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Effect of initiation of medications for opioid use disorder on hospitalization outcomes for endocarditis and osteomyelitis in a large private hospital system in the United States, 2014–18

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ABSTRACT

Background and Aims Opioid use disorder (OUD) has led to not only increases in overdose deaths, but also increases in endocarditis and osteomyelitis secondary to injection drug use (IDU). We studied the association between initiation of medications for opioid use disorder (MOUD) and treatment outcomes for people with infectious sequelae of IDU and OUD. **Design and setting** This is a retrospective cohort study reviewing encounters at 143 HCA Healthcare hospitals across 21 states of the United States from 2014 to 2018. **Participants** Adults aged 18–65 with the ICD diagnosis code for OUD and endocarditis or osteomyelitis (n = 1407). **Measurements** Main exposure was the initiation of MOUD, defined as either methadone or buprenorphine at any dosage started during hospitalization. Primary outcomes were defined as patient-directed discharge (PDD), 30-day re-admission and days of intravenous antibiotic treatment. Covariates included biological sex, age, ethnicity, other co-occurring substance use disorders, and insurance status. **Findings** MOUD was initiated among 269 (19.1%) patients during hospitalization. Initiation of MOUD was not associated with decreased odds of PDD. Initiation of MOUD did not impact 30-day re-admission. Patients who received MOUD, on average, had 5.7 additional days of gold-standard intravenous antibiotic treatment compared with those who did not [$\beta = 5.678$, 95% confidence interval (CI) = 3.563, 7.794), $P < 0.05$]. **Conclusion** For people with opioid use disorder hospitalized with endocarditis or osteomyelitis, initiation of methadone or buprenorphine appears to be associated with improved receipt of gold-standard therapy, as quantified by increased days on intravenous antibiotic treatment.

Keywords buprenorphine, gold-standard antibiotic therapy, infective osteomyelitis, infective endocarditis, injection drug use, methadone, opioid agonist therapy, opioid use disorder.

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INTRODUCTION

The overdose crisis in the United States has progressed from a prescription opioid epidemic to transition to heroin then more potent fentanyl, and now a fourth wave characterized by opioid and stimulant co-injection [1–3]. The prevalence of prescription opioid misuse prior to transition to injection of heroin has been demonstrated extensively in the literature [4–6]. Deaths from opioid overdose have hit record levels in recent years, coinciding with the rise of the dangerous synthetic opioid, fentanyl and its analogues [1].

Concomitantly, the surge in the number of Americans living with opioid use disorder (OUD) has led to significant morbidity and mortality from infectious consequences of injection drug use [7–9]. In addition to skin and soft tissue infections [10], people who inject drugs (PWID) are at a higher risk of severe injection-related infections, such as endocarditis and osteomyelitis [7–9], both conditions requiring long-term intravenous (i.v.) antibiotic therapy

as the gold standard of treatment [11]. The incidence of infective endocarditis among PWID has increased in recent years and is more than 100 times greater than in the general population [12–14]. Despite the availability of appropriate antibiotic treatments, which are typically at least 4 weeks' duration, PWID have similar all-cause mortality rates to patients with endocarditis unrelated to injecting drugs, who are older and have more comorbidities [15,16].

Infectious complications of injection drug use have a severe financial impact on the health-care system [17,18] and between 2002 and 2012, the cost of OUD-related infections more than tripled [7]. Previous reports in the literature that have reviewed hospitalization outcomes have revealed this financial impact on county safety-net health-care systems and state-wide impact [17,18] but none, to our knowledge, have investigated hospital outcomes in a multi-state private, for-profit health-care system. High-risk injection behaviors, such as sharing or re-using injection equipment, can contribute to infectious complications [19,20]. Syringe services programs (SSPs) which distribute injection equipment using a harm reduction approach have been shown to prevent transmission of viral infectious diseases as well as mitigate stigma associated with injection drug use [21]. SSPs have been supported as an evidence-based response in the United States in the wake of the current overdose crisis [22].

