Pain in Chronic Kidney Disease: A Scoping Review

Sara N. Davison,* Holly Koncicki,† and Frank Brennan‡

*Division of Nephrology & Immunology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada, †Department of Geriatrics and Palliative Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York City, New York, and ‡Department of Palliative Care, St George Hospital, Sydney, New South Wales, Australia

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
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 non-indexed 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>
<thead>
<tr>
<th>TABLE 1. Study selection by subcategories within the scope of the pain review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of records identified for title and abstract review</strong></td>
</tr>
<tr>
<td>Pain assessment and screening</td>
</tr>
<tr>
<td>Epidemiology: prevalence, severity, other characteristics, etiology, and associations</td>
</tr>
<tr>
<td>Patterns of analgesic use</td>
</tr>
<tr>
<td>Specific pain syndromes</td>
</tr>
<tr>
<td>Arthritides</td>
</tr>
<tr>
<td>Peripheral neuropathies (in general), diabetic neuropathy, and carpal tunnel syndrome</td>
</tr>
<tr>
<td>ADPKD</td>
</tr>
<tr>
<td>Pharmacokinetic/pharmacodynamic studies</td>
</tr>
<tr>
<td>Pain management: general approaches and guidelines</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>No. of Studies (total: 50), 46 study populations (6 duplications)</th>
<th>Year (44 of 50 studies ≥2000)</th>
<th>Country</th>
<th>No. of distinct patients (total: 7560)</th>
<th>Prevalence</th>
<th>Impact</th>
<th>Other Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent hemodialysis</td>
<td>36 studies</td>
<td>1993–2013</td>
<td>Asia, North America, Israel/Iran, 6 European countries</td>
<td>5244</td>
<td><em>Weighted mean prevalence:</em> 58.6%; <em>(n = 2860 in 16 populations; range 21–81%)</em> &lt;br&gt; <em>Weighted mean prevalence of mild/severe pain:</em> 48.8% <em>(n = 1701 in 6 populations; range 41–68.6%)</em> &lt;br&gt; <em>Weighted mean severity:</em> 3.69/10 <em>(n = 1506 in 6 populations; range 3.3–5.6/10)</em> &lt;br&gt; Back pain: 46.7% <em>(n = 613 in 2 populations; range 16–53%)</em> &lt;br&gt; Bone/joint pain: 32.3% <em>(n = 366 in 4 populations; range 37–61.7%)</em> &lt;br&gt; Muscle soreness: 61.6% <em>(n = 1159 in 4 populations driven predominantly by NECOSAD study; range 28–71%)</em> &lt;br&gt; Abdominal pain: 22.2% <em>(n = 202 in 2 populations)</em></td>
<td>HRQL: 9 populations; <em>(n = 2086)</em> &lt;br&gt; Pain &amp; overall symptom burden are consistently associated with lower QOL, psychosocial distress, insomnia, depression</td>
<td>Biochemical &amp; demographics: 11 populations; <em>(n = 3215)</em> &lt;br&gt; 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 <em>(n = 896)</em></td>
</tr>
<tr>
<td>Prevalent peritoneal dialysis</td>
<td>4 studies</td>
<td>2000</td>
<td>United States Canada</td>
<td>779</td>
<td><em>Prevalence:</em> 38% <em>(n = 107, 1 study)</em> &lt;br&gt; <em>Prevalence muscle soreness:</em> 64% <em>(n = 573, 1 study)</em> &lt;br&gt; <em>Severity:</em> 3.6/10 <em>(n = 1482, 2 populations; range 2.2–4.1/10)</em></td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Following withdrawal of hemodialysis</td>
<td>3 studies</td>
<td>2000</td>
<td>United States Canada</td>
<td>114</td>
<td>54% at the time of withdrawal, 42% in last 24 hrs; 23% in last 24 hours when seen by palliative care</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Conservative</td>
<td>3 studies</td>
<td>2005–2006</td>
<td>United Kingdom</td>
<td>43–66 patients</td>
<td>53% pain *(32% mild/severe); 73% last month of life <em>(41% very distressing)</em> <em>(n = 43)</em></td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>CKD (stages 1–4)</td>
<td>2 studies</td>
<td>2005, 2010</td>
<td>United States United States</td>
<td>635</td>
<td>130: 72.9% pain <em>(musculoskeletal most common), av 5.7/10; (505) Increased physical pain on SF-36</em></td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Hospitalized CKD</td>
<td>1 study</td>
<td>2007</td>
<td>Australia</td>
<td>53</td>
<td>100% had some level of pain in the past 24 hours</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>
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 concomitantly administered 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 decrements 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>
<thead>
<tr>
<th>Patient population</th>
<th>Patient number</th>
<th>Any analgesic</th>
<th>NSAID</th>
<th>Acetaminophen</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD (3 studies)</td>
<td>2342</td>
<td>–</td>
<td>24% (range 6%-54%)</td>
<td>24%</td>
<td>–</td>
</tr>
<tr>
<td>CKD with pain (1 study)</td>
<td>130</td>
<td>–</td>
<td>15%</td>
<td>33%</td>
<td>–</td>
</tr>
<tr>
<td>Incident HD/PD (2 studies)</td>
<td>4826</td>
<td>11%</td>
<td>18%</td>
<td>–</td>
<td>7% (range 5–18%)</td>
</tr>
<tr>
<td>Prevalent HD (13 studies)</td>
<td>25725</td>
<td>27% (range 18–30%)</td>
<td>5% (range 1–16%)</td>
<td>9% (range 0–14%)</td>
<td>15% (range 0–18%)</td>
</tr>
<tr>
<td>Prevalent HD with pain (7 studies)</td>
<td>755</td>
<td>56% (range 30–65%)</td>
<td>19% (range 3–42%)</td>
<td>18% (range 0–44%)</td>
<td>22% (range 0–36%)</td>
</tr>
<tr>
<td>Withdrawn from dialysis (1 study)</td>
<td>79</td>
<td>87%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Withdrawn from dialysis and followed by palliative care (1 study)</td>
<td>35</td>
<td>–</td>
<td>–</td>
<td>97%</td>
<td>–</td>
</tr>
</tbody>
</table>
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.

