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Opioid Prescribing Patterns Before, During, and After Critical Illness: An Observational Study

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OBJECTIVES: The association between opioid therapy during critical illness and persistent opioid use after discharge is understudied relative to ICU opioid exposure and modifiable risk factors. Our objectives were to compare persistent opioid use after discharge among patients with and without chronic opioid use prior to admission (OPTA) and identify risk factors associated with persistent use.

DESIGN: Retrospective cohort study.

SETTING: Medical, trauma/surgical, or neurologic ICU at an academic hospital.

PARTICIPANTS: Adult patients surviving hospital admission.

INTERVENTIONS: Opioid use during the ICU and post-ICU stays.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was persistent opioid use accounting for greater than 70% of days 4–6 months after discharge. Among 2,975 included patients, 257 (8.6%) were classified as OPTA, and 305 (10.2%) persistently filled opioid prescriptions, including 186/257 (72%) OPTA and 119/2,718 (4.4%) with no chronic opioid fills prior to admission. Among all patients, OPTA was strongly associated with persistent opioid use (odds ratio, 57.2 [95% CI, 41.4–80.0]). Multivariable logistic regression revealed that male sex, surgical procedure, and ICU opioid-free days were associated with reduced persistent opioid use for OPTA patients. Age and ICU opioid-free days were associated with reduced persistent opioid use for non-OPTA patients. Total ICU opioid dose and dose per day of ICU exposure were not associated with persistent use for either group.

CONCLUSIONS: In this mixed cohort of ICU patients, 10.2% persistently filled opioid prescriptions 4–6 months after discharge. Although ICU opioid doses were not associated with persistent use, duration of ICU opioid administration is a modifiable risk factor that may reduce persistent opioid use after critical illness.

KEY WORDS: analgesia; analgesics; epidemic; intensive care unit; opioid; opioid; pain; sedation

In the 1980s, adult survivors of ICUs frequently reported moderate or severe pain (1), prompting the first guidelines for ICU analgesia and sedation in 1995 to call attention to inadequate analgesia (2). Encouragement to improve analgesia and increase use of opioids followed (3), and subsequent guidelines promoted opioid use, identified fears of addiction as misplaced (4, 5), and emphasized that IV opioids should be considered first-line medications to treat nonneuropathic ICU pain (6). The emergence of the opioid epidemic has raised concerns regarding these recommendations (7).

Though efforts to change opioid prescribing practices have mainly focused on the outpatient setting (8), recognition that even minor surgical procedures are associated with new persistent opioid use shifted attention to hospitals (9). Reports associating ICU opioid exposure with postdischarge opioid use

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have often underreported important data such as ICU opioid doses (9–21).

The primary objective of this study was to determine the proportion of patients with and without chronic opioid use prior to ICU admission who persistently filled opioid prescriptions after critical illness, and to identify risk factors associated with persistent opioid use, including potentially modifiable factors.

MATERIALS AND METHODS

Study Design

This retrospective cohort study enrolled adult patients admitted to the 32-bed medical, trauma/surgical, and neurologic ICUs at the Maine Medical Center, Portland, Maine, between December 1, 2014, and May 31, 2019. The study was approved under the title "Intensive Care Analgesic Review and Opioid Use (ICARUS)" on January 31, 2018, by the Maine Medical Center Institutional Review Board (1183993-1), and informed consent was waived. All study procedures followed the ethical standards of the U.S. Department of Health and Human Services (45 CFR 46) and the Helsinki Declaration of 1975. This study report follows the Strengthening the Reporting of Observational Studies in Epidemiology guideline for cohort studies.

Data Sources

Patients were identified using a computer-generated report in Epic (Epic Systems Corporation, HYPERSPACE, Verona, Wisconsin, May 2019). Pre- and posthospital opioid utilizations were evaluated using the patient's home state-specific Prescription Monitoring Program (PMP) (Appriss, Lexington, Kentucky), a secure database that provides date and medication filled, quantity prescribed, prescriber, and dispensing pharmacy. Data were transcribed into Research Electronic Data Capture and merged with the electronic medical record data for analysis.

Inclusion and Exclusion Criteria

Consecutive adult patients greater than or equal to 18 years old admitted during the study period who received an oral or IV opioid in the ICU were included. Patients were excluded if they died during their admission, were discharged to hospice or another hospital, had an ICU length of stay (LOS) less than 24 hours, never received an opioid in the ICU, had missing ICU or post-ICU data, their home state did not use the PMP, they had multiple ICU admissions, they received methadone, buprenorphine, or remifentanil in the hospital (due to lack of an accepted equianalgesic dose conversion), and if opioids were administered via patient-controlled analgesia (PCA) or epidural analgesia since dosing data were not recorded in the medication administration record and were not extractable from nursing flowsheets.

