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PROGRESS IN DIALYSIS PRACTICE

Pain in Chronic Kidney Disease: A Scoping Review

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ABSTRACT

There is increasing international attention in efforts to integrate palliative care principles, including pain and symptom management, into the care of patients with advanced chronic kidney disease (CKD). The purpose of this scoping review was to determine the extent, range, and nature of research activity around pain in CKD with the goal of (i) identifying gaps in current research knowledge; (ii) guiding future research; and (iii) creating a rich database of literature to serve as a foundation of more detailed reviews in areas where the data are sufficient. This review will specifically address the epidemiology of pain in CKD, analgesic use, pharmacokinetic data of analgesics, and the management of pain in CKD. It will also capture the aspects that pertain to specific pain syndromes in CKD such as peripheral neuropathy, carpal tunnel syndrome, joint pain, and autosomal dominant polycystic kidney disease.

Dialysis is not effective in ameliorating many of the physical and psychosocial symptoms associated with advanced chronic kidney disease (CKD). Patients often have tremendous symptom burden and need quality supportive/palliative care for years before death. Of all the symptoms reported by patients with stage 5 CKD, pain is one of the most common and distressing. Despite this, there remains a lack of clinical consensus on approaches to the screening, assessment and management of pain in these patients. The development of a system of integrated supportive/palliative care is urgently required to provide quality care for patients with advanced CKD, including an approach to the management of pain.

Kidney Disease: Improving Global Outcomes (KDIGO) is focusing on efforts to develop formal international recommendations for palliative care and symptom control including pain in CKD. A comprehensive analysis of palliative and supportive care in CKD is timely and represents an area of great clinical need. As part of the development of KDIGO recommendations, a scoping review was conducted to determine the extent, range, and nature of research activity around pain in CKD. The purpose of this review was to understand existing literature with the goal of (i) identifying gaps in current research knowledge; (ii) guiding future research; and (iii) creating a rich database of literature to serve as a foundation of more detailed reviews in areas where the data are sufficient. The overall aim was to synthesize and disseminate research findings around pain in CKD to health services researchers, healthcare providers, administrators, and policy makers to promote evidence-based quality clinical care. This review will specifically address the epidemiology of pain in CKD, analgesic use, pharmacokinetic data of analgesics, and the management of pain in CKD. It will also capture aspects that pertain to specific pain syndromes in CKD such as peripheral neuropathy, carpal tunnel syndrome, joint pain, and autosomal dominant polycystic kidney disease (ADPKD).

Methods

The methodological framework of Arksey and O'Malley (1) was used to guide our scoping review. Intradialytic symptoms such as dialysis headaches and muscle cramps were not considered as part of this review. Consultation with international multidisciplinary experts brought together by KDIGO, occurred throughout all steps of this review.

Search Strategy

Our search was developed in conjunction with an experienced librarian and involved several sources including electronic databases, reference lists of

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relevant literature, hand searching websites of relevant networks, organizations, societies, and suggestions from colleagues and stakeholders. No date limits were applied. Searches were limited to articles with an English abstract. Results included guidelines, systematic reviews, health technology assessments, meta- analyses and review articles; as well as clinical trials, cohort studies, and cross-sectional studies. Case reports were removed. Databases searched included MEDLINE (in-process and other nonindexed citations), CINAHL, EMBASE, and Cochrane Library databases (see Appendix A for search strategy). Searches were run on August 5, 2013. Gray literature included guideline sites using a variety of search terms for CKD and pain (Appendix B): 997 references were identified and selected for abstract review. The number of studies selected for data synthesis in each subcategory can be seen in Table 1.

The Epidemiology of Pain in CKD

It is well documented in the literature that severe pain is prevalent amongst CKD patients: 55 publications from 1992 to 2009 representing over 7500 CKD patients highlight patients' experience with pain. Most of these data come from prevalent hemodialysis patients (with 36 studies examining over 5200 patients) and show that over 58% of CKD patients experience pain and 49% of patients rate their pain as moderate or severe. Several studies, rather than examining pain as a single concept, have used tools that ask specifically about bone or joint pain, muscle soreness, or abdominal pain. These studies represent fewer numbers of patients, but the prevalence of symptoms remains consistently high (see Table 2). Data on peritoneal dialysis patients and stage 5 CKD patients cared for conservatively without dialysis are limited although evidence suggests similar pain prevalence and severity to chronic hemodialysis patients (2–4). To date, there are no data from developing countries.

TABLE 1. Study selection by subcategories within the scope of the pain review

Total number of records identified for title and abstract review	$N = 997$
Pain assessment and screening	13
Epidemiology: prevalence, severity, other characteristics, etiology, and associations	55
Patterns of analgesic use	31
Specific pain syndromes	
Arthritidies	6
Peripheral neuropathies (in general), diabetic neuropathy, and carpal tunnel syndrome	70
ADPKD	29
Pharmacokinetic/pharmacodynamic studies	143
Pain management: general approaches and guidelines	83
Nonpharmacologic management of pain	11

Data from nine studies (5–13) representing 2086 prevalent HD patients consistently show that pain and/or overall symptom burden is strongly associated with substantially lower health-related quality of life (HRQL), and greater psychosocial distress, insomnia and depression (Table 2). Together, these data appear sufficient and robust enough to make pain management a clinical and research priority in CKD.

Pain appears to be predominantly musculoskeletal in origin, but neuropathic pain is also common and chronic pain in CKD is often mixed nociceptive/neuropathic. Data on exact causes and diagnoses of pain in CKD are lacking, which may hinder the development of targeted therapeutic interventions above general pharmacologic approaches to pain management. A systematic review of the epidemiology of pain in CKD is currently underway.

Patterns of Analgesic Use in CKD

Several large international observational studies have shown that analgesic use is not high in CKD patients despite the high prevalence of pain (14–18). However, only a few studies with small numbers of patients specifically explore analgesic prescribing in patients with pain. The identified studies provided data on approximately 42,945 patients (Table 3). The use of acetaminophen, despite its safety in CKD, remains extremely low. NSAID use appears inappropriately high, and despite severe pain, there appears to be a low prevalent use of opioids. Most opioids prescribed are weak—and those often selected are inappropriate for use in CKD patients. Prescribing patterns in conservatively cared for patients, for those who withdraw from dialysis, and in developing countries are almost nonexistent. Most of the data describe prescribing patterns rather than actual analgesic use.

The impact of analgesic use on outcomes other than pain is essentially unexplored. One study reported no association of analgesics and opioids with falls (19), while another study showed an association between opioid use and a slightly increased relative risk of fractures (16) and poorer sleep (15). None of these studies were designed to explore analgesic use or outcomes of analgesic use in the context of pain management. There are clear gaps in the literature about the major barriers in managing chronic pain. While it is evident that lack of clinician education is a problem (20), other potential obstacles have not been explored. Therefore, it remains unclear as to the best way to change clinical practice. A systematic review of analgesic prescribing and use in CKD is currently underway.

Pain Assessment Tools

Despite the high prevalence of pain, healthcare professionals continue to underestimate the frequency and severity of patients' symptoms (21). Use of regularly administered symptom assessment tools

TABLE 2. Pain epidemiology data synthesis

Patient Population	No. of Studies (total:50), 46 study populations (6 duplications)	Year (44 of 50 studies ≥2000)	Country	No. of distinct patients (total: 7560)	Prevalence	Impact	Other Associations
Prevalent hemodialysis	36 studies (32 study populations)	1993–2013	Asia, North America, Israel/Iran, 6 European countries	5244	*Weighted mean prevalence*: 58.6%; (n = 2860 in 16 populations; range 21–81%); *Weighted mean prevalence of mod/severe pain*: 48.8% (n = 1701 in 6 populations; range 41–68.6%) *Weighted mean severity:* 3.69/10 (n = 1506 in 6 populations; range 3.3–5.6/10) *Back pain*: 46.7% (n = 613 in 2 populations; range 16–53%) *Bone/joint pain*: 32.3% (n = 366 in 4 populations; range 37–61.7%) *Muscle soreness:* 61.6% (n = 1159 in 4 populations driven predominantly by NECOSAD study; range 28–71%) *Abdominal pain*: 22.2% (n=202 in 2 populations)	*HRQL*: 9 populations; n = 2086. Pain & overall symptom burden are consistently associated with lower QOL, psychosocial distress, insomnia, depression *Biochemical & demographics*: 11 populations; n = 3215. Most studies show no association with gender, age, race, ethnicity or biochemical parameters although this is inconsistent. Those that do show a statistical association, clinical significance is not clear. Statistical significance driven predominantly by NECOSAD (n = 896)	
Prevalent peritoneal dialysis	4 studies (4 populations)			779	*Prevalence*: 38% (n = 107, 1 study) *Prevalence muscle soreness*: 64% (n = 573, 1 study) *Severity*: 3.6/10 (n = 1482, 2 populations; range 2.2–4.1/10)	No data	None other than NECOSAD which analyzed PD with HD data Suggestion of slightly less prevalence of muscle soreness in PD v. HD (64–71%) and less severe pain (2.2 v. 3.3/10)
Following withdrawal of hemodialysis	3 studies (2 populations)	2000	United States Canada	114	54% at the time of withdrawal, 42% in last 24 hrs; 23% in last 24 hours when seen by palliative care	No data	No data
Conservative	3 studies (1 population)	2005–2006	United Kingdom	43–66 patients	53% pain (32% mod/severe); 73% last month of life (41% very distressing) (n = 43)	No data	No data
CKD (stages 1–4)	2 studies	2005 2010	United States United States	635	130: 72.9% pain (musculoskeletal most common), av 5.7/10; (505) Increased physical pain on SF-36	No data	No difference among stages for: prevalence or bodily pain SF scores
Hospitalized CKD	1 study	2007	Australia	53	100% had some level of pain in the past 24 hours	No data	No data

TABLE 3. Analgesic use in CKD

Patient population	Patient number	Any analgesic	NSAID	Acetaminophen	Opioids
CKD (3 studies)	2342	–	24% (range 6%-54%)	24%	–
CKD with pain (1 study)	130	–	15%	33%	–
Incident HD/PD (2 studies)	4826	11%	1.8%	–	7% (range 5–18%)
Prevalent HD (13 studies)	25725	27% (range 18–30%)	5% (range 1–16%)	9% (range 0–14%)	15% (range 0–18%)
Prevalent HD with pain (7 studies)	755	56% (range 30–65%)	19% (range 3–42%)	18% (range 0–44%)	22% (range 0–36%)
Withdrawn from dialysis (1 study)	79	87%	–	–	–
Withdrawn from dialysis and followed by palliative care (1 study)	35	–	–	–	97%

allows for effective identification of symptoms. There are eight validated symptom assessment tools for CKD patients of varying length and utility (Table 4). Tools such as the Modified Edmonton Symptom Assessment System (m-ESAS v. 2) (7,8,22) and Palliative Care Outcome Scale-Renal (POS-renal) (3,23) are appropriate for routine clinical screening for pain in renal programs and help redirect care to a more patient centered model. These assessments not only identify the presence of pain but provide the opportunity for difficult discussions about appropriate palliative and supportive care options.

