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Opioid avoidance after liver transplantation: the ever-shifting pain management paradigm

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Since the first medicinal use of opium over 8,000-years ago, public opinion regarding opium and opioids has fluctuated. Alternatively viewed as a panacea and a scourge throughout history, prescription opioids are now known to cause substantial morbidity and mortality.¹ The multifactorial contributions to the current opioid-related public health crisis, including the campaign to make pain the fifth vital sign and the expectation, fueled by pharmaceutical company marketing campaigns, that pain should be treated with a pill, have resulted in hundreds of thousands of preventable overdoses and deaths.¹ In recognition of the dire consequences of opioid over-prescribing, opioid safety initiatives and programs aim to decrease opioid-related morbidity and mortality.

Despite widespread attempts to curtail opioid use and misuse, opioid prescribing to patients with cirrhosis remains high for several interconnected reasons. First, up to 80% of patients with cirrhosis have chronic pain, and there is a paucity of safe, opioid-sparing alternative analgesics (e.g., non-steroidal anti-inflammatories) for patients with cirrhosis.^{2,3} Further, multimodal, non-pharmacologic approaches to pain management have been slow to percolate into cirrhosis care.³ Finally, historical over prescription of opioids to patients with cirrhosis (e.g., up to half of patients per year) has created a cycle wherein providers much either continue to prescribe these drugs or contend with the unique challenges and unintended consequences of their cessation.⁴

The ongoing high rate of opioid prescribing to patients with cirrhosis has been associated with hospitalization, decompensation, and death.^{2,3} Moreover, pre-transplant opioid use has been associated with post-transplant opioid use, graft loss, and death.⁵ Thus, the opioid epidemic has created a public health crisis that has adversely impacted transplant recipients.

Notably, the ill-effects of opioid prescribing are often borne out even after short-term post-operative use. Early post-operative opioid analgesia may counterintuitively worsen pain via opioid-induced hyperalgesia and can lead to ileus, delirium, and other adverse events that prolong hospitalization.^{6,7} Most alarming is the fact that postoperative opioid prescribing can result in long-term opioid use and misuse.⁶ Therefore, current surgical guidelines recommend limiting opioid prescribing in favor of an individualized pain management approach.^{6,7} Despite the existing recommendations, opioids are still commonly used as the backbone of post-operative pain management.

In this issue of *Liver Transplantation*, Kutzler *et al.* present a proof-of-concept study demonstrating that post-operative transplant pain can be managed with minimal opioid analgesia. Notably, this intervention started with a pre-transplant, multidisciplinary pain management program, including mental health providers, pain management, and pharmacy. By setting expectations early about how post-operative pain will be managed, the team was able to significantly reduce early post-operative total opioid prescriptions while simultaneously decreasing pain scores compared to a historical control group. The difference in opioid prescribing and use between historical controls and intervention recipients was largely in the early post-operative period. The intervention aimed to minimize opioid use post-operatively, and, while most transplant recipients did receive at least some rescue opioid analgesia, two patients received no opioids.

Avoiding opioids post-operatively represents a major paradigm shift for patients and providers. Ongoing barriers to implementing opioid-sparing post-operative analgesia include time, training, and communication gaps.⁸ In fact, physicians are often unaware of the adverse consequences of post-operative opioid prescribing.^{4,8} While patient demand for opioids may be perceived as a barrier to opioid avoidance, it is notable that, after receiving information about the study, 100% of the transplant candidates who were approached by Kutzler *et al.*, agreed to participate, suggesting that patients may be accepting of this approach. This finding is consistent with literature that patients generally favor lower doses of opioids compared to their providers.⁷ While patients appear to be amenable to opioid avoidance—even more so than their providers—broader implementation will require time, resources, education, and culture change.

To take the paradigm shift a step farther, it may be appropriate to implement a multidimensional approach to pain management upstream in the natural history of liver disease. Kutzler *et al.* appropriately excluded patients with opioid tolerance, or baseline opioid use, from the study. However, as in most transplant populations, very few waitlisted patients were taking long-term opioids (only one patient was excluded for this reason). While up to half of patients with cirrhosis receive chronic opioid prescriptions,² few patients taking long-term opioid therapy are ultimately transplanted. This may, in part, relate to the underlying medical issues that led to opioid prescribing. However, it is also possible that, by prescribing opioids rather than providing interdisciplinary care, clinicians are doing a disservice to patients with cirrhosis and ultimately limiting access to transplantation in programs that consider opioids to be a relative contraindication to transplant.⁹ Providing early interdisciplinary care may increase transplant eligibility and avoid post-operative opioid use. This type of approach is likely more important for patients with coexisting mental health and substance use disorders, given the additional challenges of treating pain in these populations. Given the high prevalence of co-existing mental health and substance use disorders in patients with cirrhosis (e.g., 70% in the current study), programs that address the interconnected issues of chronic pain, substance use, and mental health symptoms may improve transplant outcomes.

Despite early promising results, the specific opioid-sparing alternative analgesic approached outlined in this study is not appropriate for all patients. More work is required to ensure the safety of alternative medications, and, as the authors describe, patients must be considered

on an individual, a case-by-case basis. Though a small number of patients were included in this study, there were several significant, notable, adverse reactions to the opioid-sparing analgesic regimen. Ketamine was discontinued in three patients due to mental status changes resulting in aspiration and reintubation, mental status changes alone, and pulmonary hypertension. Other adverse events related to alternative analgesia included bradycardia due to tizanidine and confusion due to baclofen. Further comparative effectiveness research could help to optimize post-transplant pain management strategies and to determine the comparative risks of opioids versus alternative analgesic regimens. While opioids have known safety risks, it is critical that the alternative approaches mitigate these risks, rather than creating new risks.

The work presented by Kutzler *et al.* represents another step towards opioid-sparing analgesia in a population of patients at risk for adverse opioid-related events. Implementing these changes more broadly, however, will require further research to establish the evidence-base for alternative approaches, stakeholder buy-in, and active implementation support. In the interim, taking an interdisciplinary and holistic approach to considering the individual needs of patients in the pre-transplant period can help to optimize post-transplant outcomes.

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