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MAJOR ARTICLE

Outcomes Associated With Medications for Opioid Use Disorder Among Persons Hospitalized for Infective Endocarditis

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(See the Editorial Commentary by Eaton on pages 479–81.)

Background. Endocarditis, once predominately found in older adults, is increasingly common among younger persons who inject drugs. Untreated opioid use disorder (OUD) complicates endocarditis management. We aimed to determine if rates of overdose and rehospitalization differ between persons with OUD with endocarditis who are initiated on medications for OUD (MOUDs) within 30 days of hospital discharge and those who are not.

Methods. We performed a retrospective cohort study using a large commercial health insurance claims database of persons ≥18 years between July 1, 2010, and June 30, 2016. Primary outcomes included opioid-related overdoses and 1-year all-cause rehospitalization. We calculated incidence rates for the primary outcomes and developed Cox hazards models to predict time from discharge to each primary outcome as a function of receipt of MOUDs.

Results. The cohort included 768 individuals (mean age 39 years, 51% male). Only 5.7% of people received MOUDs in the 30 days following hospitalization. The opioid-related overdose rate among those who did receive MOUDs in the 30 days following hospitalization was lower than among those who did not (5.8 per 100 person-years [95% confidence interval [CI], 5.1–6.4] vs 7.3 per 100-person years [95% CI, 7.1–7.5], respectively). The rate of 1-year rehospitalization among those who received MOUDs was also lower than those who did not (162.0 per 100 person-years [95% CI, 157.4–166.6] vs 255.4 per 100 person-years [95% CI, 254.0–256.8], respectively). In the Cox hazards models, the receipt of MOUDs was not associated with either of the outcomes.

Conclusions. MOUD receipt following endocarditis may improve important health-related outcomes in commercially insured persons with OUD.

Keywords. endocarditis; opioid use disorder; opioid epidemic; medications; hospitalization.

BACKGROUND

An estimated 2.1 million people have an opioid use disorder (OUD) in the United States [1], although this may be an underestimate [2]. There has been a rise in injection drug use (IDU), specifically with nonprescription opioids such as heroin and synthetically produced fentanyl. Concurrently, mortality from infections and overdose has also risen [3].

Endocarditis is increasingly common among younger persons as complications of IDU [4–7]. Valve replacement is often necessary for endocarditis, which can result in prosthetic valve infections. An increasing proportion of mortality and cost associated with IDU is attributable to endocarditits, with hospitalization increases as high as 12-fold [4, 8, 9]. Endocarditis hospitalizations are lengthy [10] given the need for prolonged antibiotics. Rehospitalization for recurrent endocarditis and drug use-associated causes are frequent and costly [11].

Methadone, buprenorphine, and naltrexone are Food and Drug Adminisistration-approved medications for OUD (MOUDs) with evidence to support their effectiveness in improving mortality and retention in care [12–15]. Buprenorphine and methadone are especially beneficial at reducing opioid use, overdose, and death [16, 17]. Despite this, receipt of MOUDs during the peri-hospitalization period is uncommon [18, 19]. Common barriers include lack of training or knowledge [20], misperceptions about the feasibility of administering MOUDs [21], and limited resources for the transition to community-based treatment [22]. Hospitalization is a unique opportunity to initiate treatment and ensure linkage to care [23, 24]. It is unknown whether MOUD initiation during or upon discharge from an endocarditis hospitalization among persons

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with OUD improves outcomes. We aimed to determine if rates of health outcomes, including overdose and rehospitalization, differ between commercially insured persons with OUD hospitalized for endocarditis who are initiated on MOUDs in the peri-hospitalization period and those who are not initiated on MOUDs.

METHODS

Data Source

We analyzed data from the 2010–2016 MarketScan Commercial Claims and Encounters database, a nationally representative commercial insurance claims-based data set that includes ambulatory and inpatient visits, outpatient pharmacy claims, and diagnostic testing [25].