Patients with infections related to injection drug use often delay seeking treatment and have high rates of patient-directed discharge (PDD) when hospitalized due to pervasive stigma and discrimination within the health-care system [23–25]. Severe opioid withdrawal or craving, in the absence of initiation of medications for opioid use disorder (MOUD), can contribute to PDD [26]. Even if MOUD is initiated, inadequate dosing or improper initiation procedures can interfere with successful completion of treatment [27]. Methadone and buprenorphine have both been Food and Drug Administration (FDA)-approved for the treatment of OUD since 1970 and 2002, respectively, but these life-saving medications are underutilized due to stigma, lack of integrative addiction medicine services, and general physician discomfort with their application [28–31]. Hospitalization is often a missed opportunity to engage PWID with OUD in psychiatric or social services [32]. Hospital re-admission has been associated with a lack of outpatient follow-up for OUD [33,34]. In a 10-year retrospective study, interventions directed at addressing the underlying cause of endocarditis secondary to injection drug use were considered suboptimal, and rarely exceeded basic psychosocial support [29]. Endocarditis is an often fatal consequence of severe OUD, and hospitalization may be an opportune time to initiate MOUD to improve health outcomes [35]. The objective of this study is to investigate the outcomes of hospitalization for consequences of injection drug use in a large private, for-profit hospital system in the United States and explore the effects of MOUD initiation on days of gold-standard antibiotic therapy, PDD and 30-day re-admission.

METHODS

Human subjects

This study was reviewed by the Institutional Review Board of HCA Healthcare (IRB no. 2020–832) and determined to be exempt.

Study design and sample

This is a retrospective study analyzing existing inpatient encounters from HCA Healthcare facilities in the United States. The HCA Healthcare system is a for-profit operator of facilities which include 185 hospitals and other sites of care, including surgery centers, emergency rooms and physician clinics across 21 states within the United States. This study examined records throughout a 60-month period from January 2014 (which is the earliest date available to HCA research) to 31 December 2018. All patients and their data points were de-identified prior to analysis.

Data collection

We queried the HCA electronic admission, discharge, inpatient medication, and billing records during the data collection period for all patients aged 18–65 years. Patients included in the cohort required diagnosis of opioid use disorder (defined using ICD-10 code F11 or ICD-9 code 304.00–304.03) as well as concurrent endocarditis (defined using ICD-10 code I33 or ICD-9 codes 421.0 and 424.9) or osteomyelitis (defined using ICD-10 code M86 or ICD-9 code 730.0). Data were limited to hospitalized patients only. The corresponding medical records were then used to extract demographic information, discharge disposition, length of stay, consultations to specialists (only psychiatry and pain medicine because addiction medicine was not available in all institutions) and medication list to chart review; 143 distinct HCA hospitals were included in the analysis, with a median of six patients treated per hospital during the study time-period (2014–18).

Outcome measures

The main exposure was the initiation of MOUD (defined as buprenorphine or methadone at any dose) during hospitalization. Initiation during hospitalization was defined as the lack of MOUD in the list of patient-reported home medication. The primary outcome was overall adherence to inpatient treatment, which was classified as whether or not the patient had PDD, otherwise known as against

medical advice discharge, was re-admitted within 30 days of discharge, and the number of days of gold-standard i.v. antibiotic treatment. For the purpose of this study, only the patient's initial admission to an HCA facility was used.

Statistical analysis

Descriptive statistics of demographic information were generated and are listed in Table 1. Patient selection criteria are visualized in Fig. 1. Multivariable logistic regression models were used to evaluate the association of MOUD and PDD and 30-day re-admission, separately. A multivariable linear regression model was used to evaluate the association of MOUD and days on i.v. antibiotic treatment. All regression models controlled for age, biological sex, ethnicity, insurance status (uninsured, government-subsidized or commercial) and other co-occurring substance use disorders [defined as either cocaine use disorders (ICD-10 code F14 and ICD-9 code 304.2) and amphetamine use disorder (ICD-10 code F15 and ICD-9 code 304.4)]. Because the number of hospitals included for this study is large, with a relatively low number of patients treated per hospital, it was not possible to account for potential between-hospital clustering. Insurance status was included to approximate socio-economic status, and other co-occurring substance use disorders were included as these were previously shown to be associated with endocarditis and osteomyelitis secondary to injection drug use [9]. All data were analyzed by SAS version 9.4 and IBM SPSS Statistics version 24. Neither the research question nor the analysis plan was pre-registered on a publicly available platform; thus, the results should be considered exploratory.

RESULTS

A total of 1433 patients were admitted with OUD and concurrent endocarditis or osteomyelitis between 2014 and 2018. Twenty-six of these patients reported existing MOUD prescriptions and were excluded from analysis, generating this final analyzed sample size of 1407 patients. Covariate variables included age (mean 42.7 years), biological sex (56% male), race (85% white) and presence of concurrent cocaine or amphetamine use disorders [116 (8.2%) with cocaine use disorder and 110 (7.8%) with amphetamine use disorder]; 333 (23.7%) patients were uninsured, while the majority of patients (76.3%) had either government-subsidized insurance or commercial insurance (Table 1).