Pharmacokinetics and Pharmacodynamics of Analgesics in CKD

The presence of CKD, with or without dialysis, alters the pharmacokinetics and pharmacodynamics of many analgesics and most opioids profoundly and needs to be considered carefully. Unfortunately, pharmacokinetic and pharmacodynamic data of analgesics in CKD remains limited and the level of evidence for use of individual analgesics varies considerably. With the advent of new opioid analogs and other classes of analgesic medications, this remains an emerging and important area of study.

Pharmacokinetic data on analgesic medications in the context of CKD are outlined in Table 5. Suggested dose reductions are based on both clinical experience and available data. Studies of nonsteroidal anti-inflammatory drug (NSAID) use in CKD are summarized separately in Table 6. Most pharmacokinetic studies are small or are case reports of subjects with varying degrees of renal function and doses. They are typically single dose studies or studies over very short periods of time which have not been designed to evaluate efficacy and safety. Only a few studies have provided information regarding clinically relevant outcomes such as analgesic effect or adverse effects. With respect to studies of NSAIDs, a few showed depressed thromboxane B2 levels suggesting there may be increased bleeding risk; however this was not described clinically. Though limited, the available data suggest that caution should be used when using NSAIDs in patients with GFR <35 ml/minute to avoid further deterioration in residual renal function and risk of bleeding, and if possible, chronic use should be avoided.

Pharmacologic Management of Pain in CKD

Original data on the effects of treatment algorithms on clinically important outcomes such as pain, overall symptom burden, and quality of life are lacking (24) despite the numerous review articles and recommendations for the pharmacologic treatment of chronic pain in CKD (5,25–41). These recommendations are based on international evidence-based guidelines and systematic reviews for nonmalignant chronic pain that address the appropriate use of analgesic (and opioid) therapy for nociceptive and neuropathic pain in the general population (42–48). There are also evidence-based guidelines on chronic pain management and opioid use in the geriatric population (49,50). However, even these clinical guidelines are limited by the level of evidence and have been supplemented by expert consensus statements based on clinical experience. The recommendations of these general guidelines are outlined in Tables 7 and 8. These approaches have been adapted for use in CKD based on a limited number of pharmacokinetic studies of various analgesics and case reports of toxicity (5,25–41).

For the pharmacologic management of pain in CKD, the literature would support cautiously following the evidence-based guidelines for chronic, noncancer pain in the general population with specific attention paid to the choice of analgesic, taking into account the degree of renal dysfunction, interaction with coadministered medications, and comorbidity. This would include the conservative dosing of opioids with small increases in doses titrated to analgesia and side effects for patients with moderate to severe pain that does not respond to nonopioid analgesics and results in detriments to physical function and HRQL. There is insufficient evidence to provide definitive guidance about the use of various opioids and there are no studies on the long-term use of any analgesics in patients with CKD, so careful attention must be paid to issues of efficacy and safety. Although the use of NSAIDs is not recommended in CKD, there

TABLE 4. Symptom assessment tools

Description	Clinical Utility
Modified Edmonton symptom assessment system (m-ESAS v. 2) (7,8,22)	
Eleven visual analog scales with a superimposed 0–10 scale for pain, activity, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, pruritus, and sleep. The scale for each symptom is anchored by the words no and severe at 0 and 10 respectively. The sum of all scores make up the overall symptom distress score ranging from 0 to 110.	A short practical tool for symptom screening, which can be rapidly and repeatedly completed by patients and therefore incorporated easily into routine clinical care, even for patients who are preterminal. The ESAS has been translated into several languages.
Palliative Care Outcome Scale-Renal (POS-renal) (3,23)	
Assesses 17 symptoms, which are rated in terms of their impact on the patient over the last week from 0 (not at all) to 4 (overwhelmingly). Symptoms assessed include pain, shortness of breath, weakness or lack of energy, nausea, vomiting, poor appetite, constipation, mouth problems, drowsiness, poor mobility, itching, difficulty sleeping, restless legs or difficulty keeping legs still, anxiety, depression, changes in skin, and diarrhea.	This symptom-screening tool is simple to use and can be incorporated easily into routine clinical care, even for patients who are preterminal. It has been translated into several languages.
Physical symptom distress scale (PSDS) (129)	
Assesses 16 symptoms including numbness or tingling, impaired visual ability, swelling in feet, stiffness of joints, constipation or diarrhea, dizziness, headache, pain, and muscle cramps. Rated by patients on a 4 point Likert scale 0 = not bothered at all, 4 = extremely bothered.	There is not as much experience with this symptom-screening tool. There is some redundancy with respect to items pertaining to pain. It appears practical and simple enough to incorporate into routine clinical care.
Dialysis symptom index (DSI) (130)	
Assesses 30 symptoms, rating them from 1 (not at all bothered) to 5 (very much bothered). Symptoms included are constipation, nausea, vomiting, diarrhea, decreased appetite, muscle cramps, leg swelling, shortness of breath, light-headedness, restless legs, numbness, feeling tired, cough, dry mouth, bone or joint pain, chest pain, headache, muscle soreness, difficulty concentrating, dry skin, itching, worrying, nervousness, trouble falling asleep or staying asleep, feeling irritable, sad or anxious, decreased interest in sex, and difficulty becoming sexually aroused.	The tool is easy to use and can be self-completed by patients. There is some redundancy with respect to items pertaining to pain. Respondent burden is greater than for the m-ESAS or renal-POS but less than the HRQL tools. There is limited experience with it being incorporated into routine clinical care for symptom screening.
The Brief Pain Inventory (BPI) (28)	
Assesses the location, type (nociceptive v. neuropathic) and intensity of pain. It also evaluates the impact of pain on general activity, mood, walking ability, work, relationships, sleep, and enjoyment of life. The standard 32-question instrument has been condensed to a 9 questions short form.	This tool has been used successfully in clinical and research settings internationally to assess pain once identified as problem. Seriously ill patients have been successful in completing this questionnaire. The short form is simple to use with minimal respondent burden.
Short form McGill Pain Questionnaire (SF-MPQ) (131)	
Describes the quality and intensity of pain. The scale is rated from 0 to 75 with higher scores reflecting worse degrees of pain.	This is not a simple screening tool for pain and does not assess other symptoms; hence decreasing its clinical utility as a routine symptom-screening tool in CKD. It is incomplete as a pain assessment tool as it does not explore adequately the impact of the pain on function and HRQL.
Kidney Dialysis Quality of Life-Short Form/SF-36 (KDQOL-SF) (132)	
Self-reported HRQL measure developed for CKD patients as a less burdensome version of the longer KDQOL questionnaire. The tool focuses on physical and emotional symptoms, effects on daily life, burden of disease, cognitive function, work status, sexual function, quality of social interaction, and sleep. There are also 3 quality of life scales focusing on social support, staff encouragement and patient satisfaction. There are 37 questions, some with multiple stems, over 19 pages.	Takes approximately 30 minutes to complete in healthier individuals but typically requires interviewer assistance and more time in elderly, frail patients. It provides comprehensive HRQL information but is more suited to a research environment where dedicated staff can help with the administration and complex scoring. Not suitable for patients who are preterminal.
CHOICE health experience Questionnaire (CHEQ) + SF-36 (133)	
Self-reported HRQL tool that incorporates an assessment of symptoms and was designed to complement the generic SF-36 (in a fashion similar to the KDQOL).	Requires 30 minutes to complete in healthier individuals but typically requires interviewer assistance and takes longer in elderly, frail patients. It provides comprehensive HRQL information but is more suited to a research environment where dedicated staff can help with the administration and complex scoring. Not suitable for patients who are preterminal.

is likely benefit in targeting the prostaglandin mediated pain of renal colic. However, use should be limited to a few days (51). It may be reasonable, especially in the context of older patients, to adopt a more conservative dosing regimen for gabapentin than advocated by published reviews;

TABLE 5. Pharmacokinetic data on analgesic medications in the normal state and in the context of CKD

Medication	% excreted in the urine	T ½ normal (hours)	T ½ Dialysis (ESRD) (hours)	Hemodialysis	Peritoneal dialysis	Comments and recommendations on use and maximum dosing
Acetaminophen (24,27,134,135)	<5	1–4	Unchanged	Dialyzed	Not dialyzed	Accumulation of inactive metabolites. Analgesic of choice for mild-moderate pain. No dose reduction required
Codeine (136–138)	0-16	2.5–4	13–18.9	Not dialyzed	Unlikely to be dialyzed	Metabolized to morphine derivatives and known to cause profound hypotension and CNS and respiratory depression. Not recommended in CKD
Tramadol (139–141)	90 (30% unchanged 60% as metabolites)	6	11	Dialyzed	Unknown	eGFR 30-10 mls/min: 50-100mg bd. eGFR < 10mls/min (and on dialysis): 50mg bd. Hemodialysis significantly removes Tramadol so administration is best given after each dialysis.
Morphine	10	2–3	Unchanged	Parent & active metabolites dialyzed	Not dialyzed	Rapid accumulation of active metabolites in CKD resulting in clinically significant opioid toxicity including sedation, confusion, myoclonus, and respiratory depression. Not recommended in CKD.
Hydromorphone (142,143)	6	2–5	3.2 on dialysis; 5.9 nondialysis days	Active metabolite (H3G) dialyzed	Unknown	Much better tolerated in CKD than morphine with less toxic metabolites. Pharmacodynamic data have shown less neuroexcitation compared to morphine and a greater than 65% reduction in pain over dosing intervals with no clinically significant opioid toxicity when given in low doses and monitored carefully
Fentanyl (144)	<7	2–7	Possibly increased	Not dialyzed	Not dialyzed	Inactive metabolites. Most pharmacokinetic studies in CKD use parenteral rather than transdermal fentanyl. Generally considered safe for use in CKD if monitored carefully.
Alfentanil (145)	0.4	1–2	Unchanged	Not dialyzed	Not dialyzed	Although pharmacokinetics of fentanyl analogs Alfentanil and Sufentanil do not appear to differ in CKD, there is a single case report of prolonged respiratory depression in a patient with ESRD where there was an elevated plasma concentration of sufentanil.
Buprenorphine (146–149)	Minimal	30	Unchanged	Dialyzed	Dialyzed	Buprenorphine may be given in standard doses to patients with CKD. Generally considered safe for use in CKD if monitored carefully
Oxycodone (150–153)	<10	2–4	3–5	Dialyzed	Unknown	There are case reports of toxicity in association with CKD yet overall consensus from the literature is that Oxycodone is reasonably safe to use in CKD if monitored carefully.
Methadone (149,154)	15–60	13–47	Unknown	Not dialyzed	Not dialyzed	Primarily excreted in the feces. Plasma concentrations are similar in CKD compared to those with normal renal function. Generally considered safe for use in CKD if monitored carefully

