Evaluation of Clinical Outcomes of Intravenous Drug Use-Related Infective Endocarditis in Buprenorphine-Treated Patients

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ABSTRACT – Purpose: Intravenous drug use (IVDU) is an independent risk factor for infective endocarditis (IE). IVDU-related IE is associated with poor clinical outcomes, such as infection-related and drug abuse-related readmissions and mortality. Critical interventions to treat addiction, such as medication for opioid use disorder (MOUD) with buprenorphine, may prevent these unfavorable outcomes. This study aimed to establish the effectiveness of buprenorphine prescriptions at hospital discharge for patients admitted for IVDU-related IE. **Methods:** A single center, retrospective cohort study evaluated the effectiveness of discharge prescriptions of buprenorphine in adult patients (≥18 years of age) with OUD and IVDU-related IE. Outcomes of 30-day readmissions, 180-day readmissions, and mortality were compared to a cohort of patients who were not prescribed buprenorphine at hospital discharge. **Results:** The primary endpoint of all cause 30-day readmission was lower in patients who received buprenorphine (n=11/122, 9%) at hospital discharge for IVDU-related IE compared to those who did not (n=9/48, 19%), although not statistically significant (unadjusted OR 0.429, 95% CI 0.165-1.138, p=0.082). After accounting for intensive care admission, infusion unit admission, and psychiatry consultation, the odds of all cause 30-day readmission were statistically lower in patients prescribed buprenorphine (adjusted OR 0.337, 95% CI 0.125-0.909, p=0.029). Additionally, significantly more patients prescribed buprenorphine at discharge followed-up in an outpatient treatment program, 57% and 15% respectively (p<0.001). Incidence of readmission at 180 days and mortality was similar between the two cohorts. **Conclusions:** This study demonstrated that buprenorphine prescriptions at hospital discharge in patients with OUD admitted for IVDU-related IE were effective at decreasing readmission rates at 30 days and increasing outpatient treatment follow-up. Therefore, it is imperative that an emphasis on addiction-focused interventions, such as initiating buprenorphine, be considered in this patient population at hospital discharge to decrease hospital readmissions and engage patients in outpatient treatment for OUD. This study is the first to evaluate the effects of MOUD on readmission rates for patients hospitalized with IVDU-related IE and contributes to the growing body of evidence to support addiction-focused interventions for this unique patient population.

INTRODUCTION

Infective endocarditis (IE) carries a high morbidity and mortality. Intravenous drug use (IVDU) carries a 100-fold increased risk for IE relative to the general population (1). Since 2003, the incidence of IVDU-related IE in the United States increased by approximately 10 to 15% (2, 3). IVDU-related IE is associated with poor clinical outcomes including increased hospital length of stay, increased health care costs, infection-related and drug abuse-related readmissions, and mortality. Reports of thirty-day readmission rates for IVDU-related IE are as high as 23.8% (2). Compared to medically managed non-IVDU-related IE, IVDU-related IE is associated with significantly higher rates of readmission for endocarditis, septicemia, and drug abuse (absolute relative risk of 12.5%, 6.7%, and 3.6%, respectively, p < 0.001) (2). For these reasons, addiction treatment warrants as much attention as acute management for IVDU-related IE.

Addiction treatment includes psychosocial supports, harm reduction strategies, and medication for opioid use disorder (MOUD). MOUD with buprenorphine, methadone, and naltrexone have proven advantageous in treating patients with substance abuse disorders (4). Buprenorphine is a

partial mu-opioid receptor agonist that is beneficial in decreasing physical dependency to opioids, preventing withdrawal symptoms, decreasing cravings, and increasing treatment retention (4). Comparatively to other MOUD options, buprenorphine is associated with lower incidences of overdose and lower potential for misuse (5). Additionally, buprenorphine has been shown to reduce the risk of infection and decrease risk of mortality in patients with IVDU-related IE who continued to receive treatment following hospital discharge (6, 7). Despite known benefits, access to MOUD in the context of acute hospitalization remains limited. Initiation of buprenorphine during hospitalization and continuation at discharge for IVDU-related IE may improve clinical outcomes following hospital discharge.