Table 1 Descriptive statistics of all patients hospitalized for endocarditis or osteomyelitis with concurrent OUD, stratified by initiation of MOUD during hospitalization

Characteristics	*Total (N = 1407)*	*MOUD (n = 269)*	*No MOUD (n = 1138)*
Age (mean, SD)	42.7 (12.2)	40.0 (12.87)	43.4 (11.99)
Sex (*n*, %)			
Male	784 (55.7)	150 (55.8)	634 (55.7)
Female	623 (44.3)	119 (44.2)	504 (44.3)
Race/ethnicity (*n*, %)			
White	1190 (84.6)	236 (87.7)	954 (83.8)
Black	120 (8.5)	8 (3.0)	112 (9.8)
Asian	6 (0.4)	3 (1.1)	3 (0.3)
Other	91 (6.5)	22 (8.2)	69 (6.1)
Insurance type (*n*, %)			
Uninsured	333 (23.7)	66 (24.5)	267 (23.5)
Government subsidized	907 (64.5)	158 (58.7)	749 (65.8)
Private	167 (11.8)	45 (16.8)	122 (10.7)
Other substance use (*n*, %)			
Cocaine	116 (8.2)	24 (8.9)	92 (8.1)
Amphetamines	110 (7.8)	26 (9.7)	84 (7.3)
None	1181 (84.0)	219 (81.4)	962 (84.5)
Infectious diagnosis (*n*, %)			
Osteomyelitis	906 (64.4)	143 (53.2)	763 (67.0)
Endocarditis	501 (35.6)	126 (46.8)	375 (33.0)
Initiated Tx for OUD (*n*, %)			
Methadone	221 (15.7)	221 (82.2)	–
Buprenorphine	48 (3.4)	48 (17.8)	–
Received consultation (*n*, %)			
Pain management	122 (8.7)	22 (8.2)	100 (8.8)
Psychiatry	161 (11.0)	45 (16.7)	116 (10.2)

OUD = opioid use disorder; MOUD = medication for opioid use disorder; Tx = treatment; SD = standard deviation.

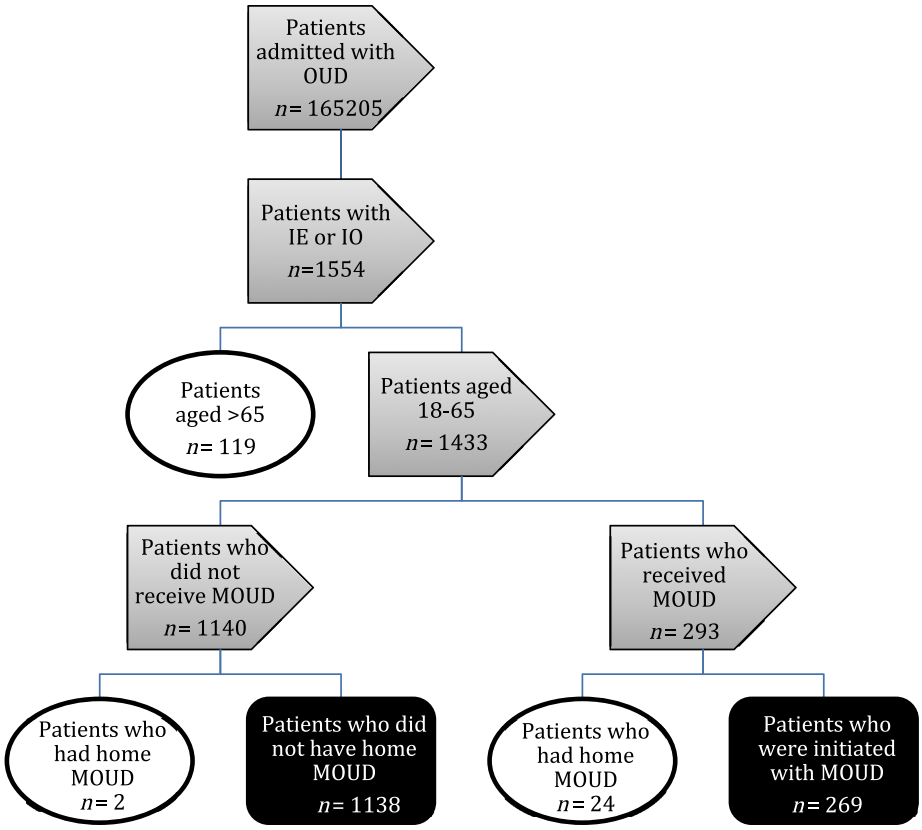

Figure 1 Flow-chart of patient selection; *n* = 1407. OUD = opioid use disorder; IE = infective endocarditis; IO = infective osteomyelitis; MOUD = medication for opioid use disorder. [Colour figure can be viewed at wileyonlinelibrary.com]

A total of 501 (35.6%) patients were diagnosed with endocarditis, while 906 (64.4%) were diagnosed with osteomyelitis; 269 (19.1%) patients were initiated with MOUD during their hospitalization, the majority of whom were given methadone (82.2%) as opposed to buprenorphine (17.8%), 122 (8.7%) patients received a pain management consultation and 161 (11.4%) received a psychiatric consultation during their hospitalization course. A total of 258 (18.3%) patients left PDD, and 527 (37.5%) patients were re-admitted within 30 days of discharge. Mean days of gold-standard i.v. antibiotic therapy for the entire study sample was 14.3. Detailed outcomes of hospitalizations are listed in Table 2.

