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Pain management in patients with chronic kidney disease and end-stage kidney disease

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Abstract

Purpose of Review—This review evaluates current recommendations for pain management in CKD and ESKD with a specific focus on evidence for opioid analgesia, including the partial agonist, buprenorphine.

Recent Findings—Recent evidence supports the use of physical activity and other nonpharmacologic therapies, either alone or with pharmacological therapies, for pain management. Nonopioid analgesics, including acetaminophen, topical analgesics, gabapentinoids, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants may be considered based on pain etiology and type, with careful dose considerations in kidney disease. NSAIDs may be used in CKD and ESKD for short durations with careful monitoring. Opioid use should be minimized and reserved for patients who have failed other therapies. Opioids have been associated with increased adverse events in this population, and thus should be used cautiously after risk/benefit discussion with the patient. Opioids that are safer to use in kidney disease include oxycodone, hydromorphone, fentanyl, methadone and buprenorphine. Buprenorphine appears to be a promising and safer option due to its partial agonism at the mu opioid receptor.

Summary—Pain is poorly managed in patients with kidney disease. Non-pharmacological and non-opioid analgesics should be first-line approaches for pain management. Opioid use should be minimized with careful monitoring and dose adjustment.

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Keywords

End-stage kidney disease; chronic kidney disease; pain; opioids; buprenorphine

Introduction

Chronic pain is a common symptom experienced by patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) [1,2]. Untreated pain in this population negatively impacts health related quality of life (HRQOL), dialysis adherence, healthcare utilization and mortality [3-5]; and may contribute to other physical and psychosocial symptoms such as depression, anxiety and fatigue [6].

There is a disproportionately high use of opioids in this population due to limited availability of non-pharmacological treatment options or safe non-opioid pharmacological options. In a study of over 400,000 ESKD patients, over half had received an opioid prescription, 3.2 times the rate in the US population [7] and 20% were on long term opioid therapy (LTOT) [8]. Chronic opioid use in patients with kidney disease has been associated with increased risk of altered mental status, falls, fractures, hospitalizations and mortality, in a dose-dependent manner [9-12]. However, closely-monitored LTOT may be warranted in some patients who fail to respond to other pain treatments. This requires careful consideration of risks and benefits.

Pain management in kidney disease is a top research priority, and is being fostered in the nephrology community by enterprises such as the Kidney Health Initiative, a public-private partnership between the American Society of Nephrology and US Food and Drug Administration [13,14]. Additionally, the recently established Hemodialysis Opioid Prescription Effort (HOPE) Consortium, funded by the National Institutes of Health's Helping to End Addiction Long term mission and the National Institute of Diabetes and Digestive and Kidney diseases (NIDDK), will address pain management and opioid safety in this population [15].

The goal of the current review is to provide practical guidance for treating pain, summarize evidence on non-pharmacological and pharmacological options for pain, and focus on safety and efficacy of medications including opioids.

Approach to Pain Management

Multiple patient, provider, and healthcare-system factors make pain management challenging in this population (Figure 1) [16]. The multifactorial etiologioes of pain and common comorbid conditions in patients with kidney disease result in varying types of pain (neuropathic, nociceptive, or both). [17-21]. Provider- and system-related factors relate to lack of training for nephrologists in treating pain, fragmentation of care and most importantly lack of scientific evidence and guidelines around pain management in CKD and ESKD [22,23].

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Pain assessment

This should start with assessment of a) pain severity using various standardized tools, most common of which is the numerical rating scale [24]; b) pathophysiologic evaluation into mechanism of injury and type of pain; c) psychosocial evaluation of co-occurring factors that contribute to pain or make treatment of pain more challenging, such as depression, anxiety, and a history of substance use disorder [25]; and d) overall impact of pain using tools such as the PEG, a validated, three-item tool assessing Pain intensity, interferences with Enjoyment in life, and General activity [26].

Prior to initiating treatment, discussions should include realistic expectations for improvements in pain and function, which can strengthen the therapeutic alliance between patient and provider [27]. When patients' anticipated pain relief does not align with their experience it requires calibration of expectations [28].

Non-pharmacologic approaches

Non-pharmacologic options range from psychosocial or behavioral based interventions (e.g.: cognitive behavioral therapy [CBT], acceptance and commitment therapy, relaxation, music therapy, mindfulness) to physically-oriented interventions (e.g.: exercise, physical therapy, yoga, acupuncture, electrical stimulation). Psychosocial interventions are supported by robust evidence from the general population as effective approaches for reducing pain severity, interference, pain-related disability and psychological distress, and have limited but promising evidence for reduction in opioid use, and even opioid misuse behaviors [29-35]. Currently, such evidence in kidney disease is very limited and of poor quality [36-39]. Two NIDDK-funded trials (Technology Assisted Collaborative Care and the HOPE Consortium trial [15]) are currently testing telemedicine-delivered CBT-based interventions for pain in patients receiving hemodialysis [40]. Physical therapy or exercise-based interventions have been successful in improving pain in the general population [41]. Few studies of exercise, physical therapy, yoga, or acupuncture in patients with kidney disease have included pain as an outcome but show promising results [42-45]. Given that non-pharmacological interventions are generally safe, further research should test the effectiveness, feasibility and acceptability of them for patients with kidney disease.

Pharmacological approaches

Review the available evidence on pharmacokinetic, efficacy, and safety profiles of analgesics in patients with kidney disease is provided in Supplementary Tables 1 and 2. Summary of dose recommendations are provided in Tables 1 and 2.

Non-opioid therapy for nociceptive pain

Acetaminophen—Acetaminophen, a common over-the-counter analgesic, and can be tried as scheduled doses for mild to moderate pain, although a Cochrane review found that efficacy in the general population may be limited [88]. It requires no dose adjustment and is generally safe in kidney disease, although may rarely cause analgesic nephropathy with long term use [89].

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NSAIDs—Potential risks of NSAIDs include gastrointestinal, cardiovascular, and renal adverse events [90]. NSAIDs inhibit prostaglandin synthesis by interfering with the cyclo-oxygenase pathway, which may increase risk of acute kidney injury, sodium retention, hypertension, hyperkalemia, and heart failure. They may also increase cardiovascular events via vasoconstriction and platelet aggregation [91]. Gastrointestinal and bleeding risks are lower with COX-2 selective agents such as celecoxib [92,93]. Recent epidemiological evidence suggests association of chronic NSAID use with increased risk of CKD progression and hospitalization in patients with CKD, albeit less than that with opioid use [12]. Similarly, in ESKD, NSAID use has been associated with increased mortality, but these findings are confounded by limitations of observational data [63].

Most of these adverse effects are rare, related to cumulative dose and likely modified by an individual's underlying risk factors, such as comorbidities and concomitant medications. Thus, short-term, cautious use of NSAIDs with consideration of individual risk factors, careful side effect monitoring, and risk/benefit discussion may be appropriate [95]. We agree with recommendations outlined by in a recent review that suggests short-acting NSAIDs could be used short-term (</= 5 days) in patients with CKD Stages 1-3; judiciously in patients with CKD Stage 4; and avoided in CKD 5 [96]. A similar case can be made for cautious use of NSAIDs in ESKD patients, in whom gastrointestinal toxicity and loss of residual renal function are the most concerning side effects. In anuric ESKD patients, there is no effect on glomerular blood flow or tubular function, thus NSAID-mediated electrolyte disturbances, volume retention, and hypertension are of less concern [60].

Topical agents—Topical agents (e.g.: topical NSAIDs, lidocaine patch, high dose capsaicin patch) may provide localized pain relief [97-100]. Topical NSAIDs are efficacious in both acute and chronic pain, have minimal systemic exposure (2-3% of oral dose), and are safe in patients with kidney disease when used over limited surface area [101].