West Virginia leads the nation in opioid abuse and misuse. The incidence of opioid-related overdose death more than doubles the national average, 42.4 versus 20.7 incidences per 100,000 persons (4). Healthcare providers in West Virginia are more likely to encounter patients with active IVDU and subsequent complications, such as IE. West Virginia was recently successful in increasing buprenorphine treatment capacity by systematically supporting the expansion of training opportunities and resources available to healthcare providers throughout the state (4). These initiatives make it easier to initiate therapy during hospitalization and enroll patients in outpatient treatment programs. This is one of few studies evaluating clinical outcomes with addiction-focused clinical interventions in IVDU-related IE, and the first study to examine the effects of buprenorphine on readmission rates for this unique patient population. By addressing addiction treatment and providing prescriptions for buprenorphine at hospital discharge for patients with IVDU-related IE and OUD, it is hypothesized that fewer patients will require readmission.

METHODS

Study Design and Participants

The local institutional review board at West Virginia University approved this study. This single center, retrospective study included adult patients ($\geq$18 years of age) with documented opioid use disorder (OUD) admitted for IVDU-related IE from January 2014 to June 2020. Documented completion of antimicrobial therapy for IE was required for study inclusion. Exclusion criteria included pregnancy, incarceration immediately prior to or following index

hospitalization, or death during index hospitalization. Patients were stratified into two groups based on whether they had documented buprenorphine prescriptions at discharge.

Data were collected by a single investigator from electronic medical records and recorded using a standardized data collection form in Microsoft Excel. Collected data were reviewed by three additional investigators for completeness and accuracy. Data evaluated included baseline demographics, psychiatric comorbid conditions of interest, urine drug screen results, infecting microorganisms, coinfection with human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus, hospital length of stay, distance from home, admission to an intensive care unit, and admission to the inpatient infusion unit. The inpatient infusion unit cares for medical patients with long-term antimicrobial infusion requirements, which oftentimes includes patients suffering behavioral health maladies such as substance abuse disorder. Patients admitted to this unit have a dedicated primary medical service with medicine and infectious diseases training and a dedicated substance use disorder service which provides a comprehensive, multidisciplinary focus to care for this unique patient population. Addiction-focused services include individual and group therapy with psychiatry and addiction specialists, peer recovery coaches, weekly Narcotics Anonymous meetings, and intensive inpatient drug detoxification. The unit is staffed with trained personnel familiar with this population that aid in reducing stigma related to their disease while hospitalized, and work to overcome barriers to successful hospital discharge by coordinating outpatient treatment follow-up, referrals to acute rehabilitation facilities, sober living housing, and recovery community networks, transportation, and prescription insurance coverage for buprenorphine. Other services are available to address the physical, spiritual, and holistic needs of this unique patient population.

The primary endpoint of the study was the incidence of all cause 30-day readmissions. Secondary endpoints included the incidence of all cause 180-day readmissions, incidence of drug abuse related-readmissions within 180 days, infection-related readmissions within 180 days, and mortality at any time point following index hospitalization for IVDU-related IE. Drug abuse related-readmissions was defined as overdose, intoxication-related injury or trauma, or elective detoxification. Infection-

related readmission was defined as infective endocarditis and skin and soft tissue infections.

Statistical Analysis

Categorical data were expressed as percentages and continuous data as percentiles. Baseline characteristics were evaluated using a Wilcoxon rank sum test for continuous variables and Chi-squared test, or Fisher's exact if needed, for categorical variables. Clinical outcomes were evaluated for significance using Fisher's exact test. In addition to univariate logistic regression analysis, multivariable logistic regression analysis was performed to investigate the association between outcomes of interest and buprenorphine prescriptions status at discharge controlling for confounding effects from intensive care admission, infusion unit admission, and psychiatry consultation. Results from the multivariable logistic regression analysis were reported as odds ratios and 95% confidence intervals (95% CI). The significance level was set at 0.05. All statistical analyses were performed in SAS 9.4 (SAS Institute, Cary NC).