In the multivariable logistic regression, initiation of MOUD was not significantly associated with PDD. Of the covariate variables, age [adjusted odds ratio (aOR) = 0.96, 95% confidence interval (CI) = 0.94, 0.97] and government (aOR = 0.45, 95% CI= 0.33, 0.61) and commercial insurance (aOR = 0.28, 95% CI = 0.16, 0.48) were significantly associated with lower odds of PDD. Initiation of MOUD did not have any association with 30-day re-admission. However, patients who were identified as white were significantly less likely to be re-admitted within 30 days (aOR = 0.69, 95% CI = 0.51, 0.93). Patients who received MOUD had significantly longer adherence time to gold-standard i.v. antibiotic therapy, with an average of 5.7 additional days (β = 5.68, 95% CI = 3.56, 7.79). Patients with government subsidized insurance plans had decreased days of i.v. antibiotics by 2.54 days, while those with commercial insurance plans were not associated with change in days on i.v. antibiotics. Results of all regression analysis are presented in Table 3.

DISCUSSION

This study of a private, for-profit hospital system with 185 hospitals across 21 states saliently demonstrates that the vast majority (80.9%) of hospitalized patients with OUD and endocarditis or osteomyelitis did not receive life-saving MOUD during their hospitalization course, consistent with studies in other settings [29]. This tremendous missed opportunity to provide gold-standard treatment for OUD carries risk for incomplete antibiotic treatment, re-admission with advanced disease and death. Continued injection drug use is associated with repeat episodes of endocarditis, a significant source of morbidity and mortality in a relative young population [36]. Hospitalization in the absence of MOUD also results in decreased tolerance to opioids and increased risk of overdose at discharge [37]. Initiation of MOUD in the hospital is critical to support

Table 2 Discharge outcomes among patients hospitalized for endocarditis or osteomyelitis with concurrent OUD

Characteristics	*Total (N = 1407)*	*MOUD (n = 269)*	*No MOUD (n = 1138)*
Mean days i.v. antibiotics	14.3	19.3	13.2
Re-admitted within 30 days (*n*, %)			
Yes	527 (37.5)	106 (39.4)	421 (37.0)
If yes, patient prior PDD	100 (7.1)	20 (7.4)	80 (7.0)
No	780 (62.5)	143 (53.2)	637 (56.0)
Discharge disposition (*n*, %)			
Home	562 (39.9)	118 (43.9)	444 (39.0)
Home with home care	219 (15.6)	37 (13.8)	182 (16.0)
PDD	258 (18.3)	49 (18.2)	209 (18.4)
Hospice/expired	47 (3.3)	10 (3.7)	37 (3.3)
Skilled nursing/stepdown	234 (16.6)	36 (13.4)	198 (17.4)
Other[a]	87 (6.2)	19 (7.1)	68 (6.0)
Given MOUD upon discharge (*n*, %)			
Yes	44 (3.1)	44 (16.4)	0

OUD = opioid use disorder; i.v. = intravenous; MOUD = medication for opioid use disorder; PDD = patient-directed discharge. [a]Other includes transfers to another in-patient level facilities, discharges to police custody, critical access hospitals and other undefined health-care facilities.

Table 3 Multivariable logistic and linear regression results for patient directed discharge, 30-day re-admission and days of i.v. antibiotic treatment