Skeletal muscle relaxants—Skeletal muscle relaxants such as baclofen, methocarbamol, and tizanidine, do not have a role in chronic pain conditions and are only recommended for short-term use in some acute pain conditions such as spasticity and spasms [102]. All skeletal muscle relaxants may cause significant sedation, muscle weakness and dizziness and should be avoided in advanced CKD and ESKD. For example baclofen, which is renally cleared, can cause severe neurotoxicity and muscle paralysis in advanced CKD and ESKD, and should be avoided.

Cannabis—While cannabis may improve some painful conditions, it has not been tested in persons with kidney disease, and its role and safety in this population is unclear [103-105].

Non-opioid therapy for neuropathic pain

In the general population, evidence supports the use of gabapentinoids (pregabalin and gabapentin), tricyclic antidepressants (TCA), and serotonin-norepinephrine reuptake inhibitors (SNRI) as first-line treatments for neuropathic pain.[99] The clearance of both gabapentin and pregabalin decreases and half-life ($t_{½}$) increases proportionately with worsening renal function, requiring renal dose adjustment (Tables 1 and Supplementary

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Table 1) [106-108]. Both medications should be dosed post-HD. These agents have been associated with increased risk of altered mental status, falls, and fractures in ESKD patients [109], and concomitant use with opioids is associated with increased hospitalization and mortality [110]. They have been associated with potential misuse and addiction and should be used with caution and close monitoring [111].

Little evidence exists regarding use of TCAs and SNRIs for patients with kidney disease (Tables 1 and 3). TCAs are associated with dose-related anticholinergic and antihistaminic side effects; SNRIs are generally better tolerated. Both of these classes may cause or exacerbate syndrome of inappropriate antidiuretic hormone secretion. The use of the SNRI duloxetine in patients with Cl_{Cr} < 30 mL/minute or on dialysis is not recommended by current FDA guidance; however, guidelines from the European Union and Canada suggest its use in severe CKD and ESKD with lower starting doses and cautious monitoring [112].

Opioid therapy for pain

Although the main indication for opioids is for nociceptive pain, they have also been shown to be effective in improving neuropathic pain, especially diabetic neuropathy, either alone or as adjuvants to gabapentinoids [113,114]. The decision to initiate LTOT should be made through a careful risk-benefit evaluation and shared decision-making. Opioids should be avoided if other options are effective, and should be used sparingly at the minimum effective doses. We recommend a similar approach to the CDC guidelines, including maximizing nonpharmacologic therapy and nonopioid analgesia, establishing clear therapeutic goals, initiating treatment with immediate-release opioids rather than long-acting, starting with low doses, and uptitrating gradually with close monitoring of side effects [8].

The benefits of treatment may include improved quality of life and better functioning. This should be balanced with the increased risks of opioids in kidney disease such as altered mental status, falls, fractures, hospitalizations, and mortality, which occurs in a dose-dependent manner and can be seen even at lower doses [9-12]. These risks may be more pronounced in the older adults, and those with concomitant sedating medications such as gabapentinoids and benzodiazepines [110,115]. LTOT can also have additional adverse effects such as hyperalgesia, sedation, overdose, and progression to opioid use disorder (OUD). An evidence-based tool to help evaluate risk of opioid misuse before initiating treatment is the Revised Opioid Risk Tool, which creates a risk category based on personal and family history of substance misuse, age, and psychological disease [116]. If OUD is suspected, we recommend referral to an addiction treatment provider.

Monitoring of long-term opioid therapy—A cornerstone of LTOT is ensuring proper monitoring. CDC guidelines recommend checking state-wide prescription drug monitoring programs to identify controlled medications prescribed by other providers [8]. Additionally, periodic drug screens are important to ensure prescribed medication use and evaluate for illicit substance use. Urine drug testing is the preferred method of screening due to high sensitivity and specificity [117]. However, this may be challenging in patients with ESKD who produce little or no urine. Oral buccal swabs or saliva testing offer a reasonable

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alternative but may have logistic issues with specimen collection as these patients frequently have xerostomia.

Specific opioid medications—The pharmacokinetic evidence of commonly used opioid medications in patients with kidney disease is summarized in Supplementary Table 2. Opioids that are safer to use in kidney disease include oxycodone, hydromorphone, fentanyl, methadone and buprenorphine. Oxycodone is one of the most commonly prescribed opioids for kidney disease patients in the US [9]. It has predominantly hepatic elimination and is poorly dialyzed (Table 2). Caution should be used with long-acting formulations and when prescribed concurrently with medications that affect CYP3A4 or CYP2D6 metabolism [118]. Similarly, hydromorphone has a reasonable safety profile in kidney disease at lower doses and is dialyzed by HD, but supplemental doses are usually not needed post-HD. Fentanyl appears to be safe in kidney disease, although evidence is limited. On the other hand, morphine and hydrocodone have high risk of accumulation and systemic exposure, thus are contraindicated in patients with CKD or ESKD.

Tramadol is an atypical, centrally-acting opioid with dual action as a weak mu-opioid receptor agonist and SNRI. Tramadol and its active M1 metabolite are renally excreted. Its metabolism can vary unpredictably depending on an individual's cytochrome P450 genetic profile [119]. Tramadol also has multiple drug interactions that may result in serotonin syndrome or seizures. Thus, we recommend it be used with extreme caution and at reduced doses, but preferably avoided.

Special Consideration: Buprenorphine and Methadone

Less commonly used opioid medications for pain are methadone (full agonist at mu-opioid receptor) and buprenorphine (partial agonist). They are more commonly used for the treatment of OUD where they reduce cravings, abate withdrawal symptoms, and prevent overdose. However, there are formulations for methadone and buprenorphine that can be used to treat chronic pain, as discussed below.

Methadone

Methadone functions as an NMDA-receptor antagonist, giving it additional efficacy for neuropathic pain. The analgesic half-life is 6-8 hours, requiring multiple daily doses. Methadone and its metabolites do not accumulate in CKD or ESKD, thus no dose adjustment is needed and it is not dialyzed out by HD (Table 2 and Supplementary Table 2). Because it can prolong the QTc interval, the electrolyte abnormalities such as hypo/hyperkalemia or hypo/hypermagnesemia that are frequently present in kidney disease may exacerbate its arrhythmia potential.

For patients without OUD, methadone as an analgesic can be prescribed by any provider with an active Drug Enforcement Administration (DEA) license, does not require patients to attend a clinic with an Opioid Treatment Program license, and can be legally filled at commercial pharmacies. In contrast, for patients with OUD, methadone is highly regulated, must be dispensed from a federally licensed Opioid Treatment Program, is dosed once a day, and initially requires patients to travel daily to receive observed dosing.

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Buprenorphine

Buprenorphine is an efficacious treatment of pain in the general population [120]. Due to its partial agonism, it has a “ceiling effect” which reduces the risks of respiratory sedation and overdose. It is metabolized in the bile duct, requires no dose adjustment in CKD, and is not dialyzed (Table 2). Given its better safety profile compared to full opioids and steady state in CKD/ESKD, it may provide a therapeutic advantage and a safer alternative for pain management in patients with kidney disease who have a physiologic dependence to opioids [121-123].

Buprenorphine prescribing for chronic pain remains low due to barriers depicted in Figure 2; potential solutions are offered. Barriers include provider confusion about available buprenorphine formulations, their indications, and federal regulations for X-waiver (Table 3) [124]. Notably, although sublingual buprenorphine-naloxone can be prescribed off-label as an analgesic, several logistical hurdles make that difficult, including requiring documentation of indication [125]. Insurance authorization may also be required for transdermal or buccal formulations of buprenorphine [126,127]. Lastly, given its traditional use as a treatment for OUD, buprenorphine may be stigmatized by patients and providers, similar to methadone [128]. The ongoing HOPE Consortium trial will provide valuable insight into the acceptability, tolerability and efficacy of buprenorphine in patients on dialysis.