RESULTS

From January 2014 to June 2020, 305 patients were identified and met inclusion criteria. After exclusion criteria were applied, a total of 170 patients with a history of OUD and a qualifying hospital admission for IVDU-related IE were included in the final analysis. Most patients were excluded from this analysis due to leaving against medical advice (AMA), and subsequently not completing antimicrobial therapy (18%, n=55). Other reasons for exclusion are listed in Figure 1. Of the patients included in the analysis, 122 (71.7%) were prescribed buprenorphine at hospital discharge and 48 (28.3%) were not prescribed buprenorphine. Baseline characteristics differed between the two groups; however, both groups remained well matched with regards to age, infectious diseases consultation, cardiac surgery consultation, infecting organisms, findings on urine drug screen, hospital length of stay, distance from home, and insurance status (Table 1). The population consisted mostly of female patients (60%) with a median age of 33 years (IQR 28-38 years) treated with intravenous antimicrobials for a hospital length of stay of 49 days (IQR 44-53 days) and lived within 131 miles (IQR 51-191 miles) from the hospital. Majority of patients (78%) were Medicaid beneficiaries. Patients in the buprenorphine treated group tended to be admitted to the inpatient infusion unit (95%) and engaged with psychiatry during admission (99%). Patients not prescribed buprenorphine at discharge tended to have significantly higher rates of intensive care unit admission (67%).
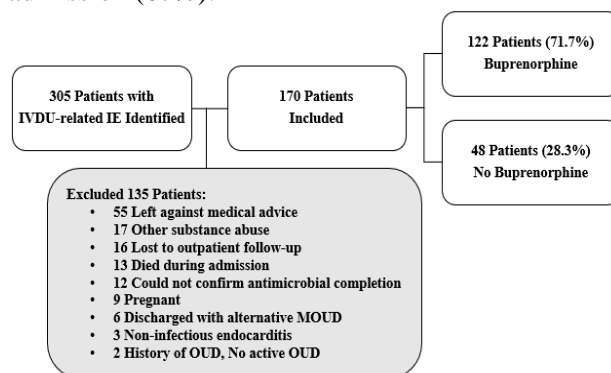

Figure 1. Study Methodology

A total of 20 incidences of the primary endpoint occurred. The primary endpoint of all cause 30-day readmissions was numerically lower in patients prescribed buprenorphine at discharge (9%) compared to 19% of patients who were not prescribed buprenorphine at discharge, although not statistically different (unadjusted OR 0.429, 95% CI 0.165-1.138, p=0.082) (Table 2). Key secondary endpoints did not clinically or statistically differ between the two groups. The incidence of all cause 180-day readmissions in the buprenorphine prescribed group was 31% compared to 38% in the no prescription of buprenorphine at discharge (unadjusted OR 0.754, 95% CI 0.376-1.532, p=0.4280). There were no differences for drug abuse related readmissions at 180-days (unadjusted OR 0.907, 95% CI 0.339-2.704, p=0.852) and infection-related readmissions at 180-days (unadjusted OR 1.080, 95% CI 0.423-2.940, p=0.872). Mortality at any time point following index hospitalization was also not statistically different (unadjusted OR 0.580 95% CI 0.093-4.508, p=0.558). While not an original endpoint of this evaluation, patients who were prescribed buprenorphine at hospital discharge tended to follow-up in an outpatient opioid treatment clinic compared to those who were not prescribed buprenorphine (57% and 15%, respectively, p<0.001).

Multivariable logistic regression was performed to attempt to control for confounding variables of ICU admission, infusion unit admission, and psychiatry consultation (Table 3). When adjusted for these confounding variables, the odds of