Demographics and Clinical Characteristics

Baseline characteristics included age, sex, ICU admit location (medical, trauma/surgical, or neurologic), surgical procedure during the ICU stay (yes/no), discharge disposition (home with or without services, inpatient rehabilitation facility, or skilled nursing facility), ICU LOS, hospital LOS, and need for and duration of invasive mechanical ventilation.

Opioid Use

Patients were classified as chronic opioid use prior to admission (OPTA) if they filled opioid prescriptions documented in the PMP accounting for greater than or equal to 70% of days in the 3 months prior to ICU admission. Patients not meeting this definition were classified as no chronic opioid fills prior to admission (non-OPTA). There is no universally accepted definition for intermittent versus chronic opioid use; Yaffe et al (10) reported in 2017 that preadmission intermittent use (<70% of days) was not associated with persistent opioid use after discharge, whereas chronic use (≥70%) was; we adopted these definitions.

We included patients receiving opioids on the hospital's formulary (**Supplementary Table 1**, http://links.lww.com/CCX/B40) and excluded patients receiving nonformulary opioids, those administered by nonoral or non-IV routes (e.g., nebulized morphine and transdermal fentanyl), and those administered for indications other than pain (e.g., belladonna alkaloids-opium for bladder spasms). A computer-generated report from the electronic medication administration record provided opioid administration data. All included opioid doses were converted to fentanyl-equivalents (FEs) in micrograms (**Supplementary Table 2**, http://links.lww.com/CCX/B40) (22).

Outcomes

The primary outcome was persistent filling of opioid prescriptions documented in the PMP accounting for greater than 70% of days from 4 to 6 months after hospital discharge. Secondary outcomes included persistent opioid prescription filling from 0 to 3 months and 7 to 12 months after discharge. Opioid exposure was quantified during the ICU, post-ICU, and the entire hospitalization as total FEs received, duration of exposure (days opioid administered), FE dose/exposure day, and opioid-free duration defined as LOS minus the opioid exposure duration for each phase of care.

Statistical Analysis

Continuous data are expressed as median (interquartile range). Univariate analysis was performed to identify variables associated with persistent opioid use 4–6 months postdischarge for the total population, and then as two separate cohorts (OPTA and non-OPTA). Differences of proportions were assessed using the chi-square test. Continuous variables were compared using Student *t* test. Multivariable logistic regression models including clinically relevant variables and those with a univariate *p* value less than or equal to 0.2 were constructed in R (Version 3.1.0, Spring Dance, Boston, Massachusetts) in the RStudio graphical user interface (Version 0.98.932) separately for the OPTA and non-OPTA patients. *p* values of less than 0.05 were considered statistically significant.

Continuous variables were examined in quintiles if significant outliers existed and were entered into the logistic regression model as follows: age (1 yr), ICU and hospital LOS (1 d), FEs (one microgram), duration of opioid exposure and opioid-free days (1 day), and duration of invasive mechanical ventilation (1 day). Categorical variables included sex (female), admitting ICU location (medical as references vs trauma/surgical or neurologic), OPTA (no), and surgical procedure (no). Collinearity was evaluated, and if Pearson correlation coefficient for variable pairs exceeded $r = 0.7$, one variable was removed with a preference for maintaining ICU variables.

RESULTS

Demographics and Clinical Characteristics

Among 10,164 ICU patient admissions during the study period, 2,975 (29.3%) were included in the data analysis (**Fig. 1**). The most frequent reasons for exclusion were no opioid exposure in the ICU (16.9%), hospital death (14.7%), and an ICU LOS less than 24 hours (10.1%). The median age was 61 years (49–71 yr), and the majority were male (55.6%) and required invasive mechanical ventilation (53.5%) (**Table 1**). Patients were admitted to the medical (25%), trauma/surgical (39%), and neurologic ICU (36%) and were most commonly discharged to either rehabilitation (29%) or home with (22%) or without (27%) services.

Opioid Administration Data

A total of 257 patients (8.6%) met criteria for OPTA, whereas 2,718 (91.4%) did not (non-OPTA) (Table 1). Patients categorized as OPTA had a higher Charlson comorbidity index (5 vs 4; $p < 0.001$), had a shorter ICU LOS (3.2 vs 3.5 d; $p = 0.02$), and were more frequently discharged home requiring services or to a skilled nursing facility ($p < 0.001$).

The combined cohort received a median of 1,100 (283–3746) total FEs during their hospitalization, including 635 (175–2941) FEs in the ICU and 76 (0–475) FEs in the post-ICU phase of care (**Table 2**). Opioid exposure duration was 2.2 days (1.2–4.7 d) in the ICU, and 1.1 days (0–4.9 d) post-ICU, whereas opioid-free days were 1.0 (0.3–2.8) in the ICU and 3.0 (1.1–6.5) post-ICU. The median ICU opioid dose per day of exposure was 276 (105–882) FEs/exposure day.