Conclusion

Pain is highly prevalent and challenging to treat among patients with kidney disease. Pain management requires careful assessment, continuous monitoring, and shared decision-making of risks and benefits of different pharmacological and non-pharmacological therapeutic options with patients. Long-term therapy with full agonist opioid treatment is associated with significantly higher adverse effects in this population, thus more research into safer alternatives such as buprenorphine is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Mercadante S, Ferrantelli A, Tortorici C, et al. Incidence of Chronic Pain in Patients with End-Stage Renal Disease on Dialysis. J Pain Symptom Manage [Internet]. 2005 10;30(4):302–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0885392405004343
2. Davison SN. Clinical Pharmacology Considerations in Pain Management in Patients with Advanced Kidney Failure. Clin J Am Soc Nephrol [Internet]. 2019;14(6):917–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30833302

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3. Davison SN, Jhangri GS. Impact of Pain and Symptom Burden on the Health-Related Quality of Life of Hemodialysis Patients. J Pain Symptom Manage [Internet]. 2010 3;39(3):477–85. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0885392410000898
4. Harris TJ, Nazir R, Khetpal P, et al. Pain, sleep disturbance and survival in hemodialysis patients. Nephrol Dial Transplant [Internet]. 2012 2 1;27(2):758–65. Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfr355
5. Weisbord SD, Mor MK, Sevick MA, et al. Associations of Depressive Symptoms and Pain with Dialysis Adherence, Health Resource Utilization, and Mortality in Patients Receiving Chronic Hemodialysis. Clin J Am Soc Nephrol [Internet]. 2014 9 5;9(9):1594–602. Available from: http://cjasn.asnjournals.org/lookup/doi/10.2215/CJN.00220114
6. Jhamb M, Abdel-Kader K, Yabes J, et al. Comparison of Fatigue, Pain, and Depression in Patients With Advanced Kidney Disease and Cancer—Symptom Burden and Clusters. J Pain Symptom Manage [Internet]. 2019 3;57(3):566–575.e3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0885392418311205
7. Daubresse M, Alexander GC, Crews DC, et al. Trends in Opioid Prescribing Among Hemodialysis Patients, 2007-2014. Am J Nephrol [Internet]. 2019;49(1):20–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30544114
8. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. JAMA [Internet]. 2016 4 19;315(15):1624 Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.1464
9. Kimmel PL, Fwu C-W, Abbott KC, et al. Opioid Prescription, Morbidity, and Mortality in United States Dialysis Patients. J Am Soc Nephrol [Internet]. 2017 12 1;28(12):3658 LP–3670. Available from: http://jasn.asnjournals.org/content/28/12/3658.abstract
10. Ishida JH, McCulloch CE, Steinman MA, et al. Opioid Analgesics and Adverse Outcomes among Hemodialysis Patients. Clin J Am Soc Nephrol [Internet]. 2018 5 7;13(5):746–53. Available from: http://cjasn.asnjournals.org/lookup/doi/10.2215/CJN.09910917
11. Vangala C, Niu J, Montez-Rath ME, et al. Hip Fracture Risk among Hemodialysis-Dependent Patients Prescribed Opioids and Gabapentinoids. J Am Soc Nephrol [Internet]. 2020 5 5;ASN.2019090904. Available from: http://www.jasn.org/lookup/doi/10.1681/ASN.2019090904
12**. Zhan M, Doerfler RM, Xie D, et al. Association of Opioids and Nonsteroidal Anti-inflammatory Drugs With Outcomes in CKD: Findings From the CRIC (Chronic Renal Insufficiency Cohort) Study. Am J Kidney Dis [Internet]. 2020 4; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638620300421This study demonstrated that opioids were associated with a much higher risk of adverse kidney disease outcomes, death, and hospitalization in comparison to the modest relationship between NSAID use and adverse outcomes.
13. Flythe JE, Hilliard T, Castillo G, et al. Symptom Prioritization among Adults Receiving In-Center Hemodialysis. Clin J Am Soc Nephrol [Internet]. 2018 5 7;13(5):735–45. Available from: http://cjasn.asnjournals.org/lookup/doi/10.2215/CJN.10850917
14. Flythe JE, Hilliard T, Lumby E, et al. Fostering Innovation in Symptom Management among Hemodialysis Patients. Clin J Am Soc Nephrol [Internet]. 2019 1 7;14(1):150–60. Available from: http://cjasn.asnjournals.org/lookup/doi/10.2215/CJN.07670618
15. NIDDK. Hemodialysis Opioid Prescription Effort (HOPE) Consortium [Internet]. [cited 2020 May 29]. Available from: https://www.niddk.nih.gov/research-funding/research-programs/hemodialysis-opioid-prescription-effort-consortium
16. Jhamb M, Tucker L, Liebschutz J. When ESKD complicates the management of pain. Semin Dial [Internet]. 2020 5 4;sdi.12881. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/sdi.12881
17. Cukor D, Saggi SJ, Ahmad R, et al. Pain experienced by dialysis patients in two culturally diverse populations. Hemodial Int [Internet]. 2019 10;23(4):510–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31374139
18. Hsu H-J, Wu I-W, Hsu K-H, et al. The association between chronic musculoskeletal pain and clinical outcome in chronic kidney disease patients: a prospective cohort study. Ren Fail [Internet]. 2019 11;41(1):257–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31014149

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19. Bristowe K, Selman LE, Higginson IJ, et al. Invisible and intangible illness: a qualitative interview study of patients' experiences and understandings of conservatively managed end-stage kidney disease. Ann Palliat Med [Internet]. 2019 4;8(2):121–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30691280
20. Ng MSN, Miaskowski C, Cooper B, et al. Distinct Symptom Experience Among Subgroups of Patients With ESRD Receiving Maintenance Dialysis. J Pain Symptom Manage [Internet]. 2020 1 23; Available from: http://www.ncbi.nlm.nih.gov/pubmed/31981596
21. Ng MSN, So WKW, Wong CL, et al. Stability and Impact of Symptom Clusters in Patients With End-Stage Renal Disease Undergoing Dialysis. J Pain Symptom Manage [Internet]. 2020;59(1):67–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31419542
22. Bourbonnais FF, Tousignant KF. Experiences of Nephrology Nurses in Assessing and Managing Pain in Patients Receiving Maintenance Hemodialysis. Nephrol Nurs J [Internet]. 47(1):37–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32083435
23. Jawed A, Moe SM, Moorthi RN, et al. Increasing Nephrologist Awareness of Symptom Burden in Older Hospitalized End-Stage Renal Disease Patients. Am J Nephrol [Internet]. 2020;51(1):11–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31743896
24. Dansie EJ, Turk DC. Assessment of patients with chronic pain. Br J Anaesth [Internet]. 2013 7;111(1):19–25. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0007091217329628
25. Jackman RP, Purvis JM, Mallett BS. Chronic nonmalignant pain in primary care. Am Fam Physician [Internet]. 2008/11/28 2008;78(10):1155–62. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19035063
26. Krebs EE, Lorenz KA, Bair MJ, et al. Development and Initial Validation of the PEG, a Three-item Scale Assessing Pain Intensity and Interference. J Gen Intern Med [Internet]. 2009 6 6;24(6):733–8. Available from: http://link.springer.com/10.1007/s11606-009-0981-1
27. Yelland MJ, Schluter PJ. Defining Worthwhile and Desired Responses to Treatment of Chronic Low Back Pain. Pain Med [Internet]. 2006 1 1;7(1):38–45. Available from: https://academic.oup.com/painmedicine/article-lookup/doi/10.1111/j.1526-4637.2006.00087.x
28. Geurts JW, Willems PC, Lockwood C, et al. Patient expectations for management of chronic non-cancer pain: A systematic review. Heal Expect [Internet]. 2017 12;20(6):1201–17. Available from: http://doi.wiley.com/10.1111/hex.12527
29. Williams AC de C, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev [Internet]. 2012 11 14; Available from: http://doi.wiley.com/10.1002/14651858.CD007407.pub3
30. Frank JW, Lovejoy TI, Becker WC, et al. Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy. Ann Intern Med [Internet]. 2017 8 1;167(3):181 Available from: http://annals.org/article.aspx?doi=10.7326/M17-0598
31. Garland EL, Brintz CE, Hanley AW, et al. Mind-Body Therapies for Opioid-Treated Pain. JAMA Intern Med [Internet]. 2020 1 1;180(1):91 Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2753680
32. Sullivan MD, Turner JA, DiLodovico C, et al. Prescription Opioid Taper Support for Outpatients With Chronic Pain: A Randomized Controlled Trial. J Pain [Internet]. 2017 3;18(3):308–18. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1526590016303285
33. Naylor MR, Naud S, Keefe FJ, et al. Therapeutic Interactive Voice Response (TIVR) to Reduce Analgesic Medication Use for Chronic Pain Management. J Pain [Internet]. 2010 12;11(12):1410–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1526590010004645
34. Guarino H, Fong C, Marsch LA, et al. Web-Based Cognitive Behavior Therapy for Chronic Pain Patients with Aberrant Drug-Related Behavior: Outcomes from a Randomized Controlled Trial. Pain Med [Internet]. 2018 12 1;19(12):2423–37. Available from: https://academic.oup.com/painmedicine/article/19/12/2423/4807510
35. Brintz C, Cukor D, Cheatle M, et al. Non-pharmacological Treatments for Opioid Reduction in Patients with Advanced Chronic Kidney Disease. Manuscript submitted for publication.
36. Ramezanzadeh D, Manshaee G. The impact of acceptance and commitment therapy on pain catastrophizing: The case of hemodialysis patients in Iran. Int J Educ Psychol Res [Internet]. 2016;2(2):69 Available from: http://www.ijeprjournal.org/text.asp?2016/2/2/69/178868

