ORIGINAL ARTICLE

Opioid Use Increases the Risk of Delirium in Critically Ill Adults Independently of Pain

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Abstract

Rationale: It is unclear whether opioid use increases the risk of ICU delirium. Prior studies have not accounted for confounding, including daily severity of illness, pain, and competing events that may preclude delirium detection.

Objectives: To evaluate the association between ICU opioid exposure, opioid dose, and delirium occurrence.

Methods: In consecutive adults admitted for more than 24 hours to the ICU, daily mental status was classified as awake without delirium, delirium, or unarousable. A first-order Markov model with multinomial logistic regression analysis considered four possible next-day outcomes (i.e., awake without delirium, delirium, unarousable, and ICU discharge or death) and 11 delirium-related covariables (baseline: admission type, age, sex, Acute Physiology and Chronic Health Evaluation IV score, and Charlson comorbidity score; daily: ICU day, modified Sequential Organ Failure Assessment, ventilation use, benzodiazepine use, and severe pain). This model was used to quantify the association between opioid use, opioid dose, and delirium occurrence the next day.

Measurements and Main Results: The 4,075 adults had 26,250 ICU days; an opioid was administered on 57.0% ($n = 14,975$), severe pain occurred on 7.0% ($n = 1,829$), and delirium occurred on 23.5% ($n = 6,176$). Severe pain was inversely associated with a transition to delirium (odds ratio [OR] 0.72; 95% confidence interval [CI], 0.53–0.97). Any opioid administration in awake patients without delirium was associated with an increased risk for delirium the next day [OR, 1.45; 95% CI, 1.24–1.69]. Each daily 10-mg intravenous morphine-equivalent dose was associated with a 2.4% increased risk for delirium the next day.

Conclusions: The receipt of an opioid in the ICU increases the odds of transitioning to delirium in a dose-dependent fashion.

Keywords: delirium; opioid; intensive care; medication; risk factor

At a Glance Commentary

Scientific Knowledge on the Subject: Delirium is prevalent in critically ill adults, and opioids are frequently administered in the ICU. Recent ICU practice guidelines have not been able to define opioids as a risk factor for delirium based on studies reporting heterogeneous results and each having important methodological limitations, including a small size; a failure to account for daily transitions between wakeful, coma, and delirium states; a failure to account for daily factors known to affect transitions to delirium; and the effect on pain on delirium occurrence.

What This Study Adds to the Field: Our analysis demonstrates that opioid use in the ICU increases the daily risk of delirium in a dose-dependent manner and that this risk is not dependent on the degree of pain present. Among ICU patients at risk for delirium, clinicians should optimize analgesic strategies known to reduce opioid exposure.

(Received in original form October 4, 2020; accepted in final form April 9, 2021)

Supported by the National Institute on Aging of the NIH under award F31AG066460 (M.S.D.) and by the American College of Clinical Pharmacy Foundation under a Student Futures Grant award (M.S.D.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the American College of Clinical Pharmacy.

Author Contributions: S.M.A.D.-K., I.J.Z., and A.J.C.S. were responsible for data acquisition. All authors contributed to study conception and design, data analysis, and drafting and approval of the manuscript.

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Am J Respir Crit Care Med Vol 204, Iss 5, pp 566–572, Sep 1, 2021

Originally published in press as DOI: 10.1164/rccm.202010-3794OC on April 9, 2021
Internet address: www.atsjournals.org

Delirium, a clinical expression of acute encephalopathy (1), occurs in up to 50% of critically ill adults, is associated with substantial burden to patients and their families, and may result in serious ICU and post-ICU complications (2, 3). The risk of delirium in the ICU depends on the presence of a number of predisposing (e.g., age) and precipitating (e.g., illness severity) factors (4, 5). Medications are important modifiable risk factors for delirium in this setting (5, 6).

Although multiple cohort studies have evaluated the association between ICU opioid use and delirium occurrence (7–17), the 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption guideline panel, after reviewing these studies, determined that current evidence is insufficient to conclude that opioid exposure is a risk factor for delirium in critically ill adults (5). Although pain after surgery is associated with increased delirium (18–21), the association between ICU pain and delirium remains unclear (22). With severity of illness, opioid administration, level of pain, and delirium occurrence often fluctuating over the course of the ICU stay and both ICU discharge or death serving as competing risks for delirium in the ICU, time-dependent analyses should be employed to investigate whether an opioid–delirium association exists in critically ill adults (6, 23, 24).

