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BRIEF RESEARCH REPORT

Pain Management and Sedation

Incidence of opioid use disorder in the year after discharge from an emergency department encounter

Brittany E. Punches PhD, RN[1,2,3] | **Rachel M. Ancona PhD**[2] | **Caroline E. Freiermuth MD, MS**[2,3] | **Jennifer L. Brown PhD**[3,4] | **Michael S. Lyons MD, MPH**[2,3]

[1] University of Cincinnati College of Nursing, Cincinnati, Ohio, USA

[2] University of Cincinnati College of Medicine Department of Emergency Medicine, Cincinnati, Ohio, USA

[3] Center for Addiction Research, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

[4] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Correspondence

Brittany E. Punches, PhD, RN, CEN, 3110 Vine Street, Cincinnati, OH 45219, USA.
Email: Brittany.Punches@uc.edu

Abstract

Objective: Therapeutic opioid exposure is associated with long-term use. How much later use is due to opioid use disorder (OUD) and the incidence of OUD without preceding therapeutic exposure are unknown. We preliminarily explored the association between emergency department opioid prescriptions and subsequent OUD.

Methods: This retrospective cohort study queried electronic health records for discharged adult patients in the year before (2014) and after (2016) their first encounter in 2015 at either of 2 EDs in a Midwestern healthcare system. OUD was defined by diagnosis codes and prescription history. Patients with OUD history before the index encounter were excluded. We report OUD incidence within 1 year, with time to first indicator of OUD among those with a repeat health system encounter post index using a Cox proportional hazards model. Secondary outcomes were sources of therapeutic opioid exposure and frequency of risk factors associated with OUD among those who developed OUD.

Results: Of the 49,904 unique, adult ED patients without history of OUD, 669 (1.3%; 95% CI, 1.2–1.4) had health records indicating OUD within 12 months. The proportion of ED patients with OUD at 12 months was 1.5% (95% CI, 1.2–1.9) if prescribed an opioid at index and 1.3% (95% CI, 1.2–1.4) if not. Of the 669 who developed OUD, 80 (12.0%) were prescribed an opioid at the index ED visit, 54 (8%) received an opioid prescription at a subsequent ED visit, and median time to OUD was 4.5 months (interquartile range 1.6-7.6, range 0.0–11.9). When controlling for demographics, mental health, and prior opioid prescriptions, there was no difference in OUD incidence between patients who did or did not receive an initial ED opioid prescription (HR, 1.1; 95% CI, 0.9–1.4).

Conclusions: A small but meaningful proportion of the ED population will develop OUD within 1 year even without ED opioid prescription. Though we found no association between ED opioid prescription and later OUD, further study is warranted given the complexity factors influencing OUD incidence, ongoing ED opioid exposure, and limitations inherent to this study design.

1 | INTRODUCTION

1.1 | Background

It is now widely accepted that opioid medications taken as directed for therapeutic indications can contribute to the development of opioid use disorder (OUD).[1-3] Opioid prescriptions, even in limited duration, are associated with later long-term use,[4-7] and individuals suffering from OUD often recall that their first exposure to opioids was through a prescription for pain.[8,9] Yet, the relationship between therapeutic opioid exposure and subsequent OUD remains largely unexplored.[1,8,10,11] For example, we do not know the degree to which later use is due to OUD, ongoing chronic pain, or new painful conditions. We also do not know the risk of OUD among similar individuals without therapeutic exposure. Emergency departments are a common source of therapeutic opioid exposure, but prescriptions are short term, low dose, and potentially unavoidable.[5,6,8,12-14] Development of OUD is a complex and extended process,[1,15-17] so the contribution of EDs to OUD incidence, if any, is presumably only indirect in the case of initial prescriptions or perhaps somewhat more direct in the case of repeat prescriptions. Information about trajectories of pain and opioid use after emergency care that could inform such questions is growing but remains limited.[18-20]

1.2 | Importance

The opioid crisis has been declared a national emergency,[21,22] with 130 deaths daily.[23] Because of increased awareness and legislation, opioid prescriptions have decreased; yet, opioid overdoses continue to climb.[23,24] Moreover, overdose deaths are likely underreported and do not capture the extensive morbidity and mortality resulting from complications of OUD and injection drug use.[25,26] Even a small improvement in the contribution of therapeutic opioid use to incident OUD would be a significant benefit given the millions exposed each year.

