In reply: We thank Swetz et al for their insightful comments. They bring forth valuable contributions to pain management in a subset of patients with liver disease who require palliative care, which we did not differentiate adequately. Because our article was intended to be an overview of outpatient (and/or transient inpatient) pain management, admittedly we did not address the extremes of pain management discussed in the letter by Swetz et al. Our goal was to provide clinicians with a broad approach to cirrhotic patients with pain (patients with abdominal pain, headaches, and joint pain, as well as those with more severe chronic pain). Given that we did not address end-of-life care or palliative care in our article, we appreciate the perspectives of Swetz et al.

To be clear to readers, although palliative care is most often thought of as end-of-life care in the medical community, it can also refer to palliation of symptoms, even in patients with ongoing aggressive medical care. This latter group is a smaller population of cirrhotic patients that we did not specifically address but whose condition is extremely difficult to manage. Obviously, with end-of-life care, opioids should be used with the goal of pain management regardless of underlying disease etiology. We would never advocate for stopping use of opioids in this population. Certainly, precipitating hepatic encephalopathy would be less of a concern in that patient population as long as the patient and family are well informed. However, the use of opioids in patients undergoing active aggressive medical care but also needing hospice or palliative care requires close monitoring for encephalopathy. The two studies on treating this group of patients, as quoted by Swetz et al, describe the same end-stage liver disease patient population at the University of California San Diego enrolled in a hospice program, but receiving aggressive medical care. Certainly, precipitating hepatic encephalopathy would be less of a concern in that patient population as long as the patient and family are well informed. However, the use of opioids in patients undergoing active aggressive medical care but also needing hospice or palliative care requires close monitoring for encephalopathy. The two studies on treating this group of patients, as quoted by Swetz et al, describe the same end-stage liver disease patient population at the University of California San Diego enrolled in a hospice program, but receiving aggressive medical care.1,2 Of the 157 patients with end-stage liver disease admitted to the hospice service, 8 (5%) were awaiting liver transplant, 6 of whom underwent transplant. The remaining patients received hospice care. Of the 157 patients, 30% developed hepatic encephalopathy while undergoing expert care and careful scrutiny.

Swetz et al rightly point out that a practitioner reading the abstract of our article in isolation may erroneously assume that opioids are to be avoided at all costs, whereas our argument is simply that they are second-line choices, as better outlined in the body of our article. Opioids should be avoided until first-line agents (eg, acetaminophen) have been tried and have failed. Opioids should be administered judiciously when used. It was not our intention to suggest that patients with liver disease and chronic unremitting pain should suffer through pain unnecessarily. Patients with cirrhosis are particularly susceptible to the adverse effects of opioids (not applicable to the end-of-life patient). One of the most common complications of end-stage liver disease is hepatic encephalopathy, which, in inexperienced hands, can be fatal. Common precipitants of encephalopathy are sedatives and opioids. As hepatologists, we see this complication very often. We maintain that if a (nonpalliative) patient with cirrhosis exhibits changes consistent with encephalopathy, immediate discontinuation of the opioid is necessary to avoid clinical deterioration, because encephalopathy is life threatening and must be treated first. Once the patient is clinically stable, resumption of opioids at lower dosing or longer intervals may be necessary, but inpatient monitoring would be required for safe dosing schedules (which was mentioned in our article). In our opinion, reliance on naloxone to manage excess sedation from opioids is impractical (with significant risk) in the outpatient setting and should be reserved for inpatients in extreme pain. Although helpful for oversedation, naloxone should not be expected to treat or reverse encephalopathy. The cited article in question also states “if acetaminophen is ineffective, opioids could be administered with careful monitoring for encephalopathy,” and the authors advocate the avoidance of opioids in the setting of hepatic encephalopathy (pages 2172 and 2173).3 In addition, the cited article by Hirschfield et al comments on advocating for a lower dose and less frequent dosing of opioid therapy when alternative analgesia is not available, in the context of avoidance of encephalopathy as well, which is similar to our viewpoint.

Patients seen in the palliative care settings and chronic pain clinics are in extreme pain, and they do need to be treated in a different manner than patients in outpatient medical clinics or in the main medical or surgical wards (the population for which our recommendations were directed). We agree with the optimal opioid choices (fentanyl and hydromorphone), as outlined by Swetz et al, and we concur with the strategy of careful titration of opioid dosing. Because our intention was to provide a practical approach to analgesia and because most patients with cirrhosis are managed in outpatient settings, intravenous fentanyl is not a feasible outpatient option. For a cirrhotic patient in extreme pain, inpatient management, in which careful monitoring and expert supervision can occur, is most appropriate, and we should have been more clear in our article on this point. The input of Swetz et al is valuable for patients with advanced liver disease in extreme pain. Our main point is that opioid and nonsteroidal anti-inflammatory drugs are commonly used as first-line pain control agents because of a misconception about acetaminophen safety in patients with liver disease. We hope our reply diminishes any confusion.

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