The relationship between pain, opioids, and delirium in the ICU remains understudied. We sought to evaluate whether opioid use is an independent risk factor for the daily transition from being awake without delirium to a state of delirium, accounting for patient levels of pain. Second, we explored the effect of both daily opioid dose and pain on the association between opioid use and delirium occurrence.

Methods

Study Population and Design

From August 2011 through June 2013 and June 2015 through March 2019, all consecutive adults admitted for at least 24 hours to the 32-bed mixed medical–surgical–cardiovascular–neurologic ICU of the University Medical Center Utrecht were considered for inclusion. All ICU days a patient was managed with comfort measures only were excluded from the analysis. Because of personnel changes, data was unavailable for patients admitted between June 2013 and May 2015. Throughout the study duration, a well-established institutional protocol was in place that advocated for applying the lowest amount of sedation and assessing all patients for delirium using the Confusion Assessment Method for the ICU (CAM-ICU) (25) at least twice daily. Patients were excluded if an acute neurological disease or another disorder precluding delirium assessment was present, such as mental retardation or the inability to speak Dutch or English. Patients transferred from another ICU were also excluded to avoid residual confounding from missing data. Given the noninterventional nature of the investigation, the local institutional review board waived the need for informed consent (#010/056/c, #12/421/c, and #18–10–23).

Mental Status Classification and Outcome

The mental status of each patient was assessed daily in the ICU by a trained researcher using a previously published, validated protocol (26). In short, patient wakefulness was evaluated every 3 hours using the Richmond Agitation and Sedation Scale (RASS), with a RASS ≤ -4 denoting an unarousable state (27). The presence of delirium during each 24-hour period was determined when the patient was maximally awake (e.g., after daily sedation interruption) using a previously validated five-step algorithm (interobserver agreement, 0.94–0.97; sensitivity, 0.85; specificity, 0.85) (27). The algorithm incorporated a review by the researcher of all CAM-ICU scores documented by the bedside nurse, whether a treatment for delirium had been initiated by the ICU physician, a chart review, and an additional CAM-ICU assessment by the investigator for any patient not yet classified using the prior steps (27). Given that a single positive CAM-ICU assessment by the bedside nurse is highly predictive of delirium (28), patients were classified as delirious at any time in the prior 24 hours when at least one CAM-ICU assessment was positive. The additional steps in the delirium recognition algorithm used for the study were present to minimize the risk of misclassification bias (27).

The mental status for each patient on each ICU admission (Day *t*) was then classified as *1*) awake without delirium, *2*) delirium, or *3*) unarousable. For the outcome day (Day $t + 1$), ICU discharge and death were added as a joint category representing "exit from the ICU," resulting in four possible outcome categories. Although the daily transition from awake without delirium to delirium served as the transition of interest in the analysis and remaining awake without delirium served as the reference, other potential daily mental status transitions were concomitantly modeled (*see* Figure E1 in the online supplement).

Other Data Collection and Definitions

Medication data, including dose, route, and time of administration, were retrieved from the electronic patient data management system. The dose for all intravenous and transdermal opioids administered on a scheduled or "as needed" basis was collected. The application of all transdermal patches was assumed to occur for 72 hours and to result in a bioavailability of 100% (29). All administered opioids were converted into equivalent intravenous morphine-equivalent (MEQ) doses (Table E1) (30–33).

Pain was collected by the bedside nurse during the course of standard ICU care. Patients who were responsive were asked to assess their pain on a visual analog scale (VAS) from 0 cm to 10 cm (34). Patients unable to communicate their pain were assessed using the Critical Care Pain Observation Tool (CPOT) (35). For modeling purposes, daily pain was categorized into the following three mutually exclusive categories: no clinically significant detected pain (VAS = 0–4 or CPOT = 0–2), moderate detected pain (VAS = 5–6 or CPOT = 3–4), and severe detected pain (VAS $\geq$ 7 or CPOT $\geq$ 5) (5, 36, 37).