1.3 | Goals of this investigation

This investigation was undertaken using available data to preliminarily explore the association between ED opioid prescriptions and subsequent OUD. We report OUD incidence at 1 year based on health record documentation among those who did and did not receive an ED opioid prescription, number of ED opioid prescriptions relative to other medical sources, time to OUD after an ED encounter, and modeling to evaluate development of OUD when controlling for demographics, mental health history, and receipt of prior opioid prescriptions.

2 | METHODS

2.1 | Study design and setting

This retrospective cohort study was conducted using electronic health records (EHR) from a single academic health system encompassing 2 Midwestern EDs (1 urban and 1 suburban). Combined ED volume is approximately 115,000 visits for 70,000 unique patients annually. The urban ED is a tertiary, level I trauma center that serves as the primary safety-net hospital in the region.

2.2 | Selection of participants

We selected all adult patients (over 18 years of age) discharged to home from either of the EDs in 2015, identifying their first ED visit as the index visit. Any patient with existing OUD at index, or in the year prior, was excluded.

2.3 | Measurements

Diagnostic codes (*International Classification of Diseases, Ninth Revision* and *Tenth Revision*) and medication lists were obtained from the EHR for all health system encounters for January 2014–December 2016 (year before and after the index ED encounter in 2015) to identify markers for OUD, mental health diagnosis, and non-opioid substance use. We identified all patients with an opioid prescription at index ED visit and the source of any additional opioid prescriptions from the health system for all patients in the year before and after the index visit. OUD was defined by composite definition that included any of the following coded diagnoses: OUD, opioid withdrawal, dependence, heroin use, or unintentional opioid overdose; or any prescription for buprenorphine or naloxone.

2.4 | Outcomes

We describe OUD incidence within 1 year of the ED encounter and time to first indicator of OUD. We then use a Cox proportional hazards model measuring the effect of ED opioid prescription at the index encounter on later OUD among those with a repeat postindex health system encounter. Secondary outcomes were sources of therapeutic

opioid exposure and frequency of risk factors associated with OUD among those who developed OUD.

2.5 | Analysis

We report the proportion of individuals who develop OUD within 1 year of index ED visit overall and stratify by whether or not an opioid was prescribed at index ED encounter. For patients who developed OUD, we describe summary statistics on systemwide opioid prescribing before and after their index ED encounter, the time from index ED encounter to first documentation of criteria meeting the study definition of OUD, and the frequency of risk factors associated with OUD (mental health condition and non-opioid substance use). Specified outcomes were reported with their respective 95% confidence intervals (CIs). Statistical analyses were conducted using R [version 4.0.2][27] in R Studio,[28] and the epiR[29] package.[30] Figures also were built in R using RStudio, using the ggplot2 package.[31]

Finally, we constructed a Cox proportional hazards model to control (to the degree possible) for other factors that might influence development of OUD.[32,33] This approach requires exclusion of any patients who did not have a visit somewhere in the health system in the 12 months post index. Model covariates included age, race, sex, mental health conditions (apart from substance use disorder), non-opioid substance use disorders, opioids prescribed (systemwide) in the 12 months before index ED visit, and opioids prescribed (systemwide) between index ED visit and end of the censored time period, defined as last system encounter or first encounter meeting study criteria for OUD.