Table 5. (Continued)

Medication	% excreted in the urine	T ½ normal (hours)	T ½ Dialysis (ESRD) (hours)	Hemodialysis	Peritoneal dialysis	Comments and recommendations on use and maximum dosing
Gabapentin (38,155,156)	Approx. 100	5–7	52–132	Dialyzed	Possibly dialyzed	Freely crosses the blood brain barrier. Dose post dialysis. eGFR 50–79: 600 mg tid eGFR 30-49: 300mg tid eGFR 15–29: 300 mg bid eGFR <15: 300 mg od For a discussion of a more conservative dosing regimen see main text.
Pregabalin (157,158)	92–99	5–6.5	Increased	Dialyzed (50% dialyzed in 4 hours)	Dialyzed	Similar mechanism of action as gabapentin. Can give supplementary dose postdialysis (75 mg) eGFR: >30: 150 mg bid eGFR 15–30: 150 mg od eGFR <15: 75 mg od For a discussion of a more conservative dosing regimen see main text.
Duloxetine (67,136)	<1	8–17	Unchanged	Not dialyzed	Not dialyzed	Reduced starting dose in CKD (30 mg) with a maximum dose of 60 mg per day. Some sources recommend avoiding in patients with a CrCl of <30 ml/minute. Others suggest start at a very low dose and increase according to response, with a maximum dose of 30 mg daily.
Ketamine (136)	2–4	2–4	Unchanged	Not dialyzed	Unlikely to be dialyzed	Dose as per normal renal function.
Amitryptyline (159,160)	<2	9–25	Unchanged	Not dialyzed	Not dialyzed	Although no dose reduction is required, a low-starting dose is recommended given likelihood of anticholinergic adverse effects.

TABLE 6. Pharmacokinetic data on nonsteroidal anti-inflammatory drugs in CKD and ESRD*

Acetic acid derivatives: including sulindac, indomethacin, etodolac, bromfenac
CKD
Four studies showed sulindac had less of a reduction in CrCl compared to indomethacin, naproxen and ibuprofen, in patients with impaired renal function (148,155,161,162)
Effective renal blood flow decreased in patients with renal disease after only a few days of use (163,164).
Dialysis
Lower plasma concentration of the active sulfide metabolite of sulindac which may be due to decreased protein binding (165,166).
These studies suggest that in ESRD, a higher dose of sulindac may be required for analgesic effect.
Studies of other acetic acid derivatives, etodolac, bromfenac and indomethacin, in CKD and ESRD patients, do not suggest that any dose adjustment is necessary (167–169).
Propionic acid derivatives (the –profens): 11 studies identified
CKD
Studies evaluating ketoprofen, ximoprofen and benoxaprofen have shown increased half-life in CKD (170–173).
One study of naproxen showed no difference in half-life, but lower serum levels and AUC in CKD (174).
Decreased serum levels of the parent drug, febufem and its metabolites were noted in CKD (175).
In mild CKD: 80% reduction in urinary prostaglandins, 28% reduction in CrCl and a 40% increase in serum creatinine after 1 week of treatment with ibuprofen (161).
All alterations in pharmacokinetics have been suggested to be related to decreased protein binding and subsequent changes in the volume of distribution and in some cases changes in metabolism of the medication (170,173–175).
Recommendations for dosing vary with no adjustments recommended for ximoprofen or naproxen, and a decrease in dose by half for benoxaprofen (170,171,173,174).
Dialysis
Ketoprofen 50 mg tid × 7 days showed accumulation of the active S-enatatomer metabolites after repeat dosing in hemodialysis patients (176).
Flurbiprofen concentration levels were decreased in patients on PD compared to normal subjects (177).
Enolic Acid derivatives: Two studies evaluating CKD and dialysis patients administered tenoxicam suggest no difference in metabolism that would necessitate change in dosing (44,178).
Selective Cox-2 inhibitors
CKD
Pharmacokinetics of Celecoxib showed an AUC 47% lower in CKD, presumed due to decreased protein binding or reduced tubular reabsorption leading to changes in hepatic clearance, reduced gastrointestinal absorption, or increased biliary excretion (179).
Dialysis
Rofecoxib administered as a single dose to 6 hemodialysis patients showed no change in pharmacokinetics compared to healthy controls, with no dose adjustments needed (180).

*There were 13 total studies identified though two we could not access and are not included in this paper's works cited: Traeger, A (08/1972). "[Pharmacokinetics of indomethacin in patients with kidney lesions]". International journal of clinical pharmacology, therapy and toxicology (0300-9718), 6 (3), p. 237; Stein, G (10/1977). "[Pharmacokinetics of indomethacin and indomethacin metabolites administered continuously to patients with healthy or damaged kidneys]". International journal of clinical pharmacology and biopharmacy (0340-0026), 15 (10), p. 470.

TABLE 7. Approach to the pharmacologic treatment of chronic nociceptive pain for adults in the general population

Adopt a stepwise approach such as that outlined in the World Health Organization (WHO) Analgesic Ladder (181), making special consideration for analgesic selection as outlined below.
Acetaminophen should the initial and ongoing pharmacotherapy. It has demonstrated effectiveness and a good safety profile (high-quality evidence; strong recommendation).
NSAIDs should be considered rarely and with extreme caution for chronic use in the elderly (high-quality evidence, strong recommendation). Older persons taking nonselective NSAIDs should be prescribed a proton pump inhibitor or misoprostol for gastrointestinal protection (high-quality evidence; strong recommendation).
Tramadol may be a reasonable choice as a step 2 analgesic. It is effective for noncancer pain with a lower risk of misuse, overdose or addiction compared to opioids.
Consider a trial of chronic opioid therapy if pain is moderate to severe, is having an adverse impact on function or HRQL, and potential therapeutic benefits outweigh or are likely to outweigh potential harm (strong recommendation; low-quality evidence)
Prior to initiating chronic opioid therapy, assess risks of substance abuse, misuse or addiction (strong recommendation; low-quality evidence).
When commencing chronic opioid therapy, informed consent should be obtained. A continuing discussion should occur with the patient regarding goals, expectations, potential risks and alternatives to opioid therapy (strong recommendation; low-quality evidence).
Opioid selection, initial dosing and titration should be individualized according to the patient's health, previous exposure to opioids, attainment of therapeutic goals and predicted or observed harms. The optimal dose of opioids is one that either reduces pain by 30% in pain ratings scale or improved functional status (strong recommendation; low-quality evidence).
Consider opioid rotation when patients experience intolerable adverse effects (weak recommendation; low-quality evidence).
Consider using breakthrough doses of short acting opioids in patients on regular opioid therapy with breakthrough pain (weak recommendation; low-quality evidence).
Wean opioid therapy when patients experience no progress towards therapeutic goals, experience intolerable adverse effects or who engage in repeated aberrant drug-related behaviors or drug abuse/diversion (strong recommendation; low-quality evidence).
The evidence of the effectiveness of long-term strong opioid use (6 months and greater) in chronic noncancer pain is variable. Overall, conclusion is a weak recommendation with high-quality evidence where benefits closely balanced burdens.
Pursue consultation, including interdisciplinary pain management, when patients may benefit from additional skills or resources that they cannot provide (strong recommendation; moderate quality evidence).

TABLE 8. Approach to the pharmacologic treatment of chronic neuropathic pain for adults in the general population

A stepwise approach is recommended.
Initiate treatment with one of the following*:
- Secondary-amine tricyclic antidepressant (TCA)
- Selective Serotonin Norepinephrine Reuptake Inhibitor (SSNRI)
- Calcium channel alpha-2-delta ligand (gabapentin, pregabalin)

Consider topical lidocaine, used alone or in combination with one of the first-line therapies for localized peripheral neuropathic pain.
For patients with acute neuropathic pain, neuropathic cancer pain or episodic exacerbations of severe pain and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies.
If no or inadequate pain relief at target dosage after an adequate trial, switch to an alternative first-line medication. No one medication is universally effective. Moreover, in most cases first-line medications provide only partial pain relief…hence, in clinical practice, two or more medications are often used in combination (46).
If trials of first-line medications alone or in combination fail, consider referral to a pain specialist or multidisciplinary pain center.

*In painful diabetic peripheral neuropathy, there is Level A evidence for Pregabalin, Level B evidence for Gabapentin, Duloxetine, Amitriptyline, Venlafaxine, Sodium Valproate, Dextromethorphan, Morphine, Tramadol, Oxycodone, Capsaicin, Isosorbide dinitrate spray, and TENS (65).

for example starting at 100 mg post dialysis in HD patients and 100 mg every second night in stage 5 CKD patients managed conservatively. Similarly, pregabalin may provide relief for some patients with doses as low as 25 mg after each dialysis or 25 mg every second night in stage 5 CKD patients managed conservatively. Recommended analgesics in CKD for each step of the WHO analgesic ladder are outlined in Figure 1.

Painful Diabetic Peripheral Neuropathy (PDN) and CKD

Epidemiology

Large community-based studies of patients with Type 1 and 2 diabetes, using well-defined criteria of painful diabetic neuropathy (PDN) and validated measures of pain severity and quality, have estimated that one-third of all patients have painful diabetic neuropathy (52) and approximately 16% of patients have symptoms present for greater than 1-year duration (53,54). There is limited literature on the prevalence of PDN in CKD patients: one study found a prevalence of 50% in dialysis patients with diabetes mellitus (55).

PDN is associated with an increased risk of lower limb amputation in both general and CKD patients. The PDN rate in diabetic patients with CKD Stage 4–5 was 10 times greater than the general diabetic population and two-thirds died within 2 years of the original amputation (56). Other associations include impaired HRQL and functional capacity (57,58), disrupted sleep (59), which may be compounded by other CKD symptoms of uremic pruritus and restless legs. Chronic persistent PDN may also be associated with depression (60) and anxiety (61).

Assessment Tools for PDN

The Michigan Neuropathy Screening Instrument (MNSI) (62) and the DN4 (63) are valid tools to diagnose DPN in the general population.

Management of Diabetic Peripheral Neuropathy in CKD

There are no data that specifically examine the treatment of PDN in CKD. Recommendations are based on applying pharmacokinetics in CKD to international evidence-based guidelines and expert consensus for management of PDN in the general population (64–66) to reach a series of conclusions (67). Current standard practice involves strict glycemic control (68–70) and a stepwise approach to pharmacologic therapy outlined in Table 8. There is clear and consistent evidence for the use of gabapentinoids in the management of PDN (71,72). There is also evidence for the efficacy of gabapentinoids in other renal-related symptoms—uremic pruritus (73), restless legs syndrome (74,75), and insomnia (74,76,77).