Demographics, presence of comorbidities, ICU admission characteristics, and daily physiological measurements and vital signs were prospectively collected by trained physicians. Daily severity of multiorgan failure was assessed using the modified Sequential Organ Failure

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Assessment (mSOFA) that excludes the neurological component to avoid adjusting for a component of the primary outcome (38). A trend imputation for missing covariables was performed because of the availability of longitudinal data before and after each observation day (39).

Statistical Analyses

Within the first-order Markov model, discharged alive from the ICU and death were combined into one category given that each represented few of the total daily transitions and neither was the outcome of interest (6, 40). The primary exposure to opioids was modeled using an interaction term of binary opioid use (yes/no) on Day *t* and mental status on Day *t*. Although the transition from awake without delirium to delirium was the transition of interest, all 12 possible transitions were included in the model, necessitating the inclusion of an interaction between opioid use and each baseline state (Table E2). Outcomes for each status on Day $t + 1$ are then reported relative to the interaction term on Day *t*. In a secondary model, exposure to opioids was modeled using an interaction term of opioids per 10 mg MEQ on Day *t* and the mental status on Day *t*. Given the skewed nature of the data, a logarithmic data transformation was performed, solving for the logarithm of $x + 1$ (with x being the MEQ dose of opioid) to allow for data transformation in patients receiving no opioids (41). We also evaluated the impact of pain as a risk factor for transitioning to delirium while controlling for the presence of opioids as a binary variable.

Multinomial logistic regression was used within the Markov model to account for covariables that might influence the presence of delirium, the use of an opioid, or its resulting pharmacodynamic response. These covariables were identified through a thorough search of the literature (4, 5, 42) and the creation of a directed acyclic graph to ensure selection of appropriate confounders and avoidance of collider bias (Figure E2). In total, six variables measured at ICU admission (admission type [medical vs. surgical], age, sex, Acute Physiology and Chronic Health Evaluation [APACHE] IV score [43], and Charlson Comorbidity Index) and five time-varying variables measured daily (ICU day, mSOFA, use of mechanical ventilation, use of a benzodiazepine, and presence of severe pain) were included in the model (Table E2). Neither depth of sedation (i.e., RASS = −3, −2, or −1) nor propofol were included as variables given the current lack of data suggesting thag either are associated with increased delirium in the ICU (5).

Five planned sensitivity analyses and one planned exploratory analysis were performed for the transition from awake without delirium to delirium. First, given that ICU practices focused on delirium recognition, prevention, and treatment were suspected to have changed over the 9-year study period (5, 44–46), the cohort was divided into 3-year epochs to evaluate the stability of an opioid–delirium association over time. Second, to explore whether the relationship between opioid exposure and delirium is one that primarily affects older adults, we conducted a second sensitivity analysis, stratifying between younger (<65 yr) and older (≥65 yr) adults. Third, to explore whether the two ways patients could exit from the ICU (i.e., death vs. discharge) influence the opioid–delirium association differently, we conducted a third sensitivity analysis in which ICU death and discharge were considered as separate outcome states. Fourth, although an association between untreated pain and delirium has been reported in postsurgical patients (18–21), the nature of this association in the ICU remains unknown. Therefore, we conducted a two-part sensitivity analysis using different pain breakpoints and descriptors, as follow: *1*) daily peak pain score and *2*) days with either moderate and/or severe pain on an ICU day. Fifth, opioids in surgical patients are more frequently administered for acute nociceptive pain; medical patients receive opioids for chronic pain, analgosedation, and depression of respiratory drive during mechanical ventilation (5). We therefore stratified on admission service (medical versus surgical populations) to determine whether delirium risk differed between these two. Sixth, as the risk of delirium may be different from synthetic (e.g., fentanyl) versus nonsynthetic (e.g., morphine) opioids (15), we explored whether opioid–delirium risk was different on ICU days when only a synthetic opioid was administered (i.e., alfentanil, fentanyl, remifentanil, and sufentantil) compared with days when only morphine was administered.

Given the high degree of missing pain scores in the studied cohort (5,916/26,250 [22.5%]), it was decided on a *post hoc* basis to compare the use of opioids and mental state on the days on which no pain score was documented with those days on which one or more pain scores were documented. Categorical variables were compared using χ^2 tests whereas continuous, nonnormally distributed variables were compared using a Mann-Whitney *U* test. SPSS 24 (IBM) and R 4.0.2 (http://www.r-project.org) were used to perform the statistical analyses. All statistical tests were performed against two-sided alternatives, and *P* values less than 0.05 were defined as statistically significant.

