		75–100%	50%	Avoid	**AVOID**
	(Dextro) Propoxyphene	Toxic metabolite, norpropoxyphene accumulates in renal failure, can cause seizures, hypoglycemia and cardiac conduction disturbances	No		Avoid	Avoid	Avoid	**AVOID**

Tramadol: Tramadol is an opioid analgesic that also inhibits serotonin and noradrenaline reuptake. It is extensively metabolized by the liver and 30% of the parent drug and 60% of active metabolites are excreted in the urine[60]. It is effective for both nociceptive and neuropathic pain and has the advantage of less sedation and respiratory depression compared to other opiates. A common side effect is nausea. A rare but important side effect is seizures, especially in patients taking medications that lower the seizure threshold, like selective serotonin reuptake inhibitors (SSRI). In addition, tramadol may precipitate serotonin syndrome[61] (a potentially life-threatening drug-interaction manifested by excess serotonin effect resulting in cognitive, autonomic and somatic effects) in patients taking SSRI[62]. In advanced CKD, the elimination half-life of tramadol may double[60] and the dose should be decreased to 100 mg every 12 hr in patients with eGFR of 30 ml/min and 50 mg every 12 hr when eGFR is <10 ml/min. Tramadol is significantly removed by dialysis and should be administered after hemodialysis on dialysis days[63].

Methadone: Methadone is a synthetic opioid with five to 10 times the potency of morphine, is highly protein bound (70–87%) and has a half-life of 30 hr. Approximately 20% after a single dose is excreted unchanged and about 30% as inactive metabolites in the urine[39]. There is a 3-fold increase in the excretion of metabolites on chronic dosing, suggesting enhanced metabolism[64]. The removal by hemodialysis is insignificant[65]. Although in 2 patients with CKD the plasma concentrations were no higher than patients with normal renal function[66], there is a well-described risk of accumulation and toxicity with methadone, even in patients with normal renal function, so experienced specialist supervision is warranted. A dose

reduction of 50% to 75% is suggested in patients with renal failure, but it is difficult to use in patients with CKD because of its long half-life and wide inter-individual variation in clearance[65]. Methadone requires a specialist in pain management with a special license to prescribe it, and is often not a practical choice for acute pain management.

Summary

Patients with CKD have a high burden of co-morbidities that modulate pain response, and when these individuals undergo operative procedures, standard orders for pain control can be written without taking into consideration the patient's kidney function. Unfortunately, the data on the effects and tolerability of various analgesic agents are limited in such individuals and, given the lack of data, the recommendations are mainly based on expert opinion[17,67] in patients with CKD with[68] and without dialysis[43]. The general principles of pain assessment and management should be adopted and analgesia should be prescribed incorporating the modified WHO analgesic ladder[20] in patients with CKD, with close and frequent monitoring for side effects of drug or its metabolite accumulation. The nephrologist and a pharmacist should be involved in the management of these patients. The non-opioid analgesics should be used early and 'by the clock', rather than 'on-demand', and the need for opioid analgesics should be re-evaluated every 24–48 hr, as most patients may tolerate the prescribed initial dose of the opioid analgesics, with toxic effects often emerging after 48 hr, when the parent drug and its metabolites starts accumulating. Vigilance in nursing is also required to monitor for early effects of opiate toxicity. Box 2 provides recommendations and practical points for acute pain management in CKD based on the available evidence.

Table 3. Pain management in CKD.

Pain intensity	WHO analgesic step	Agent(s) of choice	Comments
Mild pain Score 1–3	*Non-opioid ± Adjuvant*	Acetaminophen 500 mg q6h (by the clock) and 325 mg every 6–8h as required	Not to exceed total dose of 3g in 24-hours; If unable to take orally, then consider suppository NSAIDs/Cox-2 inhibitors are *not recommended*, but may consider, for short-term ONLY, under close observation
Moderate pain Score 4–6	*Non-opioid ± Adjuvant ± Weak opioid*	± Tramadol 50 mg every 12h, if required or Oxycodone 2.5 mg every 8–12h	Maximum dose 200 mg in stage 4 CKD and 100 mg in stage 5 CKD, dose after dialysis
Severe pain Score 7–10	*Non-opioid ± Adjuvant ± Strong opioid*	± Hydromorphone 1.3 mg every 8h or Fentanyl 25–50 mcg SQ every 4–6h or Buprenorphine 0.3 mg every 6h IM/IV 8–16 mg sublingual daily Transdermal Patch – 5 mcg/hr–20 mcg/hr or Morphine 1.25–2.5 mg every 8–12h (for short-term use)	Use laxatives to avoid constipation, when using opioids Do not write standing (or long-term) orders for opioids. Reassess the need and dose of opioids every 24–48 hours Monitoring for CNS and respiratory effects is required for protracted periods Fentanyl and methadone are highly protein bound and not dialyzable Avoid fentanyl transdermal patch in opioid-naïve patients

Box 2. Key points.

