Pain, Analgesics, and Safety in Patients with CKD

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A substantial body of literature has shown that >58% of dialysis patients report pain, and 49% of these patients rate their pain as moderate or severe (1). However, surprisingly little is known about the prevalence and nature of chronic pain in patients with earlier stages of CKD. In this issue of *CJASN*, Wu *et al.* (2) describe the prevalence, frequency, and severity of chronic pain in 308 predialysis CKD patients with GFR category 3–5 and explore the relationship between chronic pain with proper and improper opioid and nonopioid analgesic use.

Chronic pain was reported by 60.7% of patients in the study by Wu *et al.* (2). Of those individuals with chronic pain, 72.1% experienced pain at least 3–4 times a week and 48% rated their pain as severe. Chronic noncancer pain is known to be common (3,4). However, chronic pain in CKD appears more prevalent than that reported by 26%–29% of the general population (3,4), and 49.1% for people aged ≥55 years (3). As in the general population, chronic pain in these CKD patients occurred with increased frequency and severity in women, patients with arthritis, individuals taking ≥12 medications, and patients with lower physical function. Pain research suggests that chronic pain increases with age but then begins to decrease starting around age 65 years (5). This is consistent with the findings of Wu *et al.*, which showed the prevalence and severity of pain was less in patients aged ≥65 years compared with those aged <65 years. Unlike the general population, obesity was not associated with chronic pain in these CKD patients.

Chronic pain is clearly a problem for patients with CKD throughout their illness trajectory and not just for patients on dialysis in the final years of life. Chronic pain is associated strongly with considerable disability, lower health-related quality of life (HRQL), and burden to the healthcare system (1,6,7). The nephrology community has recognized this and has begun to advocate for routine screening and management of pain as a way to promote patient-centered, outcome-oriented, quality health care. This includes a growing consensus that analgesics, including opioids, are appropriate for some CKD patients with severe pain. However, due to the altered pharmacokinetics and pharmacodynamics of most analgesics in CKD, patients are at greater risk of drug-related problems and legitimate concerns remain about the safety of opioids and other analgesics for chronic pain in CKD. The findings of Wu *et al.* (2) of increased proper and improper selection and dosing of analgesics in CKD patients as the frequency and severity of chronic pain increase remind us that caution is required.

Concerns about the safety of chronic analgesic use, especially that of opioids, in CKD mirrors concerns about pain management and analgesic use in the general population. In North America, the volume of opioid prescriptions has more than doubled in the past decade and is higher than anywhere in the world (8). This increase has been associated with an increase in serious opioid-related harms, including substance abuse and accidental overdose deaths (9–11). Data from studies in elderly populations have also reported an association between opioids and an increased risk of mortality (12), infection (13), and fractures (14).

Although it is prudent to take valuable lessons from research in other populations, we need to place knowledge within the appropriate context for an individual patient with CKD in which the balance of risks and benefits may be entirely different. First, despite a clear increase in the prevalence of prescription opioid abuse in the general population, it is unclear whether the patterns of opioid abuse match the patterns of use for chronic pain and how this may relate to CKD patients. Data are highly variable, but studies have shown benefit for some patients in analgesia, function, and HRQL with long-term opioid use in which doses have been titrated slowly and carefully against pain with low incidences of substance abuse and serious adverse effects (15). The risk of psychologic dependence is typically low in the absence of a history of substance abuse. Regardless, it would seem sensible to incorporate risk assessments of patients for addiction risk and physicians should watch carefully for problematic opioid-seeking behavior. Should problematic behavior occur, careful consideration should be given to whether to wean, intensify follow-up (including regular prescription pick-up and a limitation on the number of physicians and pharmacists providing treatment), add addiction treatment, and/or involve pain and addiction specialists.

