Overdoses in Patients on Opioids: Risks Associated with Mental Health Conditions and Their Treatment

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For more than 20 years, opioid therapy has expanded beyond cancer pain treatment to widespread use for various chronic pain conditions. While opioids have improved the quality of life for many patients disabled by chronic pain, their long-term use remains controversial for several reasons. First, the long-term efficacy of opioids is unclear. Opioids provide clinically significant relief for only a minority of patients¹—many patients continue to experience severe, disabling pain despite opioid treatment. Second, opioids are associated with several problematic side effects that many patients report as intolerable. In addition, opioids may lead to adverse physiologic effects (e.g., hyperalgesia and hypogonadism) not necessarily reversed by stopping opioid therapy. Third, opioids have potential for misuse, which may occur more frequently than previously thought. Although physical dependence is an expected result of chronic opioid use, some patients develop an opioid use disorder. Fourth and most concerning, is that with the wider use of opioids, there has been a parallel increase in opioid-related overdose deaths. Between 1999 and 2009, the rate of prescription opioid overdose deaths in the U.S. rose fourfold,² reflecting an epidemic of prescription opioid overdoses.

While our understanding of the factors influencing the opioid epidemic and overdose risk is incomplete, three observational studies^{3–5} have helped clarify the relationship between opioid dose and drug overdose. These studies examined distinct patient populations and used different methods to measure exposure and outcomes. However, each study used a common metric by assessing prescribed daily opioid dose converted to morphine equivalent doses and compared the risk of confirmed opioid-related overdose across dose categories (i.e., 1–<20 milligrams (mg)/day, >20–<50 mg/day, >50–<100 mg/day, >100 mg/day). All three studies found that increasing opioid dose was associated, in a dose-response manner, with an increasing risk of opioid-related overdose, and this association was statistically significant at opioid doses above 50 mg/day. Bohnert

and colleagues³ showed in a national sample of Veterans that prescribed doses ≥ 100 mg/day of morphine (or morphine equivalent) were associated with a fourfold to 11-fold increased risk of opioid overdose death, depending on diagnostic subgroups of patients examined (substance use disorder, chronic pain, acute pain, and cancer). Of note, overdose deaths were a rare event, occurring in only 0.04 % of Veterans treated with opioids.³

State and national initiatives emerged in response to this compelling evidence that higher doses of opioids may be unsafe and strongly associated with overdose. Pain and public health experts in Washington State developed opioid treatment guidelines that recommended limiting opioid doses to less than 120 mg/day.⁶ In 2011, the White House Office of Drug Control Policy published a white paper entitled: “Epidemic: Responding to America’s Prescription Drug Abuse Crisis” that detailed plans to reduce opioid overdose deaths through educational efforts, expansion of state drug monitoring programs, safe medication disposal, and legal enforcement against illegal practices. The Veterans Health Administration (VHA) responded to this evidence, as well as data showing that concomitant use of opioids and benzodiazepines increase the risk of overdose, with the system-wide implementation of the Opioid Safety Initiative. Goals of the Initiative include: 1) limiting the use of high-dose opioids; 2) limiting the co-prescription of opioids and benzodiazepines; and 3) developing toolkits and other strategies to provide safer alternatives such as complementary and alternative medicine modalities for treating chronic pain.

In this issue of *JGIM*, Turner and Liang⁷ extend previous reports on drug overdose, especially in individuals with mental health conditions (depression, anxiety, or psychosis) or those receiving common psychiatric medications. The study examined interactions of filled prescriptions for opioids, benzodiazepines, antidepressants, and zolpidem with mental health conditions. In this national sample of Aetna Health beneficiaries with chronic pain, 1385 (0.67 %) had a drug overdose (incidence rate 421/100,000 person-years). Similar to earlier studies,^{3–5} this study found a higher rate of overdose among patients prescribed high opioid doses. The risk for overdose rose significantly with daily opioid dose for all patients, but was the highest for individuals with depression and prescribed opioids ≥ 100 mg/day (adjusted odds ratio=7.06) compared to individuals without depression and those not prescribed opioids. In

addition, longer duration of benzodiazepine use was associated with drug overdose, while antidepressant use for more than 90 days was associated with reduced odds of overdose for persons with depression. This latter finding suggests a protective effect of antidepressants, and supports efforts to improve adherence to antidepressant treatment beyond 90 days.