	Patient-directed discharge		*30-day re-admission*		*Days of i.v. antibiotic treatment*	
Characteristics	*aOR*	*95% CI*	*aOR*	*95% CI*	*Beta*	*95% CI*
MOUD initiated in hospital						
Yes	0.85	0.59, 1.22	1.14	0.87, 1.50	**5.68**	**3.56, 7.79**
No	Ref	–	Ref	–		
Age	**0.96**	**0.94, 0.97**	1.00	0.99, 1.01	**−0.13**	**−0.21, −0.06**
Biological sex						
Male	0.83	0.62, 1.11	0.89	0.71, 1.11	0.69	−1.00, 2.39
Female	Ref	–	Ref	–		
Ethnicity						
White	1.24	0.82, 1.87	0.69	**0.51, 0.93**	0.43	−1.89, 2.74
Other	Ref	–	Ref	–		
Cocaine/amphetamine use						
Yes	1.23	0.85, 1.77	0.86	0.62, 1.18	−0.28	
No	Ref	–	Ref	–		
Insurance status						
Govt funded insurance	**0.45**	**0.33, 0.61**	1.18	0.90, 1.56	**−2.71**	**−4.80, −0.61**
Commercial insurance	**0.28**	**0.16, 0.48**	1.08	0.73, 1.61	−2.54	−5.51, 0.42
Uninsured	Ref	–	Ref	–		

Bold type associations represent significance at $P < 0.05$. MOUD = medication for opioid use disorder i.v. = intravenous; aOR = adjusted odds ratio; CI = confidence interval.

PWID with OUD in increasing days of gold-standard i.v. antibiotic therapy (mean = 5.7 additional days) and decreasing the risk of fatal opioid overdose upon discharge.

The universally low rate of initiation of MOUD (19.1%) is concerning in the context of the modern overdose crisis, but can partially be explained by the even smaller percentage of patients who received either psychiatric or pain management consultations and the lack of addiction medicine services across institutions. Consultation with an addiction medicine service, or specialized infectious disease/addiction medicine teams, has been shown to improve outcomes in this population [28, 38]. Intransigent stigma and discrimination towards PWID could have prevented providers from adequately treating the underlying OUD [25]. Even in the field of infectious diseases, whereas 78% of physicians have reported treating infections in PWID, only 46% felt that infectious disease specialists should manage the underlying substance use disorder

and only 35% reported satisfactory substance use disorder management in health systems [39]. Patient- to systems-level barriers to MOUD initiation in a hospital setting [40] need to be explored further, and education efforts creating robust substance use disorder curricula in undergraduate and graduate medical education are urgently needed.

Hospitalization provides a critical opportunity to explore initiation of life-saving MOUD [41]. Importantly, our study shows the association of initiation of MOUD and the increased days of gold-standard i.v. antibiotic therapy by 5.7 days. While the mean additional days of gold-standard i.v. antibiotic therapy is small in comparison to the recommended duration of i.v. antibiotic treatment for these cases, it is substantial when compared to the length of stay in our cohort (mean = 14.3 days). This additional time in hospital can used to optimize MOUD doses, establish connections to outpatient MOUD and engage case management to create safe, cost-effective long-term discharge plans.

While initiation of MOUD was not significantly associated with decreased rates of PDD in this cohort, it is unknown whether patients received appropriate doses of MOUD to prevent withdrawal and control cravings, which can be more challenging in the era of fentanyl [42]. It is important to note that, overall, the rate of PDD was 18.3%, consistent with other studies in this population [9]. Whereas we did not explore harm reduction approaches to antibiotic therapy in PWID with OUD in this study, it is imperative that we fulfill our duty as physicians and offer the next best therapy to PWID, including oral antibiotic contingency plans for PDD [43]. Additionally, it is important to note that although 26 patients were excluded from the main analysis due to their self-reported current use of MOUD at admission, 24 of those patients were continued on MOUD during their admission and none had a PDD. In addition, we have shown that insurance, both government-subsidized and private, is associated with decreased PDD, revealing the challenges the social determinants of health play in addiction treatment, which could be compounded in a for-profit hospital setting.

Another salient finding in our cohort was high rate of 30-day re-admission (37.5%). Previous studies have shown that PDD is the strongest independent predictor for 30-day re-admission among patients hospitalized with endocarditis [44]. Surprisingly, we did not find a significant association between initiation of MOUD and decreased 30-day re-admission. However, a review of the records revealed that only 44 patients were prescribed MOUD upon discharge and there were no discharges to a treatment center for substance use disorder, presenting further missed opportunities in this cohort, if not ethical questions about initiating MOUD, and then failing to provide a prescription at discharge. Incidence of opioid overdose is found to be higher in the first 30 days after hospital discharge [45], but it is unknown if our high rate of re-admission was secondary to overdose. Even more concerning is that only patients who identified as white had a decreased rate of 30-day re-admission, consistent with prior studies showing racial disparities in re-admission in the United States for all causes [46] and decreased prescription of MOUD to patients who identify as black [47].