**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.

**Physical symptom distress scale (PDS)** (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.

**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 **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. 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.

**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.

**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).

### TABLE 4. Symptom assessment tools

<table>
<thead>
<tr>
<th>Description</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified Edmonton symptom assessment system (m-ESAS v. 2)</strong> (7,8,22)</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Palliative Care Outcome Scale-Renal (POS-renal)</strong> (3,23)</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Physical symptom distress scale (PDS)</strong> (129)</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Dialysis symptom index (DSI)</strong> (130)</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Kidney Dialysis Quality of Life-Short Form/SF-36 (KDQOL-SF)</strong> (132)</td>
<td>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.</td>
</tr>
<tr>
<td><strong>SHORT form McGill Pain Questionnaire (SF-MPQ)</strong> (131)</td>
<td>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 quality of life.</td>
</tr>
<tr>
<td><strong>CHEQ</strong> + SF-36 (133)</td>
<td>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.</td>
</tr>
<tr>
<td><strong>CHOICE health experience Questionnaire (CHEQ)</strong> + SF-36 (133)</td>
<td>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.</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Medication</th>
<th>% excreted in the urine</th>
<th>T ½ normal (hours)</th>
<th>T ½ Dialysis (ESRD) (hours)</th>
<th>Hemodialysis</th>
<th>Peritoneal dialysis</th>
<th>Comments and recommendations on use and maximum dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>&lt;5</td>
<td>1-4</td>
<td>Unchanged</td>
<td>Dialyzed</td>
<td>Not dialyzed</td>
<td>Accumulation of inactive metabolites. Analgesic of choice for mild-moderate pain. No dose reduction required.</td>
</tr>
<tr>
<td>(24,27,134,135)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>0-16</td>
<td>2.5-4</td>
<td>13-18.9</td>
<td>Not dialyzed</td>
<td>Unlikely to be dialyzed</td>
<td>Metabolized to morphine derivatives and known to cause profound hypotension and CNS and respiratory depression. Not recommended in CKD</td>
</tr>
<tr>
<td>(136–138)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>90 (30% unchanged 60% as metabolites)</td>
<td>6</td>
<td>11</td>
<td>Dialyzed</td>
<td>Unknown</td>
<td>eGFR 30-10 mls/min: 50-100mg bd. eGFR &lt; 10 mls/min (and on dialysis): 50mg bd. Hemodialysis significantly removes Tramadol so administration is best given after each dialysis.</td>
</tr>
<tr>
<td>(139–141)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rapid accumulation of active metabolites in CKD resulting in clinically significant opioid toxicity including sedation, confusion, myoclonus, and respiratory depression. Not recommended in CKD.</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>2-3</td>
<td>Unchanged</td>
<td>Parent &amp; active metabolites dialyzed</td>
<td>Not dialyzed</td>
<td>Rabit accumulation of active metabolites in CKD resulting in clinically significant opioid toxicity including sedation, confusion, myoclonus, and respiratory depression. Not recommended in CKD.</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>6</td>
<td>2-5</td>
<td>3.2 on dialysis; 5.9 nondialysis days</td>