Results

Patients and Observation Days

Among 6,289 consecutive patients admitted during the study period to the ICU for at least 24 hours, 4,075 (65%) were included in the analysis. The primary reasons 2,214 (35%) of patients were excluded were a condition hampering delirium assessment ($n = 1,619$), transfer from another ICU ($n = 325$), and no delirium assessments during the ICU admission ($n = 270$). The included patients were mostly male (64%), had an average age of 60.9 years (SD 15.4) an ICU admission APACHE IV score of 58.5 (SD 28), and a median maximum mSOFA of 7 (interquartile range [IQR], 4–9) (Table 1).

Delirium occurred in 1,430 (35%) of the 4,075 patients and was present on 6,176 (24%) of the 26,250 observation days (Table 2). Patients were exposed to an opioid on 14,975 (57%) of the observation days. On these days, the median MEQ dose was 24.6 mg (IQR, 7.5–73.8 mg); morphine was administered on 71.8%, remifentanil on 23.8%, and fentanyl on 18.2% of days on which an opioid was administered (Table E3). Covariable prevalence was similar across the epochs (Table E4). Compared with epoch 1, patients in epoch 3 were more likely to receive a higher average opioid dose and propofol and less likely to receive a benzodiazepine (Table E5).

Risk of Transitioning to Delirium

Among the 14,966 days patients were awake without delirium (57% of total ICU days), 1,296 (9%) transitions to delirium occurred the next day. In our primary model, the odds ratio (OR) of the transition from awake without delirium toward delirium associated with the use of opioids was 1.45 (95% confidence interval [CI], 1.24–1.69) (Table 3). For each 172% (1 log) increase in daily intravenous MEQ opioid dose, there was a 27% increase in the odds of transitioning to delirium the next day (OR, 1.27; 95% CI, 1.15–1.39). Using the logistic regression coefficient ($\beta = 0.24$), one can similarly report that a 1% increase in the daily intravenous MEQ opioid dose was

Table 1. Characteristics of the Study Population

	Total Cohort (*n* = 4,075)	Delirium Ever (*n* = 1,430)	Delirium Never (*n* = 2,645)
Age, median (IQR), yr	64 (53–72)	65 (55–74)	63 (51–71)
Sex, M, *n* (%)	2,591 (63.6)	949 (66.4)	1,642 (62.1)
Charlson Comorbidity Index (*n* = 2,942), median (IQR)	1 (0–2)	1 (0–2)	1 (0–2)
Body mass index (*n* = 4,025), median (IQR)	25.7 (22.8–29.1)	25.7 (22.9–28.8)	25.7 (22.8–29.2)
Admission type (*n* = 4,073), *n* (%)			
Medical	1,536 (37.7)	664 (46.4)	872 (33.0)
Elective surgery	1,746 (42.8)	397 (27.8)	1,349 (51.0)
Acute surgery	791 (19.4)	369 (25.8)	422 (16.0)
APACHE IV score (*n* = 3,698), median (IQR)	54 (39–73)	68 (52–87)	47 (35–64)
Length of ICU stay, median (IQR), d	2 (1–6)	6 (3–13)	1 (1–3)
Maximum mSOFA score (*n* = 4,059), median (IQR)	7 (4–9)	9 (7–11)	6 (4–8)
Mechanically ventilated during ICU stay, *n* (%)	3,791 (93.0)	1,381 (96.6)	2,410 (91.1)
Delirium during ICU stay, *n* (%)	1,430 (35.1)	2,645 (100)	0 (0)
Opioid use during ICU stay, *n* (%)	3,468 (85.1)	1,291 (90.3)	2,177 (82.3)
Opioid use during ICU stay, median (IQR), d	2 (1–4)	5 (2–9)	2 (1–3)
Severe pain* during ICU stay (*n* = 3,905), *n* (%)	1,122 (27.6)	506 (37.0)	616 (24.3)
Severe pain during ICU stay, median (IQR), d	0 (0–1)	0 (0–1)	0 (0–1)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range; mSOFA = modified Sequential Organ Failure Assessment.
*Severe pain is defined as a visual analog scale score ⩾7 or Critical Care Pain Observation Tool score ⩾5.

associated with a 0.24% increase in the odds of developing delirium the next day. Given that this association involved small changes in the daily intravenous MEQ dose, it is also safe to conclude that each daily 10 mg intravenous MEQ dose administered was associated with a 2.4% increased risk for delirium the next day.