Given the lack of direct evidence, we are not yet at a point of formulating evidence-based guidelines on the management of PDN in CKD. Nevertheless, we can formulate expert consensus recommendations based on extrapolation and synthesis of current guidelines for the treatment of PDN in the general population within the context CKD pharmacokinetics, especially with respect to gabapentinoids.

Arthritis and Joint Pain

Etiology of Joint Pain

Dialysis arthropathy is described as a range of symptoms including shoulder pain of no other known etiology, restricted range of motion, and inflammatory signs including morning stiffness & painful nighttime awakenings in patients maintained on dialysis for a varying duration (78,79). Shoulder imaging of dialysis patients with pain reveals thicker supraspinatus tendons on either ultrasound (78) or MRI (80,81), as compared to control populations. An association of these symptoms with carpal tunnel syndrome has also been described, specifically in patients with carpal biopsies positive for amyloid (82).

Management

Information regarding the specific pharmacologic management of arthritic pain in CKD is limited. One Cochrane systemic review evaluated the treatment of inflammatory arthritis in patients with either cardiovascular or renal disease. Despite a large and thorough search, no evidence was found to support guidelines in treating these patients (83). As it is hypothesized that some of the joint pain is due to accumulation of B2 microglobulin, a small study of eight HD patients evaluated use of a high-flux dialyzer for 6 months. Overall levels of B2 microglobulin were decreased and all patients noted improvement in pain, with the majority also noting decreased nocturnal awakenings, reduction in morning stiffness, and reduction in pain medications, though no improvement in mobility (79). In patients with shoulder pain managed with pharmacologic therapy, who continue to be symptomatic, arthroscopic synovectomy may be an option. This procedure was evaluated in seven patients for a mean follow-up of 5.5 years. The majority of patients rated their overall satisfaction post procedure as excellent with low pain scores, absence of pain at night, pain free range of motion with improvement in flexion and extension, and ability to perform their activities of daily living (84). The pathophysiology leading to the anatomic changes that are associated with joint symptoms in this population are not well described, and there is not enough available evidence to inform guidelines regarding specific pharmacologic or invasive interventions specifically targeted at arthritic or joint pain beyond general pharmacologic pain management strategies.

Carpal Tunnel Syndrome (CTS)

Pathophysiology and Epidemiology

Carpal Tunnel Syndrome is a mononeuropathy of the median nerve as it passes through the flexor retinaculum at the wrist. The predominant cause of CTS in patients with CKD is deposition of amyloid (beta-2 microglobulin) on the surface of the tenosynovium of the flexor tendons. This deposition leads to an extrinsic compression of the median nerve. Other factors proposed as causative factors of CTS in CKD include uremic tumoral calcinosis (85) and placement of arteriovenous fistulae inducing diversion of blood from the distal limbs (86,87). The symptoms of CTS include paresthesias and pain in the distribution of the median nerve, which is typically worse at night. Many patients experience these symptoms while on dialysis. On examination, there is wasting of the lateral thenar muscles and loss of sensation in the distribution of the median nerve. Some patients experience contracture of the finger joint due to amyloid arthropathy and abductor pollicus brevis muscle atrophy due to median nerve dysfunction, which may lead to loss of hand function. The incidence of CTS ranged from 9% to 63% with a weighted mean incidence of 18.6% among dialysis patients (88–92) and the incidence increases with years on dialysis: 32–50% (weighted mean incidence 37%) for patients on HD at least 10 years; (93,94) 75% for patients on HD at least 15 years; (95) and 85% for patients on HD at least 30 years (96). In a large electrophysiologic study, the prevalence of CTS was no different in patients on HD versus PD (97).

Assessment Tools for CTS

The Boston Carpal Tunnel Questionnaire (BCTQ) is a validated tool (in non-CKD patients) for assessment of CTS that incorporates 11 items that address symptoms, including pain and functional status (98).

Management Strategies

Surgical. The principal management of CTS secondary to CKD is surgical decompression. Most patients experience significant symptomatic relief (99), including pain (91), although several studies show that patients with HD-related CTS experience less relief of symptoms after surgical release than those with idiopathic CTS (100,101). CTS can recur with rates ranging from 5.6% after endoscopic decompression (102) to 21% (103) following open decompression.

Pharmacologic Management. There are no consensus guidelines on the pharmacologic management of the pain associated with CTS in the context of CKD. One author stated, without reference to a study, that the local injection of corticosteroids brings temporary relief only (91). The pain associated with CTS is neuropathic in origin and pharmacologic management falls under the general management of neuropathic pain in CKD.

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Epidemiology of ADPKD

ADPKD affects 4–6 million people worldwide, and accounts for 10–15% of ESRD in the United States (104). It is estimated that up to 70% of patients have severe pain not controlled by oral analgesics (104). Despite this, clinical trials in the management of pain and symptoms in these patients are limited.

Pain tends to be multifactorial in the majority of patients. Causes of acute pain include pyelonephritis, infected cysts, cyst hemorrhage and mass effect on the surrounding renal parenchyma, acute expansion of cysts and distension of the renal capsule, and nephrolithiasis (104–106), which occurs at higher rates (20%) (51,106) than the general population due to metabolic and anatomical abnormalities (51,106). Chronic pain in ADPKD may be due to

increased lumbar lordosis, hypertrophy of the lumbodorsal muscles and degenerative changes in the spine secondary to enlarging cysts (51). Asymmetric growth of cysts and presence of polycystic liver disease may adversely affect posture and lead to worsening back pain and disc disease as well (51). Chronic, localized pain due to mass effect of the cysts on renal parenchyma and capsule, may present with a steady discomfort, worsened by standing and exertion (51,106). Correlation with cyst size and pain severity has been described (51). Pain has also been described to include headache (48.5%), chest pain (30.4%), and leg pain, with the symptoms of radiculopathy (107). The frequency of headaches is similar to that of the general population, with imaging studies showing no correlation with the presence of aneurysms (107).

Management of Pain in ADPKD

Directed treatment of the underlying etiology of the pain is warranted such as antibiotics for cyst infections. For chronic pain, noninvasive, conservative measures with concurrent analgesia are recommended though this approach has not been validated specifically in the ADPKD population. Conservative measures include heat/ice application, whirlpools, physical therapy, and massage, use of supporting garments including corsets and lifestyle and psychobehavioral modifications if the pain is musculoskeletal (51,106). Physical interventions, such as acupuncture, may also be beneficial, though not yet studied in these patients (51). After conservative and pharmacologic management, major physical interventions may be indicated. As the nervous supply from the kidney relays through the celiac plexus, nerve block may help manage pain though efficacy is unclear (51). Other suggestions include spinal cord stimulation, neuraxial opioids, and local anesthetics, none of which have been studied in ADPKD (51).

Indications for surgical treatment vary and include uncontrolled hypertension, severe back and loin pain despite noninvasive therapies, abdominal fullness, worsening renal function due to cysts, hematuria with hemorrhage and recurrent infections (104). No formal guidelines regarding an approach to surgical treatment were found. Though the evidence is limited, surgical procedures may be beneficial, and referral/evaluations for surgery should be made on a case-by-case basis if more conservative measures fail. Several surgical options are available and are outlined below.

Cyst aspiration may temporarily relieve pain, however fluid reaccumulation due to active chloride transport will limit the long-term efficacy of this procedure (51). Sclerotherapy using agents such as ethanol, minocyclyine, and n-butyl cyanoacrylate have also been investigated in ADPKD as treatment of pain due to cysts (108–111). Generalizability of outcomes is unclear as inclusion criteria, baseline renal function, size and number or of cysts targeted and sclerosant protocol varied. Overall reduction in renal volume was noted immediately post procedure (110) and at 6–7 months (108,109) with 81% of treated cysts having a 50% reduction in volume in one study (108). Improvement in symptoms was noted with significant decrease in pain scores within the first 7 days post procedure (5.5–2.3) (110) with between 86–90% of patients reporting improvement in pain at 6 months (108,109) and others reporting relief at 12–24 months post procedure (111). The duration of these effects is unclear, as recurrence of pain and reaccumulation of volume by 12 months (109), requiring repeat procedures has been described (110). Complications varied and included hematuria (109,111), pain (111), and nephro-cutaneous fistula (110).

Approximately 117 ADPKD patients have been evaluated in studies and case series of laparoscopic decortication, though generalizability is difficult as inclusion criteria, baseline renal function, indications for intervention, size of cysts targeted and follow-up have varied (112–121). Although outcomes have varied, most studies support improvement in pain. Immediately, postoperatively to 6 months, 85% of patients reported being free of pain (115,122) with another study noting a decrease in pain score immediately postoperatively from 7.4/10 to 2.3/10 (116) and in the 6 months thereafter (117). Pain relief sustained in a majority of patients (62–80%) being pain free at 1–2 years (119) and with 81% of patients having a >50% reduction in pain score at 3 years (120). The longest follow-up of 10 years noted that 67% of patients reported a >50% reduction in their pain as compared to preoperative levels (121). Though the majority of studies suggest no detrimental effects on renal function (113,115,117,119), some have described worsening renal function in patients with preoperative CrCl <30 ml/minute, GFR $\leq$3.4 ml/minute/1.73 m^2) (120,121).

