



## Ⓜ Opioids for Sedation: Has the Pendulum Swung Too Far?

To the Editor:

For a decade, analgosedation has been a cornerstone of supportive care in the ICU. However, Duprey and colleagues' recent article is a reminder that opioids are not benign. In a cohort of 4,075 adult patients in a mixed ICU, any administration of an opioid in an awake, nondelirious patient was associated with a 45% increase in the odds of delirium the following day in a dose-dependent fashion while controlling for relevant covariates. Furthermore, total opioid use increased substantially over the course of the study (1). Here, we argue that in the shift toward analgosedation and sedative hypnotic avoidance, the pendulum may have swung too far, with important implications for opioid use in the ICU.

Analgosedation encompasses two distinct strategies that, in practice, represent significantly different approaches: 1) analgesia-first sedation, wherein an analgesic is used before a sedative, or 2) analgesia-based sedation, wherein an analgesic is used instead of a sedative (2). Analgesia-based sedation goes beyond the idea of addressing pain first and uses opioids to manage agitation or facilitate mechanical ventilation. Duprey and colleagues' evaluation mirrors a practice shift toward analgesia-based sedation; the mean opioid dose was 10 times higher from 2017 to 2019 than from 2015 to 2016—478 mg versus 56 mg—and patients were more likely to receive an opioid at a higher median dose on a day when pain scores were not documented. This trend held true even for unarousable patients, who were the most likely to receive an opioid (at the highest median dose) (1).

The push to replace sedatives with opioids has limited evidence. The largest randomized controlled trial to date failed to demonstrate the benefit of a non-sedation strategy on 90-day mortality, ICU- and ventilator-free days, and coma- and delirium-free days despite less sedative use and lighter sedation (3). Conversely, analgesia-based sedation has improved patient-centered outcomes such as pain management (4, 5) and ventilator-free days (4, 6) in a number of studies; however, these trials have notable limitations. Remifentanyl, a synthetic opioid with a 3- to 4-minute half-life independent of end-organ function, limits generalizability (4, 6). Studies often use a suboptimal comparator (e.g., midazolam-based sedation) (6) or describe cohorts with short durations of intubation, making it difficult to assess the impact of the intervention (5). Finally, retrospective pre/post-study designs may be influenced by confounders such as adoption of sedation protocols (4).

The most significant limitation of the current literature is that all studies targeted light sedation. As such, the efficacy and safety of an analgesia-based regimen in patients requiring deep sedation or long durations of mechanical ventilation are largely uncharacterized. This knowledge gap has become extremely relevant during the ongoing coronavirus disease (COVID-19) pandemic. High doses and long durations of opioid infusions may achieve deep sedation, but may also precipitate opioid tolerance, dependence, or hyperalgesia, and place patients at risk for withdrawal. Furthermore, there is no "perfect" opioid

agent when deep sedation is required; potent opioids with advantageous pharmacokinetic profiles (fentanyl, remifentanyl) induce tolerance more quickly, whereas morphine metabolites may accumulate or induce hyperalgesia.

As such, core questions regarding analgosedation remain: 1) Are there differences in outcomes between analgesia-first and analgesia-based sedation? 2) Is there a preferred sedation strategy in patients requiring deep sedation? 3) Does the choice of specific agent, class, or dosing scheme influence these outcomes?

In the push to avoid benzodiazepine use, the adverse effect profile of opioids may have been inadvertently downplayed. However, absence of evidence of harm does not constitute evidence of absence, and no drug is benign. This is a plea for consideration of how much we still do not know, and for awareness of how many times in critical care practice we have seen the pendulum swing dramatically while we trade one risk for another. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

Brian P. Murray, Pharm.D., B.C.C.C.P.\*  
University of North Carolina Medical Center  
Chapel Hill, North Carolina

Andrea Sikora Newsome, Pharm.D., B.C.P.S., B.C.C.C.P., F.C.C.M.  
University of Georgia College of Pharmacy  
Augusta, Georgia

and  
Augusta University Medical Center  
Augusta, Georgia

ORCID ID: 0000-0001-6660-9749 (B.P.M.).

\*Corresponding author (e-mail: [brian.murray@unchealth.unc.edu](mailto:brian.murray@unchealth.unc.edu)).

## References

- Duprey MS, Dijkstra-Kersten SMA, Zaal IJ, Briescacher BA, Saczynski JS, Griffith JL, et al. Opioid use increases the risk of delirium in critically ill adults independently of pain. *Am J Respir Crit Care Med* [online ahead of print] 09 April 2021; DOI: 10.1164/rccm.202010-3794OC. Published in final form as *Am J Respir Crit Care Med* 2021;204:565–571 (this issue).
- Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018;46:e825–e873.
- Olsen HT, Nedergaard HK, Strøm T, Oxlund J, Wian KA, Ytrebø LM, et al. Non-sedation or light sedation in critically ill, mechanically ventilated patients. *N Engl J Med* 2020;382:1103–1111.
- Faust AC, Rajan P, Sheperd LA, Alvarez CA, McCorstin P, Doebele RL. Impact of an analgesia-based sedation protocol on mechanically ventilated patients in a medical intensive care unit. *Anesth Analg* 2016; 123:903–909.
- Tedders KM, McNorton KN, Edwin SB. Efficacy and safety of analgosedation with fentanyl compared with traditional sedation with propofol. *Pharmacotherapy* 2014;34:643–647.
- Breen D, Karabinis A, Malbrain M, Morais R, Albrecht S, Jarnvig IL, et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanyl with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomized trial [ISRCTN47583497]. *Crit Care* 2005;9:R200–R210.

Copyright © 2021 by the American Thoracic Society

Ⓜ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern.

Originally Published in Press as DOI: 10.1164/rccm.202104-1012LE on June 7, 2021