Patients categorized as OPTA received significantly more total FEs in the ICU than non-OPTA patients (1,200 [300–3,933] vs 600 [158–2,792] FEs; $p < 0.001$). Similarly, OPTA patients had a longer duration of ICU opioid exposure (2.7 d [1.6–5.5 d] vs 2.1 d [1.2–4.5 d]; $p < 0.001$) and a shorter ICU opioid-free duration (0.26 d [0.3–0.99 d] vs 1.10 d [0.44–2.85 d]; $p < 0.001$).

For the combined cohort, 305 (10.2%) filled an opioid prescription accounting for greater than 70% of days 4–6 months after discharge, including 186 of 257 OPTA patients (72.4%), and 119 of 2,718 (4.4%; $p < 0.001$) non-OPTA patients (Table 2). Among OPTA patients, a large fraction did not persistently fill opioid prescriptions from 0 to 3 months (24%), 4 to 6 months (28%), or 7 to 12 months (34%) (**Fig. 2**).

Risk Factors for Persistent Opioid Use

In the combined cohort, OPTA was overwhelmingly associated with persistent opioid use 4–6 months

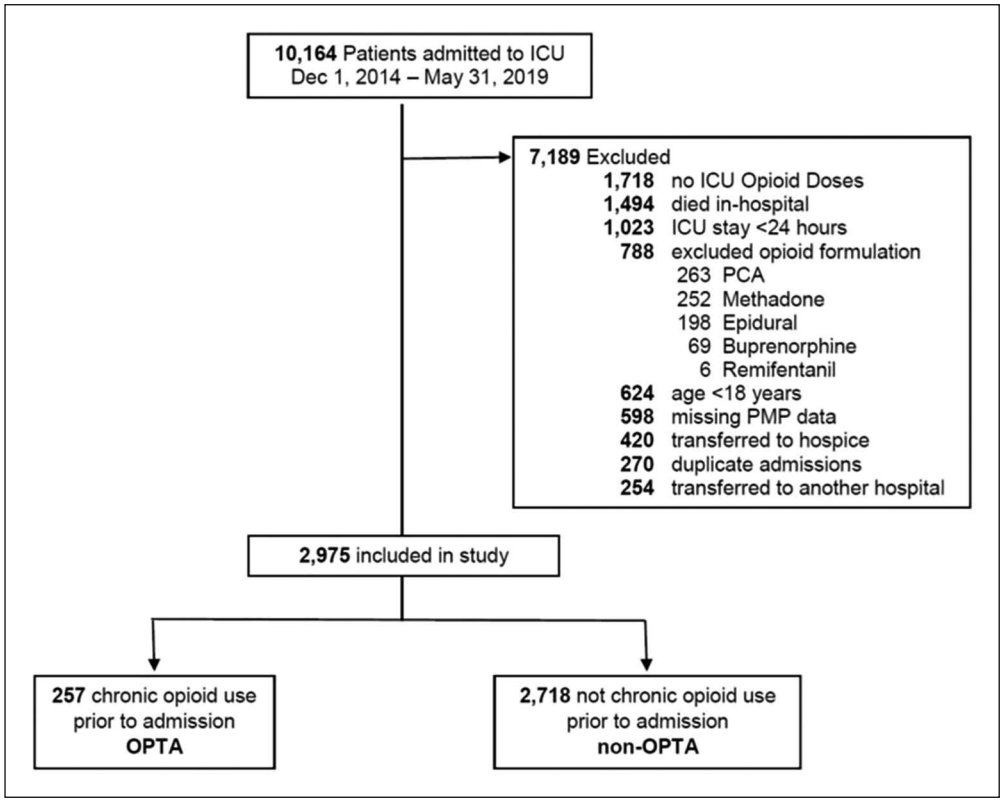

Figure 1. Flowchart for cohort formation. Non-OPTA = no chronic opioid fills prior to admission, OPTA = opioid use prior to admission, PCA = patient-controlled analgesia.

after discharge in the multivariable logistic regression model (odds ratio, 57.2 [95% CI, 41–80]); accordingly, separate models were created for the OPTA and non-OPTA cohorts. Univariate analysis of variables associated with persistent opioid use after hospital discharge is presented in **Supplementary Table 3** (http://links.lww.com/CCX/B40).

The multivariable logistic regression model for non-OPTA patients revealed age ($p = 0.009$), and ICU opioid-free days ($p < 0.001$) were associated with a reduced likelihood of persistent opioid use (**Table 3**). For the OPTA cohort, male sex ($p = 0.049$), surgery during the ICU admission ($p = 0.033$), and ICU opioid-free days ($p = 0.026$) were associated with a reduced likelihood of persistent opioid use (Table 3). For both cohorts, ICU opioid dose per day of exposure was not associated with persistent opioid use.