- Before prescribing analgesics, consider kidney function to avoid toxicity that may occur from accumulation of the parent drug or their metabolites.

- The general principles of pain assessment and management should be adopted and analgesia should be prescribed incorporating the modified WHO analgesic ladder.

- Co-analgesics like acetaminophen should be considered "by the clock" rather than "by demand".

- Do not write standing (or long-term) orders for opioids. Reassess the need and the dose of opioids every 24–48 hr.

- Avoid fentanyl transdermal patch in opioid-naïve patients.

Author contributions

MSP conceived the idea. KSP performed literature review and prepared part of the initial draft. Both authors contributed equally to modifications and approve the current version.

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References

1. Coresh J, Byrd-Holt D, Astor BC, et al.: **Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000.** *J Am Soc Nephrol.* 2005; **16**(1): 180–8.
PubMed Abstract | **Publisher Full Text**

2. Parmar MS: **Safe drug prescribing.** *CMAJ.* 2002; **166**(13): 1651; author reply 1651.
PubMed Abstract | **Free Full Text**

3. Diskin CJ, Thomas S: **Intravenous analgesic use in dialysis patients.** *Nephrol Dial Transplant.* 1999; **14**(10): 2530–2.
PubMed Abstract | **Publisher Full Text**

4. Toogood F: **The use of morphine in cardiac disease.** *Lancet.* 1898; **2**: 1393–4.
Publisher Full Text

5. Yeo I: **On the use of opium in acute and chronic diseases.** *Practitioner.* 1907; **1**: 625–40.

6. Angst MS, Buhrer M, Lotsch J: **Insidious intoxication after morphine treatment in renal failure: delayed onset of morphine-6-glucuronide action.** *Anesthesiology.* 2000; **92**(5): 1473–6.
PubMed Abstract

7. Moreau K, Morel D, Merville P, et al.: **[Cardiorespiratory arrest following ingestion of morphine sulfate in a patient with chronic renal failure].** *Presse Med.* 1997; **26**(15): 713.
PubMed Abstract

8. Osborne RJ, Joel SP, Slevin ML: **Morphine intoxication in renal failure: the role of morphine-6-glucuronide.** *Br Med J (Clin Res Ed).* 1986; **292**(6535): 1548–9.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

9. Covington EC, Gonsalves-Ebrahim L, Currie KO, et al.: **Severe respiratory depression from patient-controlled analgesia in renal failure.** *Psychosomatics.* 1989; **30**(2): 226–8.
PubMed Abstract

10. Dubs A, Wiedemeier P, Caduff B: **[Morphine poisoning in chronic kidney failure. Morphine-6-glucuronide as a pharmacologically active morphine metabolite].** *Dtsch Med Wochenschr.* 1999; **124**(30): 896–8.
PubMed Abstract | **Publisher Full Text**

11. Conway BR, Fogarty DG, Nelson WE, et al.: **Opiate toxicity in patients with renal failure.** *BMJ.* 2006; **332**(7537): 345–6.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

12. Weinger MB: **Dangers of Postoperative opioids. APSF Workshop and White Paper address prevention of postoperative respiratory complications.** 2007; **21**(4): 61–88.
Reference Source

13. Berris K: **Adverse events - Physician-prescribed opioids.** Risk Identification for all Physicians: Canadian Medical Protective Association (CMPA), April 2009, pp. 1–5.

14. Davison SN: **Pain in hemodialysis patients: prevalence, cause, severity, and management.** *Am J Kidney Dis.* 2003; **42**(6): 1239–47.
PubMed Abstract | **Publisher Full Text**

15. O'Donnell K, Chung JY: **The diagnosis of major depression in end-stage renal disease.** *Psychother Psychosom.* 1997; **66**(1): 38–43.
PubMed Abstract

16. Davison SN: **Chronic kidney disease: psychosocial impact of chronic pain.** *Geriatrics.* 2007; **62**(2): 17–23.
PubMed Abstract

17. Davison SN: **The prevalence and management of chronic pain in end-stage renal disease.** *J Palliat Med.* 2007; **10**(6): 1277–87.
PubMed Abstract | **Publisher Full Text**

