

# Factors Associated With the Prophylactic Prescription of a Bowel Regimen to Prevent Opioid-Induced Constipation

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## ABSTRACT

**OBJECTIVE:** Identify factors associated with the prophylactic prescription of a bowel regimen with an inpatient opioid prescription.

**METHODS:** This was a retrospective cohort study from June 1, 2013, to October 31, 2014 of pediatric inpatients prescribed an oral or intravenous opioid on the general medical/surgical floors. We identified patients with or without a prophylactic prescription of a bowel regimen. We obtained patient demographics, prescriber training level and service and used multivariate logistic regression to analyze the factors associated with prophylactic bowel regimen and opioid prescription.

**RESULTS:** Of the 6682 encounters that met study criteria, only 966 (14.5%) encounters had prophylactic prescriptions. Patient factors associated with prophylactic prescription include increasing age (per year; odds ratio [OR] = 1.06, 95% confidence interval [CI] 1.05–1.07) and sickle cell diagnosis (OR = 3.19, 95% CI 2.08–4.91). Medication factors associated with prophylactic prescription include a scheduled opioid prescription (OR = 1.75, 95% CI 1.46–2.1) and a prescription for oxycodone (OR = 3.59, 95% CI 2.57–5.00) or morphine (OR = 1.84, 95% CI 1.39–2.44), compared with acetaminophen-hydrocodone. Compared with medical providers, surgeons were less likely (OR = 0.43, 95% CI 0.35–0.53) and pain service providers were more likely to prescribe a prophylactic bowel regimen (OR = 4.12, 95% CI 3.13–5.43).

**CONCLUSIONS:** More than 85% of inpatient opioid prescriptions did not receive a prophylactic bowel regimen. Future research should examine factors (eg, clinical decision support tools) to increase prophylactic prescription of bowel regimens with opioids for populations found to have lower rates.

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Opioid-induced constipation, a common gastrointestinal side effect of opioids, affects 15% to 80% of patients taking opioids.<sup>1–3</sup> Previous studies show that adult patients with cancer and opioid-induced constipation have lower quality of life and higher health care utilization, including high rates of outpatient visits, longer inpatient stays, and increased total health care costs compared with adult oncologic patients without constipation.<sup>4,5</sup> Although no formal published guidelines exist for the treatment of opioid-induced constipation in noncancer patients, expert opinion recommends the prescription of a bowel regimen at the time of an opioid prescription to prevent constipation.<sup>1,6</sup> Previous studies have found that 60% of pediatric patients receiving opioid therapy while hospitalized for sickle cell crises received a laxative,<sup>7</sup> and have demonstrated lower rates of opioid-induced constipation in patients premedicated with a bowel regimen.<sup>8</sup> Despite recommendations for the prophylactic prescription of a bowel regimen,<sup>1,6</sup> the rates of prophylactic bowel regimens remain inconsistent in hospitalized children receiving opioids.

A multicenter quality improvement collaborative reduced the rates of constipation by 67% by targeting the proactive prescription of a bowel regimen at the time of prescription of the opioid.<sup>9</sup> Consistent prescription of a bowel regimen at the time of an opioid prescription requires changes in prescribing behaviors. Several studies have examined the use of clinical decision support tools and educational modalities to improve opioid prescribing practices among trainees.<sup>10,11</sup> Clinical decision support tools may be useful in improving rates of prophylactic bowel regimens at the time of an opioid prescription.

Few studies have looked at factors associated with the use of bowel regimens in pediatric patients receiving opioids. Understanding patient and prescriber factors associated with the prophylactic prescription of a bowel regimen may allow for targeted interventions that can reduce opioid-induced constipation. The purpose of this study was to describe the frequency of

use and factors associated with the prophylactic prescription of a bowel regimen with an opioid in pediatric inpatients at a tertiary-care pediatric hospital.

## **METHODS**

### **Design**

This was a retrospective cohort study from June 1, 2013, to October 31, 2014, at Children's Hospital Los Angeles (CHLA). Approval for retrospective review with waiver of consent was granted by the CHLA Institutional Review Board.

