Published in final edited form as:

Drug Alcohol Depend. 2020 October 01; 215: 108207. doi:10.1016/j.drugalcdep.2020.108207.

Impact of medications for opioid use disorder among persons hospitalized for drug use-associated skin and soft tissue infections

Joshua A. Barocas, MD^{a,b}, Mam Jarra Gai, MPH^a, Brenda Amuchi, MBBS, MPH^a, Raagini Jawa, MD, MPH^{a,b}, Benjamin P. Linas^{a,b}

^aSection of Infectious Diseases, Boston Medical Center (BMC), 801 Massachusetts Ave, 2nd Floor, Boston, MA, USA, 02118

^bBoston University School of Medicine, 801 Massachusetts Ave, 2nd Floor, Boston, MA, USA, 02118

Abstract

Background: Skin and soft tissue infections (SSTI) are common complications of injection drug use. We aimed to determine if rehospitalization and recurrent SSTI differ among persons with opioid use disorder (OUD) hospitalized for SSTI who are initiated on MOUD within 30 days of discharge and those who are not.

Methods: We performed a retrospective analysis of commercially insured adults aged 18 years and older in the U.S. with OUD and hospitalization for injection-related SSTI from 2010-2017. The primary exposure was initiation of MOUD in the 30 days following hospitalization for SSTI. The primary outcomes included 30-day and 1-year 1) all-cause rehospitalization and 2) recurrent SSTI. We calculated the incidence rates for the two groups: MOUD group and no MOUD group for the primary outcomes. We developed Cox models to determine if rehospitalization and recurrent SSTI differ between the two groups.

Results: Only 5.5% (357/6538) of people received MOUD in the month following their index SSTI hospitalization. 30-day rehospitalization incidence was higher in the MOUD group compared to no MOUD (35.9 vs 27.5 per 100 person-30 days) and one-year SSTI recurrence was lower (10.3 vs 18.7 per 100 person-years). In multivariable modeling, the MOUD group remained at significantly higher risk of 30-day rehospitalization compared to the no MOUD group and at lower risk for one-year SSTI recurrence.

Corresponding author: Joshua A. Barocas, MD, Boston University Medical Campus, 801 Massachusetts Ave, 2nd Floor, Boston, MA, 02131, Joshua.Barocas@BMC.org.

Contributors: All authors made substantial contributions to this manuscript. Dr. Barocas designed the study and directed its implementation, including quality assurance and control. Ms. Gai, Ms. Amuchi, Dr. Jawa, and Dr. Linas helped design the analytic strategy and provided content expertise. Ms. Gai helped with data analysis and data quality assurance and control. All authors were involved in manuscript preparation and review, and all authors approve the final manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of Interest: None declared

Conclusions: MOUD receipt following SSTI hospitalization decreases risk of recurrent SSTI among persons with OUD. Further expansion of these in-hospital services could provide an effective tool in the U.S. response to the opioid epidemic.

Keywords

skin infections; opioid use disorder; opioid epidemic; medications; hospitalization

1. Introduction

The U.S. opioid epidemic has expanded and evolved from oral ingestion of prescription opioids to injection of illicitly-produced synthetic opioids such as heroin and fentanyl, and stimulants such as cocaine and methamphetamine (Hedegaard, 2018). As a consequence, complications of injection drug use are rising (Centers for Disease & Prevention, 2011). In the past decade, heroin-related deaths have quadrupled (Rudd, Seth, David, & Scholl, 2016). There have been outbreaks of HIV related to injection drug use (Atkins et al., 2020; Cranston et al., 2019; Golden et al., 2019; Peters et al., 2016) and hepatitis C virus (HCV) prevalence has steadily risen (Zibbell et al., 2018).

Though opioid overdose and communicable viral diseases have received considerable attention, injection-related bacterial and fungal infections, such as endocarditis, osteomyelitis, septic arthritis, and skin and soft tissue infections (SSTI), are less often discussed; yet, they are associated with substantial morbidity, mortality, and costs (Ciccarone, Unick, Cohen, Mars, & Rosenblum, 2016; Collier, Doshani, & Asher, 2018; Ronan & Herzig, 2016). Patients with injection-related infections have longer hospitalizations, higher costs and increased risk of death compared to those with infections not attributed to injection drug use (Gray, Rogawski McQuade, Scheld, & Dillingham, 2018; Miller & Polgreen, 2018; Njoroge, Al-Kindi, Koromia, ElAmm, & Oliveira, 2018).

As the prevalence of injection drug use and its complications rise, new models of care are needed. Hospitals may be a pragmatic location to both treat opioid use disorder (OUD) and prevent the associated medical complications (Fanucchi, Walsh, Thornton, Nuzzo, & Lofwall, 2019; LaRochelle et al., 2019). As such, hospitalization may be a reachable moment to initiate medication for opioid use disorder (MOUD) (Shanahan, Beers, Alford, Brigandi, & Samet, 2010; Suzuki, 2016). The effect of post-hospitalization MOUD initiation on outcomes is not well characterized. The impact of such an intervention on health outcomes and healthcare utilization may inform decision-making by hospital administrators and other payors. We, therefore, aimed to determine if rehospitalization and recurrent SSTI differ among persons with OUD hospitalized for SSTI who are initiated on MOUDs within 30 days of discharge and those who are not.