There are several limitations to this paper. Importantly, we were unable to determine if proper induction protocols and adequate dosages of MOUD were initiated during hospitalization, which could explain the lack of differences in PDD and 30-day re-admission between the two groups. In addition, we are unable to determine patient intent to transition to outpatient MOUD at discharge, and whether patients were prescribed MOUD for medically supervised withdrawal versus continued treatment. Liebschutz *et al.* showed that patients with OUD who only received a 5-day taper (detoxification) of buprenorphine during hospitalization were less likely to enter a buprenorphine program compared to those who were actively linked to outpatient MOUD and were more likely to continue opioid use, confounding our 30-day re-admission data [41]. Thirdly, we only counted first hospitalization in this cohort, so it is unknown if these patients were admitted repeatedly over the study period, and we were also limited to HCA facilities. Due to the common practice of seeking care at an alternative facility, particularly after experiencing stigma, we probably underestimated 30-day re-admission. Importantly, this study is a specific cohort of PWID receiving care at HCA facilities and may not be generalizable to other PWID. Finally, we were unable to control for clustering within hospitals in this analysis, which may have underestimated differences in outcomes of interest between the two groups.

CONCLUSION

MOUD was greatly under-utilized in the treatment of endocarditis and osteomyelitis secondary to injection drug use. MOUD was associated with increased receipt of gold-standard i.v. antibiotic therapy; however, effects of MOUD on PDD and 30-day re-admission are less clear. Combined with proper outpatient follow-up, initiation of MOUD in the acute setting may be associated with improved morbidity and mortality associated with endocarditis and osteomyelitis due to increased days of gold-standard i.v. antibiotic therapy.

Declaration of interests

None.

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Author contributions

Young Jo: Conceptualization; investigation; methodology. **Rebecca Nosal:** Conceptualization. **Angela Vittori:** Visualization. **Leopoldo Cordova:** Investigation; methodology. **Christian Vandever:** Data curation; formal analysis. **Clara Alvarez:** Project administration; supervision. **Tyler Bartholomew:** Methodology. **Hansel Tookes:** Writing-reviewing and editing.

