

Opioid Use to Treat Migraine Headaches in Hospitalized Children and Adolescents

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ABSTRACT

OBJECTIVES: Prescription of opioids to treat pediatric migraine is explicitly discouraged by treatment guidelines but persists in some clinical settings. We sought to describe rates of opioid administration in pediatric migraine hospitalizations.

METHODS: Using data from the Pediatric Health Information System, we performed a cross-sectional study to investigate the prevalence and predictors of opioid administration for children aged 7 to 21 years who were hospitalized for migraine between January 1, 2016, and December 31, 2018.

RESULTS: There were 6632 pediatric migraine hospitalizations at 50 hospitals during the study period, of which 448 (7%) had an opioid administered during the hospitalization. There were higher adjusted odds of opioid administration in hospitalizations for non-Hispanic black (adjusted odds ratio [aOR], 1.68; $P < .001$) and Hispanic (aOR, 1.54; $P = .005$) (reference white) race and ethnicity, among older age groups (18–21 years: aOR, 2.74; $P < .001$; reference, 7–10 years), and among patients with higher illness severity (aOR, 2.58; $P < .001$). Hospitalizations during which an opioid was administered had a longer length of stay (adjusted rate ratio, 1.48; $P < .001$) and higher 30-day readmission rate (aOR, 1.96; $P < .001$). By pediatric hospital, opioid administration ranged from 0% to 23.5% of migraine hospitalizations. Hospitals with higher opioid administration rates demonstrated higher adjusted readmission rates ($P < .001$) and higher adjusted rates of return emergency department visits ($P = .026$).

CONCLUSIONS: Opioids continue to be used during pediatric migraine hospitalizations and are associated with longer lengths of stay and readmissions. These findings reveal important opportunities to improve adherence to migraine treatment guidelines and minimize unnecessary opioid exposure, with the potential to improve hospital discharge outcomes.

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Pediatric pain management guidelines have historically been aimed at improving underrecognition and inadequate treatment of pain in children. In light of increasing rates of opioid exposure in children and adolescents between 1994 and 2007,¹ as well as the recent increase in opioid-related deaths and unintentional poisonings in children and adolescents in the United States, efforts have shifted to focus on minimizing unnecessary opioid prescribing.²⁻⁴

Opioids are explicitly discouraged for the treatment of pain associated with migraine headaches. This class of medications is thought to potentiate the underlying pathophysiology of migraine, leading to a diminished response to abortive therapies and potential conversion to a chronic headache disorder.⁵⁻⁷ Evidence-based guidelines for abortive treatment of pediatric migraine headaches instead focus on use of a tiered approach to pain management by using nonsteroidal anti-inflammatory analgesics, triptans, dopamine antagonists, and ergotamines.⁵ The American Academy of Neurology recommends that opioids not be prescribed as abortive treatment of pediatric or adult migraine headaches.⁸ However, despite these recommendations, studies in the ambulatory, emergency department (ED), and, to a limited extent, the hospital setting suggest that opioids continue to be used to treat pediatric migraine headaches.⁹⁻¹³

Little is known about the continued use of opioids as abortive therapy for pediatric migraines specifically in the inpatient setting. Findings on opioid treatment of migraines in other settings may not extend to the inpatient environment where patient and provider characteristics may be qualitatively distinct.^{10,12,13} In 1 small study of 58 hospitalized children and adolescents, a quarter of pediatric patients with migraines were found to have an opioid administered during their hospital stay.¹³ These patients had significantly longer lengths of stay (LOS) than those who did not receive an opioid.¹³ This study was limited by being conducted at a single site with a small sample of patients. To date, there are no representative national studies investigating

the use and impact on discharge outcomes of opioids to treat migraine headaches in hospitalized children and adolescents.

Our objectives with this study were to (1) identify differences in patient and hospital characteristics associated with administration of an opioid during a pediatric migraine headache hospitalization; (2) describe the association between opioid administration and hospital discharge outcomes (geometric mean LOS, 30-day hospital readmission, and 7-day return rate to the ED); and (3) describe the variation in rate of opioid administration during a migraine headache hospitalization and discharge outcomes across pediatric tertiary care hospitals.

METHODS

Study Design and Setting

We performed a retrospective cross-sectional study using the Pediatric Health Information System (PHIS). The PHIS database contains administrative and billing data on discharges from 52 tertiary care children's hospitals across the United States. Data quality is maintained by a joint effort between the Children's Hospital Association (Lenexa, KS), participating hospitals, and IBM Watson Health—Truven Health (Ann Arbor, MI). Because of the use of deidentified data, this study was determined to be nonhuman subject research by the institutional review board.

