**Review Article**

# The Impact of Inpatient Medication Assisted Treatment in Opioid Use Disorder-Associated Infective Endocarditis: A Retrospective Cohort Study

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**Abstract**

**Background:** Patients admitted with opioid use disorder-associated infective endocarditis (OUD-IE) often experience opiate withdrawal putting them at risk of leaving prior to completion of IE treatment. Inpatient treatment with medication-assisted treatment (MAT), including buprenorphine or methadone, has the potential to mitigate withdrawal and decrease morbidity and mortality associated with OUD-IE.

**Methods:** In this retrospective cohort study we evaluated outcomes of adults admitted with OUD-IE who received inpatient MAT compared to those who did not receive inpatient MAT. Our primary outcomes were adherence to treatment and leaving against medical advice (AMA). We also evaluated demographics, causative organisms, and complications.

**Results:** There were 49 patients with 89 unique admissions associated with OUD-IE. Mortality rate was high with 11 inpatient deaths (22%). Admissions that resulted in death were excluded from our comparison groups (n=11). Of the 78 evaluable admissions for OUD-IE, 18 (23%) received inpatient MAT. Significantly, 14 of 18 (78%) admissions adhered to treatment when MAT was given, compared to 21 of 60 (35%) when MAT was not given (p=0.001). Furthermore, 4 of 18 (22%) left AMA when MAT was given, compared 39 of 60 (65%) when no MAT was given (p=0.001). Those who received inpatient MAT were more likely to adhere to treatment and less likely to leave AMA (OR=6.5; 95% CI=1.9, 22.27).

**Conclusions:** Patients with OUD-IE are more likely to adhere to treatment when they receive inpatient MAT. MAT should be encouraged for all patients admitted with OUD-IE.

## INTRODUCTION

As the opioid epidemic continues to spread in the US, injection drug use (IDU) and associated complications are on the rise [1-7]. Infective endocarditis (IE) is a well-known complication of injection drug use (IDU), and people who inject drugs (PWID) have a 100 fold increased risk of IE [8-10]. Hospital admissions for associated injection drug use-associated infective endocarditis (IDU-IE) have increased anywhere between two-fold to twelve-fold in the past two decades depending on the geographic regions in the US and IE is associated with significant morbidity and mortality [11-13]. Additionally, hospital costs associated with IDU-IE are substantial, with one study reporting costs an 18-fold increase in costs from 2010-2015 from 1.1 million to over 20 million annually [12].

Medications for assisted treatment (MAT) for opioid use disorder (OUD) is an integral part in addressing the converging

opioid and infectious disease epidemics including IE [14,15]. MAT includes opioid agonist therapy with buprenorphine or methadone, which have been shown to effectively treat opioid withdrawal, improve likelihood of completion of scheduled treatment, and reduce mortality associated with OUD and [16,17].

IE is often associated with prolonged hospital stays due to its associated complications, as well as the inherent duration and route of treatment. As a result, those with opioid use disorder-associated infective endocarditis (OUD-IE) may experience withdrawal upon admission, putting them at risk of leaving the hospital prior to completion of treatment. As untreated IE is almost universally fatal, medically managing the patient's OUD with medication assisted treatment (MAT) in conjunction with treatment of IE may prevent premature cessation of treatment and improve overall outcomes in those with OUD-IE.

Our study examined the role of inpatient initiation of MAT with buprenorphine or methadone for treatment of opioid withdrawal and opioid use disorder. We hypothesized that patients with OUD-IE who were initiated on MAT would be more likely to adhere to IE treatment and less likely to leave against medical advice compared to those were not initiated on MAT.

## METHODS

### Study Design

This was a retrospective cohort study conducted at the Los Angeles County-University of Southern California Medical Center, a 600-bed public teaching hospital. The study received approval from the University of Southern California Institutional Review Board.

### Participants

Forty-nine adults with 89 unique admissions for OUD-IE between 10/2015-09/2019 were included in the study. Eligible participants were adult (age ≥18 years) inpatients with admissions for management of OUD-IE. Admissions were categorized into two groups, those in which the patient received MAT and those in which the patient did not. Eight patients with admissions that resulted in inpatient death were excluded from group comparisons but were included in the evaluation of IE characteristics and complications. Additionally, three individuals with multiple admissions associated with OUD-IE died on their final admission, and those three admissions were excluded from our group comparisons given inpatient death.