3 | RESULTS

3.1 | Characteristics of study subjects

In 2015, there were 115,886 ED visits representing 71,460 unique patients. Patients were excluded for age <18 years (1775; 2%), ED disposition other than discharge home (18,074; 25%), and pre-existing OUD (1707; 2%). Of the 49,904 patients included for analysis, 55% were white, 54% were women, median age was 39 years, and 5176 (10.4%) received an opioid prescription at their index ED encounter (Table 1). Of the entire included cohort, 669 (1.3%; 95% CI, 1.2–1.4) developed OUD in the 12 months after index ED visit. The proportion developing OUD at 12 months was 1.5% (95% CI, 1.2–1.9) for patients prescribed an opioid at index and 1.3% (95% CI, 1.2–1.4) for patients who were not.

3.1.1 | Patients who developed OUD in the 12 months after index ED visit

For the 669 patients who developed OUD in this study, 80 (12.0%; 95% CI, 9.6–14.7) were prescribed an opioid at index. The majority of patients (423, 63.2%) who developed OUD did so within 6 months

The Bottom Line

Experts suggest that emergency department (ED) opioid prescriptions may be associated with new opioid use disorder (OUD). In this analysis of 49,904 ED patients, the incidence of new onset OUD at 12 months was similar between patients who did and did not receive ED opioid prescriptions (adjusted hazard ratio, 1.1; 95% confidence interval, 0.9-1.4%). Non-opioid substance use disorder, mental health conditions, and prior opioid prescriptions were stronger predictors of 12-month OUD.

after index visit and over a third (259, 38.7%) did so within 3 months (Figure 1). Median time from ED index visit to onset of OUD was 4.5 months overall (interquartile range [IQR] 1.6–7.6, range 0.0–11.9), 4.1 months (IQR 1.8–7.0, range 0.1–11.9) for those prescribed an opioid, and 4.5 (IQR 1.6–7.7, range 0.0–11.9) for those who were not (Figure 1). There were 45 (6.7%) patients who met criteria for OUD within 1 week of ED index visit, approximately evenly distributed between exposure groups. Sensitivity analysis excluding these patients did not change study findings.

Before the index encounter, 126 (18.8%) were prescribed an opioid by any prescriber type, about half of which (9.7%) originated from an ED. Post index, 135 (20.1%) were prescribed an opioid by any prescriber type and of these, 54 (8%) were from an ED (Figure 2). Among those who received health system prescriptions, repeat prescriptions both before and after the index ED encounter were common (Table 1).

3.1.2 | Patients with at least 1 follow-up visit in the year after index ED visit

In the Cox proportional hazards model, we excluded 17,782 (35.6%) patients who did not have a follow-up visit in the system in the 12 months after index ED visit, leaving 32,124 patients included. Opioid prescription at index ED visit did not have a meaningful effect on OUD (HR, 1.1; 95% CI, 0.9–1.4). The model did find that non-opioid substance use disorder (HR, 2.1; 95% CI, 1.8-2.6), a mental health condition (HR, 1.7; 95% CI, 1.4-2.0), and at least 1 opioid prescription in the 12 months before index (HR, 1.5; 95% CI, 1.2–1.8) increased the risk of developing OUD in the year after an ED visit. The meaning of study findings did not change according to whether opioid prescriptions were included as a continuous or binary variables; we report the binary variable as easier to interpret.

4 | LIMITATIONS

Although advancing current literature in important respects, our results should be interpreted in context with several important