References

1. Colon-Berezin C., Nolan M. L., Blachman-Forshay J., Paone D. Overdose deaths involving fentanyl and fentanyl analogs—New York City, 2000–2017. *Morb Mortal Wkly Rep* 2019; **68**: 37–40.
2. Lake S., Wood E., Buxton J., Dong H., Montaner J., Kerr T. Prescription opioid use and non-fatal overdose in a cohort of injection drug users. *Am J Drug Alcohol Abuse* 2015; **41**: 257–63.
3. Cano M., Huang Y. Overdose deaths involving psychostimulants with abuse potential, excluding cocaine: state-level differences and the role of opioids. *Drug Alcohol Depend* 2020; **18**: 108384.
4. Guarino H., Mateu-Gelabert P., Teubl J., Goodbody E. Young adults' opioid use trajectories: from nonmedical prescription opioid use to heroin, drug injection, drug treatment and overdose. *Addict Behav* 2018; **86**: 118–23.
5. O'Keefe D., Horyniak D., Dietze P. From initiating injecting drug use to regular injecting: retrospective survival analysis of injecting progression within a sample of people who inject drugs regularly. *Drug Alcohol Depend* 2016; **158**: 177–80.
6. Fleischauer A. T., Ruhl L., Rhea S., Barnes E. Hospitalizations for endocarditis and associated health care costs among persons with diagnosed drug dependence—North Carolina, 2010–2015. *Morb Mortal Wkly Rep* 2017; **66**: 569–73.
7. Ronan M. V., Herzig S. J. Hospitalizations related to opioid abuse/dependence and associated serious infections increased sharply, 2002–12. *Health Aff* 2016; **35**: 832–7.
8. McCarthy N. L., Baggs J., See I., Reddy S. C., Jernigan J. A., Gokhale R. H., *et al*. Bacterial infections associated with substance use disorders, large cohort of United States hospitals, 2012–2017. *Clin Infect Dis* 2020; **71**: e37–e44.
9. Serota D. P., Bartholomew T. S., Tookes H. E. Evaluating differences in opioid and stimulant use-associated infectious disease hospitalizations in Florida, 2016–2017. *Clin Infect Dis* 2020; https://doi.org/10.1093/cid/ciaa1278
10. Phillips K. T., Anderson B. J., Herman D. S., Liebschutz J. M., Stein M. D. Risk factors associated with skin and soft tissue infections among hospitalized people who inject drugs. *J Addict Med* 2017; **11**: 461–7.
11. Berbari E. F., Kanj S. S., Kowalski T. J., Darouiche R. O., Widmer A. F., Schmitt S. K., *et al*. Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis* 2015; **61**: e26–e46.
12. Gray M. E., McQuade E. T. R., Scheld W. M., Dillingham R. A. Rising rates of injection drug use associated infective endocarditis in Virginia with missed opportunities for addiction treatment Referral: a retrospective cohort study. *BMC Infect Dis* 2018; **18**: 1–9.
13. Rodger L., Glockler-Lauf S. D., Shojaei E., Sherazi A., Hallam B., Koivu S., *et al*. Clinical characteristics and factors associated with mortality in first-episode infective endocarditis among persons who inject drugs. *JAMA Netw Open* 2018; **1**: e185220–e185220.
14. Rudasill S. E., Sanaiha Y., Mardock A. L., Khoury H., Xing H., Antonios J. W., *et al*. Clinical outcomes of infective endocarditis in injection drug users. *J Am Coll Cardiol* 2019; **73**: 559–70.
15. Leahey P. A., LaSalvia M. T., Rosenthal E. S., Karchmer A. W., Rowley C. F. High morbidity and mortality among patients with sentinel admission for injection drug use-related infective endocarditis. *Open Forum Infect Dis* 2019; **6**: ofz089.
16. Straw S., Baig M. W., Gillott R., Wu J., Witte K. K., O'Regan D. J., *et al*. Long-term outcomes are poor in intravenous drug users following infective endocarditis, even after surgery. *Clin Infect Dis* 2020; **71**: 564–71.
17. Tookes H., Diaz C., Li H., Khalid R., Doblecki-Lewis S. A cost analysis of hospitalizations for infections related to injection drug use at a county safety-net hospital in Miami, Florida. *PLOS ONE* 2015; **10**: e0129360.
18. Coye A. E., Bornstein K. J., Bartholomew T. S., Li H., Wong S., Janjua N. Z., *et al*. Hospital costs of injection drug use in Florida. *Clin Infect Dis* 2020; https://doi.org/10.1093/cid/ciaa823
19. Annie F. H., Bates M. C., Uejio C. K., Bhagat A., Kochar T., Embrey S. The impact of the drug epidemic on the incidence of sepsis in West Virginia. *Cureus* 2018; **10**: e3521.
20. Larney S., Peacock A., Mathers B. M., Hickman M., Degenhardt L. A systematic review of injecting-related injury and disease among people who inject drugs. *Drug Alcohol Depend* 2017; **171**: 39–49.
21. Vidourek R. A., King K. A., Yockey R. A., Becker K. J., Merianos A. L. Straight to the point: a systematic review of needle exchange programs in the United States. *J Behav Health* 2019; https://doi.org/10.5455/jbh.20181023074620
22. Jarlais D. C. D., Nugent A., Solberg A., Feelemyer J., Mermin J., Holtzman D. Syringe service programs for persons who inject drugs in urban, suburban, and rural areas—United States, 2013. *Morb Mortal Wkly Rep* 2015; **64**: 1337–41.
23. McNeil R., Small W., Wood E., Kerr T. Hospitals as a 'risk environment': an ethno-epidemiological study of voluntary and involuntary discharge from hospital against medical advice among people who inject drugs. *Soc Sci Med* 2014; **105**: 59–66.