2. Methods

2.1. Data Source

We analyzed data from the 2010-2017 MarketScan Commercial Claims and Encounters database, a commercial health insurance database managed by Truven Health Analytics.

This database includes approximately 1 billion insurance claims per year from more than 100 commercial insurance plans in the U.S. for the continuum of ambulatory and inpatient visits, outpatient pharmacy claims, and diagnostic testing for persons under age 65. While the claims database does not include every person in the U.S., it does cover all enrollees from nearly half of health care provider-sponsored U.S. health insurance plans.

2.2. Inclusion Criteria

We selected individuals aged 18 and older with OUD (Supplemental eTable 1) who were hospitalized for an SSTI between 2010 and 2017 and had a minimum 30-day follow-up after hospital discharge. We identified individuals with an initial inpatient claim for SSTI (Supplemental eTable 2) using *International Classification of Diseases, Ninth or Tenth Revisions (ICD-9 or ICD-10)* codes. We included individuals who had a diagnosis of OUD within 6 months before or after the index SSTI hospitalization (Miller & Polgreen, 2018). We used ICD-9 or ICD-10 codes in inpatient or outpatient claims to define OUD diagnosis (Morgan, Schackman, Weinstein, Walley, & Linas, 2019). We excluded individuals who were identified as having OUD diagnosis who also had a pharmacy claim for MOUD use (Supplemental eTable 3) in the three months preceding their infection.

2.3. Outcomes

The primary outcome measures included 30-day and 1-year 1) all-cause rehospitalization and 2) recurrent SSTI. We identified rehospitalization and SSTI events using ICD-9 and ICD-10 codes on inpatient claims.

2.4. 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 (both injectable, extended release (XR-NTX) and oral formulations) and buprenorphine (mono- and co-formulated with naloxone) (Micromedex Solutions, 2018. Drug Topics Red Book, 2018). Until late 2017, methadone therapy was not covered by commercial insurance, therefore, it is not reliably included in this dataset. 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 four weeks of discharge were categorized as being in the "MOUD" group. Individuals who did not fill a prescription or filled one after four weeks post-discharge were classified as "no MOUD."

2.5. Analyses

We characterized the cohort in terms of percent initiating MOUD as well as sociodemographic and clinical characteristics including percent requiring surgical intervention and percent with an interrupted hospitalization.

We then calculated the incidence rates for the two groups: the MOUD group and the no MOUD group. We calculated the total person-time and the total number of primary

outcomes for each group. We calculated the incidence rates per 100 person-time and associated 95% confidence interval (CI) under the normality assumption.

We developed weekly timescale Cox hazards models to predict time from hospital discharge to first rehospitalization and first recurrent SSTI over the determined time period as a function of receipt of MOUDs. Individuals began contributing follow-up time at discharge for their index SSTI episode, and ceased contributing time when they encountered a primary outcome, exited their insurance plan, at the end of the study period, whichever came first. 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 and ICD-10 codes (see Supplemental eTable 4), and whether or not surgical intervention for SSTI was performed during index hospitalization identified using ICD-9, ICD-10, and Current Procedural Terminology (CPT) codes. The models adjusted for whether an individual had an interrupted hospitalization (defined as a break from discharge to readmission for SSTI ≥ 5 days). Using the interrupted hospitalization approach rather than discharge codes indicating "discharge against medical advice," since the latter would not capture provider clinical decision-making regarding the stability or resolution of the infection. We chose the 5-day cut off since a majority of SSTIs can be treated and resolve within a 5-7 day period. Therefore, an admission for a SSTI that occurs after a longer period of time (e.g., 10 days) is likely to represent a new infection. Our approach was also guided by existing evidence that readmissions after AMA discharges occur within short time periods such as 1 day (Tan, Feng, Joyce, Fisher, & Mostaghimi, 2020).

All statistical analyses were performed in SAS, version 9.4.

3. Results

The cohort included 6,538 individuals with 9,821 person-years of follow-up. Baseline statistics of the cohort overall and by comparison group are presented in Table 1. The mean age was 40 years (SD=14.5) and 48% were female. The median length of hospitalization was 4 days (IQR=5) and 14% of this population underwent a surgical procedure during their index hospitalization associated with their SSTI. Though MOUDs save lives, only 5.5% (357/6538) of people received MOUDs in the month following their index SSTI hospitalization. Approximately 84% of those in the MOUD group received buprenorphine while the remainder received either oral naltrexone or injectable naltrexone. Those who received MOUDs were younger (mean age, 30 years $\pm$ 11.4 vs 40 years $\pm$ 14.5), less likely to undergo a surgical procedure ($p=0.0007$), and more likely to have a co-occurring substance use disorder ($p<0.0001$) than those who did not receive MOUDs. The two groups were well-balanced in terms of recent hospital utilization. There was no difference between the two groups with regard to average number of hospitalizations prior to index SSTI hospitalization (MOUD group=2.57 (SD 2.4) vs. no MOUD group=2.67 (SD 2.68), p -value = 0.62). The mean MOUD prescription duration (i.e., days supplied) following discharge was 16 days (SD = 13 days).