### **Setting**

We included patients prescribed an opioid while hospitalized on the medical/surgical floors at CHLA, a 365-bed tertiary-care freestanding children's hospital, who received care by 1 of the following services: (1) pediatric hospital medicine attending physicians; (2) pediatric residents supervised by pediatric hospitalists, general pediatrics attending physicians, or pediatric subspecialty fellows and attending physicians (eg, pediatric oncology); and (3) a surgical or surgical subspecialist team, which includes surgery attending physicians, fellows, residents, and advanced practitioners, such as nurse practitioners (NPs) or physician assistants (PAs). In addition to these primary services, a pediatric pain service staffed by NPs, pediatric anesthesia fellows, and pediatric anesthesia attending physicians directly prescribed pain medications for some patients, and they were included in the analysis. We excluded the NICU, the PICU, emergency department, operating room, and radiology suite where opioids may be used for sedation purposes rather than acute pain management.

### **Patients**

Our electronic health record (CERNER Millennium version 2015.01.03) generated a prescribing report for each drug of interest that included patient encounter, medical record number, date of birth, race/ethnicity, insurance type, medication, medication order frequency, and prescriber name. We included pediatric patients under age 21 and excluded patients prescribed epidurals or 1-time opioid orders. Because the report was

generated on the basis of prescription encounters, we were unable to code for nil per os (NPO) status or admission diagnosis without doing a formal chart review of all patients.

Preliminary analysis showed a statistically significant effect with non-Hispanic Black patients. We hypothesized that the diagnosis of sickle cell disease and admission for a sickle cell–related diagnosis might be affecting our data. Thus, we reviewed the diagnoses of all non-Hispanic black patients in our data set and coded for sickle cell–related diagnosis or not. Any patient who was not non-Hispanic black was coded as not having sickle cell disease after discussion with our hematology service revealed that only a small number of the sickle cell patients (~5%) were not non-Hispanic Black.

### **Medications**

The opioids of interest were morphine, hydromorphone, oxycodone, and hydrocodone-acetaminophen. Given our focus on acute pain management, we excluded methadone because it is used for chronic pain management or withdrawal. We also excluded fentanyl because its use is restricted on our inpatient general medical-surgical wards. Tramadol constituted <1% of all inpatient opioid prescriptions; therefore, we excluded it from our study. Bowel regimens included senna, docusate, polyethylene glycol, and bisacodyl. We included both oral and rectal formulations of the bowel regimens as well as bowel regimens dosed as scheduled and pro re nata (PRN). Although we were able to code for frequency (scheduled vs PRN) of the opioid, the report generated by our electronic health records did not allow us to code for dosage form and route. We coded patients with patient-controlled analgesia (PCA) as receiving scheduled doses of opioids.

### **Prescribers**

We manually categorized the training level and prescribing service based on the name of the prescriber listed on the report. We verified the prescriber training level by cross-referencing lists obtained through the

graduate medical education office and the global directory at CHLA. Service lines for the advanced practitioners were confirmed by their individual departments. A prescriber was categorized as a trainee (if he or she was either a resident or fellow), an advanced practitioner (included NPs and PAs), or an attending physician (if he or she had completed their graduate medical education). Prescribing service was categorized as medical (including general pediatric services and any medical subspecialties), surgical (including general surgery as well as any surgical subspecialties such as orthopedics, neurosurgery, and otolaryngology), and pain/anesthesia.

### Outcome

The outcomes of interest were factors associated with prophylactic opioid and bowel regimen use. The binary outcome was presence or absence of a prophylactic order, defined as a preexisting bowel regimen at the time of an opioid order or the prescription of a bowel regimen and an opioid within 1 hour of each other. We felt that 1 hour was a reasonable period for a prescriber to enter orders in a single sitting. We identified the first prescription of an opioid and a bowel regimen for each inpatient encounter. We matched the prescription of the opioid and the prescription of a bowel regimen by unique individual inpatient encounters and calculated the time between the first opioid and bowel regimen order using the order date and times.

### Statistical Analysis

Descriptive statistics were computed for all measures, including medians and interquartile ranges (IQR) for age and frequencies and percentages for categorical variables. A series of univariate analyses assessed relationships between all predictors and the prophylactic order outcome. A  $\chi^2$  test for association with prophylactic order was conducted on opioid frequency, ethnicity, prescribing service, and training level. Variables that were associated with the outcome at  $P < .05$  were retained for investigation in a multivariate logistic regression model. Given concerns about NPO status as a possible confounder,

we did a subanalysis of patients receiving oral pain medications. SPSS version 20 was used for all analyses.