Inclusion Criteria

We selected individuals aged ≥18 years with OUD (Supplemental eTable 1) who were hospitalized for endocarditis between 2010 and 2016 and had a minimum 30-day follow-up after hospital discharge. We compared outcomes among those individuals who received MOUDs (Supplemental eTable 2) within 30 days of discharge for the index endocarditis to those who did not. We identified individuals with an initial inpatient claim for infective endocarditis (Supplemental eTable 3) using *International Classification of Diseases, Ninth or Tenth Revisions (ICD-9 or ICD-10)* codes. We included individuals who had a diagnosis of OUD either concurrent with or in the 6 months before or after the index endocarditis hospitalization [6]. OUD diagnosis was based on ICD-9/10 codes in inpatient or outpatient claims. We determined which codes to include based on expert opinion and previous literature [26]. We excluded individuals who had a pharmacy claim for MOUDs in the 3 months preceding their infection and individuals who had an ICD-9/10 diagnosis of concurrent stimulant use as treatment patterns differ in those patients.

Outcomes

The primary outcome measures included: (1) opioid-related overdose and (2) 1-year all-cause rehospitalization. We identified overdose events based on relevant ICD-9/10 codes. This outcome includes overdoses for which a medical claim was made, meaning a patient received care for an overdose at a hospital. We identified rehospitalization events using ICD-9/10 codes on inpatient claims.

Main Independent Variable

The primary independent variable was prescription for MOUD within 30 days of discharge. We used National Drug Codes to categorize MOUD and included: naltrexone (injectable extended release and oral formulations) and buprenorphine (mono- and coformulated with naloxone) [27]. Until late 2017, methadone therapy was not covered by commercial insurance; therefore, it is not reliably included in this data set. We are also not able to determine if MOUDs were initiated in the hospital.

We used outpatient prescription data to determine the date on which individuals filled their prescription following hospitalization and the days' supply in each prescription. Individuals who filled a prescription within 4 weeks of discharge were categorized as being in the "MOUD" group. Individuals who did not fill a prescription or filled one after 4 weeks postdischarge were classified as "no MOUD." In the time-to-event analyses, individuals began contributing follow-up time at discharge for their index endocarditis episode, and ceased contributing time when they encountered a primary outcome, were censored at the end of 1 year (in the case of rehospitalization) or at the end of the study period, or at exit from their insurance plan. The short-term intervention may not fully explain any differences in the long-term outcomes, and some individuals not immediately initiating MOUDs may receive an MOUD prescription later in the study period. To assess this, we performed a post hoc analysis to compare the average MOUD duration between those initiating MOUDs within 30 days of hospitalization and those who were prescribed MOUDs at a later date and who are grouped in our "no MOUD" sample.

Analyses

We calculated the overdose and all-cause rehospitalization incidence rates for the 2 groups: those who received MOUD treatment following hospitalization and those who did not. We calculated the total person-time and the total number of primary outcomes for each group. An overdose was counted at any point following the hospitalization through the end of the study, whereas rehospitalizations were limited to 1 year following index hospitalization. We calculated the incidence rates per 100 person-time and associated 95% confidence interval (CI) under the normality assumption. We also calculated the incidence rate of 30- and 90-day rehospitalization.

We developed weekly timescale Cox hazards models to predict time from hospital discharge to first overdose and first rehospitalization over the subsequent year as a function of receipt of MOUDs. The Cox models controlled for baseline demographic and clinical covariates including an individual's sex, age, and region of residence and type of commercial insurance coverage; evidence of another substance use disorder during index hospitalization identified using ICD-9/10 codes (see Supplemental eTable 4), and whether or not cardiac surgery (eg, valve replacement) was performed during index hospitalization identified using ICD-9/10 and current procedural terminology (CPT) codes. The models adjusted for whether or not an individual had an interrupted hospitalization (defined as a break from discharge to readmission for endocarditis ≤10 days). Because this was based on expert opinion, we performed post hoc sensitivity analyses in which the hospitalization interruption was ≤5 and ≤30 days to account for uncertainty.

All statistical analyses were performed in SAS, version 9.4.

