Overview of NSAID Use and Safety in Kidney Disease

Nearly 60% of patients with CKD suffer pain. Of those patients with CKD who have pain, most rate their pain as moderate or severe in intensity. Undermanaged pain is associated with higher rates of mood disorders, maladaptive coping, and decreased quality of life for patients with CKD (1). In general, nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line for analgesia and also act as antipyretics and anti-inflammatory medications. Estimates indicate that 98 million patients annually are prescribed NSAIDs (2), which likely represents only a fraction of total use given widespread nonprescription access. Epidemiologic studies suggest that 70%–80% of all NSAID users consume over-the-counter products like ibuprofen or naproxen (3,4). In the National Health and Nutrition Examination Survey, routine NSAID use was common in patients with CKD and use increased with increasing CKD severity (3).

NSAIDs have been known to have adverse effects in CKD patients. These risks can broadly be categorized into affecting the kidneys, gastrointestinal (GI) tract, or cardiovascular system. Among these risks, it is the direct and indirect nephrotoxicity that has primarily led to hesitation with the use of NSAIDs in patients with CKD. In one study, patients with CKD were more likely to receive an opioid than an NSAID or gabapentinoid across the entire spectrum of CKD (5). The highest rates of opioid prescribing were in patients with the lowest GFR. Indirect nephrotoxicity from NSAIDs is linked to altered intraglomerular hemodynamics. NSAIDs inhibit PG synthesis, which decreases afferent arteriolar vasodilation and can reduce glomerular pressure. This is especially prominent in patients with already jeopardized renal perfusion as in shock or intravascular volume depletion. For this reason, use of NSAIDs in acutely ill patients with AKI, acute kidney disease, or in the midst of renal recovery remains ill-advised. Patterns of direct nephrotoxicity include interstitial nephritis, papillary necrosis, and GN (6,7). Although these risks of NSAIDs have been reproducibly demonstrated, on a per patient level they remain rare. Less than 1%–5% of all NSAID users experience such side effects (6). Most nephrotoxicity related to NSAIDs recovers after drug withdrawal; however, the likelihood of recovery may depend on renal reserve.

Historical risk factors for NSAID-associated nephrotoxicity included higher drug doses, longer durations, concurrent use of renin-angiotensin system (RAS) inhibitors or diuretics, preexisting CKD, and advanced age (6,8). Recent evidence has refuted or at a minimum indicated that some of these risks may be less profound than once thought (7,9–12). This is likely to be due to withdrawal of phenacetin from the market, an often coadministered agent with NSAIDs that increased the nephrotoxicity of the drug combination (6). A recent multicenter propensity-matched cohort of 25,571 hospitalized adults evaluated the risk of nephrotoxicity associated with acute NSAID use in the presence or absence of RAS inhibitors. The mean duration of NSAID exposure was 2.4 days. Compared with patients treated with alternate analgesic or anti-hypertensive agents not known to affect glomerular hemodynamics (oxycodone and amlodipine, respectively), the combination of NSAID and RAS inhibitor did not worsen AKI incidence, severity, or duration (9).

In a case control study that evaluated the odds of nephrotic syndrome in 13,074 primary care patients, NSAID exposure for <15 days was not associated with greater risk (7). In the Nurse’s Health Study (11) and the Physician’s Health Study (10), greater cumulative exposure to NSAIDs over 10–20 years was not associated with long-term adverse kidney outcomes. It is difficult to account for inherent differences in prescribing behavior for NSAIDs in patients with reduced kidney function, even with rigorous covariate adjustment. However, in a study of patients with rheumatoid arthritis where chronic use of anti-inflammatory agents is the mainstay of therapy, patients with a baseline eGFR >30 ml/min per 1.73 m² treated with NSAIDs experienced comparable kidney function decline over 3.2 years compared with those not exposed to NSAIDs (12).