DISCUSSION

In this cohort of 2,975 critically ill adults treated with opioids in the ICU, the major factor associated with persistent opioid use 4–6 months after hospital discharge was chronic OPTA. Although OPTA patients made up only 8.6% of the cohort, they accounted for 61% of patients with persistent opioid use after discharge. Most prior studies included only opioid-naïve (11, 12, 14-17, 19, 21, 23–25) or chronic opioid users (13), but not both. We included patients with and without prior chronic opioid use, clarifying the relative contribution and factors associated with persistent opioid use in each group.

When adjusting for other risk factors, ICU opioid-free days were associated with reduced persistent opioid use for both the OPTA and non-OPTA groups, whereas opioid dose per day of exposure in the ICU was not associated with persistent opioid use for either cohort. Treating and preventing pain for ICU patients are a high priority, with opioids recommended as the first-line medication to do so (6). We need to identify safe and effective ways to use opioids and other treatments without contributing to the opioid epidemic or inadequately treating patient pain. This study suggests that increasing ICU time without opioids may be associated with reduced persistent opioid use, whereas opioid dose per ICU exposure day may not be associated.

Although the association between chronic OPTA and persistent use after discharge appears obvious and has been reported before in studies with a mixed cohort (10, 18, 26), many chronic users do not persistently fill opioid prescriptions after discharge. Yaffe et al (10) reported that chronic opioid use among adult ICU patients decreased from 6.2% prior to admission to 3.6% at discharge, 2.8% at 2 years, and 1.8% at 4 years. Similarly, Wang et al (13) reported that 37% of elderly chronic opioid users did not fill opioid prescriptions 6 months after ICU discharge, and another 21.5% filled prescriptions at a lower dose. In our study,

TABLE 1.
Patient Demographics and ICU Characteristics

Variable	All, *n* = 2,975	Opioid Use Prior To Admission, *n* = 257	No Chronic Opioid Fills Prior to Admission, *n* = 2,718	*p*
Age, yr	61 (49–71)	62 (54–69)	61 (49–71)	0.10
Female, *n* (%)	1,321 (44)	126 (49)	1,195 (44)	0.12
Charlson Comorbidity Index	4 (2–6)	5 (3–7)	4 (2–6)	< 0.001
Admission ICU/diagnosis[a], *n* (%)				
Medical	729 (25)	69 (27)	660 (24)	0.06
Respiratory failure	151 (21)	20 (29)	131 (20)	
Sepsis/septic shock	81 (11)	12 (17)	69 (10)	
Encephalopathy	66 (9)	4 (6)	62 (9)	
Gastrointestinal bleeding	47 (6)	3 (4)	44 (7)	
Acute kidney injury/metabolic	36 (5)	4 (6)	32 (5)	
Neurologic	1,166 (39)	83 (32)	1,083 (40)	
Subarachnoid hemorrhage	219 (19)	11 (13)	208 (19)	
Intracerebral/subdural hemorrhage[b]	162 (14)	6 (7)	156 (14)	
Ischemic stroke	147 (13)	10 (12)	137 (13)	
Traumatic brain injury/subdural/intracerebral hemorrhage	132 (11)	4 (5)	128 (12)	
Encephalopathy	78 (7)	8 (10)	70 (6)	
Seizure/status epilepticus	72 (6)	5 (6)	67 (6)	
Trauma/surgical	1,080 (36)	105 (41)	975 (36)	
Multitrauma	140 (13)	10 (10)	130 (13)	
Respiratory failure	101 (9)	12 (11)	89 (9)	
Sepsis/infection	81 (8)	7 (7)	74 (8)	
Abdominal surgery/problem	73 (7)	11 (10)	62 (6)	
Peripheral vascular crisis	52 (5)	5 (5)	47 (5)	
Thermal injury	49 (4)	2 (2)	47 (5)	
Surgical procedure, *n* (%)	1,283 (43)	104 (40)	1,179 (43)	0.37
ICU LOS, d	3.5 (2.0–6.9)	3.2 (1.9–6.0)	3.5 (2.0–7.0)	0.02
Hospital LOS, d	9 (5–16)	9 (5–15)	9 (5–17)	0.21
Mechanical ventilation, *n* (%)	1,593 (54)	123 (48)	1,470 (54)	0.06
Mechanical ventilation, d[c]	1.8 (0.8–5.0)	2.0 (0.8–5.5)	1.8 (0.8–5.0)	0.56
Discharge disposition, *n* (%)				
Home or self-care	812 (27)	58 (23)	754 (28)	< 0.001
Home with services	666 (22)	69 (27)	597 (22)	
Rehabilitation facility	874 (29)	53 (21)	821 (30)	
Skilled nursing, intermediate care, and long-term care	623 (21)	77 (30)	546 (20)	

[a]Most common admitting diagnoses in each ICU (≥4%).

[b]Nontraumatic intracerebral hemorrhage or subdural hematoma.

[c]Mechanical ventilation days do not include zero days for those not intubated.

