Safe Use of Opioids to Manage Pain in Patients With Cirrhosis

To the Editor: The duty to relieve symptoms, safely, is a preeminent one of health care professionals. We appreciate the concerns of Chandok and Watt[1] about the need for cautious use of opioids, particularly in patients with advanced liver disease. Indeed, we concur that caution should be exercised by all health care experts in use of therapeutics. However, we have concerns with the recommendations by Chandok and Watt[1] regarding opioid use. Although the fear of precipitating encephalopathy or causing excessive sedation is real, an equally cogent concern is that this fear may result in less-experienced practitioners thinking that pain must be experienced regardless, or that opioids are not safe to be used in patients with cirrhosis. Medically appropriate pain management to improve function and quality of life is acceptable for patients before they undergo transplant.[2-4] For those unsuitable for transplant (up to 85% of patients), palliative care[5,6] and occasionally hospice[7] are appropriate for many. Opioids can be used safely to relieve pain and dyspnea, even in those with advanced liver disease (as well as advanced renal, pulmonary, and cardiac disease), and are preferred to nonsteroidal anti-inflammatory agents or other drugs, especially for moderate to severe pain.[5,8] In our diverse and varied practices, we routinely use low doses of opiates such as intravenous fentanyl (with its short half-life) or oral or parenteral hydromorphone (which has less hepatic clearance than morphine) and believe that this can be done safely. The clearance of these drugs is reduced in patients with liver failure; thus, the initial dose may need to be lower, the interval between the doses may need to be increased, and such patients will need to be assessed on a regular basis.[9,10] The effect of opioids can always be reversed with naloxone, but the effect of undertreated or untreated pain on patients (or the patient's family) cannot.

Effective palliative care and pain management involve 3 key components: (1) open and honest communication about the illness, options, and medically appropriate goal setting; (2) careful attention to symptom assessment and management; and (3) appropriate care of the family, including medical, psychosocial, spiritual, and other concerns. These components are completely congruent with the best practices in hepatology.

We are concerned by the message conveyed by Chandok and Watt[1] with blanket statements such as "opioids can have deleterious effects in patients with cirrhosis…and thus they should be avoided in patients with cirrhosis," because these statements can be misleading, particularly to clinicians-in-training, and can precipitate excessive fears regarding opioid use. Long-acting opioids may be appropriate for chronic pain in patients with cirrhosis, once a safe and effective dose of short-acting opioids has been established. We disagree with the authors' recommendations for starting transdermal, continuous-release fentanyl for intractable pain (suggested in Figure 2 of their article as an acceptable "first-line" option comparable to low-dose oral hydromorphone), because introduction of a fentanyl "patch" would not be prudent until opioid requirements have been determined for the individual patient by titrating short-acting opioids to symptom relief.

Furthermore, claims of "any sign of [sedation, constipation, or early encephalopathy] necessitates immediate discontinuation of the opiate" are misleading. Indeed, in a reference cited by Chandok and Watt, those authors[8] note that "were alternative analgesia not available, [patients] should be prescribed lower doses of opioids, with extended dosing intervals." Clinical context is required in all these settings, and we concur that it is likely that clinical prudence may suggest titrating opioid doses downward, increasing dosing interval, or rotating to an alternative agent as appropriate options, rather than abruptly discontinuing opioid therapy. This is particularly critical in an end-of-life situation or when opioids have been used for a longer period, because abrupt discontinuation may not only precipitate pain but also opioid withdrawal symptoms.

End-state liver disease (cirrhosis) is incurable and irreversible, although patients can be kept "compensated" and have good quality of life. Quality of life can be maintained only if pain and non-pain symptoms are aggressively addressed and managed. Recommendations presented by Chandok and Watt can easily be taken out of context and can perpetuate fear and lack of understanding of opioids in the non-pain and palliative care community. This fear may lead to suboptimal treatment of pain and increased suffering in this fragile patient population.

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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.[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[4] comments on advocating for a lower dose and less frequent dosing of opiod 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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Gynecomastia

To the Editor: In the August and November 2009 issues of *Mayo Clinic Proceedings*, Haynes and Mookadam[1] published a Medical Image entitled "Male Gynecomastia" and Johnson and Murad[2] published a Concise Review for Clinicians entitled "Gynecomastia: Pathophysiology, Evaluation, and, Management," respectively. In response to these publications, I appreciate the journal's Editorial Board providing me an opportunity to comment on a standardized method for detecting, defining, and quantifying palpable breast tissue (PBT) in men, as well as to discuss the general prevalence of PBT, potential etiologies, and indications for further evaluation.

Incidentally, I suggest that the term *palpable breast tissue* be used instead of *gynecomastia* because the presence of breast tissue is a normal finding in men. *Gynecomastia* literally refers to the presence of a female breast in men.

Until 1979, breast tissue was considered to develop during puberty in some boys and then to regress and to be rare in men. Indeed, in the excellent review of the pathogenesis of gynecomastia in 1980 by Wilson et al,[3] the authors reported that "in normal adult man, no breast tissue can be palpated." They also stated that "it is possible that gynecomastia, if it occurs at all in elderly men, is rare." Thus, when breast tissue was identified in men, it was considered pathologic, that is, to be an adverse effect of numerous different medications or to be due to the onset of a hormonal imbalance induced by an underlying malignancy or other serious disease state affecting sex hormone production.