Nephrectomy may be curative of symptoms, but is generally reserved for patients who have been treated unsuccessfully by other therapies and who have ESRD managed either with transplant or dialysis. Open nephrectomies have been associated with high risks of morbidity (12%) and mortality (5%) and since the early 1970s, the rate of this procedure has declined (123). Since the initial description of the laparoscopic nephrectomy for ADPKD in 1996, several series have described success both with and without hand assist (117,122–126). In the six studies reviewed, approximately 46 patients had undergone laparoscopic nephrectomy with or without the addition of hand assist. Once again generalizability is limited as the patient populations were not homogenous, with varying preoperative management of symptoms and varying indications for surgery including pain (123,124,126), shortness of breath (124), gastrointestinal symptoms (124–126), hypertension (125), hematuria (125,126), and infections (123,126). Though no prospective-controlled studies have been completed comparing laparoscopic to

TABLE 9. Knowledge gaps and research agenda

Symptom (pain) epidemiology and burden in developing countries.
Symptom (pain) epidemiology and burden in conservatively cared for patients (with comparisons made to those on dialysis).
Symptom (pain) trajectories at the end-of-life.
Analgesic prescribing in CKD patients with pain.
Analgesic use and availability for CKD patients in developing countries.
Major barriers in managing chronic pain in CKD: from both healthcare provider and healthcare system perspectives; from developing and developed country perspectives.
Efficacy and safety of pain management strategies/interventions for both nociceptive and neuropathic pain. These strategies would need to evaluate various analgesics (and adjuvants) at all levels of the WHO analgesic ladder. Important outcomes would include effect on HRQL, other symptoms, and global symptom burden.
Comparison of surgical decompression to best analgesic practice for the management of the neuropathic pain associated with CTS.
Efficacy and safety of nonsurgical but invasive procedures such as spinal cord stimulation and nerve block for pain associated with ADPKD.
Larger controlled studies with standardized protocols would be of benefit in comparing various surgical procedures for the management of pain in ADPKD.

open procedures, one study had a retrospective control of 10 patients (122) and another compared outcomes to patients who had laparoscopic procedures converted to open (123). The major risk factor for conversion into an open procedure was size of kidneys (>3500 cm^3) (123). Both series describe benefits in the laparoscopic group including less blood loss (150–246 vs. 325–687 ml), less transfusions (21.4% vs. 75%), shorter hospital lengths of stay postoperatively (1.5–3.4 vs. 6.8–9 days), less postoperative nasogastric tube use (10% vs. 100%), and less narcotic use (34.2 vs. 120 mg morphine). Improvement in pain was noted in all studies, through decreased narcotic use (122), reduction in pain scores from 6.9/10 to 0.5/10 at 3 months (123), and improved pain at up to 31 months postoperatively (124), as well as resolution of other symptoms (122–126). Overall complication rates were similar, estimated to be 40–50% in the open and laparoscopic groups respectively (122). Complications from procedures varied including incisional hernias (122–124), ileus (122,123), bleeding or hematomas requiring transfusions (122,124,125), brachial plexus injury (124), pulmonary embolism (124), wound infection (123), splenic cyanosis (124), clotting of dialysis shunt (124), duodenal serosal tear (122), and ATN of renal transplant secondary to hypotension (125).

Finally, laparoscopic denervation was of benefit in 13 patients (127,128). One case report of a patient with chronic back and flank pain had benefit in relief of pain, however long-term follow-up was not reported (127). The largest report of 12 children (mean age 12.4 years) who underwent denervation reported an improvement in pain scores from 6–9/10 prior to surgery to 0–1/10 at discharge, and pain free at a mean follow-up of 25.5 months with no major complications (128).

Final Comments

With the exception of developing countries and patients being managed conservatively, the prevalence, severity and negative impacts of chronic pain have been well documented and provide a strong imperative to the nephrology community to establish pain management as a clinical and research priority. However, there are clear gaps in the literature, which should guide future research to help inform evidence-based guidelines that are specific for CKD (outlined in Table 9). The primary research priority is the development and evaluation of pain management strategies and interventions for both nociceptive and neuropathic pain that evaluates both efficacy and safety in diverse CKD patient populations. These strategies would need to evaluate various analgesics (and adjuvants) at all levels of the WHO analgesic ladder.

References

1. Arksey H, O'Malley L: Scoping studies: Towards a methodological framework. *Int J Soc Res Methodol* 8:19–32, 2005
2. Murtagh FE, Addington-Hall JM, Edmonds PM, Donohoe P, Carey I, Jenkins K, Higginson IJ: Symptoms in advanced renal disease: a cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. *J Palliat Med* 10:1266–1276, 2007
3. Murphy EL, Murtagh FE, Carey I, Sheerin NS: Understanding symptoms in patients with advanced chronic kidney disease managed without dialysis: use of a short patient-completed assessment tool. *Nephron Clin Pract* 111:c74–c80, 2009
4. Noble H, Meyer PJ, Bridge DJ, Johnson DB, Kelly DD: Exploring symptoms in patients managed without dialysis: a qualitative research study. *J Ren Care* 36:9–15, 2010
5. Davison SN: Chronic pain in end-stage renal disease. *Adv Chronic Kidney Dis* 12:326–334, 2005
6. Davison SN, Jhangri GS: Impact of pain and symptom burden on the health-related quality of life of hemodialysis patients. *J Pain Symptom Manage* 39:477–485, 2010
7. Davison SN, Jhangri GS, Johnson JA: Cross-sectional validity of a modified Edmonton symptom assessment system in dialysis patients: a simple assessment of symptom burden. *Kidney Int* 69:1621–1625, 2006
8. Davison SN, Jhangri GS, Johnson JA: Longitudinal validation of a modified Edmonton symptom assessment system (ESAS) in haemodialysis patients. *Nephrol Dial Transplant* 21:3189–3195, 2006
9. Kimmel PL, Emont SL, Newmann JM, Danko H, Moss AH: ESRD patient quality of life: symptoms, spiritual beliefs, psychosocial factors, and ethnicity. *Am J Kidney Dis* 42:713–721, 2003
10. Leinau L, Murphy TE, Bradley E, Fried T: Relationship between conditions addressed by hemodialysis guidelines and non-ESRD-specific conditions affecting quality of life. *Clin J Am Soc Nephrol* 4:572–578, 2009
11. Weisbord SD, Carmody SS, Bruns FJ, Rotondi AJ, Cohen LM, Zeidel ML, Arnold RM: Symptom burden, quality of life, advance care planning and the potential value of palliative care in severely ill haemodialysis patients. *Nephrol Dial Transplant* 18:1345–1352, 2003
12. Weisbord SD, Fried LF, Arnold RM, Fine MJ, Levenson DJ, Peterson RA, Switzer GE: Prevalence, severity, and importance of physical and emotional symptoms in chronic hemodialysis patients. *J Am Soc Nephrol* 16:2487–2494, 2005
13. Gamondi C, Galli N, Schonholzer C, Marone C, Zwahlen H, Gabutti L, Bianchi G, Ferrier C, Cereghetti C, Giannini O: Frequency and severity of pain and symptom distress among patients with chronic kidney disease receiving dialysis. *Swiss Med Wkly* 143: w13750, 2013

14. Bailie GR, Mason NA, Bragg-Gresham JL, Gillespie BW, Young EW: Analgesic prescription patterns among hemodialysis patients in the DOPPS: potential for under prescription. *Kidney Int* 65:2419–2425, 2004
15. Elder SJ, Pisoni RL, Akizawa T, Fissell R, Andreucci VE, Fukuhara S, Kurokawa K, Rayner HC, Furniss AL, Port FK, Saran R: Sleep quality predicts quality of life and mortality risk in haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol DialTransplant* 23:998–1004, 2008
16. Jadoul M, Albert JM, Akiba T, Akizawa T, Arab L, Bragg-Gresham JL, Mason N, Prutz KG, Young EW, Pisoni RL: Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 70:1358–1366, 2006
17. Plantinga L, Grubbs V, Sarkar U, Hsu CY, Hedgeman E, Robinson B, Saran R, Geiss L, Burrows NR, Eberhardt M, Powe N, CDC CKD ST: Nonsteroidal anti-inflammatory drug use among persons with chronic kidney disease in the United States. *Ann Fam Med* 9:423–430, 2011
18. US Renal Data System: USRDS Dialysis Morbidity and Mortality Study. USRDS: *Annual Data Report*. Bethesda, MD: NIH, NIDDK, 1998
19. Desmet C, Beguin C, Swine C, Jadoul M: Falls in hemodialysis patients: prospective study of incidence, risk factors, and complications. *Am J Kidney Dis* 45:148–153, 2005
20. Shah HH, Monga D, Caperna A, Jhaveri KD: Palliative care experience of US adult nephrology fellows: a national survey. *Ren Fail* 36:39–45, 2014
21. Weisbord SD, Fried LF, Mor MK, Resnick AL, Unruh ML, Palevsky PM, Levenson DJ, Cooksey SH, Fine MJ, Kimmel PL, Arnold RM: Renal provider recognition of symptoms in patients on maintenance hemodialysis. *Clin J Am Soc Nephrol* 2:960–967, 2007
22. Walke LM, Byers AL, McCorkle R, Fried TR: Symptom assessment in community-dwelling older adults with advanced chronic disease. *J Pain Symptom Manage* 31:31–37, 2006
23. Hearn J, Higginson IJ: Development and validation of a core outcome measure for palliative care: the palliative care outcome scale. Palliative Care Core Audit Project Advisory Group. *Qual Health Care* 8:219–227, 1999
24. Barakzoy AS, Moss AH: Efficacy of the World Health Organization analgesic ladder to treat pain in end-stage renal disease. *J Am Soc Nephrol* 17:3198–3203, 2006
25. Broadbent A, Khor K, Heaney A: Palliation and renal failure: Common non-opioid medication guidelines. *Prog Palliat Care* 5:9–64, 2003
26. Davison SN, Ferro CJ: Management of pain in chronic kidney disease. *Prog Palliat Care* 18:6–195, 2009
27. Davison SN, Chambers EJ, Ferro CJ: Management of pain in renal failure. In: Chambers EJ, Brown E, Germain M (eds). *Supportive Care for the Renal Patient*, 2nd edn. New York: Oxford University Press, 2010:139–188
28. Davison SN: Pain in hemodialysis patients: prevalence, cause, severity, and management. *Am J Kidney Dis* 42:1239–1247, 2003
29. Davison SN: The prevalence and management of chronic pain in end-stage renal disease. *J Palliat Med* 127:7–1287, 2007
30. Dean M: Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* 28:497–504, 2004
31. Harris D: Pain management in patients with renal impairment. *Eur J Palliat Care* 15:214–216, 2008
32. Kurella M, Bennett WM, Chertow GM: Analgesia in patients with ESRD: a review of available evidence. *Am J Kidney Dis* 42:217–228, 2003
33. Launay-Vacher V, Karie S, Fau J-B, Izzedine H, Deray G: Treatment of pain in patients with renal insufficiency: The World Health Organization three-step ladder adapted. *J Pain* 6:137–148, 2005
34. Mid-Atlantic Renal Coalition and the Kidney End-of-Life Coalition. Clinical algorithm & preferred medications to treat pain in dialysis patients, Richmond, VA: Mid-Atlantic Renal Coalition and the Kidney End-of-Life Coalition, 2009
35. Moss AH: Pain Management in ESKD. *Presentation from Kidney End-of-Life Coalition (USDA)*.
36. Murtagh FE, Addington-Hall JM, Donohoe P, Higginson IJ: Symptom management in patients with established renal failure managed without dialysis. *Edtna Erca J* 32:93–98, 2006
37. Murtagh FE, Chai MO, Donohoe P, Edmonds PM, Higginson IJ: The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother* 21:5–16, 2007
38. Naylor HK, Raymond CB: Treatment of neuropathic pain in patients with chronic kidney disease. *CANNT J* 21:34–38, 2011
39. Young BA, Hynes J, McComb T, Blagg CR: Associations with home hemodialysis modality failure and mortality. *Hemodial Int* 8:344–348, 2004
40. Niscola P, Scaramucci L, Vischini G, Giovannini M, Ferrannini M, Massa P, Tatangelo P, Galletti M, Palumbo R: The use of major analgesics in patients with renal dysfunction. *Curr Drug Targets* 11:752–758, 2010
41. Pham PC, Toscano E, Pham PM, Pham PA, Pham SV, Pham PT: Pain management in patients with chronic kidney disease. *NDT Plus* 2:111–118, 2009
42. Macintyre PE, Schug SA, Scott DA, Visser EJ, Walker SM; APM: SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2010): *Acute Pain Management: Scientific Evidence* (3rd edn). ANZCA & FPM: Melbourne
43. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C: Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 10:113–130, 2009
44. Horber FF, Guentert TW, Weidekamm E, Heizmann P, Descoeudres C, Frey FJ: Pharmacokinetics of tenoxicam in patients with impaired renal function. *Eur J Clin Pharmacol* 29:697–701, 1986
45. Daousi C, Nurmikko T: Painful diabetic neuropathy. In: Stannard C, Kalso E, Ballantyne J (eds). *Evidence – Based Chronic Pain Management*, West Sussex: BMJ Books, 2010:204–221
46. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpaa ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD: Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc* 85:S3–S14, 2010
47. Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A: Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. *Can Fam Physician* 57: 1269–1276, e1419–1228, 2011
48. Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R, Patel S, Manchikanti L: Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. *Pain physician* 11:S5–S62, 2008
49. Ferrell B, Argoff CE, Epplin J, Fine P, Gloth FM, Herr K, Katz JD, Mehr DR, Reid C, Reisner L. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc* 57: 1331–1346, 2009
50. Pergolizzi J, Boger RH, Budd K, Dahan A, Erdine S, Hans G, Kress HG, Langford R, Likar R, Raffa RB, Sacerdote P: Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract* 8:287–313, 2008
51. Bajwa ZH, Gupta S, Warfield CA, Steinman TI: Pain management in polycystic kidney disease. *Kidney Int* 60:1631–1644, 2001
52. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ: Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. *Diabetes Care* 34:2220–2224, 2011
53. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ: Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med* 21:976–982, 2004
54. Barrett AM, Lucero MA, Le T, Robinson RL, Dworkin RH, Chappell AS: Epidemiology, public health burden, and treatment of diabetic peripheral neuropathic pain: a review. *Pain Med* 8(Suppl 2): S50–S62, 2007
55. Innis J: Pain assessment and management for a dialysis patient with diabetic peripheral neuropathy. *CANNT J* 16:12–17, 2006
56. Eggers PW, Gohdes D, Pugh J: Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. *Kidney Int* 56:1524–1533, 1999
57. Van Acker K, Bouhassira D, De Bacquer D, Weiss S, Matthys K, Raemen H, Mathieu C, Colin IM: Prevalence and impact on quality of life of peripheral neuropathy with or without neuropathic pain in type 1 and type 2 diabetic patients attending hospital outpatients clinics. *Diabetes Metab* 35:206–213, 2009
58. Jensen MP, Chodroff MJ, Dworkin RH: The impact of neuropathic pain on health-related quality of life: review and implications. *Neurology* 68:1178–1182, 2007
59. Zelman DC, Brandenburg NA, Gore M: Sleep impairment in patients with painful diabetic peripheral neuropathy. *Clin J Pain* 22:681–685, 2006
60. Vileikyte L, Leventhal H, Gonzalez JS, Peyrot M, Rubin RR, Ulbrecht JS, Garrow A, Waterman C, Cavanagh PR, Boulton AJ: Diabetic peripheral neuropathy and depressive symptoms: the association revisited. *Diabetes Care* 28:2378–2383, 2005
61. Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B: Pain severity in diabetic peripheral neuropathy is associated with