Disentangling the role that mental health conditions and their treatments play in overdose risk is critical, especially in light of data demonstrating that mental health conditions increase the risk of overdose among Veterans receiving opioids for pain,⁸ and in light of the fact that mental health comorbidities are common in patients with chronic pain.⁹ Furthermore, depression complicates the management of chronic pain and is associated with poorer outcomes; depression is associated with more pain complaints, greater pain intensity, longer duration of pain, and lower likelihood of recovery among patients with chronic pain.⁹ As a result, patients with depression are more likely to be prescribed opioids for chronic pain compared to patients without depression.

Turner and Liang's⁷ analysis highlights the need to evaluate overdose risk specifically for patients with depression or those who are treated with antidepressants, benzodiazepines, or zolpidem. A particularly interesting finding in this study is the potentially higher risk period during initiation of opioids and antidepressants, but not benzodiazepines or zolpidem. One implication of this finding is that prior studies in cohorts of prevalent opioid treatment samples (instead of "new or incident users") may have underestimated the rate of overdose. Patients who stopped taking their opioids "early" after experiencing a non-fatal overdose would be under-represented relative to those who did not experience early serious adverse outcomes of opioid use.

Furthermore, a recent study by Miller et al.¹⁰ showed that patients starting long-acting opioids were more than twice as likely to overdose (hazard ratio [HR], 2.33; 95 % CI, 1.26–4.32) compared with persons initiating therapy with short-acting opioids, after adjusting for potential confounders. Furthermore, the risk associated with long-acting opioids was even greater during the first 2 weeks after starting treating (HR=5.25 (95 % CI 1.88–14.72)). Thus, patients may benefit from additional safety monitoring during the "early" period (i.e., the first 2 weeks) after initiating opioid therapy, especially a long-acting agent, or after starting an antidepressant among patients also receiving opioids.

Because overdose is the most serious adverse outcome of opioid therapy but relatively infrequent, it is necessary to use large administrative databases to study the critical research problems needed to inform overdose prevention. These data sources have limitations; however, for example, in quantifying illness and patient overdose behaviors such as taking more pills than prescribed, using multiple drugs with psychoactive or sedating effects, or snorting/injecting crushed opioids to obtain a high. These data sources are also limited in overcoming treatment by indication or severity and related selection effects. Although studies such as the one from Turner and Liang⁷

should be interpreted cautiously, they also represent the best information available to study overdose in patient populations.

The findings of Turner and Liang⁷ are particularly salient for the care of patients with comorbid chronic pain and depression, as well as those patients who are treated with benzodiazepines for anxiety. In the context of opioid therapy, the "rule" for safer medication prescribing to "start low dose and go (titrate) slow" applies with the added recommendation to try and "stay below" 100 mg of morphine or its equivalent total per day, especially for those with comorbid depression. Primary care physicians (PCPs) often struggle with opioid treatment decisions and worry about fostering drug abuse and addiction; these recent studies add even more issues for physicians to consider. Physicians will need to consider not only the daily dose, but also duration of opioid action and the early period after initiating opioids or adding antidepressants to the treatment regimen.

Turner and Liang's⁷ findings highlight the importance of assessing the balance of benefits and risks before initiating and continuing opioid therapy, especially as doses approach or exceed 100 mg/day and in patients with comorbid depression. To mitigate risks of opioid prescribing, PCPs and pain specialists may consider implementing the following strategies: 1) maximize non-opioid analgesics; 2) encourage and reinforce non-pharmacological treatments to complement analgesics; 3) view opioid initiation as an empiric trial in which the opioid will be discontinued if ineffective; 4) avoid opioid dose escalations without first assessing treatment response, side effects, and signs of misuse; 5) use opioid monitoring tools (urine drug screens, prescription drug monitoring programs, pill counts) regularly; and 6) assess and treat comorbid depression. At the health care system level, opioid risk may be further minimized if insurers increase reimbursement for non-pharmacological treatments and clinics, or if hospitals provide a broader array of pain treatment options; these include greater access to physical rehabilitation, cognitive behavioral therapy, and complementary and alternative or integrative treatments for chronic pain. This combination of system, prescriber, and patient efforts is needed to have lasting reductions in opioid overdose without compromising pain management.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government.

Conflict of Interest: Drs. Bair and Bohnert have no conflicts of interest related to this work.

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