Abandoning the use of NSAIDs in patients with kidney disease will lead to consequences from the therapeutic alternatives. Some studies have raised concerns about the potential for nephrotoxicity with acetaminophen as it is a metabolite of phenacetin, but these findings are inconsistent and of unclear clinical significance (13,14). Gabapentinoids, common agents used

Can NSAIDs Be Used Safely for Analgesia in Patients with CKD?: PRO

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for the treatment of neuropathic pain especially in patients with diabetic kidney disease, can lead to worrisome neurotoxicity. In patients with an eGFR <90 ml/min per 1.73 m² treated with gabapentinoids, approximately 6% experienced toxicity, which manifested as encephalopathy, ataxia, myoclonus, and generalized weakness (15). In the Chronic Renal Insufficiency Cohort (CRIC), opioid use, not NSAID use, was associated with a greater risk for adverse events including kidney failure requiring dialysis and death, even after adjustment for potential confounders including baseline kidney function. Worsening kidney disease and hospitalization were similar between those treated with opioids and those treated with NSAIDs (16). In a head-to-head comparison of the risk of death in patients with CKD receiving opioids versus those receiving NSAIDs, opioids were associated with a dose-dependent higher risk of death at every quintile of CKD (17). The assumption that non-NSAID therapies are consistently safer alternatives in patients with CKD is not supported by data. By broadly eliminating a useful class of analgesics for patients with CKD, we have risked exposure to excess harm from the alternatives.

Place in Therapy for NSAIDs in Patients with CKD

Rather than widespread NSAID avoidance in kidney disease, we advocate a patient-centered approach to NSAID use. Key considerations for use should include indication for therapy (type of pain), expected dose and duration, individual risk profile, suitability of alternative options, and goals of care.

Pain is classified as nociceptive (relating to tissue damage) or as neuropathic (relating to injury to nerves). Knowing which type of pain a patient has helps to both generate a differential diagnosis and guide management. The Centers for Disease Control and Prevention published guidelines in 2016 that recommend nonpharmacologic interventions as first line in all patients for the management of chronic pain regardless of type (18). Nonpharmacologic interventions such as physical therapy, acupuncture, behavior management techniques, mindfulness, and music therapy are evidenced-based for the management of chronic pain (19,20). When nonpharmacologic interventions are not possible or not effective, pharmacologic modalities are entertained. The World Health Organization (WHO) developed a pain ladder for the pharmacologic management of pain, which has been suggested for use in CKD and validated in ESKD (1,21). The first step of the WHO pain ladder includes nonopioid medications such as acetaminophen, and topical or oral NSAIDs, Step 1 also can include adjuvant medications that predominately target neuropathic pain such as tricyclic antidepressants, serotonin-NE reuptake inhibitors, gabapentinoids. Steps 2 and 3 of the WHO pain ladder include the use of opioid pain relievers.

For nociceptive pain, topical NSAIDs should be considered first line. A Cochrane review shows topical NSAIDs to be as effective as oral NSAIDs, for both acute and chronic pain, with no more GI or cardiac side effects than placebo (22). Although topical NSAIDs are limitedly absorbed, there have been no reports of clinically meaningful kidney injury with the products available on the market. Topical NSAIDs are impractical for patients with widespread pain. In these cases acetaminophen is typically used before oral NSAIDs in patients with CKD. If pain is inadequately controlled by these measures, clinicians face the crux of the clinical challenge: how to select between an oral NSAID or an opioid.