Our exploratory analysis evaluating the association between pain and delirium, controlling for opioid exposure, found pain to be inversely associated with a transition to delirium regardless of the characterization of pain employed *1*) presence of severe pain (OR, 0.72; 95% CI, 0.53–0.97), *2*) presence of moderate or severe pain (OR, 0.71; 95% CI, 0.60–0.85), and *3*) peak pain score (OR, 0.95; 95% CI, 0.92–0.98) (Table 4).

Sensitivity Analyses

The association between opioid use and delirium was stable over the entire study period, with a significant association found in all three study epochs (Table E6). The risk for a transition to delirium was similar between younger and older adults, although this relationship was no longer dose dependent in older adults (Table E7). The risk for a transition to delirium was unchanged when ICU discharge and death were considered as separate outcome states (Table E8). The association between opioid exposure and delirium was unaffected by the pain measure included in the model (Table E9).

Opioid use was associated with increased odds of a transition to delirium in both medical (OR, 1.33; 95% CI, 1.08–1.63) and surgical patients (OR, 1.61; 95% CI, 1.27–2.05) (Table E10). With respect to the type of opioid, we found that both morphine (OR, 1.09, 95% CI, 1.04–1.13 per 10 mg of morphine) and

Table 2. Characteristics of Individual ICU days (*n* = 26,250) by Mental Status Category

		Mental Status Day *t*		
Characteristic on Day *t*	All ICU Patient Days (*n* = 26,250)	Awake without Delirium (*n* = 14,966)	Delirium (*n* = 6,176)	Unarousable (*n* = 5,108)
Characteristic of opioid use				
Use of any opioid, *n* (%)	14,975 (57.0)	7,325 (49.1)	3,466 (56.1)	4,157 (81.4)
Dose (if any) in mg, median (IQR)*	24.0 (7.5–68.6)	15 (5–48)	26.5 (9.2–81.9)	47.6 (22.5–312.5)
Use of morphine, *n* (%)†	10,759 (71.8)	5,516 (75.3)	2,336 (67.4)	2,907 (69.9)
Use of a synthetic opioid, *n* (%)†	6,477 (43.3)	2,891 (39.5)	1,750 (50.5)	1,836 (44.2)
Characteristic of covariables				
mSOFA (*n* = 25,363), median (IQR)	6 (3–8)	4 (3–7)	6 (4–8)	9 (6–11)
Use of mechanical ventilation, *n* (%)	20,852 (79.4)	11,113 (74.4)	5,099 (82.6)	4,620 (90.4)
Use of a benzodiazepine, *n* (%)	8,417 (32.1)	3,914 (26.2)	1,832 (29.7)	2,671 (52.3)
Presence of severe pain, *n* (%)	1,829 (7.0)	1,124 (7.5)	381 (6.2)	52 (1.0)

Definition of abbreviations: IQR = interquartile range; mSOFA = modified Sequential Organ Failure Assessment.
*In morphine equivalents.
†Use of opioid on Day *t* is not mutually exclusive; percentages do not add up to 100%.

Table 3. Multinomial Model on Transitions of Daily Mental Status Conditional on Opioid Exposure

Mental Status				
Day *t*	Day *t* + 1	Opioid Exposure	Adjusted Odds Ratio*† (95% Confidence Interval)	*P* Value
Awake without delirium	Awake without delirium	No	Reference	—
Awake without delirium	Delirium	Yes	1.45 (1.24–1.69)	<0.001
Awake without delirium	Delirium	Log-transformed 10 mg MEQ‡	1.27 (1.15–1.39)	<0.001