TABLE 1 Demographics and characteristics of sample

	Study population		Opioid prescribed index ED visit		No Opioid prescribed index ED visit		Developed OUD[a]		No OUD[b]	
	N = 49,904 (%)		N = 5176 (%)		N = 44,728 (%)		N = 669 (%)		N = 49,235 (%)	
Demographics										
Age, y, median (IQR)	39 (28–53)		42 (30–54)		39 (27–53)		36 (29–50)		39 (28–53)	
Sex										
Female	26,801	(53.7)	2669	(51.6)	24,132	(54.0)	333	(49.8)	26,468	(53.8)
Male	23,103	(46.3)	2507	(48.4)	20,596	(46.0)	336	(50.2)	22,767	(46.2)
Race										
White/Caucasian	27,618	(55.3)	3368	(65.1)	24,250	(54.2)	129	(19.3)	27,091	(55.0)
Black/African American	18,659	(37.4)	1517	(29.3)	17,142	(38.3)	527	(78.8)	18,530	(37.6)
Hispanic	1,504	(3.0)	116	(2.2)	1388	(3.1)	6	(0.9)	1498	(3.0)
Other	2,080	(4.2)	170	(3.3)	1910	(4.3)	7	(1.0)	2073	(4.2)
Unknown/Missing	43	(0.1)	5	(0.1)	38	(0.1)	–	–	43	(0.1)
Risk factors										
History of mental health diagnosis	6,064	(12.2)	549	(10.6)	5515	(12.3)	179	(26.80)	5885	(12.0)
History of non-opioid substance use (any)	6,290	(12.6)	542	(10.5)	5748	(12.9)	160	(23.90)	6130	(12.5)
Alcohol	1,956	(3.9)	145	(2.8)	1811	(4.0)	40	(6.00)	1916	(3.9)
Marijuana	4,250	(8.5)	382	(7.4)	3868	(8.6)	84	(12.60)	4166	(8.5)
Cocaine	596	(1.2)	46	(0.9)	550	(1.2)	29	(4.30)	576	(1.2)
Hallucinogen	15	(0.0)	1	(0.0)	14	(0.0)	1	(0.10)	14	(0.0)
Stimulants	50	(0.1)	4	(0.1)	46	(0.1)	3	(0.40)	47	(0.1)
Sedatives	75	(0.2)	–	–	75	(0.2)	6	(0.90)	69	(0.1)
Inhalants	2	(0.0)	–	-	2	(0.0)	–	–	2	(0.0)
Other drug	405	(0.8)	28	(0.5)	377	(0.8)	47	(7.00)	358	(0.7)
Opioid prescribing (RX)										
Opioid RX at index	5176	(10.4)	5176	(100)	–	–	80	(12.00)	5096	(10.40)
Opioid RX within 12 months before index – any	4277	(8.6)	986	(19.0)	3291	(7.4)	126	(18.80)	4151	(8.40)
Opioid RX within 12 months before index - Non ED	2876	(5.8)	596	(11.5)	2280	(5.1)	89	(13.30)	2787	(5.70)
Opioid RX within 12 months before index – ED	1,971	(3.9)	540	(10.4)	1431	(3.2)	65	(9.70)	1906	(3.90)
Prescribed opioid post index[c] - Non ED	2,108	(4.2)	613	(11.8)	1495	(3.3)	81	(12.10)	2027	(4.10)
Prescribed opioid post index[c] - ED	1,578	(3.2)	520	(10.0)	1058	(2.4)	54	(8.10)	1524	(3.10)
Outcomes (within 12 months post index)										
OUD composite definition[d]	669	(1.3)	80	(1.5)	589	(1.3)	–	–	–	–
OUD diagnosis	427	(0.9)	51	(1.0)	376	(0.8)	–	–	–	–
Dependence	230	(0.5)	26	(0.5)	204	(0.5)	–	–	–	–
Opioid withdrawal	27	(0.1)	4	(0.1)	23	(0.1)	–	–	–	–
Heroin use	95	(0.2)	9	(0.2)	86	(0.2)	–	–	–	–
Unintentional opioid overdose	50	(0.1)	8	(0.2)	42	(0.1)	–	–	–	–
Naloxone prescription	124	(0.2)	24	(0.5)	100	(0.2)	–	–	–	–

(Continues)

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TABLE 1 (Continued)

	Study population		Opioid prescribed index ED visit		No Opioid prescribed index ED visit		Developed OUD[a]		No OUD[b]	
Buprenorphine prescription	58	(0.1)	30	(0.6)	28	(0.1)	–	–	–	–

[a]Based on first encounter with indicator or OUD.