patient functioning, symptom levels of anxiety and depression, and sleep. *J Pain Symptom Manage* 30:374–385, 2005
62. Moghtaderi A, Bakhshipour A, Rashidi H: Validation of Michigan neuropathy screening instrument for diabetic peripheral neuropathy. *Clin Neurol Neurosurg* 108:477–481, 2006
63. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lanteri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 114:29–36, 2005
64. Tesfaye S, Vileikyte L, Rayman G, Sindrup S, Perkins B, Baconja M, Vinik A, Boulton A: Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. *Diabetes Metab Res Rev* 27:629–638, 2011
65. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, Feldman E, Iverson DJ, Perkins B, Russell JW, Zochodne D: Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 76:1758–1765, 2011
66. Argoff CE, Backonja MM, Belgrade MJ, Bennett GJ, Clark MR, Cole BE, Fishbain DA, Irving GA, McCarberg BH, McLean MJ: Consensus guidelines: treatment planning and options. *Mayo Clin Proc* 81:S12–S25, 2006
67. Pop-Busui R, Roberts L, Pennathur S, Kretzler M, Brosius FC, Feldman EL: The management of diabetic neuropathy in CKD. *Am J Kidney Dis* 55:365–385, 2010
68. Diabetes Control Complications Trial (DCCT) Research Group: Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Ann Neurol* 38: 869–880, 1995
69. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
70. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD: Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 360:129–139, 2009
71. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E: Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 280:1831–1836, 1998
72. Freeman R, Durso-Decruz E, Emir B: Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care* 31:1448–1454, 2008
73. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H: Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant* 19:3137–3139, 2004
74. Micozkadioglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M: Gabapentin versus levodopa for the treatment of restless legs syndrome in hemodialysis patients: An open-label study. *Ren Fail* 26:393–397, 2004
75. Thorp ML, Morris CD, Bagby SP: A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *Am J Kidney Dis* 38:104–108, 2001
76. Biyik Z, Solak Y, Atalay H, Gaipov A, Guney F, Turk S: Gabapentin versus pregabalin in improving sleep quality and depression in hemodialysis patients with peripheral neuropathy: a randomized prospective crossover trial. *Int Urol Nephrol* 45:831–837, 2013
77. Lo HS, Yang CM, Lo HG, Lee CY, Ting H, Tzang BS: Treatment effects of gabapentin for primary insomnia. *Clin Neuropharmacol* 33:84–90, 2010
78. Barisic I, Ljutic D, Jankovic S, Vlak T, Tomic S, Kokic S, Erceg M: Relevant sonographic parameters of a painful shoulder in symptomatic dialyzed patients versus asymptomatic dialyzed and healthy volunteers. *Coll Antropol* 30:313–318, 2006
79. Hardouin P, Flipo RM, Foissac-Gegoux P, Dumont A, Duquesnoy B, Delcambre B: Dialysis-related beta 2 microglobulin-amyloid arthropathy. Improvement of clinical symptoms after a switch of dialysis membranes. *Clin Rheumatol* 7:41–45, 1988
80. Bernageau J, Bardin T, Goutallier D, Voisin MC, Bard M: Magnetic resonance imaging findings in shoulders of hemodialyzed patients. *Clin Orthop Relat Res* 9:1–96, 1994
81. Dervisoglu E, Anik Y, Erdogan S, Akansel G, Yilmaz A: Beta2-microglobulin amyloidosis in hemodialysis and peritoneal dialysis patients. *Ther Apher Dialysis* 12:306–310, 2008
82. Charra B, Calemard E, Uzan M, Terrat JC, Vanel T, Laurent G: Carpal tunnel syndrome, shoulder pain and amyloid deposits in long-term haemodialysis patients. *Proc Eur Dial Transplant Assoc Eur Ren Assoc* 21:291–295, 1985
83. Marks JL, van dH, Colebatch AN, Buchbinder R, Edwards CJ: Pain pharmacotherapy in patients with inflammatory arthritis and concurrent cardiovascular or renal disease: a Cochrane systematic review. *J Rheumatol* 90:81–84, 2012
84. Coleman SH, Madsen M, Di Carlo EF, Sullivan JF, Wickiewicz TL: Arthroscopic synovectomy for the management of shoulder arthropathy in chronic renal dialysis patients. *J Shoulder Elbow Surg* 12:144–147, 2003
85. Cofan F, Garcia S, Combalia A, Segur JM, Oppenheimer F: Carpal tunnel syndrome secondary to uraemic tumoral calcinosis. *Rheumatology* 41:701–703, 2002
86. Harding AE, Le Fanu J: Carpal tunnel syndrome related to antebrachial Cimino-Brescia fistula. *J Neurol Neurosurg Psychiatry* 40:511–513, 1977
87. Kumar S, Trivedi HL, Smith EK: Carpal tunnel syndrome: a complication of arteriovenous fistula in hemodialysis patients. *Can Med Assoc J* 113:1070–1072, 1975
88. Gilbert MS, Robinson A, Baez A, Gupta S, Glabman S, Haimov M: Carpal tunnel syndrome in patients who are receiving long-term renal hemodialysis. *J Bone Joint Surg Am* 70:1145–1153, 1988
89. Bicknell JM, Lim AC, Raroque HG Jr, Tzamaloukas AH: Carpal tunnel syndrome, subclinical median mononeuropathy, and peripheral polyneuropathy: common early complications of chronic peritoneal dialysis and hemodialysis. *Arch Phys Med Rehabil* 72:378–381, 1991
90. Asencio G, Rigout C, Ramperez P, Branger B, Oules R, Bertin R, Megy B, Leonardi C: Hemodialysis-related lesions of the hand. *Rev Rhum Engl Ed* 62:233–240, 1995
91. Sivri A, Celiker R, Sungur C, Kutsal YG: Carpal tunnel syndrome: a major complication in hemodialysis patients. *Scand J Rheumatol* 23:287–290, 1994
92. Warren DJ, Otieno LS: Carpal tunnel syndrome in patients on intermittent haemodialysis. *Postgrad Med J* 51:450–452, 1975
93. Kessler M, Netter P, Azoulay E, Mayeux D, Pere P, Gaucher A: Dialysis-associated arthropathy: a multicentre survey of 171 patients receiving haemodialysis for over 10 years. The Co-operative Group on Dialysis-associated Arthropathy. *Br J Rheumatol* 31:157–162, 1992
94. Harris SA, Brown EA: Patients surviving more than 10 years on haemodialysis. The natural history of the complications of treatment. *Nephrol Dial Transplant* 13:1226–1233, 1998
95. Ikegaya N, Hishida A, Sawada K, Furuhashi M, Maruyama Y, Kumagai H, Kobayashi S, Yamamoto T, Yamazaki K: Ultrasonographic evaluation of the carpal tunnel syndrome in hemodialysis patients. *Clin Nephrol* 44:231–237, 1995
96. Otsubo S, Kimata N, Okutsu I, Oshikawa K, Ueda S, Sugimoto H, Mitobe M, Uchida K, Otsubo K, Nitta K, Akiba T: Characteristics of dialysis-related amyloidosis in patients on haemodialysis therapy for more than 30 years. *Nephrol Dial Transplant* 24:1593–1598, 2009
97. Kwon HK, Pyun SB, Cho WY, Boo CS: Carpal tunnel syndrome and peripheral polyneuropathy in patients with end stage kidney disease. *J Korean Med Sci* 26:1227–1230, 2011
98. Levine DW, Simmons BP, Koris MJ, Daltroy LH, Hohl GG, Fossel AH, Katz JN: A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. *J Bone Joint Surg Am* 75:1585–1592, 1993
99. Shiota E, Tsuchiya K, Yamaoka K, Kawano O: Open carpal tunnel decompression in long-term haemodialysis patients. *J Hand Surg* 26:529–532, 2001
100. Hirasawa Y, Ogura T: Carpal tunnel syndrome in patients on long-term haemodialysis. *Scand J Plast Reconstr Surg Hand Surg* 34:373–381, 2000
101. Kim SJ, Shin SJ, Kang ES: Endoscopic carpal tunnel release in patients receiving long-term hemodialysis. *Clin Orthop Relat Res* 14:1–148, 2000
102. Yoshida A, Okutsu I, Hamanaka I, Motomura T: Results of endoscopic management of primary versus recurrent carpal tunnel syndrome in long-term haemodialysis patients. *Hand Surg* 9:165–170, 2004
103. Spencer JD: Amyloidosis as a cause of carpal tunnel syndrome in haemodialysis patients. *J Hand Surg* 13:402–405, 1988
104. Badani KK, Hemal AK, Menon M: Autosomal dominant polycystic kidney disease and pain - a review of the disease from aetiology, evaluation, past surgical treatment options to current practice. *J Postgrad Med* 50:222–226, 2004
105. Grantham JJ: Renal pain in polycystic kidney disease: when the hurt won't stop. *J Am Soc Nephrol* 2:1161–1162, 1992
106. Hogan MC, Norby SM: Evaluation and management of pain in autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis* 17:e1–e16, 2010