Definition of abbreviation: MEQ = morphine-equivalent.
*Adjusted for time-fixed covariables, including admission category (medical, surgical, and trauma), age, sex, Acute Physiology and Chronic Health Evaluation IV Score, body mass index, and Charlson Comorbidity Index.
†Adjusted for time-varying covariables on day *t*, including day of ICU admission, modified Sequential Organ Failure Assessment score (without neurologic component), use of mechanical ventilation, use of a benzodiazepine, and presence of severe pain.
‡Adjusted odds ratio represents the odds for a 1 log-fold increase in MEQ dose.

synthetic opioids (OR, 1.77; 95% CI, 1.33–2.35 for each 1 log-fold increase in MEQ of synthetic opioids) were associated with an increase in the odds of delirium transition (Table E11). For synthetic opioids, this represents an ~1.5% increase in the odds of transitioning to delirium for each 10-mg increase in the intravenous MEQ dose administered the prior day.

Comparison of days with pain scores present with days with missing pain scores revealed that days when pain was missing were more likely to be deemed unarousable. Patients were significantly more likely to be receiving an opioid on a day when pain was missing and to be receiving a higher median dose of morphine equivalents (Table E12).

Discussion

In a cohort of 4,075 critically ill adults, after employing a rigorous first-order Markov model with multinomial logistic regression analysis approach, we found that exposure to any opioid during the ICU stay increases the risk of delirium occurrence by 45%, independent of the administration of benzodiazepines and other variables known to influence delirium occurrence (6, 7). This risk was dose dependent, remained stable across study years and age groups, was observed in both medical and surgical patients, and was not dependent on the degree of pain present on the day preceding a transition to delirium.

Our study is not subject to the important methodological limitations of prior reports investigating the association between opioid use and delirium occurrence in the ICU (7–17). Our results are not consistent with a smaller study of 97 trauma–surgery ICU patients in which a Markov model regression analysis was also employed (17). In this study, fentanyl exposure was associated with an increased delirium risk in 45 surgical patients, whereas morphine did not increase the risk of delirium in 52 trauma patients (17). Our investigation, which included nearly 40 times as many patients, suggests that both natural opioids (i.e., morphine) and synthetic opioids (i.e., fentanyl) are associated with increased delirium risk. The dose dependency for this risk may vary by the individual opioid selected.

Our finding of an inverse relationship between pain and delirium the next day that was independent of opioid exposure was unexpected. However, it should be noted pain may change rapidly over the course of a single ICU day, and it is difficult to quantify (5). We therefore cannot exclude that our findings were not subject to bias because of the fact that pain may have been underestimated in patients about to transition to a state of delirium. Better understanding of the relationship between pain and delirium in the ICU remains an important area for further research.

Table 4. Pain as a Risk Factor for the Transition to Delirium

Mental Status					
Day *t*	Day *t* + 1	Pain Exposure	Controlled for Opioid Use	Adjusted Odds Ratio*† (95% Confidence Interval)	*P* Value
Awake without delirium	Awake without delirium	No	—	Reference	—
Awake without delirium	Delirium	Severe pain	Yes	0.72 (0.53–0.97)	<0.01
Awake without delirium	Delirium	Severe pain	No	0.76 (0.56–1.02)	0.07
Awake without delirium	Delirium	Moderate or severe pain	Yes	0.71 (0.60–0.85)	<0.01
Awake without delirium	Delirium	Moderate or severe pain	No	0.74 (0.63–0.88)	<0.01
Awake without delirium	Delirium	Peak pain score	Yes	0.95 (0.92–0.98)	<0.01
Awake without delirium	Delirium	Peak pain score	No	0.96 (0.93–0.99)	<0.01

*Adjusted for time-fixed covariables, including admission category (medical, surgical, and trauma), age, sex, Acute Physiology and Chronic Health Evaluation IV Score, body mass index, and Charlson Comorbidity Index.
†Adjusted for time-varying covariables on day *t*, including day of ICU admission, modified Sequential Organ Failure Assessment score (without neurologic component), use of mechanical ventilation, use of a benzodiazepine, and use of an opioid.

In addition to its large sample size, our investigation has the following important strengths: *1*) patients were evaluated at least twice daily for delirium on the basis of a validated assessment protocol; *2*) the model also accounted for transitions to an unarousable state and to death/ICU discharge; *3*) of 11 model covariables considered, five were time varying, which allowed us to consider daily changes in key confounding factors (e.g., severity of illness, benzodiazepine use, need for mechanical ventilation, and acute pain) that could affect daily opioid–delirium risk; and *4*) opioid dose–effect relationships were evaluated.