Cohort Definition

We included inpatient or observation stays for children and adolescents aged 7 to 21 years admitted to a PHIS hospital between January 1, 2016, and December 31, 2018, with either a primary diagnosis of migraine headache, based on the *International Classification of Diseases, 10th Revision*, or a secondary diagnosis code for migraine headache with an All Patient Refined Diagnosis-Related Group (APR-DRG; 3M Health Information Systems, Salt Lake City, UT) classification of "migraine and other headaches". For discharges that were not assigned a "migraine and other headaches" APR-DRG, we excluded those with a secondary diagnosis of migraine to limit our study to only migraine-related

hospitalizations and not hospitalizations with migraine headaches on the chronic medical problem list. We excluded children and adolescents who most likely had an opioid administered for an indication other than for pain management of their migraine headache; those with a billing or procedure code to indicate their hospitalization included an ICU stay, mechanical ventilation, terminal care, procedures that could have required sedation (on the basis of manual review of procedure codes within the study cohort), and care for traumatic injuries. Because patients with a complex chronic condition¹⁴ or a pregnancy-related diagnosis could be prescribed an opioid for an indication other than migraine headaches, children and adolescents with these diagnoses were also excluded.

Primary Exposure

Our primary exposure was administration of an opioid during a hospitalization for migraine headache. Opioid administration was defined on the basis of billing code for any opioid analgesic, which includes partial and full opioid agonists including tramadol. Discharge prescriptions were not included in our analysis.

Patient and Hospital Characteristics

We extracted the following patient characteristics: age, sex, race and ethnicity, payer type, presence of a mental health diagnosis,¹⁵ and zip code–based median annual household income quartile generated from 2010 US Census data (quartile 1: ≤\$33 311, quartile 2: \$33 312–41 386, quartile 3: \$41 387–54 013, quartile 4: ≥\$54 014). The zip code–based median household income has been previously demonstrated to be a useful proxy for socioeconomic status when individual-level data are unavailable.¹⁶ To assess severity of illness, we calculated the mean hospitalization resource intensity scores for hospitalizations (H-RISK). The H-RISK is a measure of relative resource intensity of pediatric hospital care and is a proxy measure (eg, hospitalization cost) for clinical severity.¹⁷ We extracted the hospital-level characteristic of location as defined by US Census region.

Discharge Outcomes

We investigated hospital discharge outcomes, including hospital LOS in hours, hospital readmission within 30 days, and ED return visit within 7 days of discharge.

Analysis

Descriptive statistics with frequencies and percentages were used to summarize categorical variables, and medians with interquartile range or LOS geometric mean with 95% confidence intervals (CIs) were used to summarize continuous variables. We assessed differences between continuous characteristics using Wilcoxon rank-sum tests, and we assessed differences in categorical characteristics and variation in opioid administration across hospitalizations using χ^2 or Fisher exact test. To identify patient and hospital characteristics for adjustment of hospital discharge outcomes, we used generalized linear mixed modeling to model (1) the probability of opioid administration during a migraine hospitalization, (2) hospital readmissions, and (3) ED return visits. A binomial distribution and logit link were assumed for these models. We used a log linear model to model LOS. We used linear regression to assess the relationship between hospital-level opioid administration and adjusted hospital readmission, adjusted ED return visit, and adjusted geometric mean LOS. Covariates included in all models were patient age, sex, race and ethnicity, payer type, median household income quartile, H-RISK, mental health status, and US Census region. There were 160 hospitalizations missing data for median household income quartile, which were excluded from the adjusted analyses. All statistical models also included a random intercept for each hospital to account for clustering of discharges within hospitals. All statistical tests were 2 sided, and *P* values <.05 were considered statistically significant. Statistical analyses were performed by using SAS software version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

There were 6632 hospitalizations for migraine headaches (representing 5371 unique patients) across 50 hospitals

between January 1, 2016, and December 31, 2018. Of these, 448 (7%) had an opioid administered during the hospitalization. Of all migraine hospitalizations, 6472 (97.6%) had a primary diagnosis of migraine and 160 (2.4%) had a secondary diagnosis of migraine and an APR-DRG classification of migraine and/or other headache. The most frequently prescribed opioids were

morphine sulfate (53%), fentanyl citrate (19%), tramadol hydrochloride (14%), combination opioids (eg, hydrocodone and acetaminophen; 11%), oxycodone (5%), and hydromorphone (5%). In the bivariate results, found in Table 1, there were differences in characteristics between those with administration of an opioid and those without.

