Published in final edited form as:

Crit Care Med. 2018 June ; 46(6): 1005–1006. doi:10.1097/CCM.0000000000003103.

Critical Care Outcomes among Opioid Users: Hidden Sequelae of a Growing Crisis?

Andrew J. Goodwin, MD, MSCR¹

¹Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, Suite 816, Clinical Sciences Building, MSC 630, 96 Jonathan Lucas St. Charleston, SC 29425

Keywords

Opioids; Opiates; ICU Outcomes; Critical Care; Mortality

The United States (US) is in the midst of an opioid epidemic with consumption rates that far exceed the rest of the world. A heightened focus on pain management, non-standardized prescribing patterns, and false assurances from the pharmaceutical industry about the addictive potential of prescription opioids have led to a public health emergency in which over 3.6 million people misuse opioids and more than 50,000 people die annually in the US from their overdose (1, 2). The societal impact of this growing crisis has garnered significant recent attention among policymakers, the media and the general public although its full impact on population health is unknown.

Opioid users represent a population at heightened risk for developing critical illness either from complications of the underlying conditions for which they use opioids (e.g. malignancy) or from complications from the opioids themselves. Thus, as the population of opioid users has grown, so too has the population of opioid users who develop critical illness. Recent work by Stevens et al. found that between 2009 and 2015, the number of opioid overdoses requiring critical care in the US increased by 34% while the average cost per ICU overdose admission increased from \$58,500 to \$92,400 (3). In addition to overdose, opioid use has been associated with a number of complications which could adversely affect the prognosis of critically ill patients including myocardial infarction (4), cerebrovascular accident (5), and infection (6–8). However, the impact of opioid use on critical illness outcomes has previously been unexplored.

In this issue of *Critical Care Medicine*, Munch et al. (9) examine the association between pre-admission opioid use and mortality in a heterogeneous, non-surgical critically ill population. The investigators combined data from the Danish National Patient Registry and the Danish National Prescription Registry in order to stratify subjects into four distinct groups: 1) current opioid users (redeemed an opioid prescription within 30 days prior to hospital admission), 2) recent opioid users (redeemed an opioid prescription within 31–365 days prior to hospital admission), 3) former users (at least one prior opioid prescription

redeemed, but none in the 365 days prior to admission) and 4) non-users. Current users were further sub-typed into new (first prescription within the 30 days prior to admission) and long-term users. Intriguingly, they found that 30-day all-cause mortality increased across all opioid use categories with non-users experiencing a 20.6% mortality rate and current users experiencing a 34.8% mortality rate. After adjustment for demographics, comorbidities and concomitant medication use, current users were at an elevated risk of 30-day mortality compared to non-users (Hazard Ratio = 1.20) with new users experiencing the highest risk (HR = 1.35). Further, current (HR = 1.47) and recent (HR = 1.20) users who survived the first 30 days were at a persistently increased risk of death during the year after hospitalization with critical illness. The primary immediate cause of death for all groups was “disease of the airways” which includes lower respiratory tract infections.

Although this study’s findings are merely associative, the observation that opioid users experience an elevated risk of mortality after critical illness is provocative and could potentially be explained by several possible theories. First, opioids are known to have immunosuppressive properties through a number of proposed mechanisms including modulation of the hypothalamic-pituitary-adrenal axis, alteration of sympathetic tone and potentially through direct effects on immune cells, although this last mechanism remains controversial (10). Pre-clinical data suggest that the immunosuppressive potential of opioids varies by agent although its clinical impact in human disease is uncertain. Several studies have demonstrated an association between opioid use and the development of severe infection including recent work by Wiese et al. who observed that opioid users are at increased risk for invasive pneumococcal infection (6, 11, 12). However, as these risks of infection and the association with mortality seen in the current study exist when opioids with minimal immunosuppressive properties are used (9, 11, 12), immunosuppression alone seems unlikely to fully explain the current observations.

Opioid use may also indirectly worsen critical illness outcomes by increasing the risk of complications associated with mortality such as aspiration and delirium (13, 14). This possibility is supported by the investigators’ observation that new users and users of high potency opioids experience the highest risk of death as these subjects may also be those at greatest risk of opioid complications. However, due to limitations in administrative coding accuracy, they were unable to accurately examine this possibility. Finally, one cannot rule out the possibility that the association between opioid use and mortality seen in this study is the result of residual confounding by indication. Opioids are commonly used by patients with malignancy and severe chronic lung disease for symptom control and the presence of these underlying diagnoses could be responsible for the increased mortality seen among critically ill opioid users. The investigators’ careful dissection of risk among patients with and without these chronic diseases, however, demonstrates that even opioid users without cancer or chronic lung disease are at an increased risk of death from critical illness.