Table 1. Baseline Characteristics

Demographic	Buprenorphine (n = 122)	No Buprenorphine (n = 48)	P-Value
Age, Median (IQR)	33 (28-37)	32 (29-39)	0.398
Female Sex, n (%)	73 (60)	33 (67)	0.516
Comorbid Conditions, n (%)			
Anxiety	52 (43)	12 (25)	0.050
Bipolar Disorder	16 (13)	4 (8)	0.544
Depression	47 (39)	19 (40)	0.999
Polysubstance Abuse	85 (70)	27 (57)	0.185
Post-Traumatic Stress Disorder	20 (16)	7 (15)	0.954
Schizophrenia	3 (3)	2 (4)	0.929
ICU Admission, n (%)	56 (46)	32 (67)	0.023
Infusion Unit Admission, n (%)	116 (95)	40 (83)	0.028
Outpatient Clinic Follow-up, n (%)	70 (57)	7 (15)	<0.001
Consultations, n (%)			
Psychiatry	121 (99)	44 (92)	0.035
Infectious Diseases	121 (99)	46 (96)	0.398
Outpatient Parenteral Antimicrobial Therapy	26 (21)	11 (23)	0.983
Cardiac Surgery	110 (90)	44 (92)	0.992
Coinfections, n (%)			
Hepatitis B	12 (10)	4 (8)	0.992
Hepatitis C	67 (55)	19 (40)	0.103
HIV	4 (3)	2 (4)	0.999
Microorganisms, n (%)			
Staphylococcal species	64 (53)	20 (42)	0.273
Streptococcal species	15 (12)	5 (10)	0.938
Enterococcal species	1 (1)	4 (8)	0.035
Gram-Negative Organism	15 (12)	3 (6)	0.381
Other bacterial species	4 (3)	0 (0)	0.479
Candida species	3 (2)	2 (4)	0.929
Urine Drug Screen Findings, n (%)			
Amphetamines	31 (25)	7 (15)	-
Benzodiazepines	17 (14)	11 (23)	-
Buprenorphine	41 (34)	10 (21)	-
Cannabinoids	16 (13)	6 (13)	-
Opiates	58 (48)	26 (54)	-
Heroin	1 (1)	0 (0)	-
Fentanyl	5 (4)	0 (0)	-
Methadone	1 (1)	0 (0)	-
Oxycodone	9 (7)	4 (8)	-
None	25 (20)	15 (31)	-
Rifampin Use, n (%)	8 (7)	2 (4)	0.851
Hospital Length of Stay (days), Median (IQR)	49 (44-54)	47 (39-52)	0.130
Distance from Home (miles), Median (IQR)	139 (53-192)	103 (46-173)	0.351
Medicaid Insurance, n (%)	99 (81)	34 (71)	0.153

HIV: human immunodeficiency virus, ICU: intensive care unit, IQR: Interquartile range

all cause 30-day readmissions for patients prescribed buprenorphine at discharge were 33.7% compared to those who were not prescribed buprenorphine (OR 0.337, 95% CI 0.125-0.909, p=0.029). No difference was observed for incidence of all cause 180-day readmission (OR 0.692, 95% CI 0.330-1.464, p=0.330), drug abuse related 180-day readmission (OR 0.717, 95% CI 0.264-2.113, p=0.520), infection related 180-day readmission (OR 1.032, 95% CI 0.415-2.783, p=0.948), and mortality following hospital discharge (OR 0.603, 95% CI 0.415-2.783, p=0.536).

DISCUSSION

This is the first study designed to examine the effects of buprenorphine on readmission rates for OUD in patients hospitalized for IVDU-related IE. Additionally, this is one of few studies evaluating clinical outcomes with addiction-focused clinical interventions in IVDU-related IE. The results demonstrate an absolute risk reduction of 10% in all cause 30-day readmission in patients prescribed buprenorphine at hospital discharge compared to those who were not, although not statistically significant. However, prescriptions for buprenorphine at hospital discharge was associated with statistically and clinically significant increases in outpatient treatment follow-up for OUD. The results showed no statistically significant differences in the incidences of all cause, drug abuse-related, and infection-related readmissions at 180-days and mortality at any time point following index hospitalization for IVDU-related IE.