18. Woolf CJ: **Pain: moving from symptom control toward mechanism-specific pharmacologic management.** *Ann Intern Med.* 2004; **140**(6): 441–51.
PubMed Abstract | **Publisher Full Text**

19. McCaffery M, Beebe A: **Pain: Clinical Manual for Nursing Practice.** Baltimore: V. V. Mobsy Company, 1993.

20. Launay-Vacher V, Karie S, Fau JB, et al.: **Treatment of pain in patients with renal insufficiency: the World Health Organization three-step ladder adapted.** *J Pain.* 2005; **6**(3): 137–48.
PubMed Abstract | **Publisher Full Text**

21. Barakzoy AS, Moss AH: **Efficacy of the world health organization analgesic ladder to treat pain in end-stage renal disease.** *J Am Soc Nephrol.* 2006; **17**(11): 3198–203.
PubMed Abstract | **Publisher Full Text**

22. Henrich WL, Agodoa LE, Barrett B, et al.: **Analgesics and the kidney: summary and recommendations to the Scientific Advisory Board of the National Kidney Foundation from an Ad Hoc Committee of the National Kidney Foundation.** *Am J Kidney Dis.* 1996; **27**(1): 162–5.
PubMed Abstract

23. Bannwarth B, Pehourcq F: **[Pharmacologic basis for using paracetamol: pharmacokinetic and pharmacodynamic issues].** *Drugs.* 2003; **63**(Spec No 2): 5–13.
PubMed Abstract

24. Chandok N, Watt KD: **Pain management in the cirrhotic patient: the clinical challenge.** *Mayo Clin Proc.* 85(5): 451–8.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

25. Broadbent A, Khor K, Heaney A: **Palliation and chronic renal failure: Opioid and other palliative medications-Dosage guidelines.** *Prog Palliat Care.* 2003; **11**(4): 183–90.
Publisher Full Text

26. Henry D, Page J, Whyte I, et al.: **Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects. Results of a case-control study.** *Br J Clin Pharmacol.* 1997; **44**(1): 85–90.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

27. Parmar MS: **Chronic renal disease.** *BMJ.* 2002; **325**(7355): 85–90.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

28. Crowe E, Halpin D, Stevens P: **Early identification and management of chronic kidney disease: summary of NICE guidance.** *BMJ.* 2008; **337**: a1530.
PubMed Abstract | **Publisher Full Text**

29. Lee A: **Constipation in patients on peritoneal dialysis: a literature review.** *Ren Soc Aust J.* 2011; **7**(3): 122–129.
Reference Source

30. Glare PA, Walsh TD: **Clinical pharmacokinetics of morphine.** *Ther Drug Monit.* 1991; **13**(1): 1–23.
PubMed Abstract

31. Gong QL, Hedner T, Hedner J, et al.: **Antinociceptive and ventilatory effects of the morphine metabolites: morphine-6-glucuronide and morphine-3-glucuronide.** *Eur J Pharmacol.* 1991; **193**(1): 47–56.
PubMed Abstract

32. Bodd E, Jacobsen D, Lund E, et al.: **Morphine-6-glucuronide might mediate the prolonged opioid effect of morphine in acute renal failure.** *Hum Exp Toxicol.* 1990; **9**(5): 317–21.
PubMed Abstract

33. Huwyler J, Drewe J, Klusemann C, et al.: **Evidence for P-glycoprotein-modulated penetration of morphine-6-glucuronide into brain capillary endothelium.** *Br J*

Pharmacol. 1996; **118**(8): 1879–85.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

34. Lotsch J, Schmidt R, Vetter G, *et al.*: **Increased CNS uptake and enhanced antinociception of morphine-6-glucuronide in rats after inhibition of P-glycoprotein.** *J Neurochem.* 2002; **83**(2): 241–8.
PubMed Abstract | **Publisher Full Text**

35. Lotsch J, Zimmermann M, Darimont J, *et al.*: **Does the A118G polymorphism at the mu-opioid receptor gene protect against morphine-6-glucuronide toxicity?** *Anesthesiology.* 2002; **97**(4): 814–9.
PubMed Abstract

36. Oertel BG, Schmidt R, Schneider A, *et al.*: **The mu-opioid receptor gene polymorphism 118A>G depletes alfentanil-induced analgesia and protects against respiratory depression in homozygous carriers.** *Pharmacogenet Genomics.* 2006; **16**(9): 625–36.
PubMed Abstract

37. Szeto HH, Inturrisi CE, Houde R, *et al.*: **Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure of cancer.** *Ann Intern Med.* 1977; **86**(6): 738–41.
PubMed Abstract | **Publisher Full Text**