Rehospitalization rates

There were differences in 30-day and one-year rehospitalization rates between the two groups. The 30-day rehospitalization rate in the no MOUD group was 27.5 per 100 person-months (95% CI 27.4-27.7) and for the MOUD group was 35.9 (95% CI 35.3-36.6). The one-year rehospitalization rate in the no MOUD group was 192.9 per 100 person-years (95% CI, 192.5-193.3) and for those who did was 169.4 per 100 person-years (95% CI, 167.9-171.0). We found that opioid withdrawal and non-fatal overdose accounted for 35% of the rehospitalizations among the MOUD group in the first 30 days following SSTI and 62% of the rehospitalizations at one year. Conversely, opioid withdrawal and non-fatal overdose accounted for 15% of the 30-day rehospitalizations in the no MOUD group and 26% of the rehospitalization at one year.

3.1. Recurrent SSTI rates—In the 30 days following hospitalization, the SSTI recurrence rate was 2.8 per 100 person-months (95% CI, 2.73-2.81) in the no MOUD group and 1.13 per 100 person-months (95% CI, 1.02-1.24) in the MOUD group. In the 1 year following hospitalization, SSTI recurrence rate was 18.7 per 100 person-years (95% CI, 18.53-18.78) in the no MOUD group and 10.3 per 100 person-years (95% CI, 9.87-10.64) in the MOUD group.

3.2. Cox-adjusted models—In the adjusted models, there was a statistically significant increased hazard in 30-day rehospitalization (adjusted hazard ratio [aHR] = 1.29, 95% CI 1.05-1.59) (Table 2) and a reduced hazard in one-year SSTI recurrence (aHR = 0.62, 95% CI 0.42-0.91) (Table 3, Figure 1). The receipt of MOUDs was not associated with decreased time to one-year rehospitalization (aHR = 0.96, 95% CI 0.83-1.11) or 30-day recurrent SSTI (aHR = 0.49, 95% CI 0.18-1.233) (Supplemental Appendix).

We examined clinical covariates to determine whether they were predictive of the primary outcomes. Persons who had a co-occurring substance use disorder were at increased risk compared to those who did not for 30-day and one-year rehospitalization (aHR = 1.29, 95% CI 1.11-1.50; aHR = 1.31, 95% CI 1.18-1.44, respectively). Persons who had a procedure related to their SSTI were at increased risk, compared to those who did not, to be rehospitalized at 30 days (aHR = 1.80, 95% CI 1.58-2.05) and one-year (aHR = 1.76, 95% CI 1.61-1.92) and to have a recurrent infection at 30 days (aHR = 1.79, 95% CI 1.24-2.60) and one-year (aHR = 1.75, 95% CI 1.48-2.06). Finally, persons with a hospital interruption of 5 days were also at increased risk compared to those who did not have an interruption for 30-day and one-year rehospitalization (aHR = 5.15, 95% CI 4.40-6.02, aHR = 3.05, 95% CI 2.66-3.40, respectively).

4. Discussion

We assessed the impact of receipt of MOUD in the immediate post-hospitalization period among people with OUD who were hospitalized for SSTI. First, we found that even among individuals admitted to the hospital with a known complication of injection drug use, only 5.5% initiated either buprenorphine or naltrexone within 30-days of the admission. While this is not the first study to document under-utilization of MOUD, the degree to which medications are overlooked or avoided remains striking. Previous studies have demonstrated

similarly low rates of MOUD receipt (Barocas et al., 2020; Rosenthal, Karchmer, Theisen-Toupal, Castillo, & Rowley, 2016). Both patient- and system-level factors are associated with MOUD receipt (Priest, Lovejoy, Englander, Shull, & McCarty, 2020). We also found that among those who did start an MOUD within 30-days of their hospital admission for SSTI, there was an increase in 30-day rehospitalization, but a statistically significant reduction in one-year rehospitalization. We also found a small reduction in the incidence of recurrent SSTI at both 30 days and one-year. These findings lend further support to the growing literature that MOUDs can improve healthcare utilization and health outcomes that are associated with OUD and should be standard of care for patients with injection-related infections (Hadland et al., 2018; Wakeman et al., 2020).

While there were reductions in the incidence of most primary outcomes, only 30-day rehospitalization and one-year recurrent SSTI outcomes were significant in the adjusted Cox models. Interestingly, MOUD receipt was associated with an increased hazard of 30-day rehospitalization but a decreased hazard of one-year recurrent SSTI. One explanation for the increased hazard of 30-day rehospitalization lies in the causes of rehospitalization between the two groups. People in the MOUD group had a greater proportion of rehospitalizations that was due to either opioid withdrawal or non-fatal overdose at both 30-days and one-year compared to people in the no MOUD group. Unfortunately, we are not able to accurately capture fatal overdoses in this claims dataset because a number of fatal overdoses occur outside the healthcare setting. Nevertheless, this finding demonstrates that post-hospitalization initiation of MOUD is not sufficient to prevent rehospitalization, especially as it relates to OUD. Initiation of MOUD must be accompanied by linkage to care services in order to improve outcomes otherwise it serves only as a temporary bandage that prolonged an inevitable withdrawal or overdose event. Additionally, aside from opioid-related rehospitalizations MOUD initiation may result in a short-term increase in healthcare utilization. For many OUD patients, MOUD allows for stabilization of their use disorder which can allow them to better engage in healthcare and give them an opportunity to prioritize getting medical care for their co-morbidities. This effect may be seen in the short-term when there is overlap between MOUD initiation and rehospitalization.