Table 2. Univariable logistic regression analysis of primary and secondary endpoint

Endpoint	Buprenorphine (n = 122)	No Buprenorphine (n = 48)	OR (95% CI)	P-Value
All Cause 30-Day Readmission, n (%)	11 (9)	9 (19)	0.429 (0.165-1.138)	0.082
Secondary Endpoints (180-Day Readmission), n (%)				
All Cause Readmission	38 (31)	18 (38)	0.754 (0.376-1.532)	0.428
Drug Abuse Related Readmission	14 (11)	6 (13)	0.907 (0.339-2.704)	0.852
Infection Related Readmission	19 (16)	7 (15)	1.080 (0.423-2.940)	0.872
Mortality following hospital discharge	3 (2)	2 (4)	0.580 (0.093-4.508)	0.558

CI: Confidence interval, IQR: Interquartile range, OR: Odds ratio

Table 3. Multivariable logistic regression analysis of primary and secondary endpoints controlling for potential confounding effects from ICU admission, infusion service admission, and psychiatric consultation

Endpoint	OR (95% CI)	P-Value
All Cause 30-Day Readmission, n (%)	0.337 (0.125-0.909)	0.029
Secondary Endpoints (180-Day Readmission), n (%)		
All Cause Readmission	0.692 (0.330-1.464)	0.330
Drug Abuse Related Readmission	0.717 (0.264-2.113)	0.520
Infection Related Readmission	1.032 (0.415-2.783)	0.948
Mortality following hospital discharge	0.603 (0.108-3.881)	0.536

CI: Confidence interval, IQR: Interquartile range, OR: Odds ratio

Drug abuse is one of the major reasons for 30-day and 180-day readmissions in IVDU-related IE (2). Other common causes of readmission include recurrent and new infections that may be related to persistent drug abuse. The overall incidence of drug abuse-related readmission in this analysis was 5.9% at 180 days and is consistent with previous reports (2, 8, 9, 10). However, this statistic is likely an underestimation due to strict definitions of admission for drug abuse and is not reflective of probable indicators for persistent drug abuse. Rarely are addiction services offered during hospitalization for IVDU-related IE. One institution reports that less than 25% of patients received a consultation by an addiction or psychiatry specialist during hospitalization for IVDU-related IE, 55.9% of patients' discharge summary plans address addiction, and 7.8% of patients had a plan for MOUD following hospitalization for IVDU-related IE (11). Comparatively, patients included in this analysis were frequently evaluated by psychiatry (97%), admitted to the inpatient infusion unit (92%), and arranged outpatient treatment clinic follow-up (45%). Additionally, more patients in this cohort were prescribed buprenorphine at discharge (72%).

One retrospective observational review evaluated the effects on inpatient MOUD on discharges AMA and readmission rates (12). Patients included in this analysis were admitted for IVDU-related complications, of which IE only accounted for 21.8% (n=32) of admissions. MOUD included methadone and buprenorphine. Inpatient MOUD led to decreased rates of AMA discharges compared to individuals receiving supportive care (RR 0.50, 95% CI 0.34-0.74). Additionally, all cause 30-day readmission rates were lower in patients who were prescribed MOUD at discharge compared to those who were not, 18.8% and 35.1%, respectively (RR 0.54, 95% CI 0.32-0.96). All cause 90-day readmission was not statistically significantly different between these two cohorts (27.3% vs. 42.7%, RR 0.64, 95% CI 0.40-1.03). Another retrospective review evaluated MOUD use on mortality after hospitalization of IVDU-related IE. MOUD included buprenorphine, methadone, and naltrexone received within three months after IVDU-related IE hospitalizations (7). Only 24.3% (n=165) of patients were prescribed MOUD following hospitalizations for IVDU-related IE. Of these patients, 67.9% (n=112) received buprenorphine. Mortality rate was 9.2 deaths per 100 person-years, and MOUD within 3 months after discharge was not associated with reduced mortality (adjusted HR 1.29, 95% CI 0.61-2.72). However, MOUD was associated with reduced mortality in the month that the patient received therapy (adjusted HR 0.30, 95% CI 0.10-0.89). Our findings add to this body of evidence to support MOUD with buprenorphine to improve clinical outcomes following hospitalization for IVDU-related IE. Similar to previous reports, buprenorphine prescriptions at discharge yielded lower rates of 30-day readmission and increased

outpatient treatment follow-up (12). However, long-term outcomes such as 180-day readmission rates and mortality did not confer the same benefit.