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37. Heidarigorji A, Heidari Gorji M, Davanloo Aa. The efficacy of relaxation training on stress, anxiety, and pain perception in hemodialysis patients. Indian J Nephrol [Internet]. 2014;24(6):356 Available from: http://www.indianjnephrol.org/text.asp?2014/24/6/356/132998
38. Rambod M, Sharif F, Pourali-Mohammadi N, et al. Evaluation of the effect of Benson's relaxation technique on pain and quality of life of haemodialysis patients: A randomized controlled trial. Int J Nurs Stud [Internet]. 2014 7;51(7):964–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0020748913003544
39. Burrai F, Lupi R, Luppi M, et al. Effects of Listening to Live Singing in Patients Undergoing Hemodialysis: A Randomized Controlled Crossover Study. Biol Res Nurs [Internet]. 2019;21(1):30–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30249121
40. Roumelioti M-E, Steel JL, Yabes J, et al. Rationale and design of technology assisted stepped collaborative care intervention to improve patient-centered outcomes in hemodialysis patients (TĀCcare trial). Contemp Clin Trials [Internet]. 2018 10;73:81–91. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1551714418302921
41. Searle A, Spink M, Ho A, et al. Exercise interventions for the treatment of chronic low back pain: a systematic review and meta-analysis of randomised controlled trials. Clin Rehabil [Internet]. 2015 12 13;29(12):1155–67. Available from: http://journals.sagepub.com/doi/10.1177/0269215515570379
42. Painter P, Carlson L, Carey S, et al. Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. Am J Kidney Dis [Internet]. 2000 3;35(3):482–92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638600702022
43. Yurtkuran M, Alp A, Yurtkuran M, et al. A modified yoga-based exercise program in hemodialysis patients: A randomized controlled study. Complement Ther Med [Internet]. 2007 9;15(3):164–71. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0965229906000732
44. Bullen A, Awdishu L, Lester W, et al. Effect of Acupuncture or Massage on Health-Related Quality of Life of Hemodialysis Patients. J Altern Complement Med [Internet]. 2018 11;24(11):1069–75. Available from: https://www.liebertpub.com/doi/10.1089/acm.2018.0030
45. Kim KH, Lee MS, Kim T-H, et al. Acupuncture and related interventions for symptoms of chronic kidney disease. Cochrane Database Syst Rev [Internet]. 2016 6 28; Available from: http://doi.wiley.com/10.1002/14651858.CD009440.pub2
46. Randinitis EJ, Posvar EL, Alvey CW, et al. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol [Internet]. 2003 3;43(3):277–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12638396
47. Lal R, Sukbuntherng J, Luo W, et al. Clinical pharmacokinetics of gabapentin after administration of gabapentin enacarbil extended-release tablets in patients with varying degrees of renal function using data from an open-label, single-dose pharmacokinetic study. Clin Ther [Internet]. 2012 1;34(1):201–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22206794
48. Blum RA, Comstock TJ, Sica DA, et al. Pharmacokinetics of gabapentin in subjects with various degrees of renal function. Clin Pharmacol Ther [Internet]. 1994 8;56(2):154–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8062491
49. Wong MO, Eldon MA, Keane WF, et al. Disposition of gabapentin in anuric subjects on hemodialysis. J Clin Pharmacol [Internet]. 1995 6;35(6):622–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7665723
50. Lobo ED, Heathman M, Kuan H-Y, et al. Effects of varying degrees of renal impairment on the pharmacokinetics of duloxetine: analysis of a single-dose phase I study and pooled steady-state data from phase II/III trials. Clin Pharmacokinet [Internet]. 2010 5;49(5):311–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20384393
51. Nichols AI, Richards LS, Behrle JA, et al. The pharmacokinetics and safety of desvenlafaxine in subjects with chronic renal impairment. Int J Clin Pharmacol Ther [Internet]. 2011 1;49(1):3–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21176719
52. Troy SM, Schultz RW, Parker VD, et al. The effect of renal disease on the disposition of venlafaxine. Clin Pharmacol Ther [Internet]. 1994 7;56(1):14–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8033490