### RESULTS

We identified 6682 inpatient encounters that met inclusion criteria during our 16-month study period. Table 1 shows patient and provider demographic information. Median age for the cohort was 9 years (interquartile range: 4–14 years). More than 50% were Hispanic/Latino and >71% had public insurance. The most commonly prescribed opioid was morphine (57.1%),

followed by hydrocodone-acetaminophen combination (18%), hydromorphone (14.5%), and oxycodone (10.4%). The majority of prescriptions were written by trainees (58.7%), followed by advanced practitioners (25.8%) and attending physicians (15.4%). The surgical services wrote half of the prescriptions (50.3%), followed by the medical services (35.4%) and the pain service (14.2%). Among advanced practitioners, almost half (47.5%) of orders were written by NPs on the pediatric pain service. We found an overall association between type of opioid and

**TABLE 1** Demographic Characteristics of Pediatric Patients Stratified by Prescription of a Bowel Regimen at the Time of an Opioid Prescription.

Variable	Total	%	Simultaneous	%	Not Simultaneous	%	P
Age in y, median (IQR)	9 (4–14)	—	12 (7–16)	—	8 (3–14)	—	<.001
Sex							.65
Male	3441	51.5	504	14.6	2937	85.4	
Female	3241	48.5	462	14.3	2779	85.7	
Race/ethnicity							<.001
White/non-Hispanic	1180	17.7	173	14.7	1007	85.3	
Black/non-Hispanic	625	9.4	162	25.9	463	74.1	
Hispanic	3597	53.8	470	13.1	3127	86.9	
Other	1280	19.2	161	12.6	1119	87.4	
Insurance							.22
Public	4758	71.5	667	14.0	4091	86.0	
Private	1815	27.3	281	15.5	1534	84.5	
Other	78	1.2	14	17.9	64	82.1	
Sickle cell disease							<.001
Yes	251	3.8	102	40.6	149	59.4	
No	6431	96.2	864	13.4	5567	86.6	
Opioid frequency							
Scheduled opioid	1154	17.2	349	30.2	805	69.8	
PRN opioid	5528	82.7	617	11.2	4911	88.8	
Opioid type							<.001
Acetaminophen-hydrocodone	1203	18.0	74	6.2	1129	93.8	
Oxycodone	692	10.4	120	17.3	572	82.7	
Morphine	3816	57.1	616	16.1	3200	83.9	
Hydromorphone	971	14.5	156	16.1	815	83.9	
Training level							<.001
Trainee	3925	58.7	452	11.5	3473	88.5	
Advanced practitioner (NP/PA)	1725	25.8	432	25.0	1293	75.0	
Attending physician	1032	15.4	82	7.9	950	92.1	
Prescribing service							<.001
Medical	2364	35.4	372	15.7	1992	84.3	
Surgical	3356	50.3	194	5.8	3162	94.2	
Pain/anesthesia	949	14.2	398	41.9	551	58.1	

—, not applicable.

prescribing service (Fig 1;  $P < .001$ ). Although morphine was the most commonly prescribed opioid across all prescribing services, the pain service prescribed morphine more frequently than other services ( $P < .05$ ), the medical service prescribed hydromorphone more than either other service ( $P < .05$ ), and the surgical services prescribed hydrocodone more frequently than other services ( $P < .05$ ).

A minority ( $n = 966$ , 14.5%) of inpatient encounters had a prophylactic prescription of a bowel regimen and opioid. On unadjusted analysis, older age was associated with increased likelihood of having a prophylactic order (per year; odds ratio [OR] = 1.06, 95% confidence interval [CI] 1.05–1.07;  $P < .001$ ). Patients admitted for a sickle cell diagnosis were more likely to receive a prophylactic prescription of an opioid and a bowel regimen (40.6% vs 13.4%;  $P < .001$ ). Patients with scheduled opioids were more likely to have a prophylactic bowel regimen than those with a PRN opioid (30.2% vs 11.2%;  $P < .001$ ). Patients receiving hydrocodone-acetaminophen (6.2%) were less likely compared with patients receiving oxycodone (17.3%), morphine (16.1%), or hydromorphone (16.1%) to have a bowel regimen at the time of the opioid prescription ( $P < .001$ ). NPs (25%) were more likely than trainees (11.5%) or attending physicians (7.9%) to write a prophylactic order ( $P < .001$ ). Members of the pain service

(41.9%) were more likely than the medical (15.7%) and surgical services (5.8%) to write a prophylactic order ( $P < .001$ ). There were no associations between prophylactic orders and gender ( $P = .65$ ) or insurance type ( $P = .22$ ).

