

EDITORIALS

Growing Concerns Regarding Long-term Opioid Use: The Hospitalization Hazard

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Overall rates of opioid use and chronic use for non-cancer pain have increased markedly in the last 1 to 2 decades.^{1,2} Recognition of such rapidly increasing use has prompted a flurry of investigations examining the impact of what has been referred to as the “opioid epidemic.”^{1,3,4} Patients receiving chronic opioid analgesics have previously been demonstrated to consume disproportionate shares of healthcare resources, including significantly more emergency room visits and days in the hospital.⁵ In this issue of the *Journal of Hospital Medicine*, Liang and Turner⁶ further demonstrate the impressive scope of healthcare resources consumed by this patient population, and extend these findings by examining the relationship between opioid dose and subsequent hospitalization in a large national cohort of middle-aged health maintenance organization enrollees with noncancer pain. This is the first study to investigate the relationship in a general cohort of patients.

Perhaps the most striking finding of the study was an all-cause hospitalization rate of 1120 per 10,000 person-years among their cohort of opioid users. Considering that 5 to 8 million Americans use long-term opioids,⁷ this translates to about 500,000 to 900,000 admissions per year. The degree to which opioids themselves contribute to such hospitalizations (attributable risk) is uncertain, and it is likely that some of this risk can be explained by the idea that opioids are a marker for comorbidity, and that the conditions prompting opioid use independently increase risk of hospitalization. Studies examining more homogeneous patient populations could serve to shed light on this question. The issue of attributable risk notwithstanding, it is clear that this is a patient population that should have the attention of physicians, hospital administrators, and policy makers.

The main finding of their study is that the total opioid dose in any given 6-month interval was more strongly associated with subsequent all-cause hospitalization than the daily dose. This suggests that cumulative exposure is important, and possibly more

important than the strength of any given prescription, at least when it comes to the outcome of hospitalization. That is not to say that the daily dose is unimportant, and the authors appropriately caution against such an interpretation. Daily dose matters, and to conclude otherwise would be incorrect for several reasons. First, among patients receiving high total doses of opioids, higher daily doses did seem to confer additional risk. Second, hospitalization is only 1 measure of risk, and multiple prior studies and a recent systematic review have concluded that higher opioid doses are strongly associated with adverse events, including overdose, abuse, addiction, motor vehicle accidents, and myocardial infarction.⁸ Last, their finding that total dose more strongly predicts hospitalization than daily dose may reflect confounding by indication and underlying patient characteristics not captured in their analysis. Patients receiving a daily dose of 100 mg or more, but with a total dose of <1830 mg over 6 months, would necessarily have received opioids for a relatively brief period of time (<20 days). The indications for—and patients receiving—such short-course, high-dose therapy are likely to be vastly different from those for longer-course, high-dose therapy, in ways that could be meaningfully associated with hospitalization risk. Nonetheless, their results suggest that cumulative exposure is important as an additional metric by which to predict possible adverse consequences of opioid use.

That cumulative exposure and percent of time on opioids are associated with increased risk of subsequent hospitalization casts further doubt on the already questionable risk-to-benefit ratio of long-term use of opioids for noncancer pain. A recent systematic review of the effectiveness and risks of long-term opioid therapy for chronic pain found existing evidence insufficient to determine effectiveness for chronic pain and function, owing to lack of a single study evaluating long-term outcomes in patients on opioid therapy versus no opioid therapy, and found evidence for a dose-dependent risk for serious harms.⁸ The authors conclude that the lack of scientific evidence on effectiveness of long-term opioid therapy for chronic pain is in striking contrast to its widespread use in this setting. Studies examining the effect of long-term opioid therapy on pain and function, and defining patient subgroups that may benefit from such therapy, are imperative and long overdue.

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In the absence of data showing benefit, and in the face of a growing body of evidence demonstrating harm, we are obligated to reevaluate opioid prescribing for chronic noncancer pain. Until studies have evaluated the impact of opioid use on long-term outcomes, physicians are missing a key piece of the risk-benefit calculation, and prescribing must be done judiciously. Curbing the opioid epidemic will require initiatives of epidemic proportions, involving the entire spectrum of healthcare, from the primary care setting to the emergency department (where up to 25% of patients with chronic pain receive their opioids⁷), from researchers to policy makers, and ultimately from patient expectations to physician decision making.

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