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

53. Lieberman JA, Cooper TB, Suckow RF, et al. Tricyclic antidepressant and metabolite levels in chronic renal failure. Clin Pharmacol Ther [Internet]. 1985 3;37(3):301–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3971655
54. Sandoz M, Vandel S, Vandel B, et al. Metabolism of amitriptyline in patients with chronic renal failure. Eur J Clin Pharmacol [Internet]. 1984;26(2):227–32. Available from: http://link.springer.com/10.1007/BF00630290
55. Dawling S, Lynn K, Rosser R, et al. Nortriptyline metabolism in chronic renal failure: metabolite elimination. Clin Pharmacol Ther [Internet]. 1982 9;32(3):322–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7105623
56. Dawlilng S, Lynn K, Rosser R, et al. The pharmacokinetics of nortriptyline in patients with chronic renal failure. Br J Clin Pharmacol [Internet]. 1981 7;12(1):39–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7248140
57. Tutor-Crespo MJ, Hermida J, Tutor JC. Relative Proportions of Serum Carbamazepine and its Pharmacologically Active 10,11-Epoxy Derivative: Effect of Polytherapy and Renal Insufficiency. Ups J Med Sci [Internet]. 2008 1 12;113(2):171–80. Available from: http://www.tandfonline.com/doi/full/10.3109/2000-1967-225
58. Lee CS, Wang LH, Marbury TC, et al. Hemodialysis clearance and total body elimination of carbamazepine during chronic hemodialysis. Clin Toxicol [Internet]. 1980 10;17(3):429–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7449356
59. Vlavonou R, Perreault MM, Barrière O, et al. Pharmacokinetic characterization of baclofen in patients with chronic kidney disease: dose adjustment recommendations. J Clin Pharmacol [Internet]. 2014 5;54(5):584–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24414993
60. Chauvin KJ, Blake PG, Garg AX, et al. Baclofen has a risk of encephalopathy in older adults receiving dialysis. Kidney Int [Internet]. 2020 5; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253820305524
61. Wolf E, Kothari NR, Roberts JK, et al. Baclofen Toxicity in Kidney Disease. Am J Kidney Dis [Internet]. 2018;71(2):275–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28899601
62. Brvar M, Vrtovec M, Kovac D, et al. Haemodialysis clearance of baclofen. Eur J Clin Pharmacol [Internet]. 2007 12;63(12):1143–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17764008
63. Narabayashi M, Saijo Y, Takenoshita S, et al. Opioid rotation from oral morphine to oral oxycodone in cancer patients with intolerable adverse effects: an open-label trial. Jpn J Clin Oncol [Internet]. 2008 4;38(4):296–304. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18326541
64. Kurita GP, Lundström S, Sjøgren P, et al. Renal function and symptoms/adverse effects in opioid-treated patients with cancer. Acta Anaesthesiol Scand [Internet]. 2015 9;59(8):1049–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25943005
65. Malhotra BK, Schoenhard GL, de Kater AW, et al. The pharmacokinetics of oxycodone and its metabolites following single oral doses of Remoxy®, an abuse-deterrent formulation of extended-release oxycodone, in patients with hepatic or renal impairment. J Opioid Manag [Internet]. 11(2):157–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25901481
66. Leuppi-Taegtmeyer A, Duthaler U, Hammann F, et al. Pharmacokinetics of oxycodone/naloxone and its metabolites in patients with end-stage renal disease during and between haemodialysis sessions. Nephrol Dial Transplant [Internet]. 2019;34(4):692–702. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30189012
67. Samolsky Dekel BG, Donati G, Vasarri A, et al. Dialyzability of Oxycodone and Its Metabolites in Chronic Noncancer Pain Patients with End-Stage Renal Disease. Pain Pract [Internet]. 2017;17(5):604–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27589376
68. Kirvela M, Lindgren L, Seppala T, et al. The pharmacokinetics of oxycodone in uremic patients undergoing renal transplantation. J Clin Anesth [Internet]. 1996 2;8(1):13–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/0952818095000925
69. Darwish M, Yang R, Tracewell W, et al. Effects of Renal Impairment and Hepatic Impairment on the Pharmacokinetics of Hydrocodone After Administration of a Hydrocodone Extended-Release Tablet Formulated With Abuse-Deterrence Technology. Clin Pharmacol drug Dev [Internet]. 2016 3;5(2):141–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27138027

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

70. Ashby M, Fleming B, Wood M, et al. Plasma morphine and glucuronide (M3G and M6G) concentrations in hospice inpatients. J Pain Symptom Manage [Internet]. 1997 9;14(3):157–67. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9291702
71. Bastani B, Jamal JA. Removal of morphine but not fentanyl during haemodialysis. Nephrol Dial Transplant [Internet]. 1997 12;12(12):2802–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9430910
72. Lee MA, Leng ME, Tiernan EJ. Retrospective study of the use of hydromorphone in palliative care patients with normal and abnormal urea and creatinine. Palliat Med [Internet]. 2001 1;15(1):26–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11212464
73. Paramanandam G, Prommer E, Schwenke DC. Adverse effects in hospice patients with chronic kidney disease receiving hydromorphone. J Palliat Med [Internet]. 2011 9;14(9):1029–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21823925
74. Perlman R, Giladi H, Brecht K, et al. Intradialytic clearance of opioids: methadone versus hydromorphone. Pain [Internet]. 2013 12;154(12):2794–800. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23973378
75. 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 [Internet]. 4(6):335–6, 339–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19192761
76. Joh J, Sila MK, Bastani B. Nondialyzability of fentanyl with high-efficiency and high-flux membranes. Anesth Analg [Internet]. 1998 2;86(2):447 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9459269
77. Kreek MJ, Schecter AJ, Gutjahr CL, et al. Methadone use in patients with chronic renal disease. Drug Alcohol Depend [Internet]. 1980 3;5(3):197–205. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6986247
78. Opdal MS, Arnesen M, Müller LD, et al. Effects of Hemodialysis on Methadone Pharmacokinetics and QTc. Clin Ther [Internet]. 2015 7 1;37(7):1594–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25963997
79. Furlan V, Hafi A, Dessalles MC, et al. Methadone is poorly removed by haemodialysis. Nephrol Dial Transplant [Internet]. 1999 1;14(1):254–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10052536
80. Melilli G, Samolsky Dekel BG, Frenquelli C, et al. Transdermal opioids for cancer pain control in patients with renal impairment. J Opioid Manag [Internet]. 10(2):85–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24715663
81. Hand CW, Sear JW, Uppington J, et al. Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. Br J Anaesth [Internet]. 1990 3;64(3):276–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2328175
82. Filitz J, Griessinger N, Sittl R, et al. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. Eur J Pain [Internet]. 2006 11;10(8):743–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16426877
83. Moller PL, Sindet-Pedersen S, Petersen CT, et al. Onset of acetaminophen analgesia: comparison of oral and intravenous routes after third molar surgery. Br J Anaesth [Internet]. 2005 5;94(5):642–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15790675
84. Koncicki HM, Unruh M, Schell JO. Pain Management in CKD: A Guide for Nephrology Providers. Am J Kidney Dis [Internet]. 2017 3;69(3):451–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27881247
85. Kienzler J-L, Gold M, Nollevaux F. Systemic bioavailability of topical diclofenac sodium gel 1% versus oral diclofenac sodium in healthy volunteers. J Clin Pharmacol [Internet]. 2010 1;50(1):50–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19841157
86. Lugo RA, Kern SE. The pharmacokinetics of oxycodone. J Pain Palliat Care Pharmacother [Internet]. 2004;18(4):17–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15760805

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

87. Kinnunen M, Piirainen P, Kokki H, et al. Updated Clinical Pharmacokinetics and Pharmacodynamics of Oxycodone. Clin Pharmacokinet [Internet]. 2019;58(6):705–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30652261

88. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus placebo for knee and hip osteoarthritis. Cochrane Database Syst Rev [Internet]. 2019 2 25; Available from: http://doi.wiley.com/10.1002/14651858.CD013273

89. McCrae JC, Morrison EE, MacIntyre IM, et al. Long-term adverse effects of paracetamol - a review. Br J Clin Pharmacol [Internet]. 2018 10;84(10):2218–30. Available from: http://doi.wiley.com/10.1111/bcp.13656

90. Whelton A Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med [Internet]. 1999 5;106(5):13S–24S. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002934399001138

91. Gunter BR, Butler KA, Wallace RL, et al. Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis. J Clin Pharm Ther [Internet]. 2017 2;42(1):27–38. Available from: http://doi.wiley.com/10.1111/jcpt.12484

92. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and Upper Gastrointestinal Effects of Celecoxib in Rheumatoid Arthritis. JAMA [Internet]. 1999 11 24;282(20):1921 Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.282.20.1921

93. Leese PT, Hubbard RC, Karim A, et al. Effects of Celecoxib, a Novel Cyclooxygenase-2 Inhibitor, on Platelet Function in Healthy Adults: A Randomized, Controlled Trial. J Clin Pharmacol [Internet]. 2000 2;40(2):124–32. Available from: http://doi.wiley.com/10.1177/00912700022008766

94. Lai KM, Chen T-L, Chang C-C, et al. Association between NSAID use and mortality risk in patients with end-stage renal disease: a population-based cohort study. Clin Epidemiol [Internet]. 2019;11:429–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31213924

95. Sriperumbuduri S, Hiremath S. The case for cautious consumption. Curr Opin Nephrol Hypertens [Internet]. 2019 3;28(2):163–70. Available from: http://journals.lww.com/00041552-201903000-00011

96**. Baker M, Perazella MA. NSAIDs in CKD: Are They Safe? Am J Kidney Dis [Internet]. 2020 5; Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638620307241This article outlined the effects of NSAIDs on potential nephrotoxic events at each CKD Stage with a concurrent recommendation for NSAID use. The authors also give recommendations for NSAID dosing in CKD.