The method in which *gynecomastia* was diagnosed often was unclear. Frequently, a painful or tender breast was confused with the presence of gynecomastia, that is, with the mere presence of any PBT. Also, commonly the presence of pain and/or tenderness was considered to represent new-onset gynecomastia, although data were often lacking to document this. A painful breast, ie, *mastodynia* and/or breast tenderness, generally is a self-limiting condition of unknown etiology. Acute onset of breast enlargement associated with mastodynia likely represents an inflammatory process of unknown etiology, at least in some patients.[4] In any regard, these conditions do not require further investigation other than possibly determination of serum estradiol, luteinizing hormone (LH), and β-human chorionic gonadotropin concentrations.

When PBT is first noted by the patient or health care professional, regardless of whether pain and/or tenderness is present, commonly a mammogram is ordered. This is indicated only if the PBT is clearly of recent onset, very firm, irregular, and unilateral and particularly if associated with skin retraction, ie, with clinical suspicion of malignancy, a very rare occurrence.[5]

In 1979, I published a report indicating that PBT was present in 36% of healthy young and middle-aged fertile men.[6] It was asymptomatic and generally had not been noticed by these men. This high prevalence has subsequently been documented by others.[7]

The method I used to identify and quantify the amount of breast tissue present was not indicated in detail.[6] However, it was explicitly explained subsequently in an article authored by my former research fellow, Niewoehner, and me.[8] An illustration of the procedure was presented in a review article by Braunstein[9] in the *New England Journal of Medicine*. A summary of the technique follows.

The presence of PBT is defined as a palpable discrete disc of firm homogeneous, subareolar breast tissue at least 2 cm in diameter. It is measured as follows: with a finger at the superior inner quadrant and thumb at the inferior outer quadrant, a pincerlike movement is made to pick up a firm disc of breast tissue from the chest wall, the diameter of which is then measured with a flexible rule. Somewhat arbitrarily, if the tissue is smaller than 2 cm, gynecomastia (PBT) was considered not to be present. The limit of 2 cm was chosen to ensure the presence of PBT. Breast tissue is composed of stroma and ductal structures as well as fat; thus, the density of breast tissue is greater than that of fat. If breast firmness cannot be differentiated from fat tissue, the consistency of fat tissue itself can be determined by compression of the axillary fold using the same technique.[10] This methodology has been performed by others.[7,11-13]

In the article that Niewoehner and I wrote,[8] we demonstrated that the prevalence of PBT increased with age and adiposity. In older men, the mean was 65% but was as high as 85% in those with a body mass index (calculated as the weight in kilograms divided by height in meters squared) greater than 25.

The increase in the prevalence of PBT with aging has been attributed to the relative and absolute increase in fat mass with aging, and thus an increase in fat cell steroid aromatase activity. This in turn results in an increase in estrogen production,[8,10] a plausible but not proven mechanism.

Although numerous drugs have been implicated in the genesis of gynecomastia, most articles are case reports, and others are poorly documented. Of medications currently in use, only spironolactone, possibly cimetadine,[14] and estrogens have been clearly shown to induce breast enlargement. In addition, spironolactone-induced breast enlargement is dose dependent.[15,16] Furthermore, PBT (gynecomastia) is so common it would be difficult to ascribe the gynecomastia to a medication unless a randomized control trial or rechallenge test were performed.

In my opinion, the presence of PBT does not require an evaluation for thyroid, liver, primary, hypothalamic, or pituitary gonadal abnormalities. Also, if estrogen production is increased, an evaluation for malignancies is not indicated unless the PBT clearly is new and/or progressive.

Incidentally, to my knowledge, hyperthyroidism has not been shown to be a pathologically important cause of gynecomastia. Although thyrotoxicosis can induce changes in sex hormone concentrations,[17] the prevalence of gynecomastia in these patients is similar to that in the general population. Nevertheless, and regardless of the potential etiology, if breast enlargement is bilateral and clearly of recent onset or is progressive, a potential etiological evaluation should be con-

sidered, beginning with determination of estradiol, LH, and β-human chorionic gonadotropin concentrations, as indicated previously.

A low circulating testosterone concentration, particularly in the setting of a normal estradiol concentration, has been suggested to result in gynecomastia. However, to my knowledge, an enlargement in breast tissue mass secondary to a loss of inhibition by testosterone, allowing an estrogen stimulatory effect to be expressed by a normal, unchanged estrogen concentration, has not been documented. In addition, estrogen is a potent inhibitor of LH secretion in men. In many cases in which an estrogen-testosterone ratio is high and is due to a low or low-normal testosterone concentration, the decreased testosterone could be due to a modest increase in estrogen concentration resulting in feedback inhibition of LH.[18] In this context, an increase in breast mass would be due to the elevation in estrogen concentration, not the result of a low testosterone value, per se.

In summary, PBT is common in men, increases with age and/or adiposity, and is rarely due to commonly used medications unless they increase the circulating estradiol concentration or produce an estrogen-mimetic substance. A hormonal evaluation is unnecessary unless the observed breast enlargement is clearly of recent origin or is increasing. Mammography is never indicated unless there is a strong clinical suspicion of a breast malignancy. Finally, before the publication by Niewoehner and me,[8] a standardized assessment of the presence of gynecomastia often was not clearly defined. Many of the medication-associated reports appeared earlier, and the detection methodology was not described, thus complicating an interpretation of the data.

On the basis of the observed high prevalence of PBT in the general male population, implication of a medication in the genesis of gynecomastia will require a large population-based study or knowledge that PBT was not present before introduction of that medication into a treatment regimen. Preferably, a rechallenge test also should be performed to document a cause-and-effect relationship.

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Editor's Note: When publishing a letter that comments on an article published previously in *Mayo Clinic Proceedings*, it is the journal's policy to invite the author(s) of the reference article to publish a response. Drs Haynes and Mookadam and Johnson and Murad elected to not respond in print.

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