107. Bajwa ZH, Sial KA, Malik AB, Steinman TI: Pain patterns in patients with polycystic kidney disease. *Kidney Int* 66:1561–1569, 2004
108. Kim SH, Moon MW, Lee HJ, Sim JS, Kim SH, Ahn C: Renal cyst ablation with n-butyl cyanoacrylate and iodized oil in symptomatic patients with autosomal dominant polycystic kidney disease: preliminary report. *Radiology* 226:573–576, 2003
109. Uemasu J, Fujihara M, Munemura C, Nakamura E, Kawasaki H: Cyst sclerotherapy with minocycline hydrochloride in patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 11:843–846, 1996
110. Singh I, Mehrotra G: Selective ablation of symptomatic dominant renal cysts using 99% ethanol in adult polycystic kidney disease. *Urology* 68:482–487, 2006
111. Lee YR, Lee KB: Ablation of symptomatic cysts using absolute ethanol in 11 patients with autosomal-dominant polycystic kidney disease. *Korean J Radiol* 4:239–242, 2003
112. Chehval MJ, Neilsen C: Laparoscopic cyst decompression in polycystic kidney disease. *J Endourol* 9:281–282, 1995
113. Hemal AK, Gupta NP, Rajeev TP, Aron M, Bhowmik D, Jain R: Retroperitoneoscopic management of infected cysts in adult polycystic kidney disease. *Urol Int* 62:40–43, 1999
114. Sulikowski T, Kaminski M, Rozanski J, Zietek Z, Domanski L, Majewski W, Sienko J, Romanowski M, Mizerski A, Myslak M, Tejchman K, Pabisiak K, Nowacki M, Ostrowski M, Ciechanowski K: Laparoscopic removal of renal cysts in patients with ADPKD as an alternative method of treatment and patient preparation for kidney transplantation: preliminary results. *Transpl Proc* 38:23–27, 2006
115. Brown JA, Torres VE, King BF, Segura JW: Laparoscopic marsupialization of symptomatic polycystic kidney disease. *J Urol* 156:22–27, 1996
116. McNally ML, Erturk E, Oleyourryk G, Schoeniger L: Laparoscopic cyst decortication using the harmonic scalpel for symptomatic autosomal dominant polycystic kidney disease. *J Endourol* 15:597–599, 2001
117. Elashry OM, Nakada SY, Wolf JS Jr, McDougall EM, Clayman RV: Laparoscopy for adult polycystic kidney disease: a promising alternative. *Am J Kidney Dis* 27:224–233, 1996
118. Teichman JM, Hulbert JC: Laparoscopic marsupialization of the painful polycystic kidney. *J Urol* 153:1105–1107, 1995
119. Elzinga LW, Barry JM, Torres VE, Zincke H, Wahner HW, Swan S, Bennett WM: Cyst decompression surgery for autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2:1219–1226, 1992
120. Lee DI, Andreoni CR, Rehman J, Landman J, Ragab M, Yan Y, Chen C, Shindel A, Middleton W, Shalhav A, McDougall EM, Clayman RV: Laparoscopic cyst decortication in autosomal dominant polycystic kidney disease: impact on pain, hypertension, and renal function. *J Endourol* 17:345–354, 2003
121. Haseebuddin M, Tanagho YS, Millar M, Roytman T, Chen C, Clayman RV, Miller B, Desai A, Benway B, Bhayani S, Figenshau RS: Long-term impact of laparoscopic cyst decortication on renal function, hypertension and pain control in patients with autosomal dominant polycystic kidney disease. *J Urol* 188:1239–1244, 2012
122. Gill IS, Kaouk JH, Hobart MG, Sung GT, Schweizer DK, Braun WE: Laparoscopic bilateral synchronous nephrectomy for autosomal dominant polycystic kidney disease: The initial experience. *J Urol* 165:1093–1098, 2001
123. Lipke MC, Bargman V, Milgrom M, Sundaram CP: Limitations of laparoscopy for bilateral nephrectomy for autosomal dominant polycystic kidney disease. *J Urol* 177:627–631, 2007
124. Dunn MD, Portis AJ, Elbahnasy AM, Shalhav AL, Rothstein M, McDougall EM, Clayman RV: Laparoscopic nephrectomy in patients with end-stage renal disease and autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 35:720–725, 2000
125. Jenkins MA, Crane JJ, Munch LC: Bilateral hand-assisted laparoscopic nephrectomy for autosomal dominant polycystic kidney disease using a single midline HandPort incision. *Urology* 59:32–36, 2002
126. Rehman J, Landman J, Andreoni C, McDougall EM, Clayman RV: Laparoscopic bilateral hand assisted nephrectomy for autosomal dominant polycystic kidney disease: initial experience. *J Urol* 166:42–47, 2001
127. Valente JF, Dreyer DR, Breda MA, Bennett WM: Laparoscopic renal denervation for intractable ADPKD-related pain. *Nephrol Dial Transplant* 16:160, 2001
128. Casale P, Meyers K, Kaplan B: Follow-up for laparoscopic renal denervation and nephropexy for autosomal dominant polycystic kidney disease-related pain in pediatrics. *J Endourol* 22:991–993, 2008
129. Chiou CP: Development and psychometric assessment of the physical symptom distress scale. *J Pain Symptom Manage* 16:87–95, 1998
130. Weisbord SD, Fried LF, Arnold RM, Rotondi AJ, Fine MJ, Levenson DJ, Switzer GE: Development of a symptom assessment instrument for chronic hemodialysis patients: the Dialysis Symptom Index. *J Pain Symptom Manage* 27:226–240, 2004
131. Melzack R: The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1:277–299, 1975
132. Joshi VD, Mooppil N, Lim JF: Validation of the kidney disease quality of life-short form: a cross-sectional study of a dialysis-targeted health measure in Singapore. *BMC Nephrol* 11:36, 2010
133. Wu AW, Fink NE, Cagney KA, Bass EB, Rubin HR, Meyer KB, Sadler JH, Powe NR: Developing a health-related quality-of-life measure for end-stage renal disease: the CHOICE Health Experience Questionnaire. *Am J Kidney Dis* 37:11–21, 2001
134. Prescott LF: Analgesic nephropathy: a reassessment of the role of phenacetin and other analgesics. *Drugs* 23:75–149, 1982
135. Prescott LF, Speirs GC, Critchley JA, Temple RM, Winney RJ: Paracetamol disposition and metabolite kinetics in patients with chronic renal failure. *Eur J Clin Pharmacol* 36:291–297, 1989
136. Ashley C, Currie AE: *The Renal Drug Handbook*. Oxford: Radcliffe Publishing, 2009
137. Way EL, Adler TK: The pharmacologic implications of the fate of morphine and its surrogates. *Pharmacol Rev* 12:383–446, 1960
138. Guay DR, Awni WM, Findlay JW, Halstenson CE, ABRAHAM PA, Opsahl JA, Jones EC, Matzke GR: Pharmacokinetics and pharmacodynamics of codeine in end-stage renal disease. *Clin Pharmacol Ther* 43:63–71, 1988
139. Schug SA, Morgan J: Treatment of cancer pain: Special considerations in patients with renal disease. *Am J Cancer* 3:247–256, 2004
140. Izzedine H, Launay-Vacher V, Abbara C, Aymard G, Bassilios N, Deray G: Pharmacokinetics of tramadol in a hemodialysis patient. *Nephron* 92:755–756, 2002
141. Gibson TP: Pharmacokinetics, efficacy, and safety of analgesia with a focus on tramadol HCl. *Am J Med* 101:47S–53S, 1996
142. Paramanandam G, Prommer E, Schwenke DC: Adverse effects in hospice patients with chronic kidney disease receiving hydromorphone. *J Palliat Med* 14:1029–1033, 2011
143. 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* 4:335–336, 2008
144. Davies G, Kingswood C, Street M: Pharmacokinetics of opioids in renal dysfunction. *Clin Pharmacokinet* 31:410–422, 1996
145. Chauvin M, Lebrault C, Levron JC, Duvaldestin P: Pharmacokinetics of alfentanil in chronic renal failure. *Anesth Analg* 66:53–56, 1987
146. Filitz J, Griessinger N, Sittl R, Likar R, Schuttler J, Koppert W: Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. *Eur J Pain* 10:743–748, 2006
147. Mordarski S: Efficacy and safety of buprenorphine in patients receiving haemodialysis. *J Appl Res* 7:46–51, 2009
148. Berg KJ, Talseth T: Acute renal effects of sulindac and indomethacin in chronic renal failure. *Clin Pharmacol Ther* 37:447–452, 1985
149. Kreek MJ, Schecter AJ, Gutjahr CL, Hecht M: Methadone use in patients with chronic renal disease. *Drug Alcohol Depend* 5:197–205, 1980
150. Fitzgerald J: Narcotic analgesics in renal failure. *Conn Med* 55:701–704, 1991
151. Foral PA, Ineck JR, Nystrom KK: Oxycodone accumulation in a hemodialysis patient. *South Med J* 100:212–214, 2007
152. Kirvela M, Lindgren L, Seppala T, Olkkola KT: The Pharmacokinetics of Oxycodone in uremic patients undergoing renal transplantation. *J Clin Anesth* 8:13–18, 1996
153. Kaiko R, Benziger D, Cheng C, Hou Y, Grandy R: Clinical Pharmacokinetics of Controlled-Release Oxycodone in Renal Impairment. *Clin Pharmacol Ther* 59:130–130, 1996
154. Inturrisi CE, Verebely K: Disposition of methadone in man after a single oral dose. *Clin Pharmacol Ther* 13:923–930, 1972
155. Wong MO, Eldon MA, Keane WF, Turck D, Bockbrader HN, Underwood BA, Sedman AJ, Halstenson CE: Disposition of gabapentin in anuric subjects on hemodialysis. *J Clin Pharmacol* 35:622–626, 1995
156. Blum RA, Comstock TJ, Sica DA, Schultz RW, Keller E, Reetze P, Bockbrader H, Tuerck D, Busch JA, Reece PA, Sedman AJ: Pharmacokinetics of gabapentin in subjects with various degrees of renal function. *Clin Pharmacol Ther* 56:154–159, 1994
157. MIMS: *MIMS Annual*. St. Leonards, NSW: UBM Medica Australia, 2010
158. Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN: Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol* 43:277–283, 2003
159. Lieberman JA, Cooper TB, Suckow RF, Steinberg H, Borenstein M, Brenner R, Kane JM: Tricyclic antidepressant and metabolite levels in chronic renal failure. *Clin Pharmacol Ther* 37:301–307, 1985