24. Biancarelli D. L., Biello K. B., Childs E., Drainoni M., Salhaney P., Edeza A., *et al.* Strategies used by people who inject drugs to avoid stigma in healthcare settings. *Drug Alcohol Depend* 2019; **198**: 80–6.
25. Muncan B., Walters S. M., Ezell J., Ompad D. C. 'They look at us like junkies': influences of drug use stigma on the healthcare engagement of people who inject drugs in New York City. *Harm Reduct J* 2020; **17**: 1–9.
26. Fanucchi L. C., Lofwall M. R., Nuzzo P. A., Walsh S. L. In-hospital illicit drug use, substance use disorders, and acceptance of residential treatment in a prospective pilot needs assessment of hospitalized adults with severe infections from injecting drugs. *J Subst Abuse Treat* 2018; **92**: 64–9.
27. Simon R., Snow R., Wakeman S. Understanding why patients with substance use disorders leave the hospital against medical advice: a qualitative study. *Subst Abuse* 2020; **41**: 519–25.
28. Marks L. R., Munigala S., Warren D. K., Liang S. Y., Schwarz E. S., Durkin M. J. Addiction medicine consultations reduce readmission rates for patients with serious infections from opioid use disorder. *Clin Infect Dis* 2019; **68**: 1935–7.
29. Rosenthal E. S., Karchmer A. W., Theisen-Toupal J., Castillo R. A., Rowley C. F. Suboptimal addiction interventions for patients hospitalized with injection drug use-associated infective endocarditis. *Am J Med* 2016; **129**: 481–5.
30. Jicha C., Saxon D., Lofwall M. R., Fanucchi L. C. Substance use disorder assessment, diagnosis, and management for patients hospitalized with severe infections due to injection drug use. *J Addict Med* 2019; **13**: 69–74.
31. Miller A. C., Polgreen P. M. Many opportunities to record, diagnose, or treat injection drug–related infections are missed: a population-based cohort study of inpatient and emergency department settings. *Clin Infect Dis* 2019; **68**: 1166–75.
32. Eaton E. F., Mathews R. E., Lane P. S., Paddock C. S., Rodriguez J. M., Taylor B. B., *et al.* A 9-point risk assessment for patients who inject drugs and require intravenous antibiotics: focusing inpatient resources on patients at greatest risk of ongoing drug use. *Clin Infect Dis* 2019; **68**: 1041–3.
33. Raven M. C., Carrier E. R., Lee J., Billings J. C., Marr M., Gourevitch M. N. Substance use treatment barriers for patients with frequent hospital admissions. *J Subst Abuse Treat* 2010; **38**: 22–30.
34. Tiako M. J. N., Mori M., Mahmood S. U. B., Shioda K., Mangi A., Yun J., *et al.* Recidivism is the leading cause of death among intravenous drug users who underwent cardiac surgery for infective endocarditis. *Semin Thorac Cardiovasc Surg* 2019; **31**: 40–5.
35. Kimmel S. D., Walley A. Y., Li Y., Linas B. P., Lodi S., Bernson D., *et al.* Association of treatment with medications for opioid use disorder with mortality after hospitalization for injection drug use-associated infective endocarditis. *JAMA Netw Open* 2020; **3**: e2016228–e2016228.
36. Alagna L., Park L., Nicholson B., Keiger A., Strahilevitz J., Morris A., *et al.* Repeat endocarditis: analysis of risk factors based on the international collaboration on endocarditis–prospective cohort study. *Clin Microbiol Infect* 2014; **20**: 566–75.
37. Barocas J. A., Morgan J. R., Wang J., McLoone D., Wurcel A., Stein M. D. Outcomes associated with medications for opioid use disorder among persons hospitalized for infective endocarditis. *Clin Infect Dis* 2020; https://doi.org/10.1093/cid/ciaa062
38. Barocas J. A., Morgan J. R., Fiellin D. A., Schackman B. R., Yazdi G. E., Stein M. D., *et al.* Cost-effectiveness of integrating buprenorphine-naloxone treatment for opioid use disorder into clinical care for persons with HIV/hepatitis C co-infection who inject opioids. *Int J Drug Policy* 2019; **72**: 160–8.
39. Rapoport A. B., Fischer L. S., Santibanez S., Beekmann S. E., Polgreen P. M., Rowley C. F. Infectious diseases physicians' perspectives regarding injection drug use and related infections, United States, 2017. *Open Forum Infect Dis* 2018; **5**: ofy132.
40. Hassamal S., Goldenberg M., Ishak W., Haglund M., Miotto K., Danovitch I. Overcoming barriers to initiating medication-assisted treatment for heroin use disorder in a general medical hospital: a case report and narrative literature review. *J Psychiatr Pract* 2017; **23**: 221–9.
41. Liebschutz J. M., Crooks D., Herman D., Anderson B., Tsui J., Meshesha L. Z., *et al.* Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. *JAMA Intern Med* 2014; **174**: 1369–76.
42. Randhawa P. A., Brar R., Nolan S. Buprenorphine–naloxone 'microdosing': an alternative induction approach for the treatment of opioid use disorder in the wake of North America's increasingly potent illicit drug market. *Can Med Assoc J* 2020; **192**: E73–E73.
43. Iversen K., Ihlemann N., Gill S. U., Madsen T., Elming H., Jensen K. T., *et al.* Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med* 2019; **380**: 415–24.
44. Pasupula D. K., Bhat A. G., Malleshappa S. K. S., Lotfi A., Slawsky M., Buffer S., *et al.* Trends and predictors of 30-day readmission among patients hospitalized with infective endocarditis in the United States. *Cureus* 2019; **11**: e4962.
45. Mudumbai S. C., Lewis E. T., Oliva E. M., Chung P. D., Harris B., Trafton J., *et al.* Overdose risk associated with opioid use upon hospital discharge in veterans health administration surgical patients. *Pain Med* 2019; **20**: 1020–31.
46. Basu J., Hanchate A., Bierman A. Racial/ethnic disparities in readmissions in US hospitals: the role of insurance coverage. *Inquiry* 2018; **55**: 0046958018774180.
47. Lagisetty P. A., Ross R., Bohnert A., Clay M., Maust D. T. Buprenorphine treatment divide by race/ethnicity and payment. *JAMA Psychiatry* 2019; **76**: 979–81.