A couple plausible explanations exist for the decreased hazard of recurrent SSTI. First, only SSTIs for which a medical claim was made were captured. For this to occur, a patient must have received care for an SSTI at a hospital. Many patients with active OUD delay seeking medical care for fear of long wait times, stigma and discrimination, and inadequately treated opioid withdrawal. Some patients choose to attempt to take care of their infection without seeking medical care. In some cases, individuals will lance and drain their own abscess to avoid interacting with the healthcare system (Binswanger, Kral, Bluthenthal, Rybold, & Edlin, 2000; Monteiro et al., 2020). While this may not cause an imbalance in our results (i.e., infections are missed equally in both groups), it does steal power from our analysis. Second, methadone maintenance treatment is only covered by insurance if used for treatment of pain, not for maintenance therapy for OUD. As a result, it is not reliably included in commercial claims data. Since we were unable to determine whether or not an individual was prescribed methadone following hospitalization, those individuals were, therefore, included in the no MOUD group. As such, this may have biased our result toward

the null hypothesis and against the overall effectiveness of MOUDs. These explanations also highlight some of the limitations of the claims database.

There were significant findings among the covariates. First, we note that nearly half of the overall cohort was female (48%). This is a higher proportion than is found in other cohorts of people with OUD (Burnett, Broz, Spiller, Wejnert, & Paz-Bailey, 2018) though similar proportions have been found among injection drug-use associated endocarditis (Barocas et al., 2020; Shah et al., 2020). Further research is needed to explore the possible explanations behind these findings. Second, persons who had a co-occurring substance use disorder were at increased risk compared to those who did not for rehospitalization. Recent evidence suggests that co-occurring substance use disorder is common among persons with opioid-related overdoses (Barocas et al., 2019). Stimulants, benzodiazepines, and alcohol are among the most common substances used in this population. Importantly, many other substance use disorders do not have robust evidence-based pharmacotherapeutic options. Patients may present to the hospital as a result of polysubstance use. This highlights the need for improved pharmacotherapy of other substance use disorders.

A first step in making hospital-based or post-hospitalization MOUD prescribing more common is to demonstrate the potential economic impact to hospitals or healthcare systems. A recent analysis done by MassHealth, the public payor in Massachusetts that includes Medicaid and the Children's Health Insurance Program, found significant savings associated with MOUD treatment. In fiscal year 2017, patients with OUD who were on an MOUD had lower costs than those who were not on an MOUD, which was largely driven by a reduction in acute care service utilization (Harvey & Stoler, 2019). Patients with SSTI frequently require acute care services such as urgent care, emergency departments, and inpatient hospitalization, therefore, hospitals and payors may see additional benefits if these patients are prescribed an MOUD at the time of service receipt.

Another important step in increasing access to MOUD is decreasing provider- and system-level barriers to prescribing. Access to two of the three medications approved by the U.S. Food and Drug Administration (FDA) for OUD—buprenorphine and methadone—is limited by regulations and prescribing requires special training outside of postgraduate programs. In the case of buprenorphine (often co-formulated with naloxone), a “X waiver” from the Drug Enforcement Administration (DEA) is needed. Most physicians do not have a DEA X waiver, and those who do, tend to not prescribe at all (Rapoport et al., 2018). An effort to eliminate the DEA waiver (“X the X Waiver”) is currently underway, which will clear the path for more buprenorphine prescribing, but physician-level barriers will remain. These barriers to prescribing include lack of training or knowledge (Cunningham, Sohler, McCoy, & Kunins, 2006), misperceptions about the feasibility of administering MOUDs in the hospital (Hassamal et al., 2017), and limited resources for the transition to community-based treatment (Winetsky, Weinrieb, & Perrone, 2018). A coordinated effort to integrate treatment for addiction into medical education at all levels, increase awareness of addiction among hospital administrators, and destigmatize addiction in the community at-large is needed.

While MOUDs are crucial, they are just one component of treatment for OUD. These life-saving medications should be included in a package of interventions that have demonstrated

effectiveness including overdose education and naloxone distribution, sterile syringe and injection equipment distribution, safe injection education, behavioral counseling, and HIV and HCV testing (Lurie, Gorsky, Jones, & Shomphe, 1998; Turner et al., 2015; Walley et al., 2013). All of these are low cost interventions that, if coupled with linkage to outpatient services, could significantly reduce healthcare utilization and costs at all levels—for patients, providers, hospitals, and insurance payors. More importantly, such a package would likely reduce morbidity and mortality from overdose and other medical complications of drug use.