Continuous variables reported as median (interquartile range) and proportions as number (%).

p values compare opioid use prior with admission and no chronic opioid fills prior to admission patients.

TABLE 2.
ICU, Post-ICU, Total Hospital, and Postdischarge Opioid Exposure Data

Variable	All, *n* = 2,975	Opioid Use Prior To Admission, *n* = 257	No Chronic Opioid Fills Prior to Admission, *n* = 2,718	*p*
ICU care and opioid exposure				
LOS, d	3.5 (2.0–6.9)	3.2 (1.9–6.0)	3.5 (2.0–7.0)	0.02
Exposure duration, d	2.2 (1.2–4.7)	2.7 (1.6–5.5)	2.1 (1.2–4.5)	< 0.001
Total FEs, µg	635 (175–2,941)	1,200 (300–3,933)	600 (158–2,792)	< 0.001
FEs per day exposed, µg/d	276 (105–882)	452 (150–1,060)	265 (101–858)	< 0.001
Opioid-free duration, d[a]	1.04 (0.32–2.78)	0.26 (0.03–0.99)	1.10 (0.44–2.85)	< 0.001
Post-ICU care and opioid exposure				
LOS, d	5.6 (3.0–10.4)	5.1 (2.9–10.3)	5.6 (3.0–10.4)	0.75
Opioid exposure duration, d[b]	1.1 (0–4.9)	1.2 (0–4.9)	1.1 (0–4.9)	0.94
Total FEs, mcg[c]	76 (0–475)	504 (107–2,069)	53 (0–375)	< 0.001
FEs per day exposed, µg/d[c]	100 (53–183)	177 (94–344)	94 (50–167)	< 0.001
Opioid-free duration, d	3.0 (1.1–6.5)	1.0 (0.3–2.8)	3.2 (1.3–6.8)	< 0.001
Hospital care and opioid exposure				
LOS, d	9 (5–16)	9 (5–15)	9 (5–17)	0.21
Exposure duration, d	4.3 (2.0–8.6)	6.9 (3.4–10.9)	4.0 (1.9–8.1)	< 0.001
Total FEs, µg	1,100 (283–3,746)	2,496 (662–7,390)	996 (262–3,501)	< 0.001
FEs per day exposed, µg/d	232 (100-667)	346 (141–750)	224 (97–658)	< 0.001
Postdischarge persistent opioid exposure, mo, *n* (%)				
0–3[d]	301/2,975 (10)	195/257 (76)	106/2,718 (3.9)	< 0.001
4–6[d]	305/2,975 (10)	186/257 (72)	119/2,718 (4.4)	< 0.001
7–12[d]	279/2,876 (9.7)	155/235 (66)	124/2,641 (4.7)	< 0.001

FEs = fentanyl-equivalents, LOS = length of stay.

[a]Four hundred eighty-eight patients received opioids every day in the ICU—their zero opioid-free days were not included.

[b]Three hundred forty-two patients were discharged from the ICU, post-ICU exposure data include 2,633 patients.

[c]Nine hundred ninety-three patients received no opioids post-ICU, total, and per-exposure day fentanyl equivalent doses included the remaining 1,640 patients.

[d]Denominators represent patients still alive at 3, 6, and 12 mo.

p values for comparison between no chronic opioid fills prior to admission and opioid use prior to admission groups.

28% of OPTA patients did not persistently fill opioid prescriptions 4–6 months after discharge, and persistent use decreased from 76% to 66% over 12 months, similar to data from Dunn et al (26).

Few studies evaluating persistent opioid use after critical illness reported ICU opioid doses (23–25); among opioid-naïve patients, Krancevich et al (23) and Witcraft et al (24) found no association between ICU opioid dose and persistent opioid use), and Tollinche et al (25) observed that patients who received opioids in the ICU were less likely to receive an opioid prescription at discharge. Witcraft et al (24) found that intubation and hospital (but not ICU) opioid dose were associated with continuing opioids at discharge. In our multivariable analyses, neither of these factors was associated with persistent opioid use for OPTA or non-OPTA patients.

Additional reports evaluated the duration of opioid exposure during hospitalization (11–19). Kram et al (11) identified that discharge with opioids was associated with enteral but not IV opioid exposure duration. Donohue et al (19) identified a lower risk of persistent opioid use if opioids were administered on a smaller percent of hospital days, and if the opioid-free duration prior to discharge exceeded 24 hours. Both Kram et al (11) and Donohue et al (19) studied opioid-naïve

TABLE 3.
Multivariable Analysis of Factors Associated With Persistent 4–6 Month Opioid Fills