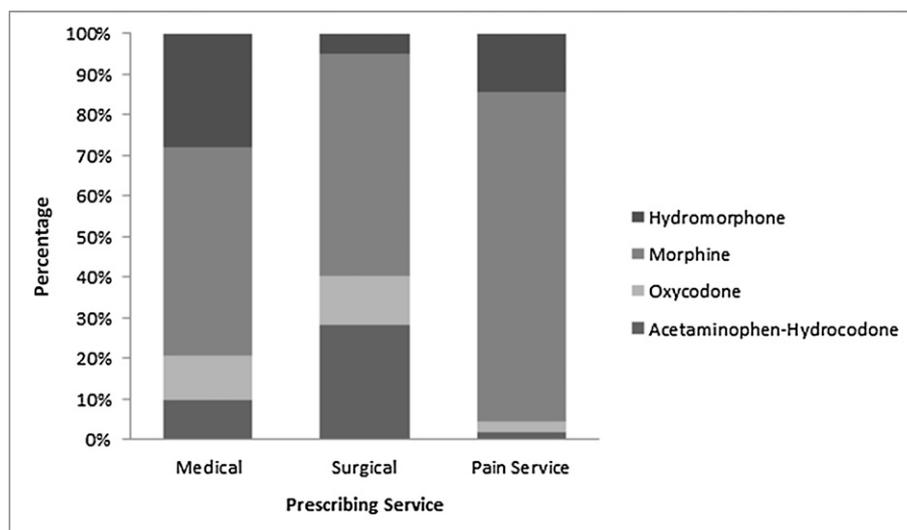
On multivariate logistic regression, increasing patient age, a sickle cell–related diagnosis, scheduled opioid prescription, opioid type, training level, and prescribing services were found to be associated with the prophylactic prescription of opioids and a bowel regimen (Table 2). Compared with patients receiving hydrocodone-acetaminophen, patients receiving oxycodone (OR = 3.59, 95% CI 2.57–5.00;  $P < .001$ ) and morphine (OR = 1.84, 95% CI 1.39–2.44;  $P < .001$ ) were more likely to have a prophylactic bowel regimen. Compared with trainees, attending physicians were less likely to prescribe a prophylactic bowel regimen (OR 0.40, 95% CI 0.31–0.53;  $P < .01$ ). Compared with medical providers, surgeons were less likely (OR = 0.43, 95% CI 0.35–0.53;  $P < .001$ ) and the pain service more likely (OR = 4.12, 95% CI 3.13–5.43;  $P < .001$ ) to prescribe a prophylactic bowel regimen. As depicted in Fig 2, trainees on the medical and surgical services were more likely to prescribe a prophylactic order when compared with trainees on the pain service. Conversely, NPs and attending physicians on the pain service were more likely to prescribe a prophylactic bowel regimen than NPs

or attending physicians on the other 2 services.

Our subanalysis of patients initially receiving oral opioids (therefore, not NPO and eligible to receive an oral bowel regimen) demonstrated that, of the 1895 included, 194 (10.2%) had a prophylactic bowel regimen at the time of the opioid prescription. The results of our multivariate logistic regression were similar to our main results (Table 3). There continues to be a statistically significant association between increasing age, scheduled opioid, sickle cell diagnosis, and opioid type (oxycodone). There were no changes in the associations between training level and prescribing service, except that the significantly increased odds for a prophylactic prescription for the pain service were no longer statistically significant (OR = 1.40, 95% CI 0.62–3.16).

## DISCUSSION

In our single-center retrospective study, >85% of encounters did not have a prophylactic prescription for a bowel regimen at the time of an opioid prescription. This is much lower than a previous study that found that approximately one-third of pediatric sickle cell inpatients did not receive at least 1 bowel regimen.<sup>7</sup> Increasing age and sickle cell–related diagnosis were patient factors independently associated with the proactive