38. Hassan H, Bastani B, Gellens M: **Successful treatment of normeperidine neurotoxicity by hemodialysis.** *Am J Kidney Dis.* 2000; **35**(1): 146–9.
PubMed Abstract

39. Davies G, Kingswood C, Street M: **Pharmacokinetics of opioids in renal dysfunction.** *Clin Pharmacokinet.* 1996; **31**(6): 410–22.
PubMed Abstract

40. Cone EJ, Phelps BA, Gorodetzky CW: **Urinary excretion of hydromorphone and metabolites in humans, rats, dogs, guinea pigs, and rabbits.** *J Pharm Sci.* 1977; **66**(12): 1709–13.
PubMed Abstract

41. Davison SN, Mayo PR: **Pain management in chronic kidney disease: the pharmacokinetics and pharmacodynamics of hydromorphone and hydromorphone-3-glucuronide in hemodialysis patients.** *J Opioid Manag.* 2008; **4**(6): 335–6, 339–44.
PubMed Abstract

42. Fainsinger R, Schoeller T, Boiskin M, *et al.*: **Palliative care round: cognitive failure and coma after renal failure in a patient receiving captopril and hydromorphone.** *J Palliat Care.* 1993; **9**(1): 53–5.
PubMed Abstract

43. Murtagh FE, Chai MO, Donohoe P, *et al.*: **The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice.** *J Pain Palliat Care Pharmacother.* 2007; **21**(2): 5–16.
PubMed Abstract

44. Vree TB, Verwey-van Wissen CP: **Pharmacokinetics and metabolism of codeine in humans.** *Biopharm Drug Dispos.* 1992; **13**(6): 445–60.
PubMed Abstract

45. Guay DR, Awni WM, Findlay JW, *et al.*: **Pharmacokinetics and pharmacodynamics of codeine in end-stage renal disease.** *Clin Pharmacol Ther.* 1988; **43**(1): 63–71.
PubMed Abstract

46. Matzke GR, Chan GL, Abraham PA: **Codeine dosage in renal failure.** *Clin Pharm.* 1986; **5**(1): 15–6.
PubMed Abstract

47. Talbott GA, Lynn AM, Levy FH, *et al.*: **Respiratory arrest precipitated by codeine in a child with chronic renal failure.** *Clin Pediatr (Phila).* 1997; **36**(3): 171–3.
PubMed Abstract

48. Park GR, Shelly MP, Quinn K, *et al.*: **Dihydrocodeine–a reversible cause of renal failure?** *Eur J Anaesthesiol.* 1989; **6**(4): 303–14.
PubMed Abstract

49. Barnes JN, Goodwin FJ: **Dihydrocodeine narcosis in renal failure.** *Br Med J (Clin Res Ed).* 1983; **286**(6363): 438–9.
PubMed Abstract | **Free Full Text**

50. Kaiko RF, Benziger DP, Fitzmartin RD, *et al.*: **Pharmacokinetic-pharmacodynamic**

relationships of controlled-release oxycodone. *Clin Pharmacol Ther.* 1996; **59**(1): 52–61.
PubMed Abstract | **Publisher Full Text**

51. Niscola P, Scaramucci L, Vischini G, *et al.*: **The use of major analgesics in patients with renal dysfunction.** *Curr Drug Targets.* 2010; **11**(6): 752–8.
PubMed Abstract | **Publisher Full Text**

52. Popio KA, Jackson DH, Ross AM, *et al.*: **Hemodynamic and respiratory effects of morphine and butorphanol.** *Clin Pharmacol Ther.* 1978; **23**(3): 281–7.
PubMed Abstract

53. Nagashima H, Karamanian A, Malovany R, *et al.*: **Respiratory and circulatory effects of intravenous butorphanol and morphine.** *Clin Pharmacol Ther.* 1976; **19**(6): 738–45.
PubMed Abstract

54. Talbert RL, Peters JI, Sorrells SC, *et al.*: **Respiratory effects of high-dose butorphanol.** *Acute Care.* 1988; **12**(Suppl 1): 47–56.
PubMed Abstract

55. Gaver RC, Vasiljev M, Wong H, *et al.*: **Disposition of parenteral butorphanol in man.** *Drug Metab Dispos.* 1980; **8**(4): 230–5.
PubMed Abstract

56. Filitz J, Griessinger N, Sittl R, *et al.*: **Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine.** *Eur J Pain.* 2006; **10**(8): 743–8.
PubMed Abstract | **Publisher Full Text**

57. Scholz J, Steinfath M, Schulz M: **Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update.** *Clin Pharmacokinet.* 1996; **31**(4): 275–92.
PubMed Abstract