	Opioid Use Prior to Admission			No Chronic Opioid Fills Prior to Admission		
Variable	**OR (95% CI)**		***p***	**OR (95% CI)**		***p***
Age, yr	1.02 (0.91–1.05)		0.34	0.98 (0.97–1.00)		0.009
Charlson Comorbity Index	0.95 (0.84–1.08)		0.42	1.06 (1.00–1.13)		0.057
Sex						
Female	1 (Reference)			1 (Reference)		
Male	0.54 (0.29–1.00)		0.049	0.77 (0.53–1.13)		0.18
Surgical procedure						
No	1 (Reference)			1 (Reference)		
Yes	0.51 (0.27–0.95)		0.033	1.25 (0.85–1.84)		0.25
Admission ICU						
Medical	1 (Reference)		0.84	1 (Reference)		0.26
Neurologic	1.14 (0.45–2.88)			0.74 (0.44–1.23)		
Trauma/surgical	1.32 (0.52–3.39)			1.07 (0.68-–1.70)		
	Quintile Range	OR (95% CI)	*p*	Quintile Range	OR (95% CI)	*p*
Mechanical ventilation, d	0	1 (Reference)	0.67	0	1 (Reference)	0.13
	0.02–0.71	1.67 (0.54–5.99)		0.01–0.66	0.42 (0.17–0.91)	
	0.71–1.44	1.06 (0.36–3.49)		0.66–1.29	0.64 (0.28–1.36)	
	1.44–3.07	0.47 (0.15–1.53)		1.29–2.64	0.50 (0.20–1.17)	
	3.07–6.76	1.19 (0.32–4.91)		2.64-6.37	1.00 (0.44–2.23)	
	6.76–215	0.96 (0.27–3.58)		6.37-89	0.80 (0.31–1.97)	
ICU fentanyl-equivalents per day exposed, µg/d	11.1–128	1 (Reference)	0.053	10–84	1 (Reference)	0.23
	128–283	2.15 (0.84–5.75)		84–179	1.13 (0.63-2.07)	
	283–631	2.08 (1.06–8.12)		179–417	0.65 (0.32-1.32)	
	631–1,240	2.41 (0.83–7.37)		417–1,070	1.39 (0.65-2.99)	
	1,240–8,390	5.76 (1.75–20.7)		1,070–12,000	1.53 (0.64-3.75)	
ICU Opioid-free duration, d	0	1 (Reference)	0.026	0	1 (Reference)	<0.001
	0.01–0.2	1.20 (0.43–3.65)		0.01–0.21	1.31 (0.76–2.27)	
	0.02–0.13	1.36 (0.49–4.05)		0.21–0.87	0.42 (0.20–0.85)	
	0.13–0.62	2.01 (0.66–7.07)		0.87–1.71	0.61 (0.31–1.16)	
	0.62–1.09	0.60 (0.24–1.55)		1.71–3.58	0.62 (0.32–1.19)	
	1.09–10.2	0.28 (0.10–0.76)		3.58–36.9	0.32 (0.14–0.71)	

OR = odds ratio.

patients; our data confirm the association between ICU opioid-free time and reduced persistent opioid use for both OPTA and non-OPTA patients.

The association of ICU or hospital LOS with persistent opioid use has varied in prior studies, and LOS is part of the calculation of opioid-free duration. Yaffe (10), Wang et al (13), and Witcraft et al (24) reported that ICU LOS was not associated with persistent opioid use; in contrast, Wunsch et al (17) reported that ICU stays longer than 7 days were associated with greater risk of persistent opioid use. Krancevich et al (23) and Tollinche et al (25) reported that LOS after transfer to a non-ICU bed was associated with persistent opioid use, as was total hospital LOS for Witcraft et al (24). Due to collinearity, LOS data were not included in our multivariable model, but opioid-free days were associated