[b]Last follow-up visit in 12 months (no OUD/Dep, at least 1 subsequent visit), or 12 months postindex visit (no OUD and no subsequent visit).

[c]Number of prescriptions between index and first onset of OUD or last follow up visit within 12 months (no OUD)

[d]dd; OUD classified as (1) ICD-9/10 diagnosis of: OUD, opioid dependence, opioid withdrawal, heroin use, or unintentional opioid overdose; or (2) prescription for naloxone or buprenorphine.

Abbreviations: ED, emergency department; ICD-9/10, *International Classification of Diseases, Ninth Revision/Tenth Revision*; IQR, interquartile range; OUD, opioid use disorder.
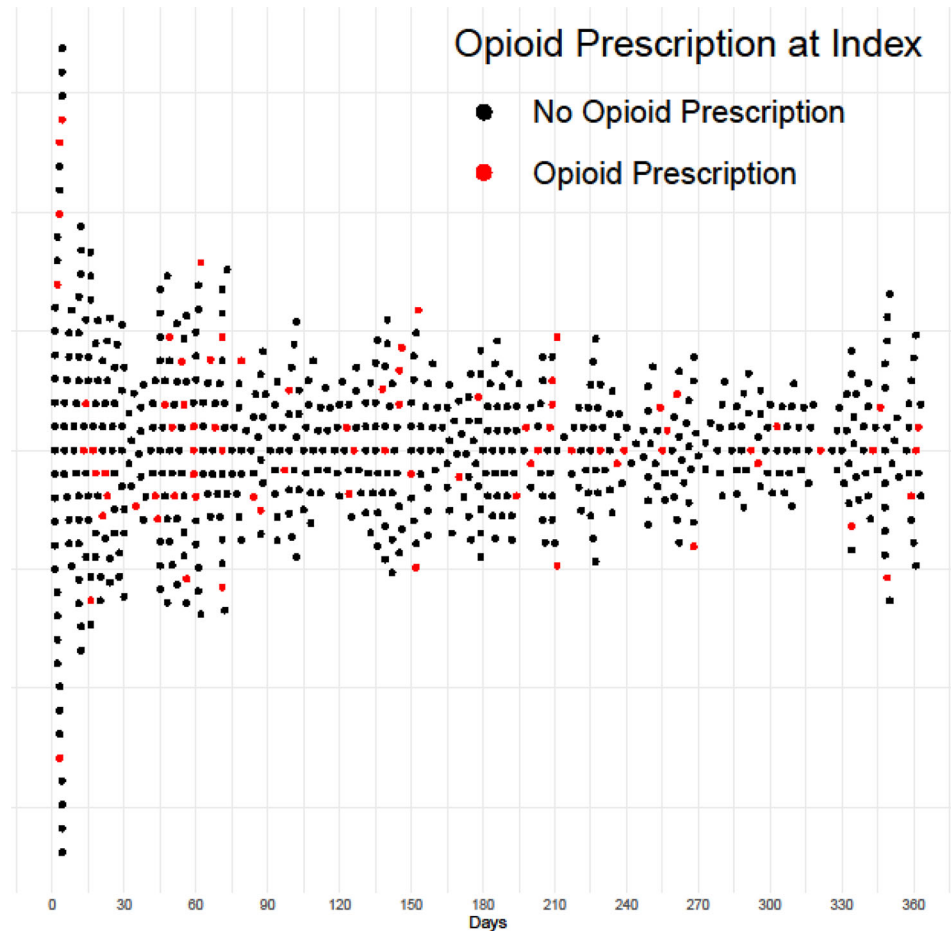