Our analysis also has several potential limitations. First, regarding study design, as for any first-order Markov analysis, within-patient correlations were ignored, as transitions are assumed to be independent of the patient history beyond the prior day (6, 23, 24). We acknowledge that results from a single-center analysis may not be generalizable to other centers having patients with differing underlying risk factors for delirium or where the use of nonpharmacologic strategies known to reduce delirium (e.g., ABCDEF bundle) differ (5, 45). However, our cohort of patients has a similar case mix and opioid utilization pattern to those of reports conducted in other settings and countries (5, 46, 47). Second, with regard to study determinants, other than evaluating the effect of synthetic versus nonsynthetic opioids, we did not evaluate the impact of individual opioids and therefore cannot comment on the differential impact of different medications or dosing strategies (e.g., administration of an i.v. bolus vs. an increase in the continuous infusion dose) on delirium. Although pain assessments were not documented on 23% of days, an unarousable state (a mental status often precluding pain assessment by bedside clinicians) was documented on more than half of these days. It should be acknowledged that analysis excluding these days could bias the results. Future research surrounding how to consider missing pain scores in an analysis such as ours is needed.

Third, classifying the study outcome (a patients' mental state on a daily basis) as being either awake without delirium, delirious, or unarousable may be a simplification, as mental status may vary on each ICU day and may not be categorizable. Although mental status was evaluated at multiple times over each 24-hour period to minimize misclassification bias and patients were routinely evaluated for delirium while maximally awake, some of the delirium detected in the cohort may have been rapidly reversible and potentially clinically irrelevant (48). Because delirium tends to fluctuate, some patients with delirium may have been missed during the CAM-ICU assessment. However, this is unlikely, given the use of a validated delirium recognition algorithm that advocated frequent CAM-ICU assessment and incorporated additional criteria to define delirium (26).

Fourth, although the list of covariables included in the multivariable analysis was derived from a previous systematic review of the literature together with expert consensus, it is possible, as in any observational study, that unmeasured confounding could have influenced the reported results (4, 5, 42). For example, we did not have information on daily pain/sedation targets and could therefore not adjust for these in our models. Nonopioid analgesics were not included in our analyses. Calculation of an *E*-value shows that such an unmeasured confounder would need to have an adjusted OR for 1.7 to nullify the effect of the categorical opioid analysis and an adjusted OR of 1.86 to nullify the effect of opioid dose. We also were unable to control for the propofol dose and any potential dose interaction between sedative and opioid exposure. Future studies with increased granularity are needed to evaluate this potential interaction more closely.

A number of important considerations exist for ICU clinicians seeking to adopt the results of our investigation in clinical practice. Despite our observation of an increased opioid-related risk of delirium, opioids should generally remain part of the treatment plan for critically ill adults with acute pain (5). In accordance with guideline-based care, if opioids are used, patients should be routinely monitored for delirium given their increased risk for developing it (5). The association between opioid use and delirium was stronger in surgical patients than in medical patients. Although opioids are most likely to be administered solely for pain in surgical patients, in medical patients, they are often used as sedatives and to help promote ventilator synchrony. Multimodal, nonopioid analgesic strategies, shown to reduce opioid dose and duration, should be considered, particularly in surgical populations, in which evidence for this approach is strongest and in which opioids are most frequently used for acute nociceptive pain (5, 45, 47). Opioid use should be regularly titrated to ensure patients are wakeful and pain free (5). If opioids are being used for analgosedation, a nonsedation approach may be just as effective and safe in some patients (49). For mechanically ventilated adults who require continuous sedation, dexmedetomidine, with its analgesic properties and reduced delirogenic potential, may be a better option than continuous opioids (5, 47). Lastly, ICU clinicians should continue to focus their efforts on applying other evidence-based strategies known to reduce delirium in their patients (5, 45).

In conclusion, after controlling for multiple baseline and time-varying variables known to affect delirium and for competing risks for delirium occurrence, our analysis of 4,075 patients over 26,250 ICU days demonstrates that opioid use increases the risk of delirium in a dose-dependent manner. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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