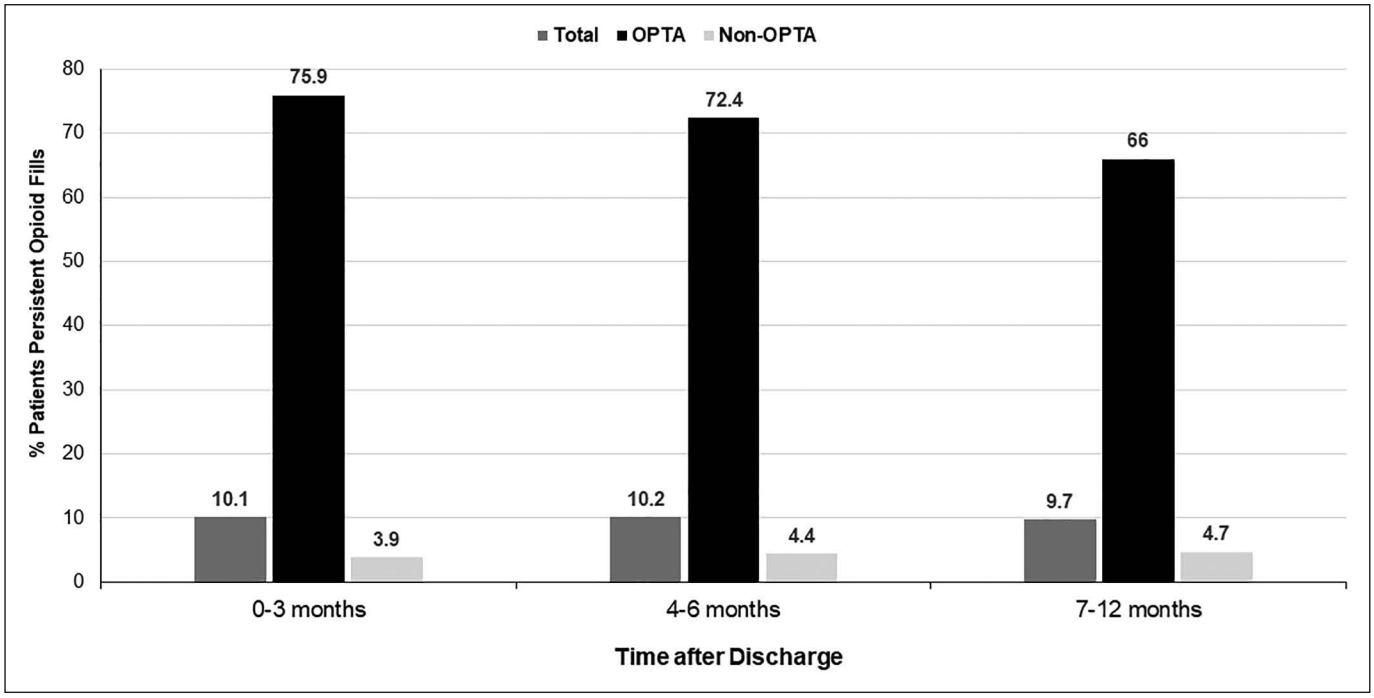

Figure 2. Persistent opioid fills 0–3, 4–6, and 7–12 mo after discharge for the total cohort (*dark gray*), the chronic opioid use prior to admission (OPTA) cohort (*black*), and the no chronic opioid fills prior to admission (non-OPTA) cohort (*light gray*).

with a reduced risk of persistent opioid fills, suggesting more aggressive opioid weaning, rather than limiting daily dose, may be a promising method to reduce persistent opioid use, but this has not been tested.

The strengths of this study were the large sample size, including patients with and without chronic OPTA, a wide range of adult ages, and detailed opioid dosing including ICU, post-ICU, and PMP-based data for 3 months before admission to 12 months after discharge. Limitations of our study include a retrospective design at a single teaching hospital, and including nonintubated patients and chronic or intermittent opioid users that differs from many study designs. We adjusted for different opioid medications using equianalgesic dosing conversions but did not evaluate indication for opioid use, quality of analgesia or etiology of pain, use of nonopioid analgesics, or multimodal pain relief, and did not assess whether Integrated Medication-Assisted Treatment was provided during ICU or post-ICU care or the reasons for chronic OPTA or persistent opioid use after ICU discharge. Although the PMP enabled us to follow patients before and after hospital discharge, it lacked data on methadone or nonprescription opioid use, and may not reliably capture opioid dosing during inpatient rehabilitation or through the Veterans Health Administration. Because several important groups were excluded (such as the 2.6% with PCAs or 1.9% receiving epidural analgesia), our results may not be generalizable to all patient populations and may be subject to bias. Future studies may benefit from assessing these therapies. Many states have passed legislation to limit dose and/or duration of opioids that can be prescribed; we did not take these evolving changes into account in our analyses.

We are not certain why a surgical procedure during the ICU stay was related to a reduced risk for persistent opioid use among OPTA patients; perhaps longer stays requiring tracheostomy or percutaneous gastrostomy tubes allowed more time to wean off opioids, or surgical procedures may have resolved a cause of pain. In our study, the median ICU dose of opioids per day of exposure was 276 FEs μg; using the conversion that 100-μg IV fentanyl = 10-mg IV morphine and 30-mg oral morphine, 276-μg IV fentanyl is equivalent to 83-mg oral morphine (22). These opioids were used to provide analgosedation that has been shown to improve outcomes, address pain and discomfort, and potentially reduce sedative medications (6, 27). Our observational data must be considered hypothesis-generating, and any changes in our approach to opioids in the ICU must prospectively evaluate the adequacy of patient analgesia and confirm the ultimate impact on persistent opioid use. Other strategies may include the use of pain management protocols with valid and reliable assessment

tools, incorporation of a multimodal analgesia strategy, and minimization of continuously infused opioids.

CONCLUSIONS

In a heterogeneous cohort of adult ICU patients, the major factor associated with opioid use 4–6 months after discharge was OPTA. Few prior studies had reported ICU opioid doses, which we found were not associated with persistent opioid use, whether patients were OPTA or not. The number of opioid-free days in the ICU was associated with a reduced likelihood of persistent use for both groups. Protocols to facilitate reducing opioid duration in the ICU may help reduce persistent opioid use, but this requires prospective study.