FIGURE 1 Days from index ED encounter to first indicator of opioid use disorder in health records, based on ED prescription at index encounter disorder in health records, based on ED prescription at index encounter. There were 669 patients who developed OUD, each dot represents an individual patient. Abbreviations: ED, emergency department; OUD, opioid use disorder

limitations. Most important, the inaccuracies inherent to retrospective records review and especially diagnosis coding are well known.[34-36] It is logical to assume these inaccuracies are even greater for behavioral health diagnoses, screening for which is not a traditional or structured focus in emergency care. Consequently, misclassification of patients in terms of OUD, both before and after the index encounter, is likely in this study design. This misclassification bias, likely leading to under-reporting of OUD, could bias the overall proportion of persons with

OUD toward the null. Moreover, our composite definition of OUD is unlikely to correlate precisely with OUD; we do not have data on non-medical opioid exposure over the same study period. The problem of data quality in existing records also applies to other patient characteristics that may affect the relationship between therapeutic opioid exposure and eventual OUD. As we included electronic health record data from only 2 hospitals within a health system, the patterns of opioid exposure we report may not generalize beyond the single system we

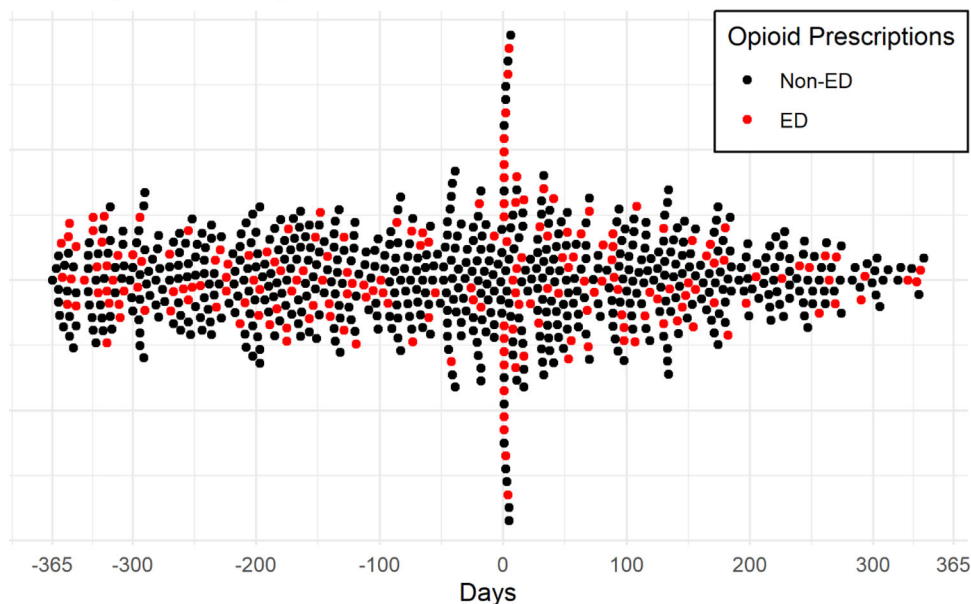## Opioid Prescriptions in the Year Before and After Index Visit

FIGURE 2 Timing and source of opioid prescriptions before and after index ED visit among patients who developed opioid use disorder. Each dot represents a prescription event for a person who ultimately developed opioid use disorder after an index ED encounter, only a subset of whom received an opioid prescription at the index ED encounter. Prescription events after development of opioid use disorder not shown. Opioid prescriptions given at the index ED encounter not shown. Abbreviations: ED, emergency department

investigated, although the nature of any causal relationship between therapeutic opioid exposure and subsequent OUD within any single person is unlikely to vary by treatment location. Finally, the authors acknowledge the data are dated, yet adhere the time for analysis was extensive given the size and complexity of the project, and we do not believe that there would be any change over time this period of time in the degree to which opioid therapy leads to OUD.

5 | DISCUSSION

The question of whether and how short-term opioid therapy is causally related to later OUD and the degree to which this can be avoided is central for policy and practice in episodic care settings such as the ED. Discovering the answer to such questions requires longitudinal study that accounts for (1) inclusion of exposed and unexposed groups, (2) better characterization of therapeutic exposure source, timing, and intensity, (3) concurrent understanding of both therapeutic and non-medical exposure, and (4) precise classification distinguishing episodic use, chronic use/dependence, and OUD at study entry and conclusion of follow-up.