There are several limitations to our study. First, MarketScan is a database that includes only commercially insured individuals, which does not include governmental insurance, including Medicare or Medicaid. Medicaid populations in contrast to commercial populations, tend to be younger and more socioeconomically disadvantaged. Given that a growing proportion of persons with OUD are insured through Medicaid (Feder et al., 2017), our estimates may not be generalizable to uninsured or publicly insured populations. Inadequate health insurance coverage for substance use services can be a significant barrier to treatment. Second, MarketScan does not include data on race or ethnicity, so evaluation of confounding by these variables was not possible. As the opioid epidemic continues to evolve and disproportionately affect black and Latinx populations (Alexander, Kiang, & Barbieri, 2018; Barocas et al., 2019), future studies should evaluate disparities in outcomes in these populations compared to the white, non-Latinx population. Third, our strict inclusion and exclusion criteria for this cohort may have limited the statistical power. Our definition, however, allowed us to understand the impact of MOUDs on individuals with OUD who were not recently on treatment. Additionally, we are not able to determine if MOUD were initiated during the hospitalization though previous studies have demonstrated low rates of inpatient initiation of MOUD (Rosenthal et al., 2016). We also examined the combined effect of buprenorphine and naltrexone rather than the effect of each on the stated outcomes. There were so few naltrexone prescriptions in this group that it would be difficult to derive any meaningful results by examining the separate effects. Finally, while we used a strong statistical design, we cannot rule out the possibility of unmeasured confounders that may exist in any observational study.

5. Conclusions

In conclusion, we found an impact of post-hospitalization MOUD receipt among persons with OUD hospitalized for SSTI. Our study design enabled the analysis to characterize both changes in incidence in rehospitalization and recurrent infection, as well as significant changes in time to event for acute rehospitalization and long-term recurrent SSTI. These results contribute to the nascent but growing body of evidence that MOUD receipt around the time of an acute infection or hospitalization can improve health outcomes, but will also impact healthcare utilization. MOUDs are but one component of a potential bundle of evidence-based interventions for hospitalized persons with OUD. Further expansion of these in-hospital services and development of patient-tailored approaches to address barriers to receipt and retention in treatment, could provide an effective tool in the U.S. response to the opioid epidemic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

This work was supported by the National Institute on Drug Abuse at the National Institutes of Health [1K01DA051684-01 to J.A.B.; R01DA046527 to B.P.L.; R01DA046527-02S1 to J.A.B., M.J.G.; and P30DA040500 to B.P.L.] and the Charles A. King Trust to J.A.B.

6. References

- Alexander MJ, Kiang MV, & Barbieri M (2018). Trends in Black and White Opioid Mortality in the United States, 1979-2015. *Epidemiology*, 29(5), 707–715. doi:10.1097/EDE.0000000000000858 [PubMed: 29847496]
- Atkins A, McClung RP, Kilkenny M, Bernstein K, Willenburg K, Edwards A, ... Oster AM. (2020). Notes from the Field: Outbreak of Human Immunodeficiency Virus Infection Among Persons Who Inject Drugs - Cabell County, West Virginia, 2018-2019. *MMWR Morb Mortal Wkly Rep*, 69(16), 499–500. doi:10.15585/mmwr.mm6916a2 [PubMed: 32324723]
- Barocas JA, Morgan JR, Wang J, McLoone D, Wurcel A, & Stein MD (2020). Outcomes Associated with Medications for Opioid Use Disorder Among Persons Hospitalized for Infective Endocarditis. *Clin Infect Dis*. doi:10.1093/cid/ciaa062
- Barocas JA, Wang J, Marshall BDL, LaRochelle MR, Bettano A, Bernson D, ... Walley AY. (2019). Sociodemographic factors and social determinants associated with toxicology confirmed polysubstance opioid-related deaths. *Drug Alcohol Depend*, 200, 59–63. doi:10.1016/j.drugalcdep.2019.03.014 [PubMed: 31100636]
- Binswanger IA, Kral AH, Bluthenthal RN, Rybold DJ, & Edlin BR (2000). High prevalence of abscesses and cellulitis among community-recruited injection drug users in San Francisco. *Clin Infect Dis*, 30(3), 579–581. doi:10.1086/313703 [PubMed: 10722447]
- Burnett JC, Broz D, Spiller MW, Wejnert C, & Paz-Bailey G (2018). HIV Infection and HIV-Associated Behaviors Among Persons Who Inject Drugs - 20 Cities, United States, 2015. *MMWR Morb Mortal Wkly Rep*, 67(1), 23–28. doi:10.15585/mmwr.mm6701a5 [PubMed: 29324726]
- Centers for Disease, C., & Prevention. (2011). Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morb Mortal Wkly Rep*, 60(43), 1487–1492. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/22048730> [PubMed: 22048730]
- Ciccarone D, Unick GJ, Cohen JK, Mars SG, & Rosenblum D (2016). Nationwide increase in hospitalizations for heroin-related soft tissue infections: Associations with structural market conditions. *Drug Alcohol Depend*, 163, 126–133. doi:10.1016/j.drugalcdep.2016.04.009 [PubMed: 27155756]
- Collier MG, Doshani M, & Asher A (2018). Using Population Based Hospitalization Data to Monitor Increases in Conditions Causing Morbidity Among Persons Who Inject Drugs. *J Community Health*. doi:10.1007/s10900-017-0458-9
- Cranston K, Alpre C, John B, Dawson E, Roosevelt K, Burrage A, ... DeMaria A Jr. (2019). Notes from the Field: HIV Diagnoses Among Persons Who Inject Drugs - Northeastern Massachusetts, 2015-2018. *MMWR Morb Mortal Wkly Rep*, 66(10), 253–254. doi:10.15585/mmwr.mm6810a6
- Cunningham CO, Sohler NL, McCoy K, & Kunins HV (2006). Attending physicians' and residents' attitudes and beliefs about prescribing buprenorphine at an urban teaching hospital. *Fam Med*, 38(5), 336–340. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/16673195> [PubMed: 16673195]
- Fanucchi LC, Walsh SL, Thornton AC, Nuzzo PA, & Lofwall MR (2019). Outpatient Parenteral Antimicrobial Therapy Plus Buprenorphine for Opioid Use Disorder and Severe Injection-Related Infections. *Clin Infect Dis*. doi:10.1093/cid/ciz654
- Feder KA, Mojtabai R, Krawczyk N, Young AS, Kealhofer M, Tormohlen KN, & Crum RM (2017). Trends in insurance coverage and treatment among persons with opioid use disorders following the