Little is currently known about the use and safety of analgesics, including opioids, in CKD, and the effect of analgesic use on clinically relevant outcomes such as analgesic effect, HRQL, physical function, or adverse events is essentially unexplored. One study reported no association of opioid and nonopioid analgesic use with falls (16), whereas another study showed an association between opioid use and a slightly increased relative risk of fractures (17) and poorer sleep (18). However, none of

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these studies were designed to explore analgesic use or outcomes of analgesic use in the context of pain management. There are also concerns that long-term opioid use does not consistently alleviate chronic noncancer pain (15,19). This may be less of a concern for CKD patients with more advanced disease and a decreased life expectancy. Clinicians also need to be mindful that survival may not be the most important outcome for a given patient and that improving symptom burden, physical function, and overall HRQL may be the patient's primary goal.

Wu *et al.* recognize their small sample size, but this work is an important step in understanding the patterns of analgesic use and misuse. Several large international observational studies have shown that analgesic use is not high (with the exception of nonsteroidal anti-inflammatory drugs [NSAIDs]) in CKD despite the high prevalence of pain (17,18,20–23). However, only a few studies with small numbers of patients specifically explore analgesic prescribing in patients with pain. Wu *et al.* found that over-the-counter and/or prescription analgesics were used by 40%–72% of patients with pain, depending upon the frequency of pain. Analgesics were also used by 29% of patients who reported no pain, although it is not clear whether this represented well controlled pain or inappropriate analgesic use. Acetaminophen was the most commonly used analgesic (34% of the entire CKD cohort), followed by tramadol (15%), strong opioids (12%), NSAIDs (5%), and codeine (3%). Despite greater prevalence of pain, analgesic use in this cohort is less than that seen in the general population (3,4). Although this may not be the best comparison, it appears that the use of acetaminophen, despite its safety in CKD, remains low, NSAID use may be inappropriately high, and despite severe pain, there remains a relatively low prevalent use of strong opioids. It is hoped that the longitudinal follow-up of the Wu *et al.* CKD cohort will elucidate clinical outcomes associated with analgesic use.

As shown by Wu *et al.*, as the frequency and severity of pain increases, there is greater proper and improper analgesic use, potentially placing patients at risk for analgesic-related harms. When faced with a CKD patient with chronic pain, several key issues should be considered to mitigate potential harm (1). Analgesics should be used as part of a comprehensive treatment program that includes physical therapy and psychologic and behavioral approaches to pain management. This occurs best with a multidisciplinary approach and the assessment of complicating symptoms such as depression and anxiety. A comprehensive approach to pain should also include negotiation of realistic pain treatment goals and patient education. When considering chronic analgesic therapy, attention to the choice of analgesic is critical, taking into account the degree of renal failure, interaction with coadministered medications, and comorbidity. There also needs to be careful consideration of the risks and benefits for the individual patients. Much pain can be well controlled with acetaminophen and/or low-dose adjuvant therapy (*e.g.*, gabapentin) with careful titration. Opioids can be considered for CKD patients with severe pain that does not respond to nonpharmacologic or nonopioid treatment and results in detriments to physical function and HRQL. Clinical experience suggests that low doses are typically effective for the majority of CKD patients with severe pain. The five essentials of analgesic dosing should be adhered to as follows: (*1*) by mouth: whenever possible, drugs should be given orally; (*2*) by the clock: schedule doses over 24 hours on a regular basis with additional as needed doses; (*3*) by the ladder: titrate stepwise according to the World Health Organization analgesic ladder; (*4*) for the individual: dose carefully to analgesic effect while avoiding adverse effects; and (*5*) attention to detail. Patients will require ongoing reassessment for the benefits and risks of treatment. This takes time and dedicated resources, including education of nephrology staff. There is no quick fix for the management of chronic pain.

The effective treatment of chronic pain holds the promise for substantial improvement in CKD patients' HRQL (24). The burden of opioids and other analgesics must be balanced with their benefit. The nephrology community clearly needs to develop effective clinical strategies to optimize outcomes most relevant to the patient while minimizing analgesic-related harms. The effectiveness of chronic analgesic use for chronic pain is essentially unexplored in CKD and further research is urgently required to guide clinical decisions on the basis of evidence. We need to be able to identify patients who may benefit from long-term analgesic use and patients who may be particularly vulnerable to possible analgesic-related harms. It is hoped that ongoing research will also help us understand the pathways through which analgesics affect morbidity and mortality so that we can better address these risks.

Disclosures

None.

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