<td>Active metabolite (H3G) dialyzed</td>
<td>Unknown</td>
<td>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.</td>
</tr>
<tr>
<td>(142,143)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>&lt;7</td>
<td>2-7</td>
<td>Possibly increased</td>
<td>Not dialyzed</td>
<td>Not dialyzed</td>
<td>Inactive metabolites. Most pharmacokinetic studies in CKD use parenteral rather than transdermal fentanyl. Generally considered safe for use in CKD if monitored carefully.</td>
</tr>
<tr>
<td>(144)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alfentanil</td>
<td>0.4</td>
<td>1-2</td>
<td>Unchanged</td>
<td>Not dialyzed</td>
<td>Not dialyzed</td>
<td>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.</td>
</tr>
<tr>
<td>(145)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Minimal</td>
<td>30</td>
<td>Unchanged</td>
<td>Dialyzed</td>
<td>Dialyzed</td>
<td>Buprenorphine may be given in standard doses to patients with CKD. Generally considered safe for use in CKD if monitored carefully. 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.</td>
</tr>
<tr>
<td>(146-149)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>&lt;10</td>
<td>2-4</td>
<td>3-5</td>
<td>Dialyzed</td>
<td>Unknown</td>
<td>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.</td>
</tr>
<tr>
<td>(150–153)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>15–60</td>
<td>13-47</td>
<td>Unknown</td>
<td>Not dialyzed</td>
<td>Not dialyzed</td>
<td></td>
</tr>
<tr>
<td>(149,154)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>% excreted in the urine</td>
<td>T ½ normal (hours)</td>
<td>T ½ Dialysis (ESRD) (hours)</td>
<td>Hemodialysis</td>
<td>Peritoneal dialysis</td>
<td>Comments and recommendations on use and maximum dosing</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------</td>
<td>--------------------</td>
<td>-----------------------------</td>
<td>----------------</td>
<td>--------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Gabapentin (38,155,156)</td>
<td>Approx. 100</td>
<td>5–7</td>
<td>52–132</td>
<td>Dialyzed</td>
<td>Possibly dialyzed</td>
<td>Freely crosses the blood brain barrier. Dose post dialysis. eGFR 50–79: 600 mg tid eGFR 30–49: 300 mg tid eGFR 15–29: 300 mg bid eGFR &lt;15: 300 mg od For a discussion of a more conservative dosing regimen see main text.</td>
</tr>
<tr>
<td>Pregabalin (157,158)</td>
<td>92–99</td>
<td>5–6.5</td>
<td>Increased</td>
<td>Dialyzed</td>
<td>Dialyzed</td>
<td>Similar mechanism of action as gabapentin. Can give supplementary dose postdialysis (75 mg) eGFR &gt;30: 150 mg bid eGFR 15–30: 150 mg od eGFR &lt;15: 75 mg od For a discussion of a more conservative dosing regimen see main text.</td>
</tr>
<tr>
<td>Duloxetine (67,136)</td>
<td>&lt;1</td>
<td>8–17</td>
<td>Unchanged</td>
<td>Not dialyzed</td>
<td>Not dialyzed</td>
<td>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 &lt;30 ml/minute. Others suggest start at a very low dose and increase according to response, with a maximum dose of 30 mg daily.</td>
</tr>
<tr>
<td>Ketamine (136)</td>
<td>2–4</td>
<td>2–4</td>
<td>Unchanged</td>
<td>Not dialyzed</td>
<td>Unlikely to be dialyzed</td>
<td>Dose as per normal renal function.</td>
</tr>
<tr>
<td>Amitriptyline (159,160)</td>
<td>&lt;2</td>
<td>9–25</td>
<td>Unchanged</td>
<td>Not dialyzed</td>
<td>Not dialyzed</td>
<td>Although no dose reduction is required, a low-starting dose is recommended given likelihood of anticholinergic adverse effects.</td>
</tr>
</tbody>
</table>
TABLE 6. Pharmacokinetic data on nonsteroidal anti-inflammatory drugs in CKD and ESRD*