TABLE 1 Characteristics of Pediatric Migraine Hospitalizations by Opioid Administration

Characteristic	Overall	No Opioid	Opioid	<i>P</i>
Hospitalizations, <i>n</i> (%)	6632	6184 (93.2)	448 (6.8)	—
Age, y, median (IQR)	14 (12–16)	14 (12–16)	15 (12–17)	<.001
Age category, y, <i>n</i> (%)				<.001
7–10	984 (14.8)	924 (14.9)	60 (13.4)	—
11–14	2510 (37.8)	2370 (38.3)	140 (31.3)	—
15–17	2699 (40.7)	2508 (40.6)	191 (42.6)	—
18–21	439 (6.6)	382 (6.2)	57 (12.7)	—
Sex, <i>n</i> (%)				.336
Female	4837 (72.9)	4519 (73.1)	318 (71.0)	—
Male	1795 (27.1)	1665 (26.9)	130 (29.0)	—
Payer type, <i>n</i> (%)				.018
Government	2558 (38.6)	2368 (38.3)	190 (42.4)	—
Commercial	3729 (56.2)	3501 (56.6)	228 (50.9)	—
Self-pay	102 (1.5)	89 (1.4)	13 (2.9)	—
Other	243 (3.7)	226 (3.7)	17 (3.8)	—
Race and ethnicity, <i>n</i> (%)				<.001
Non-Hispanic white	4243 (64.0)	4004 (64.7)	239 (53.3)	—
Non-Hispanic black	922 (13.9)	833 (13.5)	89 (19.9)	—
Hispanic	984 (14.8)	887 (14.3)	97 (21.7)	—
Asian American	78 (1.2)	70 (1.1)	8 (1.8)	—
Other	405 (6.1)	390 (6.3)	15 (3.3)	—
Mental health diagnosis, <i>n</i> (%)				.004
No	4223 (63.7)	3966 (64.1)	257 (57.4)	—
Yes	2409 (36.3)	2218 (35.9)	191 (42.6)	—
H-RISK, mean (SE)	0.81 (0.00)	0.81 (0.00)	0.84 (0.01)	<.001
Median household income quartile, <i>n</i> (%)				.317
Q1	1239 (18.7)	1159 (18.7)	80 (17.9)	—
Q2	1371 (20.7)	1270 (20.5)	101 (22.5)	—
Q3	1688 (25.5)	1571 (25.4)	117 (26.1)	—
Q4	2169 (32.7)	2024 (32.7)	145 (32.4)	—
Missing	165 (2.5)	160 (2.6)	5 (1.1)	—
Hospital region, <i>n</i> (%)				<.001
Midwest	1519 (22.9)	1451 (23.5)	68 (15.2)	—
Northeast	1201 (18.1)	1164 (18.8)	37 (8.3)	—
South	2815 (42.4)	2566 (41.5)	249 (55.6)	—
West	1097 (16.5)	1003 (16.2)	94 (21.0)	—

P values comparing between no opioid versus opioid administration. IQR, interquartile range; Q, income quartile; —, not applicable.

Adjusted Characteristics

There was a higher adjusted odds ratio (aOR) of administration of an opioid among older ages (18–21 years; aOR, 2.74 [95% CI: 1.8–4.15]; $P < .001$), those of non-Hispanic black (aOR, 1.68 [95% CI: 1.26–2.24]; $P < .001$) and Hispanic (aOR, 1.54 [95% CI: 1.14–2.08]; $P = .005$) race and ethnicity, and those with a higher mean H-RISK score (aOR, 2.58 [95% CI: 2.38–2.67]; $P < .001$) (Table 2). In terms of regional

variations, there were lower adjusted odds of administration of an opioid among hospitalizations from the northeast (aOR, 0.37 [95% CI: 0.23–0.6]; $P < .001$) and among those from the Midwest region (aOR, 0.6 [95% CI: 0.4–0.91]; $P = .015$).