A strength of our evaluation was that patients were only included if they had documented completion of antimicrobial therapy. This reduced the likelihood that readmissions related to infection were due to inadequate initial treatment and a greater predictor of persistent drug abuse, although this was unable to be confirmed in all cases. A large proportion of patients were admitted to the inpatient infusion unit, and most patients were evaluated by multiple disciplines that addressed the acute management of IE and substance abuse. As described previously, the inpatient infusion unit is a medical unit that employs a multidisciplinary approach for the care of patients suffering from substance abuse. Similar models exist at other institutions. One institution demonstrated that a bundle of care model yielded lower rates of 30-day readmissions in patients with comorbid substance abuse compared to usual care (15.5% vs. 30.0%, respectively, p<0.001) and increased outpatient treatment entry at three months (50.3% vs. 35.3%, p=0.014) (13). However, the genesis of our infusion unit occurred towards the end of 2017 with advancements in behavioral health services gradually increasing. For this reason, not all patients included in this analysis received the same spectrum of services. After accounting for these potential confounders in the multivariable analysis, a significant association between all cause 30-day readmission and buprenorphine prescription status at discharge was observed favoring buprenorphine for OUD at discharge.

Limitations of our review included many patients had comorbid polysubstance abuse in which MOUD may not be effective and the retrospective, single center design. It has been reported that polysubstance abuse may decrease outpatient treatment retention and subsequently increase rates of IVDU-related complications (14). Additionally, we were not able to assess adherence to buprenorphine therapy following hospital discharge, nor outpatient treatment retention beyond first follow-up appointment at an affiliated clinic. This may be a cause of higher rates of readmission within 180-days following hospital discharge for IVDU-related IE. Furthermore, a greater percentage of patients in the no buprenorphine cohort required ICU admission which may suggest that the population was sicker at baseline, but duration of ICU admission was not evaluated. Comparatively to the univariable analysis, the multivariable analysis that included

ICU admission yielded consistent point estimates and subsequent confidence intervals. Therefore, the observed reduction in 30-day readmission rates in patients prescribed buprenorphine at discharge is reassuring regardless of ICU admission. In our review, patients in both groups lived greater than 100 miles from our hospital. Though outpatient follow-up was commonly arranged in the buprenorphine group, access to care in rural areas is a significant barrier. Although this study included the highest numbers of patients with IVDU-related IE discharged on buprenorphine for OUD to date, we were unable to meet power. While the results may suggest substantially lower readmission rates for patients within the first month following index hospitalization for IVDU-related IE, the certainty of the reported outcomes should be exercised cautiously. Additional larger retrospective studies, and randomized, controlled prospective studies are warranted to evaluate addiction-focused interventions in this patient population. Lastly, buprenorphine was the only MOUD evaluated, and therefore extrapolation of results to methadone-treated and naltrexone-treated patients cannot be concluded.

Through buprenorphine prescriptions at discharge, 30-day readmissions may be prevented in a high-risk patient population. Strategies to improve outpatient treatment retention and increase access to outpatient treatment are warranted, particularly in rural areas, as 180-day readmission rates did not yield similar results. Substance abuse disorders continue to cause significant morbidity and mortality. This evaluation demonstrates that improvements may be achieved in the care of these patients through addiction-focused interventions. With these results, health systems and healthcare providers should place a higher emphasis on addiction-focused interventions, such as buprenorphine prescriptions at discharge, in patients hospitalized for IVDU-related IE.

CONCLUSIONS

The potentially clinically relevant difference in 30-day readmissions when prescribing buprenorphine at discharge for IVDU-related IE did not reach statistical significance, but this study was underpowered. After accounting for potentially confounding variables, a positive association was observed for buprenorphine prescriptions at discharge and all cause 30-day readmissions which may warrant future investigation. There was a

clinically relevant and statistically significant increase in outpatient treatment follow-up in those prescribed buprenorphine at hospital discharge. This study is the first to evaluate the effects of MOUD on readmission rates for patients hospitalized with IVDU-related IE and contributes to the growing body of evidence to support addiction-focused interventions for this unique patient population.

CONFLICT OF INTEREST. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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