97. Derry S, Moore RA, Gaskell H, et al. Topical NSAIDs for acute musculoskeletal pain in adults. Cochrane Database Syst Rev [Internet]. 2015 6 15; Available from: http://doi.wiley.com/10.1002/14651858.CD007402.pub3

98. Derry S, Conaghan P, Da Silva JAP, et al. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev [Internet]. 2016 4 22; Available from: http://doi.wiley.com/10.1002/14651858.CD007400.pub3

99. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol [Internet]. 2015 2;14(2):162–73. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1474442214702510

100. Aitken E, McColl G, Kingsmore D. The Role of Qutenza® (Topical Capsaicin 8%) in Treating Neuropathic Pain from Critical Ischemia in Patients with End-Stage Renal Disease: An Observational Cohort Study. Pain Med [Internet]. 2016 7 14;pnw139. Available from: https://academic.oup.com/painmedicine/article-lookup/doi/10.1093/pm/pnw139

101. Kienzler J-L, Gold M, Nollevaux F. Systemic Bioavailability of Topical Diclofenac Sodium Gel 1% Versus Oral Diclofenac Sodium in Healthy Volunteers. J Clin Pharmacol [Internet]. 2010 1;50(1):50–61. Available from: http://doi.wiley.com/10.1177/0091270009336234

102. Fudin J, Raouf M. A Review of Skeletal Muscle Relaxants for Pain Management [Internet]. Practical Pain Management. 2017 Available from: https://www.practicalpainmanagement.com/treatments/pharmacological/non-opioids/review-skeletal-muscle-relaxants-pain-management

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

103. Rein JL, Wyatt CM. Marijuana and Cannabinoids in ESRD and Earlier Stages of CKD. Am J Kidney Dis [Internet]. 2018 2;71(2):267–74. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638617308107

104. The Health Effects of Cannabis and Cannabinoids [Internet]. Washington, D.C.: National Academies Press; 2017 Available from: https://www.nap.edu/catalog/24625

105. Bachhuber MA, Saloner B, Cunningham CO, et al. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010. JAMA Intern Med [Internet]. 2014 10 1;174(10):1668 Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2014.4005

106. Cheikh Hassan HI, Brennan F, Collett G, et al. Efficacy and Safety of Gabapentin for Uremic Pruritus and Restless Legs Syndrome in Conservatively Managed Patients With Chronic Kidney Disease. J Pain Symptom Manage [Internet]. 2015 4;49(4):782–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S088539241400445X

107. Gunal AI, Ozalp G, Yoldas TK, et al. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant [Internet]. 2004 12 1;19(12):3137–9. Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfh496

108. Simonsen E, Komenda P, Lerner B, et al. Treatment of Uremic Pruritus: A Systematic Review. Am J Kidney Dis [Internet]. 2017 11;70(5):638–55. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638617307813

109. Ishida JH, McCulloch CE, Steinman MA, et al. Gabapentin and Pregabalin Use and Association with Adverse Outcomes among Hemodialysis Patients. J Am Soc Nephrol [Internet]. 2018 7;29(7):1970–8. Available from: http://www.jasn.org/lookup/doi/10.1681/ASN.2018010096

110**. Waddy SP, Becerra AZ, Ward JB, et al. Concomitant Use of Gabapentinoids with Opioids Is Associated with Increased Mortality and Morbidity among Dialysis Patients. Am J Nephrol [Internet]. 2020 5 19;1–9. Available from: https://www.karger.com/Article/FullText/507725This study highlights the risks of opioid and gabapentinoid co-prescribing in patients receiving dialysis.

111. Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. Ann Pharmacother [Internet]. 2016 3 31;50(3):229–33. Available from: http://journals.sagepub.com/doi/10.1177/1060028015620800

112. Nguyen T, Shoukhardin I, Gouse A. Duloxetine Uses in Patients With Kidney Disease. Am J Ther [Internet]. 2019;26(4):e516–9. Available from: http://journals.lww.com/00045391-201908000-00014

113. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: A randomized controlled trial. Neurology [Internet]. 2003 3 25;60(6):927–34. Available from: http://www.neurology.org/cgi/doi/10.1212/01.WNL.0000057720.36503.2C

114. Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain [Internet]. 2008 8;12(6):804–13. Available from: http://doi.wiley.com/10.1016/j.ejpain.2007.12.010

115. Muzaale AD, Daubresse M, Bae S, et al. Benzodiazepines, Codispensed Opioids, and Mortality among Patients Initiating Long-Term In-Center Hemodialysis. Clin J Am Soc Nephrol [Internet]. 2020 6 8;15(6):794–804. Available from: http://cjasn.asnjournals.org/lookup/doi/10.2215/CJN.13341019

116. Cheatle MD, Compton PA, Dhingra L, et al. Development of the Revised Opioid Risk Tool to Predict Opioid Use Disorder in Patients with Chronic Nonmalignant Pain. J Pain [Internet]. 2019 7;20(7):842–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1526590018306229

117. Hadland SE, Levy S. Objective Testing – URINE AND OTHER DRUG TESTS. Child Adolesc Psychiatr Clin N Am [Internet]. 2016 7;25(3):549–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1056499316300256

118. Kinnunen M, Piirainen P, Kokki H, et al. Updated Clinical Pharmacokinetics and Pharmacodynamics of Oxycodone. Clin Pharmacokinet [Internet]. 2019 6 17;58(6):705–25. Available from: http://link.springer.com/10.1007/s40262-018-00731-3

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

119. Miotto K, Cho AK, Khalil MA, et al. Trends in Tramadol. Anesth Analg [Internet]. 2017 1;124(1):44–51. Available from: http://journals.lww.com/00000539-201701000-00010

120. Aiyer R, Gulati A, Gungor S, et al. Treatment of Chronic Pain With Various Buprenorphine Formulations. Anesth Analg [Internet]. 2018 8;127(2):529–38. Available from: http://journals.lww.com/00000539-201808000-00036

121*. O'Brien MB, FRCPI T, Ahn JS, Chye, MBBS, FRACP, FFPMANZCA, FAChPM R, et al. Understanding transdermal buprenorphine and a practical guide to its use for chronic cancer and non-cancer pain management. J Opioid Manag [Internet]. 2019 3 1;15(2):147–58. Available from: https://www.wmpllc.org/ojs/index.php/jom/article/view/2402This review article provides an overview of transdermal buprenorphine and suggests that buprenorphine can be used in patients with renal disease without specific dose adjustment recommendations.

122. Breivik H, Ljosaa TM, Stengaard-Pedersen K, et al. A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naïve to potent opioids. Scand J Pain [Internet]. 2010 7 1;1(3):122–41. Available from: http://www.degruyter.com/view/j/sjpain.2010.1.issue-3/j.sjpain.2010.05.035/j.sjpain.2010.05.035.xml

123. Rauck RL, Potts J, Xiang Q, et al. Efficacy and tolerability of buccal buprenorphine in opioid-naive patients with moderate to severe chronic low back pain. Postgrad Med [Internet]. 2016 1 2;128(1):1–11. Available from: http://www.tandfonline.com/doi/full/10.1080/00325481.2016.1128307

124. Mancher M, Leshner AI, editors. Medications for Opioid Use Disorder Save Lives In: Medications for Opioid Use Disorder Save Lives [Internet]. Washington (DC); 2019 Available from: https://www.ncbi.nlm.nih.gov/pubmed/30896911

125. Rudolf GD. Buprenorphine in the Treatment of Chronic Pain. Phys Med Rehabil Clin N Am [Internet]. 2020 5;31(2):195–204. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1047965120300085

126. Pergolizzi JV, Coluzzi F, Taylor R. Transdermal buprenorphine for moderate chronic noncancer pain syndromes. Expert Rev Neurother [Internet]. 2018 5 4;18(5):359–69. Available from: https://www.tandfonline.com/doi/full/10.1080/14737175.2018.1462701