RESULTS

The cohort included 768 individuals with 978 person-years of follow-up. Baseline statistics of the cohort overall and by comparison group are presented in Table 1. The mean age was 39 years (standard deviation [SD] = 15.5), and 51% were male. The median length of hospitalization was 8 days (interquartile range [IQR] = 11), and 12% of this population underwent cardiac surgery during their index hospitalization associated with their endocarditis. Approximately 6% (44/768) of people received MOUDs in the 30 days following their index hospitalization for endocarditis. Those who received MOUDs were younger (mean age, 25 years ± 6.5) than those who did not receive MOUDs (40 years ± 15.5) ($P < .0001$). The mean MOUD prescription duration following discharge was 17.7 days (SD = 10.4 days). Buprenorphine was prescribed in 41 people of the 44 people who received MOUDs. Persons in the MOUD group (prescribed an MOUD within 30 days of hospitalization) had a longer average MOUD duration in the year following hospitalization than those in the "no MOUD" group who were prescribed an MOUD later in the year (9.7 weeks vs 8.6 weeks, $P< .42$).

Overdose Rates

We found 41 overdoses among those who did not receive MOUDs, leading to a rate of 7.3 overdoses per 100-person years (95% CI, 7.1–7.5). Comparatively, there was a rate of 5.8 overdoses per 100 person-years (95% CI, 5.1–6.4) among those who did receive MOUDs.

Rehospitalization Rates

There was a significant difference in 1-year rehospitalization rates between the 2 groups. The rate of 1-year rehospitalization among those who did not receive MOUDs was 255.4 per 100 person-years (95% CI, 254.0–256.8), and for those who did was 162.0 per 100 person-years (95% CI, 157.4–166.6). The rate of 30-day rehospitalization among those who did not receive MOUDs was 40.5 per 100 person-30 days (95% CI, 40.0–40.9) and for those who did was 32.6 per 100 person-30 days (95% CI, 30.9–34.3). The rate of 90-day rehospitalization among those who did not receive MOUDs was 85.8 per 100 person-90 days (95% CI, 85.1–86.5) and for those who did was 59.5 per 100 person-90 days (95% CI, 57.1–61.9).

Cox-Adjusted Models

Without controlling for covariates, there was not a significant risk reduction in overdose for the MOUD group compared to the "no MOUD" group (hazard ratio [HR] = 1.18; 95% CI, .36–3.80). There was a risk reduction in 1-year rehospitalization for the MOUD group compared to the "no MOUD" group that approached significance (HR = .71, 95% CI, .45–1.11) (Figure 1). In the adjusted models, the receipt of MOUDs was not associated with overdose (Table 2) or 1-year all-cause rehospitalization

Table 1. Characteristics of Cohort of Individuals With OUD Who Were Hospitalized for Infective Endocarditis, 2010–2016

	Total	No MOUD	MOUD in 30 days	*P* value
Overall number	768	724 (94.3)	44 (5.7)	
Age (mean years ± SD)	39 (±15.5)	40 (±15.5)	25 (±6.5)	<.01
Length of stay (median days, IQR)	8 (11)	8 (11)	6 (9)	
Sex, n (%)				
Male	394 (51.3)	374 (51.7)	20 (45.5)	.42
Female	374 (48.7)	350 (48.3)	24 (54.6)	
Region, n (%)				
Northeast	193 (25.1)	178 (24.6)	15 (34.1)	.17
North Central	140 (18.2)	132 (18.2)	8 (18.2)	
South	287 (37.4)	277 (38.4)	10 (22.7)	
West	148 (19.3)	137 (18.9)	11 (25.0)	
Insurance type, n (%)				
HMO	91 (11.9)	82 (11.3)	9 (20.5)	.32
POS	54 (7.0)	52 (7.2)	2 (4.6)	
PPO	453 (59.0)	429 (59.3)	24 (54.6)	
Other	170 (22.1)	161 (22.2)	9 (20.5)	
Cardiac surgery,[a] n (%)				
No	674 (87.8)	633 (87.4)	41 (93.2)	.26
Yes	94 (12.2)	91 (12.6)	3 (6.8)	
Other substance use disorders,[b] n (%)				
No	713 (92.8)	674 (93.1)	39 (88.6)	.27
Yes	55 (7.2)	50 (6.9)	5 (11.4)	