Ultimately this decision amounts to an individualized risk-benefit analysis between the drug classes (Figure 1). The nephrotoxicity risk of NSAIDs is just one facet of this decision. GI and cardiovascular side effects must also be considered, alongside the potential for respiratory depression, central nervous system depression, and dependence with opioids. In patients with stages 1 through 3 CKD, evidence from large cohorts indicate that use of NSAIDs does not accelerate CKD progression (12,23). As noted from the CRIC data, where the mean ± SD eGFR was 43 ± 13 ml/min per 1.73 m², opioids rather than NSAIDs were associated with a greater risk of kidney failure requiring dialysis and death than NSAIDs at all levels of CKD (16). For these reasons and the known risk of opioids, in patients with stages 1 through 3 CKD, we generally favor a trial of oral NSAIDs for the next step in pain management. Even in the presence of known risk factors beyond evident CKD, NSAIDs may still be preferred to opioids. For example, consider a 69-year-old man with stage 3 CKD from nephrotic syndrome, a prior myocardial infarction, active alcohol substance use disorder, and untreated obstructive sleep apnea. Despite at least two expected risks associated with NSAIDs (kidney and cardiovascular), the potential complications of opioids, particularly the risks for respiratory depression and additive central nervous system depression, are likely more substantial. This balance must be considered as part of shared decision making.

Patients with stage 4 and 5 CKD likely represent a subpopulation at increased risk for complications from NSAIDs. These patients may have diminished renal reserve and a decreased ability to recover from a nephrotoxic event. Unfortunately, this assumption is largely speculative on the basis of the limited available evidence. These patients also exhibit heightened risks with opioids so the decision remains challenging. We propose two illustrative cases to highlight the need for individualization. The first case is a 34-year-old woman with stage 4 CKD from FSGS and prior heroin addiction who needs pain management for menstrual cramps. In her situation, the risk-benefit analysis likely favors once-monthly NSAID use rather than use of an opioid despite her stage 4 CKD. In a second case, a 70-year-old man with stage 5 CKD, prior peptic ulcer disease, and resistant hypertension struggling with calciphylaxis would likely be better suited to treatment with an opioid.

As with all analgesics, NSAIDs should be appropriately dosed on the basis of kidney function. The lowest dose should be used for the shortest duration possible. Dose equivalence across NSAIDs may be estimated with the Assessment of Spondyloarthritis International Society NSAID equivalent score (24). There is little evidence to support the use of one NSAID over another. The risk of kidney injury is not significantly different between the cyclooxygenase-2 versus the nonselective NSAIDs (25). Intensity of monitoring should be tailored to risk. In low-risk scenarios (i.e., short duration of therapy or less-severe kidney disease), approximately yearly kidney function and electrolytes, similar to the non-CKD population, is likely
sufficient. There is little evidence to support thresholds for a “short duration,” but we offer 2 weeks of use as a clinically relevant benchmark. The greater the potential for risk with NSAIDs, the more frequent and comprehensive the monitoring should be. In very high-risk cases, monitoring (to include kidney function, electrolytes, and clinical assessment of ongoing benefit versus harm), should mirror the approach to opioids (e.g., monthly for 3 months and then every 3 months thereafter if stable). Patients and caregivers should be engaged, and educated, about the risks and benefits of analgesic therapy. Key teaching points should include the differences between nonprescription analgesics (i.e., acetaminophen, aspirin, and NSAIDs), need for kidney evaluation, self-care, and planned monitoring strategy.

Figure 1. | Proposed algorithm for analgesic selection in patients with CKD. We suggest that in patients with stage 1–3 CKD where the risk of NSAID-associated nephrotoxicity appears similar to the general population, there must be a high burden of risk to justify opioids over an initial trial of NSAIDs. All analgesic decisions should be individualized and include patient and caregiver education, a structured monitoring plan, and reassessment of pain control. GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; RAS, renin-angiotensin system.
Conclusions
Pharmacologic pain management for patients with CKD requires a careful individualized risk-benefit analysis. Although it is tempting to avoid NSAIDs in patients with CKD altogether, the counterbalance of exposure to alternative analgesics such as opioids may be to the patient’s detriment. Moving forward, clinicians must recalibrate their risk barometer for pharmacologic pain management in patients with CKD. Oral NSAIDs remain an essential and highly efficacious class of medication for pain management in appropriately selected individuals with CKD.

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Author Contributions
E. Barreto and M. Feely conceptualized the manuscript, wrote the original draft, and reviewed and edited the manuscript.

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