127. Fishman MA, Scherer A, Topfer J, et al. Limited Access to On-Label Formulations of Buprenorphine for Chronic Pain as Compared with Conventional Opioids. Pain Med [Internet]. 2020 5 1;21(5):1005–9. Available from: https://academic.oup.com/painmedicine/article/21/5/1005/5614401

128. Woo J, Bhalerao A, Bawor M, et al. "Don't Judge a Book by Its Cover": A Qualitative Study of Methadone Patients' Experiences of Stigma. Subst Abus Res Treat [Internet]. 2017 1 23;11:117822181668508. Available from: http://journals.sagepub.com/doi/10.1177/1178221816685087

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Key Points

- Pain management in patients with kidney disease is challenging due to multiple patient, provider, and structural factors.
- Nonpharmacologic management of pain includes behavioral-based and physically-oriented interventions.
- Preferred nonopioid analgesia in CKD and ESKD include acetaminophen, topical analgesics, gabapentinoids, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants.
- Before starting opioids, providers should have risk/benefit discussions regarding opioid analgesia, including complete psychosocial assessment and regular monitoring for benefits and adverse effects with evidence-based tools and urine or oral drug screening.
- Preferred opioid analgesics include oxycodone, hydromorphone, fentanyl, methadone, and buprenorphine.

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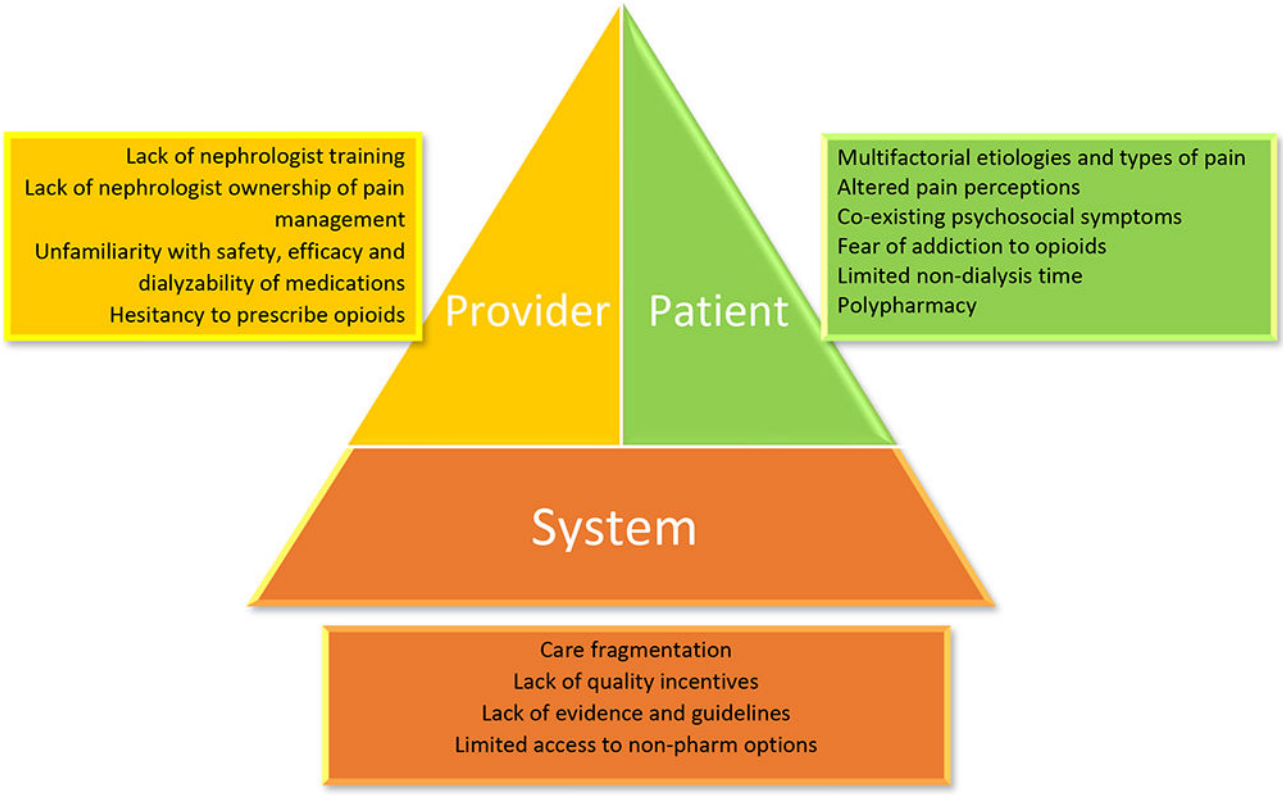

Fig 1.
Challenges in pain management in patients with kidney disease

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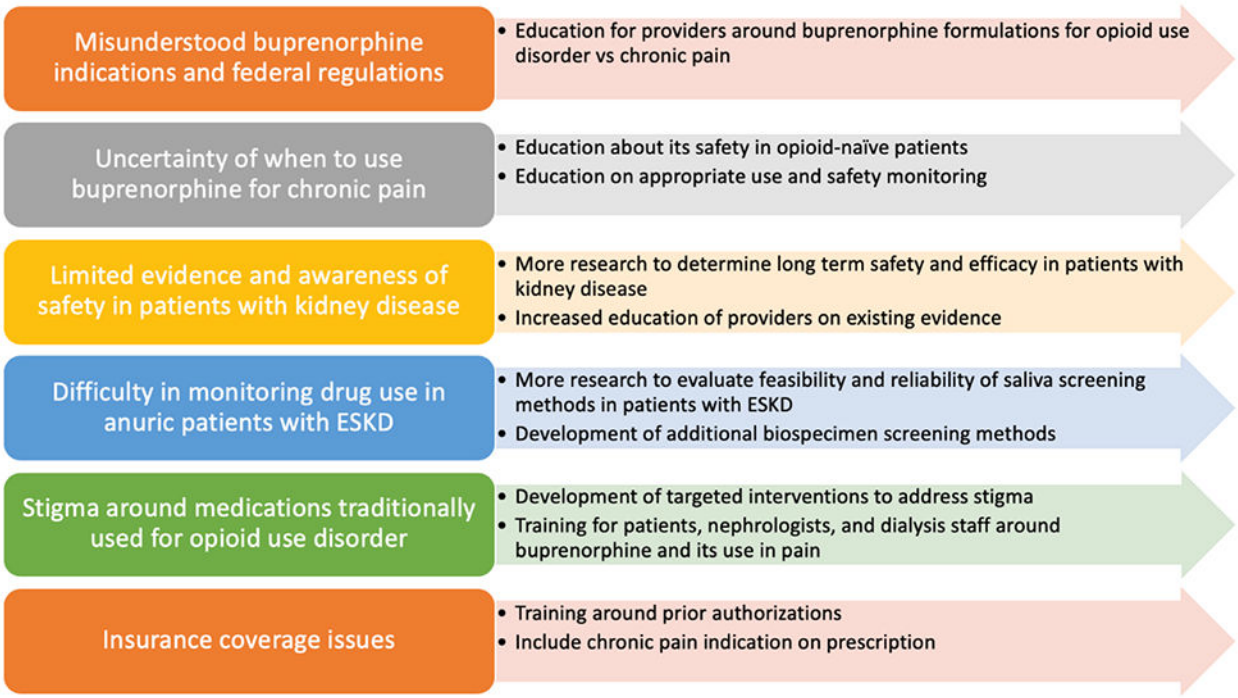

Fig 2.

Barriers and potential solutions for increasing use of buprenorphine for chronic pain in patients with kidney disease

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Table 1.