This investigation, although limited to existing data and exceedingly preliminary, is to our knowledge the first attempt to disentangle these factors in a longitudinal study design that goes beyond associating an initial prescription and later use of unknown cause and without a concurrent control. We found that 1.3% of all patients developed indicators of OUD within 12 months of an ED visit, with the median time to documentation of OUD being 4.5 months. Opioid prescriptions were

common in the year before and year after the ED visit for individuals developing OUD. As expected based on existing literature,[32,33] the frequency of mental health conditions and non-opioid substance use was high in the group that developed OUD. We urge caution when interpreting our primary finding that an ED opioid prescription at the index visit did not increase risk for subsequent diagnosis of OUD within the following year. Although this report should provide guidance for future prospective study, the quality and completeness of data available in existing health records are insufficient for definitive conclusion.

Individuals may have already been suffering from unrecognized OUD at the index visit and newly developed OUD may have been unrecognized in follow-up. Known limitations in diagnosis coding would affect both measures, as would the lack of data from other health systems, lack of follow-up in any health system, and no data source to characterize other non-medical sources of opioid exposure. The significant number of individuals who met criteria for OUD immediately after an index visit is a convincing illustration of the potential for misclassification in this study design.

There is also the potential for individuals without OUD to have been classified as such inappropriately. For example, naloxone could be prescribed to individuals without opioid use disorder, although this was anecdotally uncommon in this health system during the study period. Also, we chose to include diagnoses of opioid dependence in the composite definition given inaccuracies in diagnosis coding and difficulty disentangling OUD from opioid dependence, even though patients with physiologic opioid dependence may not meet criteria for OUD.[37,38]

Our analysis of therapeutic opioid exposure was limited to opioid prescription and did not consider opioid administration or patients who

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were hospitalized after the ED encounter. A single episode of opioid administration is even more limited in dose and duration than a prescription, but administration may still contribute to trajectories leading to OUD. For example, repeated dosing occurs within and across health encounters, neuropsychological effects may be even more pronounced with parenteral administration, and some individuals might theoretically be unusually primed for rapidly triggered addiction or relapse while in ongoing recovery. Administration and prescription of opioids in hospital settings is not directly controlled by the ED. However, ED practice might have influence in setting ongoing patient and practitioner expectations or even influencing the degree of future pain. If this is not the case, there is still the analogous question of whether and how prescriptions for opioids at hospital discharge contribute to OUD incidence.

An additional factor, unexplored by this study, is the potential selection bias introduced by the prescription itself. It is possible for clinicians to differentially limit opioid therapy according to perceived risk of opioid use disorder. Although understandable and even desirable, the resulting selection bias would inhibit the ability to detect an effect of the opioid prescription and further illustrates the need to adequately control for differences between groups in other characteristics influencing the development of OUD.

In summary, a small but meaningful proportion of the ED population will develop OUD within 1 year even without ED opioid prescription. We found no association between an initial ED opioid prescription and later OUD. However, accurate understanding of patient characteristics and evolution of those characteristics overtime is exceptionally difficult in a retrospective approach, given the complexity factors influencing OUD incidence and opioid exposure. Although this study is an important initial advance in the investigation of whether and how short-term opioid exposure is causally related to later OUD, a prospective longitudinal study design with a control group will be essential to accurately classify participants with respect to exposure, outcome, and other contributory factors.

AUTHOR CONTRIBUTIONS

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AUTHOR BIOGRAPHY

Brittany Punches, PhD, RN, an Assistant Professor at the University of Cincinnati, is a doctorally prepared nurse scientist and emergency care researcher with significant experience in emergency department clinical operations, patient perceptions of ED care, and qualitative methods.