Abbreviations: HMO, health maintenance organization; ICD, International Classification of Diseases, Ninth or Tenth Revisions; IQR, interquartile range; MOUD, medications for OUD; OUD, opioid use disorder; POS, point of service; PPO, preferred provider organization; SD, standard deviation.

[a]Complete list of ICD-9 and ICD-10 codes found in Supplemental eTable 3.

[b]Defined as evidence of another substance use disorder (including alcohol, antidepressants, cannabis, hallucinogens, or sedatives). Complete list of ICD-9 and ICD-10 codes found in Supplemental eTable 4.

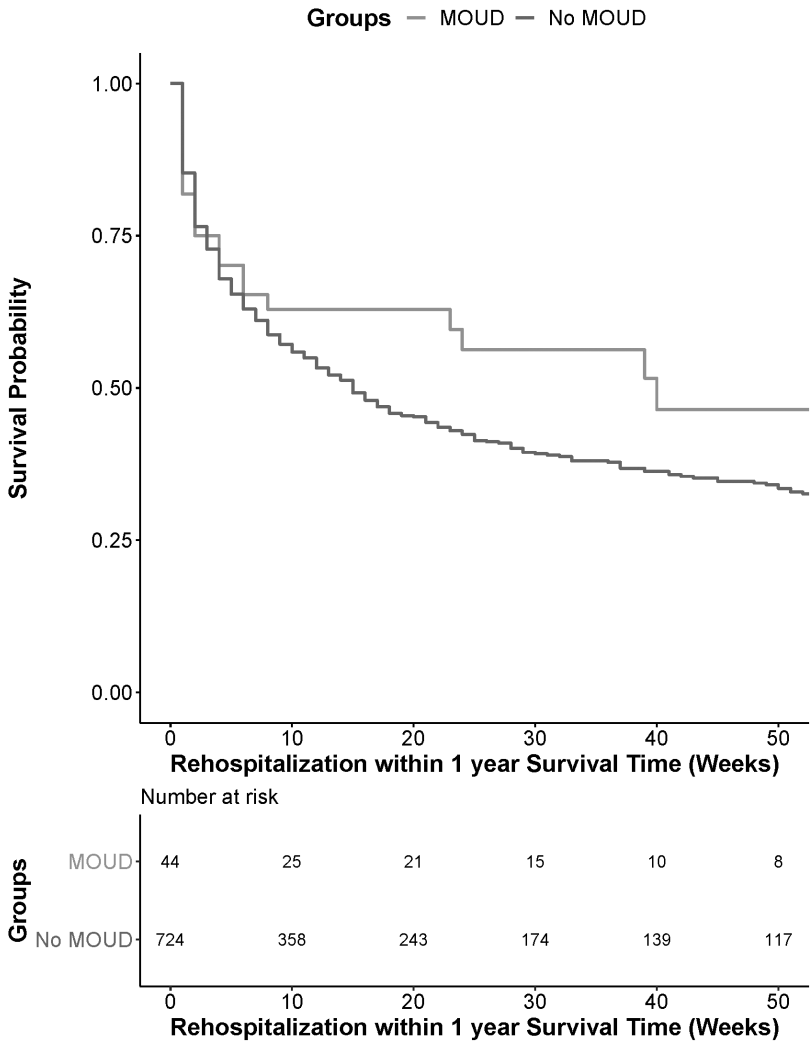

Figure 1. Kaplan–Meier curve of 1-year rehospitalization for persons who received MOUDs following hospitalization compared to no MOUDs. Time-to-event analysis for 1-year rehospitalization compared individuals with infective endocarditis who received MOUDs in the peri-hospitalization period to those who did not receive MOUDs. Without controlling for covariates, those who received MOUDs (gray line) had a lower risk of one-year rehospitalization than those who did not receive MOUDs (black line). Abbreviation: MOUD, medication for opioid use disorder.