Recommended non-opioid medications in patients with kidney disease

Medication	Metabolism and PK comments	Dosing in CKD	Dosing in ESKD	Comments
Medications for nociceptive pain				
Acetaminophen	Hepatic, excreted in the urine primarily as non-toxic metabolites High oral bioavailability 85-98% Median onset 11 minutes and median duration of action ~ 4 hours after 1000 mg oral dose [83]	Cl_{Cr} 10-50 mL/min: 650 mg q 6h prn Max daily dose 4000 mg	Cl_{Cr} < 10 mL/min or dialysis: 650 mg q 8h prn Max daily dose 4000 mg [84]	Use scheduled doses instead of as needed for continuous pain control Use with caution and Lower max daily dose (2000 mg) if liver disease or daily alcohol
NSAIDs, preferably COX-2 selective agents such as celecoxib		Reduce dose and increase dosing interval, use for short term (</= 5 days only) Contraindicated in CKD stage 5	No dose adjustment, use for short term only	Monitor for volume retention, cardiotoxicity, renal and gastrointestinal toxicity
Topical analgesics (NSAIDs, lidocaine, capsaicin)	Systemic exposure with topical NSAIDs is 2-3% than with oral, but increases with higher dose applied to larger surface area [85]			Avoid high dose topical NSAID use over large surface area
Medications for neuropathic pain				
Pregabalin	Negligible, 90% excreted renally as unchanged drug High oral bioavailability ≥ 90% Onset of pain relief ~ 1 week	Max daily dose: Cl_{Cr} 30-60 mL/min: 300 mg daily (2-3 divided doses) Cl_{Cr} 15 to 30 mL/min: 150 mg daily (1-2 divided doses) Cl_{Cr} < 15 mL/min: 75 mg daily (single dose)	Start at 25 mg once daily, Maximum dose 75 mg once daily Well dialyzed, Dose post-HD	Start at low dose and uptitrate every 1-2 weeks, monitor for altered mental status and falls
Gabapentin	Not metabolized, excreted renally as unchanged drug Bioavailability is dose dependent: is upto 80% with 300mg/d but decreases as dose increases to <50% above 1200 mg/d	Max daily dose: Cl_{Cr} 50-79 mL/min: 1800 mg daily (3 divided doses) Cl_{Cr} 30-49 mL/min: 900 mg/day (2-3 divided doses) Cl_{Cr} 15-29 mL/min: 600 mg/day (1-2 divided doses) Cl_{Cr} < 15 mL/min: 300 mg/day (single dose)	Maximum dose 300 mg once daily Well dialyzed, Dose post-HD	Start at low dose and uptitrate every 1-2 weeks, monitor for altered mental status and falls
Duloxetine	Extensively metabolized in the liver via CYP1A2 and 2D6 to inactive metabolites, Oral bioavailability 30-80%, >90% protein bound Excretion: renal 70%, fecal 20%	Start with 20 mg daily Max daily dose: 60 mg Cl_{Cr} 30-80 mL/min: no dose adjustment necessary Cl_{Cr} < 30 mL/min: avoid use	Avoid use (limited data)	Monitor for hyponatremia, can rarely cause serotonin syndrome
Venlafaxine	Hepatically metabolized via CYP2D6 to active metabolite, O-desmethylvenlafaxine. Bioavailability is ~ 13% for immediate release and 45% for extended release, primarily excreted renally	Extended release: Start at 37.5 mg once daily Max daily dose: Cl_{Cr} 30-89 mL/min: 150 mg daily Cl_{Cr} <30 mL/minute: 112.5 mg daily	Extended release: Start at 37.5 mg once daily Max daily dose: 112.5 mg daily Poorly dialyzed	Monitor for hyponatremia, can rarely cause serotonin syndrome

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Medication	Metabolism and PK comments	Dosing in CKD	Dosing in ESKD	Comments
Desvenlafaxine (active metabolite of venlafaxine)	Hepatically metabolized Oral bioavailability approximately 80%. Excreted renally approximately 45% as unchanged drug and 24% as metabolites	Max daily dose: Cl_{Cr} 30-50 mL/min: 50 mg once daily Cl_{Cr} <30 mL/min: 25 mg once daily or 50 mg every other day	Max daily dose: 25 mg once daily or 50 mg every other day. Poorly dialyzed	Monitor for hyponatremia, can rarely cause serotonin syndrome
Amitriptyline	Hepatically metabolized to nortriptyline (active metabolite) Oral doses are completely and rapidly absorbed, > 90% protein bound. Excreted renally as metabolites, 18% as unchanged drug.	Start at 10 mg once daily at bedtime, No dose adjustment recommended Maximum dose 150 mg daily.	Start at 10 mg once daily at bedtime, No dose adjustment recommended Maximum dose 150 mg daily. Poorly dialyzed	Limited evidence in CKD The Beers Criteria recommends avoidance in older adults (strong anticholinergic properties, sedation, orthostatic hypotension, urinary retention)

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Table 2.

Recommended opioid medications in patients with kidney disease

Medication	Metabolism and PK comments	Dosing in CKD	Dosing in ESRD	Comments
Oxycodone (short-acting)	Hepatically metabolized via mainly CYP3A4 to noroxycodone (weakly active) and some by CYP2D6 to oxymorphone (strongly active), High oral bioavailability of 50-87% , $t_{1/2}$ prolonged to ~ 7 hours in ESKD [86]	Start at 2.5-5 mg every 12 hours, Recommend prolonged dosing interval in severe renal impairment	Start at 2.5-5 mg every 12 hours, Recommend prolonged dosing interval in ESKD Poorly dialyzed	Caution should be used with long acting formulations and when used concurrently with medications that affect CYP3A4 or CYP2D6 metabolism. [87]
Hydromorphone	Hepatically metabolized, Oral bioavailability is Low to moderate	Start at 2.5-5 mg every 6-8 hours	Start at 2.5-5 mg every 6-8 hours, well dialyzed but no supplemental dose required post HD	Use caution with high doses
Fentanyl (transdermal)	Hepatically metabolized, 10-20% excreted renally, low oral bioavailability	Dose equivalent dose of patient's oral narcotics, wean oral opioids after 1-2 days	Dose equivalent dose of patient's oral narcotics, wean oral opioids after 1-2 days Poorly dialyzed	Do not start in opioid naïve patient
Methadone	Hepatically metabolized to inactive metabolites, >80% oral bioavailability	Start 1-2 mg once or twice a day	Start 1-2 mg once or twice a day Poorly dialyzed	Do not start in opioid naïve patient. Obtain a baseline EKG and a follow-up EKF 2-4 weeks after starting to monitor for prolonged QT interval. Monitor and correct electrolyte abnormalities
Buprenorphine	Hepatically metabolized to B3G (inactive) and norbuprenorphine (active but does not cross blood brain barrier), low oral bioavailability but effective as sublingual or transdermal formulation, excreted mostly fecally (bile)	See Table 3	See Table 3 Poorly dialyzed	Do not start in opioid naïve patient. Lesser risk of overdose and respiratory and CNS depression as compared to other opioids

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Table 3.

Comparison of Commonly Prescribed Buprenorphine Products

Trade Name	Generic Name	Route	FDA Indication	X-Waiver Required?	Starting Dose
Butrans[a]	Buprenorphine	Transdermal patch	Chronic pain	No	5ug/hr week
Belbuca[b]	Buprenorphine	Buccal tablet	Chronic pain	No	75ug once daily
Suboxone[c]	Buprenorphine-naloxone[#]	Sublingual film or tablet	Opioid use disorder	Yes[*]	2mg-0.5mg
Subutex[c]	Buprenorphine	Sublingual tablet	Opioid use disorder in patients who cannot tolerate naloxone	Yes	2mg

[a] Purdue Pharma L.P., Stamford, CT, USA

[b] BioDelivery Sciences International, Inc, Raleigh, NC, USA

[c] Reckitt Benckiser Pharmaceuticals Incorporation, Richmond, VA, USA

[#] When taken sublingually, the effect of buprenorphine predominates; if injected however, the effect of naloxone predominates.

[*] No X-waiver needed if used off-label for treatment of pain [125]