Adjusted Discharge Outcomes

After adjusting for patient and hospital characteristics, hospitalizations with administration of an opioid demonstrated a

longer adjusted geometric mean LOS (49.1 hours [95% CI: 43.5–55.5] vs 35.6 hours [95% CI: 32.2–39.5]; $P < .001$) and higher adjusted odds of 30-day readmission (aOR, 2.0 [95% CI: 1.5–2.6]; $P < .001$) compared with those without administration of an opioid (Supplemental Table 3). There was no difference in adjusted rates of return ED visits within 7 days between hospitalizations with opioid administration and those without opioid administration ($P = .126$).

Hospital-Level Variations and Outcomes

There was significant variation in the frequency of opioid administration across hospitals, ranging from 0% to 23.5% ($P < .001$), with a mean of 6.8% (Fig 1). After adjusting for patient and hospital characteristics, the mean adjusted rate of opioid administration remained nearly the same at 6.4%, and the adjusted variation between hospitals ranged from 4.8% to 8.8%. Hospitals with higher opioid administration rates demonstrated higher adjusted readmission rates ($P < .001$) and higher adjusted rates of return ED visits ($P = .026$) compared with hospitals with lower opioid prescribing rates (Figs 2 and 3).

DISCUSSION

Despite national guidelines recommending against opioid use to treat migraine headaches, we found that 7% of pediatric hospitalizations for migraine headaches involved administration of an opioid. To our knowledge, this is the first national study investigating use of opioids to treat migraine headaches in children and adolescents hospitalized at pediatric hospitals.

Previous studies investigating opioid use among hospitalized children for any diagnosis have demonstrated that >40% of children are prescribed an opioid while hospitalized.^{18,19} In 1 small single-site study, researchers found that opioids were administered to treat migraine headaches in 26% of hospitalized children.¹³ After adjusting for patient characteristics in our study, there was less interhospital variation in opioid administration; therefore, the difference in opioid administration between hospitals may be primarily driven by

TABLE 2 Adjusted Probabilities and Odds Ratios of Opioid Administration for Pediatric Migraine Hospitalizations

Characteristic	aProbability (95% CI)	aOR (95% CI)	P
Age category, y			
7–10	0.057 (0.039–0.083)	Reference	—
11–14	0.054 (0.038–0.074)	0.94 (0.68–1.30)	.700
15–17	0.066 (0.048–0.090)	1.17 (0.85–1.61)	.342
18–21	0.142 (0.097–0.202)	2.74 (1.80–4.15)	<.001
Sex			
Female	0.069 (0.050–0.093)	0.86 (0.68–1.08)	.187
Male	0.079 (0.057–0.109)	Reference	—
Payer type			
Government	0.058 (0.044–0.076)	Reference	—
Commercial	0.057 (0.043–0.074)	0.98 (0.78–1.23)	.856
Self-pay	0.105 (0.055–0.193)	1.92 (0.97–3.81)	.061
Other	0.084 (0.047–0.147)	1.50 (0.80–2.80)	.203
Race and ethnicity			
Non-Hispanic white	0.060 (0.045–0.078)	Reference	—
Non-Hispanic black	0.096 (0.070–0.131)	1.68 (1.26–2.24)	<.001
Hispanic	0.089 (0.064–0.122)	1.54 (1.14–2.08)	.005
Asian American	0.104 (0.048–0.210)	1.83 (0.82–4.07)	.138
Other	0.040 (0.022–0.069)	0.65 (0.37–1.14)	.131
Mental health diagnosis			
No	0.075 (0.056–0.101)	Reference	—
Yes	0.072 (0.051–0.100)	0.96 (0.76–1.21)	.724
H-RISK	—	2.58 (2.38–2.67)	<.001
Median household income quartile			
Q1	0.063 (0.043–0.090)	0.79 (0.57–1.10)	.158
Q2	0.078 (0.055–0.109)	Reference	—
Q3	0.076 (0.054–0.106)	0.97 (0.72–1.31)	.857
Q4	0.079 (0.056–0.110)	1.02 (0.76–1.36)	.907
Hospital region			
Midwest	0.064 (0.043–0.094)	0.60 (0.40–0.91)	.015
Northeast	0.041 (0.026–0.064)	0.37 (0.23–0.60)	<.001
South	0.109 (0.079–0.148)	1.08 (0.77–1.51)	.653
West	0.101 (0.071–0.142)	Reference	—

Results are adjusted for age, sex, race and ethnicity, payer type, mental health status, median household income quartile, US region, and H-RISK. aProbability, adjusted probability; Q, income quartile; —, not applicable.