**FIGURE 1** Percentage of prescribed opioid type for each service.

**TABLE 2** Results of the Multivariate Logistic Regression Analysis of Predictors of an Empirical Bowel Regimen

Variable	OR	95% CI	P
Age	1.06	1.05–1.07	<.001
Race/ethnicity			
White/non-Hispanic	Reference	—	—
Black/non-Hispanic	1.10	0.77–1.56	.61
Hispanic	1.12	0.91–1.38	.29
Other	0.94	0.72–1.21	.62
Sickle cell	3.19	2.08–4.91	<.001
Scheduled opioid	1.75	1.46–2.1	<.001
Opioid type			
Acetaminophen-hydrocodone	Reference	—	—
Oxycodone	3.59	2.57–5.00	<.001
Morphine	1.84	1.39–2.44	<.001
Hydromorphone	1.09	0.79–1.5	.62
Training level			
Trainee	Reference	—	—
Advanced practitioner (NP/PA)	1.08	0.84–1.39	.54
Attending physician	0.40	0.31–0.53	<.001
Prescribing service			
Medical	Reference	—	—
Surgical	0.43	0.35–0.53	<.001
Pain/anesthesia	4.12	3.13–5.43	<.001

prescription of a bowel regimen. Medication factors included opioid type and a scheduled opioid prescription. Attending physicians and prescribers on the surgical service were less likely to be associated with the prophylactic prescription of an opioid and bowel regimen when compared with trainees and prescribers on the medical service, respectively.

Patients receiving morphine and oxycodone were more likely to receive a prophylactic bowel regimen. Hydromorphone, which is the most potent of the opioids studied, had no significant association with a prophylactic prescription of an opioid and bowel regimen. Few studies examined differences in rates of opioid-induced constipation among different types of opioids in the inpatient. A single multicenter study found that compared with oxycodone, extended release oral morphine formulations were more likely to be associated with constipation.<sup>9</sup> Different prescribing services appear to have preferences for the type of opioids (Fig 1). Variations in prescribing practice among

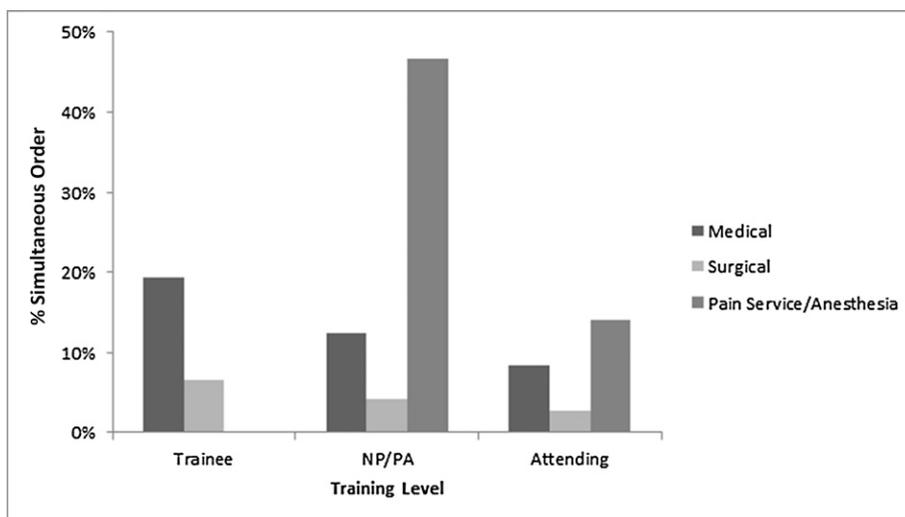
the services may affect the rates of a prophylactic bowel regimen at the time of opioid prescription. Patients prescribed scheduled opioids were more likely to receive a prophylactic bowel regimen, which suggests that prescribers recognize that multiple scheduled doses of opioids puts patients at higher risk of developing opioid-induced constipation. Because our study design does not allow us to account for the total opioid doses, some patients prescribed opioids on a PRN basis may have received as many doses as those prescribed scheduled opioids.

There were significant differences in prophylactic bowel regimens among the prescribing services and training levels. Surgeons, compared with medical providers, and attending physicians, compared with trainees, were less likely to prescribe a bowel regimen at the time of an opioid prescription. These associations persisted when we examined only patients who received oral opioids. Differences in prescribing rates are likely attributable to different practices among the services. The

rotating surgical residents may be less familiar with management and dosing of laxatives in children, compared with adults. The surgical services at our institution consist of a large body of rotating residents, making it challenging to create sustainable changes in prescribing practices solely through educational interventions. Whereas Ury et al showed that an educational curriculum alone was unable to improve prescribing rates of an empirical bowel regimen among trainees,<sup>12</sup> Rosenbluth and colleagues demonstrated that the use of pocket-sized reference card was effective in changing opioid prescribing practices in both medical and surgical trainees.<sup>11</sup> Increasing the prescribing rates of prophylactic bowel regimen among the surgical services will likely need to involve other modalities, such as clinical decision support tools or changes to our electronic ordering system.