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REFERENCES

1. Puntillo KA: Pain experiences of intensive care unit patients. *Heart Lung* 1990; 19:526–533
2. Shapiro BA, Warren J, Egol AB, et al: Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: An executive summary. Society of Critical Care Medicine. *Crit Care Med* 1995; 23:1596–1600
3. Baker DW: History of The Joint Commission's Pain Standards: Lessons for today's prescription opioid epidemic. *JAMA* 2017; 317:1117–1118
4. Jacobi J, Fraser GL, Coursin DB, et al; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), American Society of Health-System Pharmacists (ASHP), American College of Chest Physicians: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30:119–141
5. Porter J, Jick H: Addiction rare in patients treated with narcotics. *N Engl J Med* 1980; 302:123
6. Barr J, Fraser GL, Puntillo K, et al; American College of Critical Care Medicine: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; 41:263–306
7. Mattson CL, Tanz LJ, Quinn K, et al: Trends and geographic patterns in drug and synthetic opioid overdose deaths - United States, 2013-2019. *MMWR Morb Mortal Wkly Rep* 2021; 70:202–207
8. Dowell D, Haegerich TM, Chou R: CDC guideline for prescribing opioids for chronic pain–United States, 2016. *JAMA* 2016; 315:1624–1645
9. Brummett CM, Waljee JF, Goesling J, et al: New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg* 2017; 152:e170504
10. Yaffe PB, Green RS, Butler MB, et al: Is admission to the intensive care unit associated with chronic opioid use? A 4-year follow-up of intensive care unit survivors. *J Intensive Care Med* 2017; 32:429–435
11. Kram B, Weigel KM, Kuhrt M, et al: Discharge prescribing of enteral opioids after initiation as a weaning strategy from continuous opioid infusions in the intensive care unit. *J Opioid Manag* 2018; 14:35–42
12. Ladha KS, Neuman MD, Broms G, et al: Opioid prescribing after surgery in the United States, Canada, and Sweden. *JAMA Netw Open* 2019; 2:e1910734
13. Wang HT, Hill AD, Gomes T, et al: Opioid use after ICU admission among elderly chronic opioid users in Ontario: A population-based cohort study. *Crit Care Med* 2018; 46:1934–1942
14. Karamchandani K, Pyati S, Bryan W, et al: New persistent opioid use after postoperative intensive care in US veterans. *JAMA Surg* 2019; 154:778–780
15. Academia EC, Gabriel CJ, Mueller A, et al: Opioid prescribing after discharge in a previously mechanically ventilated, opioid-naïve cohort. *Ann Pharmacother* 2020; 54:1065–1072
16. Brown CR, Chen Z, Khurshan F, et al: Development of persistent opioid use after cardiac surgery. *JAMA Cardiol* 2020; 5:889–896
17. Wunsch H, Hill AD, Fu L, et al: New opioid use after invasive mechanical ventilation and hospital discharge. *Am J Respir Crit Care Med* 2020; 202:568–575
18. von Oelreich E, Eriksson M, Sjölund KF, et al: Opioid use after intensive care: A nationwide cohort study. *Crit Care Med* 2021; 49:462–471
19. Donohue JM, Kennedy JN, Seymour CW, et al: Patterns of opioid administration among opioid-naive inpatients and associations with postdischarge opioid use: A cohort study. *Ann Intern Med* 2019; 171:81–90
20. Raebel MA, Newcomer SR, Reifler LM, et al: Chronic use of opioid medications before and after bariatric surgery. *JAMA* 2013; 310:1369–1376

21. Sun EC, Darnall BD, Baker LC, et al: Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. *JAMA Intern Med* 2016; 176:1286–1293
22. McPherson ML: *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing*. Bethesda, MD: American Society of Health-System Pharmacists; 2009
23. Krancevich NM, Belfer JJ, Draper HM, et al: Impact of opioid administration in the intensive care unit and subsequent use in opioid-naïve patients. *Ann Pharmacother* 2022; 56:52–59
24. Witcraft EJ, Gonzales JP, Seung H, et al: Continuation of opioid therapy at transitions of care in critically ill patients. *J Intensive Care Med* 2021; 36:879–884
25. Tollinche LE, Seier KP, Yang G, et al: Discharge prescribing of enteral opioids in opioid naïve patients following non-surgical intensive care: A retrospective cohort study. *J Crit Care* 2022; 68:16–21
26. Dunn LK, Taylor DG, Smith SJ, et al: Persistent post-discharge opioid prescribing after traumatic brain injury requiring intensive care unit admission: A cross-sectional study with longitudinal outcome. *PLoS One* 2019; 14:e0225787
27. Devlin JW, Skrobik Y, Gélinas C, 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