- Affordable Care Act. *Drug Alcohol Depend*, 179, 271–274. doi:10.1016/j.drugalcdep.2017.07.015 [PubMed: 28823834]
- Golden MR, Lechtenberg R, Glick SN, Dombrowski J, Duchin J, Reuer JR, ... Buskin SE. (2019). Outbreak of Human Immunodeficiency Virus Infection Among Heterosexual Persons Who Are Living Homeless and Inject Drugs - Seattle, Washington, 2018. *MMWR Morb Mortal Wkly Rep*, 68(15), 344–349. doi:10.15585/mmwr.mm6815a2 [PubMed: 30998671]
- Gray ME, Rogawski McQuade ET, Scheld WM, & Dillingham RA (2018). 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*, 18(1), 532. doi:10.1186/s12879-018-3408-y [PubMed: 30355291]
- Hadland SE, Bagley SM, Rodean J, Silverstein M, Levy S, Larochelle MR, ... Zima BT. (2018). Receipt of Timely Addiction Treatment and Association of Early Medication Treatment With Retention in Care Among Youths With Opioid Use Disorder. *JAMA Pediatr*. doi:10.1001/jamapediatrics.2018.2143
- Harvey P, & Stoler A (2019). MassHealth Medication Assisted Treatment Analysis: MAT Commission Presentation. MassHealth. Massachusetts Retrieved from <https://www.mass.gov/files/documents/2019/05/22/MAT-Slides-5-21-MassHealth.pdf>
- Hassamal S, Goldenberg M, Ishak W, Haglund M, Miotto K, & Danovitch I (2017). 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*, 23(3), 221–229. doi:10.1097/PRA.0000000000000231 [PubMed: 28492461]
- Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M (2018). Drugs most frequently involved in drug overdose deaths: United States, 2011-2016. Retrieved from Hyattsville, MD:
- LaRochelle MR, Bernstein R, Bernson D, Land T, Stopka TJ, Rose AJ, ... Walley AY. (2019). Touchpoints – opportunities to predict and prevent opioid overdose: a cohort study. *Drug Alcohol Depend*, Epub ahead of print.
- Lurie P, Gorsky R, Jones TS, & Shomphe L (1998). An economic analysis of needle exchange and pharmacy-based programs to increase sterile syringe availability for injection drug users. *J Acquir Immune Defic Syndr Hum Retrovirol*, 18 Suppl 1, S126–132. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/9663635> [PubMed: 9663635]
- Micromedex Solutions, 2018 Drug Topics Red Book. (2018). Retrieved from www.micromedexsolutions.com
- Miller AC, & Polgreen PM (2018). 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*. doi:10.1093/cid/ciy632
- Monteiro J, Phillips KT, Herman DS, Stewart C, Keosaian J, Anderson BJ, & Stein MD (2020). Self-treatment of skin infections by people who inject drugs. *Drug Alcohol Depend*, 206, 107695. doi:10.1016/j.drugalcdep.2019.107695 [PubMed: 31786397]
- Morgan JR, Schackman BR, Weinstein ZM, Walley AY, & Linas BP (2019). Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. *Drug Alcohol Depend*, 200, 34–39. doi:10.1016/j.drugalcdep.2019.02.031 [PubMed: 31082666]
- Njoroge LW, Al-Kindi SG, Koromia GA, ElAmm CA, & Oliveira GH (2018). Changes in the Association of Rising Infective Endocarditis With Mortality in People Who Inject Drugs. *JAMA Cardiol*, 3(8), 779–780. doi:10.1001/jamacardio.2018.1602 [PubMed: 29926083]
- Peters PJ, Pontones P, Hoover KW, Patel MR, Galang RR, Shields J, ... Indiana, H. I. V. O. I. T. (2016). HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015. *N Engl J Med*, 375(3), 229–239. doi:10.1056/NEJMoa1515195 [PubMed: 27468059]
- Priest KC, Lovejoy TI, Englander H, Shull S, & McCarty D (2020). Opioid Agonist Therapy During Hospitalization Within the Veterans Health Administration: a Pragmatic Retrospective Cohort Analysis. *J Gen Intern Med*. doi:10.1007/s11606-020-05815-0
- Rapoport AB, Fischer LS, Santibanez S, Beekmann SE, Polgreen PM, & Rowley CF (2018). Infectious Diseases Physicians' Perspectives Regarding Injection Drug Use and Related Infections,