160. Sandoz M, Vandel S, Vandel B, Bonin B, Hory B, St HY, Volmat R: Metabolism of amitriptyline in patients with chronic renal failure. *Eur J Clin Pharmacol* 26:227–232, 1984
161. Ciabattoni G, Cinotti GA, Pierucci A, Simonetti BM, Manzi M, Pugliese F, Barsotti P, Pecci G, Taggi F, Patrono C: Effects of sulindac and ibuprofen in patients with chronic glomerular disease. Evidence for the dependence of renal function on prostacyclin. *N Engl J Med* 310:279–283, 1984
162. Bunning RD, Barth WF: Sulindac. A potentially renal-sparing nonsteroidal anti-inflammatory drug. *JAMA* 248:2864–2867, 1982
163. Swainson CP, Griffiths P: Acute and chronic effects of sulindac on renal function in chronic renal disease. *Clin Pharmacol Ther* 37:298–300, 1985
164. Klassen DK, Stout RL, Spilman PS, Whelton A: Sulindac kinetics and effects on renal function and prostaglandin excretion in renal insufficiency. *J Clin Pharmacol* 29:1037–1042, 1989
165. Ravis WR, Diskin CJ, Campagna KD, Clark CR, McMillian CL: Pharmacokinetics and dialyzability of sulindac and metabolites in patients with end-stage renal failure. *J Clin Pharmacol* 33:527–534, 1993
166. Gibson TP, Dobrinska MR, Lin JH, Entwistle LA, Davies RO: Biotransformation of sulindac in end-stage renal disease. *Clin Pharmacol Ther* 42:82–88, 1987
167. Brater DC, Lasseter KC: Profile of etodolac: pharmacokinetic evaluation in special populations. *Clin Rheumatol* 8(Suppl 1):25–35, 1989
168. Ermer JC, Boni JP, Cevallos WH, DeCleene S, Burghart P, Rudnick MR, Fruncillo RJ, Berns JS, Cohen RM: Bromfenac disposition in patients with impaired kidney function. *Clin Pharmacol Ther* 61:312–318, 1997
169. Skoutakis VA, Acchiardo SR, Carter CA, Wojciechowski NJ, Straughn AB, Meyer MC: Dialyzability and pharmacokinetics of indomethacin in adult patients with end-stage renal disease. *Drug Intell Clin Pharm* 20:956–960, 1986
170. Taylor IW, Taylor T, James I, Doyle G, Dorf G, Darragh A, Chasseaud LF: Pharmacokinetics of the anti-inflammatory drug ximoprofen in healthy subjects and in disease states. *Eur J Clin Pharmacol* 40:101–106, 1991
171. Aronoff GR, Ozawa T, DeSante KA, Nash JF, Ridolfo AS: Benoxaprofen kinetics in renal impairment. *Clin Pharmacol Ther* 32:190–194, 1982
172. Stafanger G, Larsen HW, Hansen H, Sorensen K: Pharmacokinetics of ketoprofen in patients with chronic renal failure. *Scand J Rheumatol* 10:189–192, 1981
173. Taylor IW, Chasseaud LF, Taylor T, James I, Dorf G, Darragh A: Pharmacokinetics of the anti-inflammatory drug ximoprofen in healthy young and elderly subjects: comparison with elderly rheumatic patients. *Br J Clin Pharmacol* 32:242–245, 1991
174. Anttila M, Haataja M, Kasanen A: Pharmacokinetics of naproxen in subjects with normal and impaired renal function. *Eur J Clin Pharmacol* 18:263–268, 1980
175. Rogers HJ, Savitsky JP, Glenn B, Spector RG: Kinetics of single doses of fenbufen in patients with renal insufficiency. *Clin Pharmacol Ther* 29:74–80, 1981
176. Grubb NG, Rudy DW, Brater DC, Hall SD: Stereoselective pharmacokinetics of ketoprofen and ketoprofen glucuronide in end-stage renal disease: evidence for a 'futile cycle' of elimination. *Br J Clin Pharmacol* 48:494–500, 1999
177. Cefali EA, Poynor WJ, Sica D, Cox S: Pharmacokinetic comparison of flurbiprofen in end-stage renal disease subjects and subjects with normal renal function. *J Clin Pharmacol* 31:808–814, 1991
178. al-Ghamdi MS, al-Mohanna FA, al-Mustafa ZH, al-Saeed IS: The effect of haemodialysis on the pharmacokinetics of tenoxicam in patients with end-stage renal disease. *Eur J Clin Pharmacol* 43:197–199, 1992
179. Davies NM, McLachlan AJ, Day RO, Williams KM: Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclooxygenase-2 inhibitor. *Clin Pharmacokinet* 38:225–242, 2000
180. Gottesdiener K, Agrawal N, Porras A, Wong P, Rogers JD, Gertz BJ, Redfern JS, Marbury T: Effects of renal insufficiency and hemodialysis on the pharmacokinetics of rofecoxib. *Am J Ther* 10:252–258, 2003
181. Udayaraj UP, Steenkamp R, Caskey FJ, Rogers C, Nitsch D, Ansell D, Tomson CR: Blood pressure and mortality risk on peritoneal dialysis. *Am J Kidney Dis* 53:70–78, 2009

Appendix A
Search strategies

1 *Kidney Failure, Chronic/
2 *renal insufficiency, chronic/
3 exp *Renal Dialysis/
4 *Hemofiltration/
5 *Renal Replacement Therapy/
6 (ckd or dialysis or hemodialysis or haemodialysis or esrd or renal disease* or kidney disease* or renal failure or kidney failure or renal replacement).ti.
7 (ckd or dialysis or hemodialysis or haemodialysis or esrd or chronic renal disease* or end stage renal disease or chronic kidney disease* or (renal failure not acute renal failure) or (kidney failure not acute kidney failure)).ab./freq = 2
8 limit 7 to ("in data review" or in process or "pubmed not medline")
9 (or/1-6) or 8
10 (pain or painful or pains).ti.
11 (pain or painful or pains).ab./freq = 3
12 exp *pain/or *pain management/or *pain measurement/or *pain clinics/
13 symptom*.ti. and (pain or pains or painful).tw.
14 global symptom assessment*.tw.
15 Edmonton symptom assessment scale.tw.
16 Dialysis symptom index.tw.
17 (Patient outcome scale adj4 (renal or kidney)).tw.
18 exp *Analgesia/
19 exp *Analgesics/
20 (analges* or opioid* or morphine or ibuprofen or naproxen or nsaid* or nonsteroidal anti-inflammatory or nonsteroidal anti-inflammatory or nonsteroidal anti-inflammatory or nonsteroidal anti-inflammatory or tylenol or acetaminophen or paracetamol).ti.
21 analgesic ladder.tw.
22 or/10-21
23 exp *Osteoarthritis/
24 (osteoarthritis or arthritis).ti.
25 *peripheral nervous system diseases/or *diabetic neuropathies/or *neuralgia/or *peripheral nerve injuries/or *peripheral nervous system neoplasms/or *polyneuropathies/
26 neuropath*.ti.
27 (malignanc* or neoplasm* or cancer*).ti.
28 exp *Neoplasms/
29 (pain or pains or painful).mp. and (or/23-28)
30 22 or 29
31 9 and 30
32 (rat or rats or mouse).ti.
33 limit 31 to animals
34 limit 33 to humans
35 31 not ((33 not 34) or 32)
36 Practice Guideline/or clinical protocols/or critical pathways/
37 guideline*.tw. or (recommendations or guideline*).ti. or ((clinical or critical or care or management or nursing) adj2 (protocol or path)).tw.
38 35 and (36 or 37)
39 (overview or pubmed or medline or scopus or psycinfo or cochrane).tw. or (systematic* adj3

review*).mp. or meta-analy*.pt,mp. or search*.ab.
40 technology assessment, biomedical/
41 (hta or technology assessment).tw.
42 technology assessment.jw.
43 35 and (or/39-42)
44 35 and review.pt.
45 38 or 43 or 44
46 limit 45 to english language = 161
47 case reports/
48 (case adj4 (study or report*)).tw.
49 (old adj3 (female or male or child or woman or man or girl or boy or baby)).ab.
50 case report*.jw.
51 35 not (45 or (or/47-50))
52 exp Clinical trial/or randomized.tw. or placebo.tw. or dt.fs. or randomly.tw. or trial.tw. or groups.tw.
53 51 and 52
54 Epidemiologic studies/
55 exp cohort studies/or Cross-sectional studies/
56 cohort*.tw.
57 (Follow-up adj (study or studies)).mp.
58 (observational adj (study or studies)).mp.
59 (Longitudinal or prospective or retrospective or Cross-sectional).mp.
60 51 and (or/54-59)
61 53 or 60
62 limit 61 to english language = 484

Appendix B
Guideline sites

National Guidelines Clearinghouse http://www.guideline.gov

Alberta – TOPGuidelines http://www.topalbertadoctors.org/cpgs/

BC – BCGuidelines.ca http://www.bcguidelines.ca/

CMA Infobase http://www.cma.ca/clinicalresources/practiceguidelines

Australia – Clinical Practice Guidelines Portal: http://www.clinicalguidelines.gov.au

NICE Guidance (UK) http://guidance.nice.org.uk/

NICE Pathways http://pathways.nice.org.uk/; eGuidelines.co.uk; http://www.eguidelines.co.uk; SIGN http://www.sign.ac.uk/guidelines/index.html.