This study has several strengths. Denmark’s comprehensive national database system allowed for seamless linkage between the inpatient registry, the outpatient pharmacy registry, and vital records. This powerful resource enabled an innovative analysis of both outpatient and inpatient data with near complete follow up and serves as a model for how well-integrated governmental databases can facilitate pragmatic research on important

clinical questions. Additionally, Denmark's National Health Service provides universal healthcare to its citizens. Although this may limit the generalizability of some findings, the elimination of potential confounding due to limited access to care should be viewed as a strength in this study.

As with every study, limitations also exist. The observations made here are only associative and, thus, are subject to residual confounding as previously discussed. Further, while the Danish registry system is well-integrated, it remains dependent upon the accuracy of coding by the hospitals that contribute to it. Inaccurate coding of inpatient diagnoses such as delirium prevented the authors from being able to explore possible mechanistic links between opioid use and mortality through mediation analysis. Lastly, the pharmacy data could only provide insight into opioid prescribing and filling practices whereas data on how opioids were being taken was not available. Thus, associations between the correct use and misuse of opioids with mortality could not be identified.

The opioid epidemic has become a crisis in the US with far-reaching public health implications. Using Danish registry data, Munch et al. provide novel insights into the potential negative impact that opioid use has on critical illness outcomes, findings that can be used to better characterize the impact of this crisis on population health. While further research is needed to better understand the biologic mechanisms underlying this association, ongoing policy initiatives aimed at reducing opioid use could translate into improved ICU outcomes and should be supported by the critical care community.

Acknowledgments

Copyright form disclosure: Dr. Goodwin received support for article research from the National Institutes of Health.

References

1. Center for behavioral health statistics and quality. 2016 national survey on drug use and health: Detailed tables. Substance Abuse and Mental Health Administration; Rockville MD: 2017.
2. Hedegaard, H., Warner, M., Minino, AM. NCHS Data Brief No 294. Hyattsville, MD: National Center for Health Statistics; 2017. Drug overdose deaths in the united states, 1999–2016.
3. Stevens JP, Wall MJ, Novack L, Marshall J, Hsu DJ, Howell MD. The critical care crisis of opioid overdoses in the united states. *Annals of the American Thoracic Society*. 2017; 14:1803–1809. [PubMed: 28800256]
4. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. *Journal of internal medicine*. 2013; 273:511–526. [PubMed: 23331508]
5. Lee CW, Muo CH, Liang JA, Sung FC, Kao CH. Association of intensive morphine treatment and increased stroke incidence in prostate cancer patients: A population-based nested case-control study. *Japanese journal of clinical oncology*. 2013; 43:776–781. [PubMed: 23797791]
6. Dublin S, Walker RL, Jackson ML, Nelson JC, Weiss NS, Von Korff M, Jackson LA. Use of opioids or benzodiazepines and risk of pneumonia in older adults: A population-based case-control study. *J Am Geriatr Soc*. 2011; 59:1899–1907. [PubMed: 22091503]
7. Horn SD, Wright HL, Couperus JJ, Rhodes RS, Smout RJ, Roberts KA, Linares AP. Association between patient-controlled analgesia pump use and postoperative surgical site infection in intestinal surgery patients. *Surgical infections*. 2002; 3:109–118. [PubMed: 12519477]

8. Schwacha MG, McGwin G Jr, Hutchinson CB, Cross JM, MacLennan PA, Rue LW 3rd. The contribution of opiate analgesics to the development of infectious complications in burn patients. *American journal of surgery*. 2006; 192:82–86. [PubMed: 16769281]
9. Munch T, Christiansen CF, Pedersen L, Sorensen HT. Impact of pre-admission opioid treatment on one-year mortality following non-surgical intensive care. *Critical Care Medicine*. 2018 In press.
10. Al-Hashimi M, Scott SW, Thompson JP, Lambert DG. Opioids and immune modulation: More questions than answers. *British journal of anaesthesia*. 2013; 111:80–88. [PubMed: 23794649]
11. Wiese AD, Griffin MR, Stein CM, Mitchel EF Jr, Grijalva CG. Opioid analgesics and the risk of serious infections among patients with rheumatoid arthritis: A self-controlled case series study. *Arthritis & rheumatology*. 2016; 68:323–331. [PubMed: 26473742]
12. Wiese AD, Griffin MR, Schaffner W, Stein CM, Greevy RA, Mitchel EF Jr, Grijalva CG. Opioid analgesic use and risk for invasive pneumococcal diseases: A nested case-control study. *Ann Intern Med*. 2018
13. Komiya K, Rubin BK, Kadota JI, Mukae H, Akaba T, Moro H, Aoki N, Tsukada H, Noguchi S, Shime N, Takahashi O, Kohno S. Prognostic implications of aspiration pneumonia in patients with community acquired pneumonia: A systematic review with meta-analysis. *Scientific reports*. 2016; 6:38097. [PubMed: 27924871]
14. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004; 291:1753–1762. [PubMed: 15082703]