- United States, 2017. *Open Forum Infect Dis*, 5(7), ofy132. doi:10.1093/ofid/ofy132 [PubMed: 30018999]
- Ronan MV, & Herzig SJ (2016). Hospitalizations Related To Opioid Abuse/Dependence And Associated Serious Infections Increased Sharply, 2002-12. *Health Aff (Millwood)*, 35(5), 832–837. doi:10.1377/hlthaff.2015.1424 [PubMed: 27140989]
- Rosenthal ES, Karchmer AW, Theisen-Toupal J, Castillo RA, & Rowley CF (2016). Suboptimal Addiction Interventions for Patients Hospitalized with Injection Drug Use-Associated Infective Endocarditis. *Am J Med*, 129(5), 481–485. doi:10.1016/j.amjmed.2015.09.024 [PubMed: 26597670]
- Rudd RA, Seth P, David F, & Scholl L (2016). Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*, 65(5051), 1445–1452. doi:10.15585/mmwr.mm655051e1 [PubMed: 28033313]
- Shah M, Wong R, Ball L, Puka K, Tan C, Shojaei E, ... Silverman M (2020). Risk factors of infective endocarditis in persons who inject drugs. *Harm Reduct J*, 17(1), 35. doi:10.1186/s12954-020-00378-z [PubMed: 32503573]
- Shanahan CW, Beers D, Alford DP, Brigandi E, & Samet JH (2010). A transitional opioid program to engage hospitalized drug users. *J Gen Intern Med*, 25(8), 803–808. doi:10.1007/s11606-010-1311-3 [PubMed: 20237960]
- Suzuki J (2016). Medication-assisted treatment for hospitalized patients with intravenous-drug-use related infective endocarditis. *Am J Addict*, 25(3), 191–194. doi:10.1111/ajad.12349 [PubMed: 26991660]
- Tan SY, Feng JY, Joyce C, Fisher J, & Mostaghimi A (2020). Association of Hospital Discharge Against Medical Advice With Readmission and In-Hospital Mortality. *JAMA Netw Open*, 3(6), e206009. doi:10.1001/jamanetworkopen.2020.6009 [PubMed: 32525546]
- Turner BJ, Taylor BS, Hanson JT, Perez ME, Hernandez L, Villarreal R, ... Fiebelkorn K (2015). Implementing hospital-based baby boomer hepatitis C virus screening and linkage to care: Strategies, results, and costs. *J Hosp Med*, 10(8), 510–516. doi:10.1002/jhm.2376 [PubMed: 26033458]
- Wakeman SE, Larochelle MR, Ameli O, Chaisson CE, McPheeters JT, Crown WH, ... Sanghavi DM. (2020). Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. *JAMA Netw Open*, 3(2), e1920622. doi:10.1001/jamanetworkopen.2019.20622 [PubMed: 32022884]
- Walley AY, Xuan Z, Hackman HH, Quinn E, Doe-Simkins M, Sorensen-Alawad A, ... Ozonoff A (2013). Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ*, 346, f174. doi:10.1136/bmj.f174 [PubMed: 23372174]
- Winetsky D, Weinrieb RM, & Perrone J (2018). Expanding Treatment Opportunities for Hospitalized Patients with Opioid Use Disorders. *J Hosp Med*, 13(1), 62–64. doi:10.12788/jhm.2861 [PubMed: 29073311]
- Zibbell JE, Asher AK, Patel RC, Kupronis B, Iqbal K, Ward JW, & Holtzman D (2018). Increases in Acute Hepatitis C Virus Infection Related to a Growing Opioid Epidemic and Associated Injection Drug Use, United States, 2004 to 2014. *Am J Public Health*, 108(2), 175–181. doi:10.2105/AJPH.2017.304132 [PubMed: 29267061]

Highlights

Only 5.5% of people received medications for opioid use disorder in the month following their index skin and soft tissue infection hospitalization.

30-day rehospitalization incidence was higher in the medication group compared to no medication (35.9 vs 27.5 per 100 person-30 days) and one-year infection recurrence was lower (10.3 vs 18.7 per 100 person-years).

There was a statistically significant increased hazard in 30-day rehospitalization and a reduced hazard in one-year skin and soft tissue infection recurrence in people who received medications for opioid use disorder compared to those who did not.

Figure 1. Kaplan-Meier curve of a) 30-day rehospitalization and b) 1-year recurrent SSTI for persons who received MOUDs following hospitalization compared to no MOUDs

1a. 30-day rehospitalization

1b. 1 year recurrent SSTI

NOTES: Time-to-event analysis for 30-day rehospitalization (Figure 1a) and 1-year recurrent SSTI (Figure 1b) comparing individuals with SSTI who received MOUDs in the post-hospitalization period to those who did not receive MOUDs. Controlling for covariates, those who received MOUDs (red line) had a significantly higher risk of 30 day rehospitalization and reduced risk of one-year recurrent SSTI than those who did not receive MOUDs (blue line).