We suspect that preexisting clinical decision support for the pain service and sickle cell patients affected rates of prophylactic prescription. There is no formal sickle cell crisis order set in our electronic health records; however, our residents use paper guidelines that direct them to the appropriate admission orders. Although we typically think of clinical decision support as tools built into our electronic health records, this paper tool provides a basic form of clinical decision support. In addition, our pain service has specialized electronic order sets for PCA that contains prompts for side effect management. Several previous studies have shown that low-cost point-of-care decision support tools in the form of a pocket cards can change prescribing practices.<sup>11,13</sup> Utilization of the PCA order set by our pain service is consistent with a study by Overhage et al that showed that embedding “corollary orders” into the computerized physician order entry system can decrease prescribing errors of omissions.<sup>14</sup> Our findings are consistent with previous studies that demonstrate changes in prescribing practices through various forms of clinical decision support.

One of the strengths of the study is the large heterogeneous study population that was



**FIGURE 2** Percentage of simultaneous orders stratified by training level and prescribing service.

not limited to specific disease process. This allowed us to capture the broad range of hospitalized patients in a children's hospital that may be affected by opioid-induced constipation. Future studies should look at

this topic in targeted populations of hospitalized patients. One of the major limitations to our data set was the inability to extract information about a patient's NPO status without doing a formal chart review

on our study population. This affects our analysis in that we were unable to determine which patients receiving intravenous opioids were unable to receive a bowel regimen given their NPO status. However, our subanalysis of patients receiving oral opioids found lower rates of prophylactic bowel regimens and similar associations between prescribing service and training level, suggesting that NPO status may not be confounding the association. Given our inability to determine differences in constipation rates between patients who received a prophylactic prescription and those who did not, subsequent studies should examine whether there are differences in clinical outcomes (eg constipation) between these 2 groups. Another limitation is that the study design does not allow us to identify why the associations or pattern exist. Future research efforts should focus on why different drugs or providers are associated with different prescribing practices. We focused on acute pain management on medical/surgical floors and excluded the ICU or patients on methadone or fentanyl; future studies should examine the prescribing factors associated with the side effect management in these patients. Our study was limited to a single institution, which may limit the generalizability of our results. However, some of the challenges, including rotating groups of trainees, and multiple

**TABLE 3** Multivariate Logistic Regression Subanalysis of Predictors, Examining Patients Only Receiving Oral Opioids (*n* = 1895)

Variable	OR	95% CI	<i>P</i>
Age	1.04	1.01–1.07	.009
Race/ethnicity			
White/non-Hispanic	Reference	—	—
Black/non-Hispanic	0.64	0.28–1.46	.29
Hispanic	0.89	0.58–1.39	.62
Other	0.64	0.35–1.18	.15
Sickle cell	7.80	2.88–21.15	<.001
Scheduled opioid	1.91	1.2–3.0	.004
Opioid type			
Acetaminophen-hydrocodone	Reference	—	—
Oxycodone	3.69	2.55–5.33	<.001
Morphine	n/a	n/a	
Hydromorphone	n/a	n/a	
Training level			
Trainee	Reference	—	—
Advanced practitioner (NP/PA)	1.1	0.69–1.88	.61
Attending physician	0.56	0.34–0.91	.02
Prescribing service			
Medical	Reference	—	—
Surgical	0.34	0.23–0.50	<.001
Pain/anesthesia	1.40	0.62–3.16	0.42

n/a, not applicable.

subspecialty service lines, are not unique to our institution and are found at other large tertiary-care children's hospitals.

Despite these limitations, our study shows that a significant number of hospitalized pediatric patients receiving opioids do not receive a bowel regimen at the time of an opioid prescription, putting them at risk for developing opioid-induced constipation. We found specific patient, medication and provider factors were associated with the proactive prescription of a bowel regimen. Our results suggest that preexisting clinical decision support tools may influence prescribing practices and increase the likelihood of a prophylactic bowel regimen at the time of an opioid prescription. Identification of prescribing populations less likely to prescribe a bowel regimen allows development of targeted interventions to increase prophylactic prescription of a bowel regimen to prevent opioid-induced constipation.

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## **Factors Associated With the Prophylactic Prescription of a Bowel Regimen to Prevent Opioid-Induced Constipation**

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