(Table 3) (adjusted hazard ratio [aHR] of overdose = 0.86; 95% CI, .26–2.91; aHR for 1-year rehospitalization = 0.81; 95% CI, .51–1.28). The results were not qualitatively different in the sensitivity analyses in which the hospitalization interruption was ≤5 days (overdose: aHR = 0.80; 95% CI, .24–2.68; 1-year rehospitalization: aHR = 0.76; 95% CI, .48–1.21) or when it was ≤30 days (overdose: aHR = 0.84; 95% CI, .25–2.84; 1-year rehospitalization: aHR = 0.84; 95% CI, .53–1.34).

Several covariates were examined to determine whether they were predictive of experiencing an overdose or rehospitalization. Persons who had a ≤10 or ≤30 day interruption in their index hospitalization were at increased risk compared to those who did not have an interruption for overdose (aHR = 3.56, 95% CI, 1.61–7.88, and aHR = 2.46, 95% CI, 1.12–45.39, respectively) and 1-year rehospitalization (aHR = 5.49, 95% CI, 4.00–7.52, and aHR = 5.47, 95% CI, 4.15–7.22, respectively). Persons who underwent cardiac surgery were not more likely to overdose (aHR = 0.44; 95% CI, .15–1.32) or be rehospitalized at 1 year (aHR = 1.01; 95% CI, .76–1.34) than those without surgery.

DISCUSSION

In this analysis of commercially insured individuals with OUD and endocarditis, we found that while overall receipt of MOUDs following hospitalization for endocarditis was low, those who did receive MOUDs had lower incidence of overdose and 1-year rehospitalization than those who did not. This study suggests that incorporating MOUDs into the treatment paradigm for endocarditis may improve outcomes. It may also stand to reason that integrating MOUDs into the treatment paradigm for other infections related to opioid use may also improve outcomes. The mechanism being that MOUDs lead to decreased injection

Table 2. Results of Cox Hazards Model for Opioid-Related Overdose

Parameter	Adjusted Hazard Ratio	95% Confidence Interval		*P* value
Treatment				
MOUD within 4 weeks	0.86	.26	2.91	.81
No MOUD within 4 weeks	Reference			
Clinical characteristics				
Other substance use disorder[a]				
Yes	0.86	.26	2.84	.81
No	Reference			
Cardiac surgery[b]				
Yes	0.44	.15	1.32	.14
No	Reference			
Hospital interruption[c]				
Yes	3.56	1.61	7.88	<.01
No	Reference			
Nonclinical characteristics				
Age (years)	0.97	.95	0.99	.01
Sex				
Male	Reference			
Female	0.89	.47	1.63	.68
Region				
Northeast	Reference			
North Central	0.87	.40	1.86	.71
South	0.37	.16	0.85	.02
West	0.36	.14	0.93	.04
Insurance type				
POS	Reference			
PPO	1.50	.44	5.12	.52
HMO	1.12	.27	4.61	.87
Other	1.77	.47	6.59	.40

Abbreviations: CPT, current procedural terminology; HMO, health maintenance organization; ICD, International Classification of Diseases, Ninth or Tenth Revisions; MOUD, medication for opioid use disorder; POS, point of service; PPO, preferred provider organization.

[a]Defined as evidence of another substance use disorder (including alcohol, cannabis, hallucinogens, or sedatives). Complete list of ICD-9 and ICD-10 codes found in Supplemental eTable 4.

[b]Complete list of ICD-9, ICD-10, and CPT codes found in Supplemental eTable 3.

[c]Interruption of index hospitalization ≤10 days.