Table 1.

Characteristics of cohort of individuals with OUD who were hospitalized for SSTI, 2010-2017

	Total	No MOUD	MOUD in 30 days	p-value
Overall number	6538	6181 (94.5)	357 (5.5)	
Age (mean years $\pm$ SD)	40 ($\pm$ 14.5)	40 ($\pm$ 14.5)	30 ($\pm$ 11.4)	<0.0001
Length of Stay (median days, IQR)	4 (5)	4 (6)	4 (4)	
Sex, n (%)				
Male	3400 (52.0)	3210 (51.9)	190 (53.2)	0.64
Female	3138 (48.0)	2971 (48.1)	167 (46.8)	
Region, n (%)				
Northeast	1324 (20.3)	1252 (20.3)	72 (20.2)	0.005
North Central	1258 (19.2)	1164 (18.8)	94 (26.3)	
South	2686 (41.1)	2557 (41.4)	129 (36.1)	
West	1270 (19.4)	1208 (19.5)	62 (17.4)	
Insurance Type, n (%)				
HMO	776 (11.9)	733 (11.9)	43 (12.0)	0.73
POS	479 (7.3)	448 (7.3)	31 (8.7)	
PPO	3871 (59.2)	3667 (59.3)	204 (57.1)	
Other	1412 (21.6)	1333 (21.6)	79 (22.1)	
SSTI Procedure, n (%)				
No	5651 (86.4)	5321 (86.1)	330 (92.4)	0.0007
Yes	887 (13.6)	860 (13.9)	27 (7.6)	
Other Substance Use Disorders ^a , n (%)				
No	5817 (89.0)	5529 (89.5)	288 (80.7)	<0.0001
Yes	721 (11.0)	652 (10.6)	69 (19.3)	

NOTES: HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization^aDefined 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 Supplementary Appendix eTable 4.

Table 2.

Results of Cox hazards model for 30-day all-cause rehospitalization.

	Adjusted hazard ratio	95% confidence interval		p-value
<i>Treatment</i>				
MOUD within 4 weeks	1.29	1.05	1.59	0.02
No MOUD within 4 weeks	<i>Reference</i>			
<i>Clinical characteristics</i>				
Other substance use disorder ^a				
Yes	1.29	1.11	1.50	<0.01
No	<i>Reference</i>			
SSTI procedure				
Yes	1.80	1.58	2.05	<0.01
No	<i>Reference</i>			
Hospital interruption ^b				
Yes	5.15	4.40	6.02	<0.01
No	<i>Reference</i>			
<i>Non-clinical characteristics</i>				
Age (years)	1.0	0.99	1.00	0.84
Sex				
Male	<i>Reference</i>			
Female	1.25	1.13	1.39	<0.01
Region				
Northeast	<i>Reference</i>			
North Central	0.96	0.82	1.12	0.57
South	0.79	0.69	0.91	<0.01
West	0.92	0.78	1.08	0.28
Insurance Type				
POS	<i>Reference</i>			
PPO	0.99	0.82	1.12	0.96
HMO	0.96	0.69	0.91	0.72
Other	1.10	0.78	1.08	0.41

NOTES: MOUD = medication for opioid use disorder; HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization

^aDefined as evidence of another substance use disorder (including alcohol, cannabis, hallucinogens, or sedatives). Complete list of ICD-9 and ICD-10 codes found in Supplementary Appendix eTable 4.

^bInterruption of index hospitalization 5 days

Table 3.

Results of Cox hazards model for one-year recurrent skin and soft tissue infection (SSTI).

	Adjusted hazard ratio	95% confidence interval		p-value
<i>Treatment</i>				
MOUD within 4 weeks	0.62	0.42	0.91	0.01
No MOUD within 4 weeks	<i>Reference</i>			
<i>Clinical characteristics</i>				
Other substance use disorder ^a				
Yes	0.89	0.71	1.12	0.33
No	<i>Reference</i>			
SSTI procedure				
Yes	1.75	1.48	2.06	<0.01
No	<i>Reference</i>			
Hospital interruption ^b				
Yes	1.27	0.94	1.72	0.12
No	<i>Reference</i>			
<i>Non-clinical characteristics</i>				
Age (years)	1.01	1.01	1.01	<0.01
Sex				
Male	<i>Reference</i>			
Female	1.10	0.96	1.25	0.18
Region				
Northeast	<i>Reference</i>			
North Central	0.92	0.74	1.14	0.43
South	0.85	0.71	1.02	0.08
West	1.00	0.81	1.24	0.99
Insurance Type				
POS	<i>Reference</i>			
PPO	1.03	0.79	1.34	0.84
HMO	1.14	0.83	1.56	0.42
Other	1.06	0.79	1.41	0.71

NOTES: MOUD = medication for opioid use disorder; HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization

^aDefined as evidence of another substance use disorder (including alcohol, cannabis, hallucinogens, or sedatives). Complete list of ICD-9 and ICD-10 codes found in Supplementary Appendix eTable 4.

^bInterruption of index hospitalization 5 days