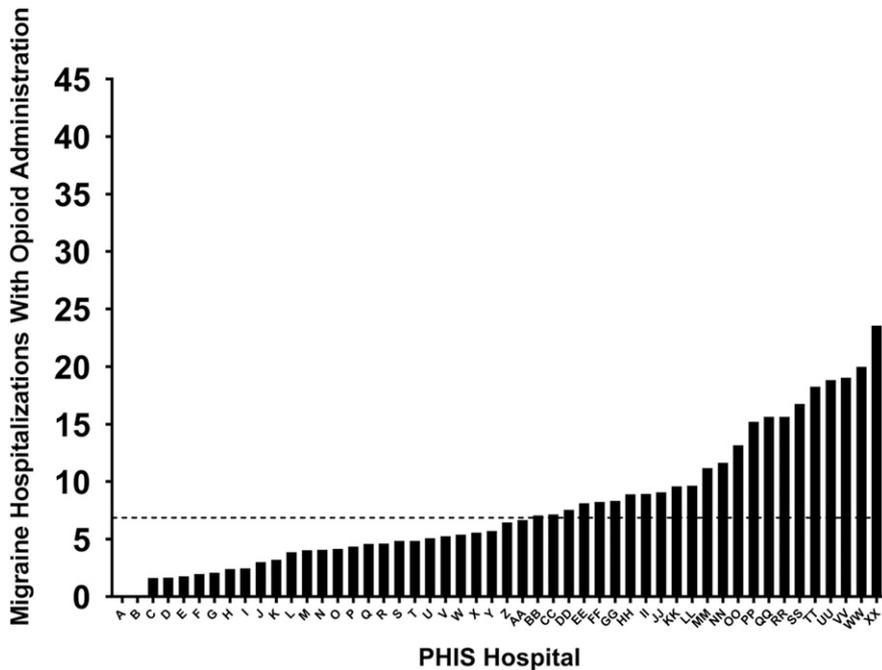


FIGURE 1 Variation by hospital in opioid administration for pediatric migraine hospitalizations. There was variation between hospitals in unadjusted rates of opioid administration for pediatric migraine hospitalizations, ranging from 0% to 23.5%, with a median of 6.8% (dotted line).

differences in patient characteristics as opposed to provider- or institutional-level factors.

Hospitalizations involving non-Hispanic black and Hispanic children were found in our study to have higher adjusted odds of

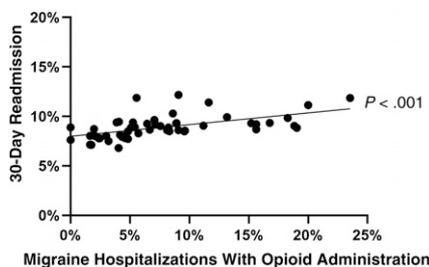


FIGURE 2 Variation by hospital in adjusted rates of readmissions by opioid administration for pediatric migraine hospitalizations. Each point represents a pediatric hospital. At the hospital level, there was an increase in the adjusted proportion of hospital readmissions (within 30 days) with increasing opioid administration during pediatric hospitalizations for migraine headaches ($P < .001$).

opioid administration. This finding differs from past studies in which researchers have demonstrated undertreatment of pain, including migraine headaches, among children of minority race and ethnicity (eg, non-Hispanic black) in the inpatient and ED settings.^{10,12,18} Our finding may indicate variation in adherence to migraine headache management guidelines among hospitalized children on the basis of differences in race and ethnicity. Racial disparities in guideline adherence have been described in management of pediatric asthma and bronchiolitis, with less adherence to treatment guidelines seen in care for those of non-Hispanic black and Hispanic race and ethnicity compared with non-Hispanic white.^{20,21} Additionally, there was a higher adjusted probability of opioid administration among hospitalizations in the South compared with other regions, which is similar to regional differences in opioid use for pediatric migraine in the ED.¹² Hospitalizations among patients with a higher H-RISK clinical severity score were associated with higher adjusted odds of an opioid prescription. This is consistent with

literature in which higher resource use overall is demonstrated, including pharmacy, among more clinically severe patients, including hospitalized children and those with complex chronic diseases.^{22,23} This finding could be indicative of the inpatient provider perceiving that a more clinically severe patient may warrant opioid administration despite migraine treatment guidelines. Given the retrospective use of administrative data, it is difficult to assess the clinical appropriateness of opioid prescription in these patients. However, our study population was limited to only those with a primary diagnosis of migraine and specifically excluded patients with other diagnoses or clinical procedures in whom opioid administration could be appropriate. Thus, this finding is of concern and represents potentially harmful opioid exposure.