<table>
<thead>
<tr>
<th>Acetic acid derivatives: including sulindac, indomethacin, etodolac, bromfenac</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CKD</strong></td>
</tr>
<tr>
<td>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)</td>
</tr>
<tr>
<td>Effective renal blood flow decreased in patients with renal disease after only a few days of use (163,164)</td>
</tr>
<tr>
<td><strong>Dialysis</strong></td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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).</td>
</tr>
<tr>
<td><strong>Propionic acid derivatives</strong> (the –profens): 11 studies identified</td>
</tr>
<tr>
<td><strong>CKD</strong></td>
</tr>
<tr>
<td>Studies evaluating ketoprofen, ximoprofen and benoxaprofen have shown increased half-life in CKD (170–173).</td>
</tr>
<tr>
<td>One study of naproxen showed no difference in half-life, but lower serum levels and AUC in CKD (174).</td>
</tr>
<tr>
<td>Decreased serum levels of the parent drug, febuxem and its metabolites were noted in CKD (175).</td>
</tr>
<tr>
<td>In mild CKD: 80% reduction in urinary prostaglandins, 28% reduction in CrCl and a 40% increase in serum creatinine after 7 days showed accumulation of the active S-enatatomer metabolites after repeat dosing in hemodialysis patients (176).</td>
</tr>
<tr>
<td>Flurbiprofen concentration levels were decreased in patients on PD compared to normal subjects (177).</td>
</tr>
<tr>
<td><strong>Enolic acid derivatives</strong> Two studies evaluating CKD and dialysis patients administered tenoxicam suggest no difference in metabolism that would necessitate change in dosing (44,178).</td>
</tr>
<tr>
<td><strong>Selective Cox-2 inhibitors</strong></td>
</tr>
<tr>
<td><strong>CKD</strong></td>
</tr>
<tr>
<td>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).</td>
</tr>
<tr>
<td><strong>Dialysis</strong></td>
</tr>
<tr>
<td>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).</td>
</tr>
</tbody>
</table>


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 be 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).
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.

**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 pollicis 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 lumbo-dorsal 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, minocycline, 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 ≤3.4 ml/minute/1.73 m² (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 homogeneous, 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
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 cm³) (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


Table 9. Knowledge gaps and research agenda

| Symptom (pain) epidemiology and burden in developing countries. | Symptom (pain) epidemiology and burden in conservatively cared 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. |
40. Pham PC, Toscano E, Pham PM, Pham PA, Pham SV, Pham PT: Pain management in patients with chronic kidney disease. *NDT Plus* 2010; 11:752–758


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 haemodialysis or haemodialysis or esrd or 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.
15. Edmonton symptom assessment scale.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 nonsteroidal anti-inflammatory or nonsteroidal anti-inflammatory or tylanol 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/
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 pla-
cebo.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

guideline.gov
Alberta – TOPGuidelines http://www.topalberta-
doctors.org/cpgs/
BC – BCGuidelines.ca http://www.bcguidelines.ca/
CMA Infobase http://www.cma.ca/clinicalresourc-
es/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/; eG
uidelines.co.uk; http://www.eguidelines.co.uk; SIGN