58. Bastani B, Jamal JA: **Removal of morphine but not fentanyl during haemodialysis.** *Nephrol Dial Transplant.* 1997; **12**(12): 2802–4.
PubMed Abstract | **Publisher Full Text**

59. Joh J, Sila MK, Bastani B: **Nondialyzability of fentanyl with high-efficiency and high-flux membranes.** *Anesth Analg.* 1998; **86**(2): 447.
PubMed Abstract

60. Lee CR, McTavish D, Sorkin EM: **Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states.** *Drugs.* 1993; **46**(2): 313–40.
PubMed Abstract

61. Boyer EW, Shannon M: **The serotonin syndrome.** *N Engl J Med.* 2005; **352**(11): 1112–20.
PubMed Abstract | **Publisher Full Text**

62. Gillman PK: **Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity.** *Br J Anaesth.* 2005; **95**(4): 434–41.
PubMed Abstract | **Publisher Full Text**

63. Izzedine H, Launay-Vacher V, Abbara C, *et al.*: **Pharmacokinetics of tramadol in a hemodialysis patient.** *Nephron.* 2002; **92**(3): 755–6.
PubMed Abstract | **Publisher Full Text**

64. Berkowitz BA: **The relationship of pharmacokinetics to pharmacological activity: morphine, methadone and naloxone.** *Clin Pharmacokinet.* 1976; **1**(3): 219–30.
PubMed Abstract

65. Furlan V, Hafi A, Dessalles MC, *et al.*: **Methadone is poorly removed by haemodialysis.** *Nephrol Dial Transplant.* 1999; **14**(1): 254–5.
PubMed Abstract | **Publisher Full Text**

66. Kreek MJ, Schecter AJ, Gutjahr CL, *et al.*: **Methadone use in patients with chronic renal disease.** *Drug Alcohol Depend.* 1980; **5**(3): 197–205.
PubMed Abstract | **Publisher Full Text**

67. Pham PCT, Toscano E, Pham PMT, *et al.*: **Pain management in patients with chronic kidney disease.** *NDT Plus.* 2009; **2**: 111–8.
Publisher Full Text

68. Dean M: **Opioids in renal failure and dialysis patients.** *J Pain Symptom Manage.* 2004; **28**(5): 497–504.
PubMed Abstract | **Publisher Full Text**

Current Referee Status: ☑ ?

Referee Responses for Version 1

Paul E Carns, The Department of Anesthesiology and The Division of Pain Medicine, Mayo Clinic in Rochester, Rochester, MN, USA

Approved with reservations: 20 February 2013

Ref Report: 20 February 2013

- The first clinical scenario includes meperidine as a drug used in the patient. The use of meperidine has significantly been reduced in the USA and is monitored as a negative finding when used in patients over 60. Thus hospitals have made efforts to reduce or eliminate its use except in treatment of rigors and given in low doses only. I am not sure if this would be the best scenario to start the article, although its issues with renal insufficiency are substantial.

- I would refrain from the use of the word 'narcotic' in your discussion in favor of the word opioid.

- In the discussion regarding 'adjuvant medications' there is no mention that nearly all these medications require dose adjustments in renal insufficiency. Since the article focuses on this topic, I believe it should be included beyond just mentioning that some patients may be using these medications.

- The last sentence in the 'Acetaminophen' section gives specific dosing recommendations to give half of the daily dose followed by round the clock dosing. Is this opinion or should a reference be included?

- Since propoxyphene is no longer available, I would consider eliminating it from the discussion. I am unsure if it is still being used in other countries. If so, I guess I would leave it in.

- The Codeine/Dihydrocodeine paragraph makes no mention of the active metabolite morphine from codeine. Discussion of other drugs in this section refer to actual names of metabolites. Given that morphine was discussed earlier in the document, including this information is important in my view.

- The chart indicating % amounts in the column headed by eGFR/ml rates does not really say that the percentages indicate a percent dose reduction. It should be made more clear even though obvious to me.

- The methadone section says that it requires a special license to prescribe. This is not entirely true. The special license is only required when treating opioid addiction. If methadone is used for pain control, no special license is needed. I would also include that methadone is not to be used in opioid naïve patients as you do with the fentanyl patch.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Howard S Smith, Albany Medical College, New York, NY, USA
Approved: 19 February 2013

Ref Report: 19 February 2013
I approve this article. However, on table 3 and figure 1, oxycodone with acetaminophen is considered step 2 of the WHO analgesic ladder but oxycodone by itself is considered step 3. I would change this.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.