Hospitalizations during which an opioid was administered had a longer adjusted LOS and higher probability of 30-day readmission in this population. A small single-site study in pediatric migraine headache patients in the hospital also revealed a longer LOS associated with opioid use.¹⁵ A past study among all hospitalized children similarly revealed a longer LOS among children prescribed an opioid during their hospital stay; however, this study was of a different patient population including children with medically complex conditions, cancer diagnoses, ICU stays, and terminal hospitalizations.¹⁸ We limited our patient population to those with a primary diagnosis of migraine headaches, and thus opioid use is explicitly advised against, hence these discharge outcomes are of concern. Furthermore, at the hospital level, opioid administration in pediatric migraine headache hospitalizations was associated with higher adjusted readmissions and ED revisit rates. Although our outcome findings differ at the hospitalization level (longer LOS and higher readmission rates) and hospital level (higher readmission rates, higher ED revisit rates), these findings are concerning in regard to patient outcomes as well as health care use and cost outcomes. Although we did not investigate health care costs, hospital readmissions, prolonged LOS, and ED revisits are all associated with

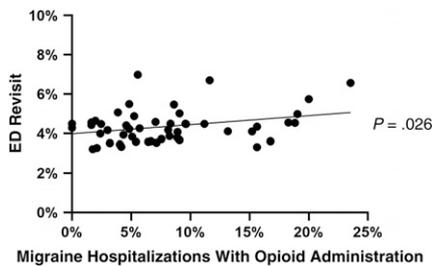


FIGURE 3 Variation by hospital in adjusted rates of ED revisits by opioid administration for pediatric migraine hospitalizations. Each point represents a pediatric hospital. At the hospital level, there was an increase in the adjusted proportion of ED revisits (within 7 days of discharge) with increasing opioid administration during pediatric migraine hospitalizations ($P = .013$).

increased costs.²⁴ Thus, minimizing these potentially avoidable outcomes may lead to a decrease in health care use as well as costs. Because opioids may potentiate the underlying pathophysiology of migraine, interventions to improve treatment guideline adherence by minimizing opioid exposure may also reduce unnecessary hospital days, readmissions, and health care costs in this population.

Our study should be viewed in light of these limitations. Because of the use of administrative data, we relied on accuracy of billing codes, which has been proven to be variable because of incompleteness of data, clerical error, and limited precision. Consequently, our data are subject to possible misclassification bias. We used a primary diagnosis of migraine headache and APR-DRG diagnosis of other headache to define our migraine headache study cohort, leading to risk for misclassification and potential underestimation of all migraine headache cases (eg, secondary diagnosis). Our data are limited to migraine hospitalizations at pediatric hospitals within the PHIS network; thus, our findings may not be generalizable to other clinical settings (eg, community hospitals). Additionally, our findings may underestimate readmissions or ED revisits among our study cohort because our data do not capture those readmissions or ED revisits to other

non-PHIS hospitals. To minimize the risk for misclassification of opioid administration for treatment of migraine headaches, we excluded all patients with diagnoses and procedures who could have been prescribed an opioid for reasons other than acute pain related to their headache. We have limited ability to make inferences regarding relevant health outcomes and clinical appropriateness of opioid prescription because our data source is an administrative database with limited relevant clinical and health outcome information.

Our study reveals critical opportunities for further investigation into use of opioids for pediatric migraines. Further study is needed to better understand how race and ethnicity impacts adherence to pediatric migraine treatment guidelines and opioid use to treat pediatric migraines in the hospital setting. Additional investigation is also warranted to further assess the drivers and clinical outcomes related to opioid administration among hospitalized children and adolescents with migraine headaches and higher clinical severity. Future investigation should be focused on identification of underlying factors driving the correlation between opioid exposure and LOS and readmissions among pediatric migraine headache hospitalizations.

CONCLUSIONS

Because opioids are explicitly discouraged as treatment of migraine headaches in children and adolescents, our findings reveal important opportunities for improved adherence to evidence-based guidelines for treatment of migraine headaches among hospitalized children and adolescents to minimize unnecessary and potentially harmful opioid exposure in this population, with the potential to improve hospital discharge outcomes.

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