Table 3. Results of Cox Hazards Model for 1-Year Rehospitalization

Parameter	Adjusted Hazard Ratio	95% Confidence Interval		*P* value
Treatment				
MOUD within 4 weeks	0.81	.51	1.28	.36
No MOUD within 4 weeks	Reference			
Clinical characteristics				
Other substance use disorder[a]				
Yes	1.11	.78	1.59	.55
No	Reference			
Cardiac surgery[b]				
Yes	1.01	.76	1.34	.96
No	Reference			
Hospital interruption[c]				
Yes	5.49	4.00	7.52	<.01
No	Reference			
Nonclinical characteristics				
Age (years)	1.01	1.00	1.01	.05
Sex				
Male	Reference			
Female	1.18	.98	1.43	.08
Region				
Northeast	Reference			
North Central	0.96	.71	1.28	.76
South	1.00	.78	1.27	.97
West	1.00	.81	1.33	1.00
Insurance type				
POS	Reference			
PPO	1.20	.81	1.78	.37
HMO	1.12	.70	1.78	.65
Other	1.16	.76	1.56	.48

Abbreviations: CPT, current procedural terminology; HMO, health maintenance organization; ICD, International Classification of Diseases, Ninth or Tenth Revisions; MOUD, medication for opioid use disorder; POS, point of service; PPO, preferred provider organization.

[a]Defined as evidence of another substance use disorder (including alcohol, cannabis, hallucinogens, or sedatives). Complete list of ICD-9 and ICD-10 codes found in Supplemental eTable 4.

[b]Complete list of ICD-9, ICD-10, and CPT codes found in Supplemental eTable 3.

[c]Interruption of index hospitalization ≤10 days.

use, thus decreasing the likelihood of introducing bacteria or fungus into the body.

Overall, only 5.7% of persons in this cohort received MOUDs in the 30 days following hospitalization for endocarditis. This is consistent with other data detailing MOUD receipt following endocarditis [18] but lower than other studies examining MOUD receipt among people in contact with the healthcare system. LaRochelle and colleagues found that nearly 30% of people who experience a nonfatal overdose received MOUDs in the year following hospitalization [28]. Hadland et al [29] found that approximately 25% of youth ages 13–22 received a MOUD within 3 months of their OUD diagnosis. These studies demonstrate the infrequency of MOUD prescribing, despite the worsening drug overdose epidemic and increased awareness of the efficacy of MOUDs.

The recent increasing endocarditis prevalence among people who use drugs (PWID) has been well described [7, 10, 30]. These studies show that a larger proportion of cases of endocarditis are among PWID, which is, in turn, lowering the overall average age of this infection. This has implications for healthcare costs and long-term patient outcomes. For example, because valve replacement is a common component of endocarditis treatment, younger age at valve replacement lengthens the exposure period for risks associated with prosthetic valves, which can be costly and highly morbid. Other studies have compared the clinical outcomes among those with endocarditis who do and not use drugs. Rudasill et al [11] examined readmission rates among people with IDU-associated infective endocarditis (IDU-IE) and non-IDU-IE and found no significant differences between the 2 groups. Importantly, the authors did not examine outcomes stratified by MOUD receipt in the IDU-IE group.

Our study is among the first to our knowledge to demonstrate improvement in crucial outcomes—opioid overdose and 1-year rehospitalization—when treatment for endocarditis

includes peri-hospitalization MOUD. In our study, healthcare utilization was assessed over a short period of time (1-year) because peri-hospitalization MOUDs may not have an impact on rehospitalization at a more distal time point. Overdose was assessed at any point following hospitalization because MOUDs do change the trajectory of OUD and may impact overdose at distal time points. Our findings argue that the peri-hospitalization period for a serious infections may be 1 high-value time point for MOUD initiation. MOUDs and addiction treatment should be considered essential components of treatment for injection-related infections. If the underlying substance use disorder remains untreated, patients are likely to experience poor outcomes.

