The Conundrum of Pain, Opiate Use, and Delirium
Analgosedation or Analgesia-First Approach?

Critical illness, regardless of etiology, is a painful condition. Many mechanically ventilated patients therefore receive opioids to manage the discomfort of having an endotracheal tube or for procedures they undergo in line with the Society of Critical Care Medicine's pain, agitation/sedation, delirium, immobility, and sleep disruption (PADIS) guidelines (1). These guidelines also recommend targeting light levels of sedation, thus minimizing overall sedative medication exposure (in particular, benzodiazepines). Specific recommendations in the PADIS guidelines were developed on the basis of well-conducted studies showing an association between deep sedation and worse outcomes (2), including the role of benzodiazepines in delirium (3). Recent large-scale implementation of the ABCDEF bundle (assessment and management of pain, both awakening and breathing trials, choice of sedation, delirium assessment and management, exercise, family engagement), a pragmatic framework for operationalizing the PADIS guidelines, has shown significant improvements in patient outcomes, including delirium and mortality, yet found that patients were more awake and complained of pain more often (4). Unfortunately, pain is also associated with worse delirium outcomes (5), though this has not been clearly demonstrated in ICU patients. As more focus is directed toward the assessment and treatment of pain in the critically ill while minimizing sedative medications, it is now more important than ever to understand the role of opioids, and the pain they are used to treat, in delirium. Two approaches often recommended are an analgosedation approach, in which opioid medications are used for their sedative properties and often administered beyond what is needed for the management of pain, or the analgesia-first approach, in which pain is addressed first and only after it is treated are sedatives administered for agitation. Yet, it is unclear whether one approach is better or worse than the other.

In this issue of the *Journal*, Duprey and colleagues (pp. 566–572) report on a large cohort of adult patients admitted to a mixed tertiary-level medical-surgical ICU in the Netherlands, where the authors sought to understand the relationship between opioid use in the ICU and transitions from an awake, nondelirious state to delirium while accounting for the level of pain (6). As a secondary analysis, the authors also assessed the impact of pain on delirium, accounting for opiate use. Patients were assessed for level of pain, agitation and sedation, and delirium using well-validated instruments. Detailed patient demographic data and that of the ICU and hospital course, including exposure to opioid medications and their doses, were collected. Multinomial regression analyses, accounting for important confounders, including time-varying daily ICU variables, were used to study the associations of opioid use on a given day and the transition from being awake and nondelirious on that day to having delirium the following day. Competing risks such as coma, discharge, or death, which would prevent a patient from being assessed for delirium, were accounted for in the modeling strategy. Sensitivity analyses were performed to address, among other variables, the long study duration and effect of changes in sedation and delirium practices over that time, implication of age, the impact of being on a surgical service, and whether the risk of delirium differed depending on the use of synthetic versus nonsynthetic opioids. Among almost 6,000 patients, 4,000 were included in the final analysis; the majority of those excluded had a neurological condition precluding delirium assessment. Of the almost 15,000 days patients were awake and nondelirious, the authors reported delirium occurring on 1,300 subsequent days. Opioid use was associated with 45% increased odds of this transition to delirium. Increased opioid dose was also associated with increased odds of this transition, though it would require almost doubling of the median daily dose administered (an additional 20.8 mg of intravenous morphine equivalents) to increase the risk nominally by 5%. The dose dependency varied by individual opioids; synthetic opioids were associated with lower odds of an increase compared with morphine (1.5% vs. 9% for every 10 mg of intravenous morphine equivalent). Surprisingly, the authors found an inverse association between the intensity of pain and delirium, which could relate to patients with better brain function more accurately reporting pain. The aforementioned sensitivity analyses did not result in any qualitative change in the associations, with opioids being associated with delirium across the entire study period, in younger and elderly patients, in both surgical and medical patients, and with both synthetic and nonsynthetic opioids.

This study adds to the growing body of evidence showing an association between opioid administration and delirium (7, 8), with many methodological advances. The large sample size, use of validated instruments, account of time-varying confounders and competing risks, and the additional exploratory sensitivity analysis all add to the strength of the study and the confidence in the results. On the contrary, the association of increasing pain with a lower probability of delirium belies any pathophysiological basis and raises concerns about bias and unmeasured confounders. Furthermore, up to 25% of pain assessments were missing, rates of delirium (34%) were lower than those usually reported in tertiary ICUs with high severity of illness, and nonopiate pain management techniques were not accounted for, limiting, to some extent, the generalizability of these findings.

As healthcare providers reduce their dependency on sedative medications and patients are more awake and communicative, attention to appropriate pain management while avoiding overzealous opiate use is now the next challenge facing clinicians. How can we use the results of this study to shape our practice? Although some have advocated analgosedation techniques to reduce the exposure to sedative medications, perhaps it is time to cautiously rethink this strategy; substituting one deliriogenic medication (e.g., a benzodiazepine) with another (opiate) may not appear to confer much benefit (though it likely depends on doses required) if you extrapolate the findings of this study. In particular, when pain scores were not assessed, patients received more opiates and were less arousable, supporting this

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argument that opiates may have been used secondarily for sedation and portended unfavorable endpoints. It may therefore be prudent to incorporate an analgesia-first approach using validated pain assessment tools to guide the administration of analgesics targeted to treat pain and pain alone (5) and using a multimodal pain management technique (pharmacological and nonpharmacological) to reduce opiate use (1). Once pain is addressed if sedation is required because of agitation and inability to redirect patients, one can then use either propofol or dexmedetomidine—both agents with similar risks for delirium yet with a superior profile over benzodiazepines (9–11). Although the study by Duprey and colleagues does not prove causation or compare head to head an analgosedation and an analgesia-first approach, it provides clinicians with a clearer understanding of the risks associated with opiates and sets the stage for a comparative trial of these two approaches in critically ill patients to determine the best strategies to address pain in this era of light sedation. ■

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Atrial Fibrillation, Obstructive Sleep Apnea, and Continuous Positive Airway Pressure: No Easy Fix

Sleep apnea (SA) and atrial fibrillation (AF) are common conditions that frequently coexist; the relationship between the two is complex and probably bidirectional (1, 2). However, whether treating patients with SA with continuous positive airway pressure (CPAP) influences the amount or duration of AF is unknown. In this issue of the *Journal*, Traaen and colleagues (pp. 573–582) report the first randomized controlled trial (RCT) to determine the effects of CPAP on AF in patients with paroxysmal AF. They convincingly demonstrate that CPAP treatment does not affect the burden of AF after 5 months of therapy (3).

This is an important area of research. Both AF and SA are not only related to debilitating symptoms in some but are also associated with embolic stroke risk. Risk management is key to stroke prevention. The trial was well designed; patients with AF were recruited from secondary care, either from cardiology clinics or patients referred for catheter ablation. All patients were screened for SA with two nights of respiratory polygraphy at home. Patients were enrolled with a mean AHI of >15 events/hour conventionally used to categorize moderate and severe SA;

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