Although the receipt of peri-hospitalization MOUDs did lower the incidence rates, it did not have an impact on the adjusted time-to-event analyses for either outcome. This may be attributed to low overall event occurrences. Another plausible explanation for this finding is the lack of methadone treatment information in the claims database. Because we were unable to determine whether or not an individual was prescribed methadone following hospitalization, those individuals were therefore included in the "no MOUDs" group. Existing data are scarce regarding use of methadone and buprenorphine within the same year to treat OUD. One study that used the National HIV Behavioral Surveillance system found that 1.8% of persons had used both medications in the previous year [31]. This provides some supporting evidence that persons who were treated with methadone in our cohort are unlikely to also have been treated with buprenorphine in the same year. Although this is a limitation of the data set, the inclusion of persons who received methadone in the "no MOUD" group would have biased our result toward the null hypothesis and against the effectiveness of MOUDs. Analyses of publicly insured individuals might therefore have different results than ours.

There were significant findings among the covariates. Notably, we found that hospitalization interruption was associated with an increased risk of primary outcomes. The 10-day interruption window was selected to model a possible discharge against medical advice (increasingly being referred to as "patient directed discharge") with then a return to the hospital for continued treatment for endocarditis. In the sensitivity analyses in which the hospital interruption was ≤5 and ≤30 days, the results did not qualitatively change. Often, treatment interruptions or discharges against medical advice are the result of untreated opioid withdrawal or cravings. As such, efforts to avoid these treatment interruptions should include inpatient initiation of MOUDs. We also found that geographic region, specifically the West and South, were associated with decreased risk of overdose compared to the Northeast. This may be explained by fentanyl that was present throughout much of the study in the Northeast but not in the West or the South [32].

Although it is encouraging that MOUDs improved outcomes, OUD is a chronic relapsing disease, and 1-time receipt of medications is but 1 component of treatment. Many people experience multiple relapses and reinitiate MOUDs numerous times. Short treatment durations such as those noted in this study are unlikely to promote sustained recovery [33]. Much like the continua of care for other chronic diseases like human immunodeficiency virus and hepatitis C virus, efforts are needed to improve retention in care. One potential approach is to develop a comprehensive inpatient treatment package at the time of endocarditis that includes infectious diseases and addiction medicine consultations, initiation of MOUD, linkage services to outpatient addiction care, and social work involvement to help address underlying social and structural issues such as homelessness, untreated mental illness, and co-occurring substance use disorders that are often barriers to retention and recovery [19]. Additionally, an integrated approach in the outpatient setting that involves colocated treatment for both the substance use disorder and the drug use-associated infection would also likely improve outcomes [34–36]. A first crucial step is to improve low barrier access to MOUD as early initiation of MOUD should be standard of care for persons with OUD-related infections.

In addition to the discussion of methadone, there were some limitations that merit discussion. First, as a commercial claims database, Marketscan does not include individuals who are uninsured or on public insurance (eg, Medicaid). Inadequate health insurance coverage for substance use services can be a barrier to treatment. In the years following the implementation of the Patient Protection and Affordable Care Act, the odds of being uninsured among persons with heroin use disorder decreased by 40%, largely due to an increase in prevalence of Medicaid coverage [37]. In fact, uninsured rates for individuals with OUD are close to commercially insured rates, our study population [38]. Thus, a large proportion of people who inject opioids are publicly insured [39] rather than uninsured. Studies have shown that OUD treatment length among persons on Medicaid are similar to commercially insured persons [40, 41]. Nonetheless, there may be differences between the commercially insured, publicly insured, and uninsured populations regarding MOUD dosing or posthospital linkage and access to care that may affect the outcomes and limit generalizability. Additionally, we are unable to evaluate associations with overdose fatalities as we cannot identify whether an overdose was fatal since individuals may exit the data set due to death or when they dis-enrolled from an employer sponsored insurance plan. Finally, although a growing problem in the United States, we are not able to fully explore polysubstance overdose given the lack of toxicology in claims data.

In conclusion, this analysis using a commercial claims data set suggested an impact of MOUDs in the peri-hospitalization period for endocarditis among people with OUD. Addressing OUD is a key element of comprehensive care. More work is need to integrate care for infections associated with drug use

that address the infection, the OUD, and the structural issues that inhibit retention in care and long-term recovery.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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