### Data Collection

Vizient clinical database classified admissions associated with IE-OUD using International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes (supplemental index Table 1). Cases identified from the database received manual chart review using electronic health records to confirm presence of OUD-IE using the modified Duke criteria for IE and evidence of active opioid use, as defined by opioid use within the past month prior to admission. The primary outcomes included: 1) treatment adherence, defined as completion of treatment while inpatient or transfer to a recuperative care or acute care facility for completion of treatment and, 2) leaving against medical advice prior to completion of treatment for infective endocarditis.

### Statistical Analysis

We examined the sample of patients through descriptive statistics. We assessed group differences on adherence to IE treatment and leaving against medical advice. SPSS was used for statistical analyses. Chi-square and t tests examined differences between the groups. Odds ratios (OR) with 95% confidence intervals (CI) evaluated the influence of MAT on targeted outcomes.

## RESULTS

An initial data query listed 3,187 admissions associated with opioid use and 518 admissions associated with IE between October, 1 2015 and September 30, 2019. Chart review confirmed 49 patients with 89 unique admissions who had OUD-IE. Eleven admissions met exclusion criteria from comparison groups due to inpatient death and inability to measure outcomes. Among the 78 evaluable admissions, 18 (23%) received inpatient MAT and 60 (77%) did not (Figure 1). The majority of patients were male (76%) and the median age was 42 years (range 20-72 years). There was no significant difference in age, sex, race, or ethnicity between the groups (Table 1). A large proportion were experiencing homelessness (63%) and were hepatitis C antibody positive (82%). Those who were experiencing homelessness were less likely to receive inpatient MAT (55% vs 88% of non-homeless, p <.05). Additionally, most individuals had documentation of other substance use, with methamphetamine use being the most common.

All admissions, including those of deceased patients, were included in our description of infective endocarditis characteristics and complications (Table 2). The most common valve affected was the tricuspid valve (51%), followed by the mitral (29%) and aortic (29%) valves. Staphylococcus aureus was the most common microorganism implicated (36%) with methicillin-resistant S. aureus (MRSA) found in 16% of cases. There were 11 inpatient deaths (22%) and no inpatient deaths among those who were given inpatient MAT. Additionally, there were a broad range of associated complications with the most common being septic pulmonary emboli (35%), septic shock (27%) and heart failure (14%).

The median number of admissions for OUD-IE was 1 (range 1-13). Of the 89 total admissions for OUD-IE, the median inpatient length of stay (LOS) was 9 days (range 1-249). Of those who adhered to IE treatment, the median LOS was 44 days (range 6-249).

Among those admissions where MAT was given, 14 of 18 (78%) adhered to IE treatment, compared to 21 of 60 (35%) where MAT was not given (p=0.001, Table 3). Furthermore, only 4 of 18 (22%) left AMA when MAT was given, compared 39 of 60

**Supplemental Table 1:** IE-OUD ICD 9 and ICD 10 Codes

| ICD-9 Codes | ICD-10 Codes |
|---|---|
| 96501,E8500,E9350,3040,30400,30401, 30402,30403,3047,30470,30471,30472, 30473,3048,30480,30481,30482,304833055, 30550,30551,30552,30553,9650,96500, 96502,96509,9701,E8502,E9352,E9401 | F11,F111,F1110,F1111,F1112,F11120,F11121,F11122,F11129,F1114,F1115,F11150,F11151,F11159,F1118,F11181,F11 182,F11188,F1119,F112,F1120,F1121,F1122,F11220,F11221,F11222,F11229,F1123,F1124,F1125,F11250,F11251,F112 59,F1128,F11281,F11282,F11288,F1129,F119,F1190,F1192,F11920,F11921,F11922,F11929,F1193,F1194,F1195,F1195 0,F11951,F11959,F1198,F11981,F11982,F11988,F1199,T402X1S,T402X2,T402X2A,T402X2D,T402X2S,T402X3,T402X3A ,T402X3D,T402X3S,T402X4,T402X4A,T402X4D,T402X4S,T402X5,T402X5A,T402X5D,T402X5S,T402X1D,T402X1A,T402X 1,T401,T401X,T401X1,T401X1A,T401X1D,T401X1S,T401X2,T401X2A,T401X2D,T401X2S,T401X3,T401X3A,T401X3D,T4 01X3S,T401X4,T401X4A,T401X4D,T401X4S |

**Table 1:** Patient Characteristics

| | Inpatient MAT (n=15) | No Inpatient MAT (n=26) | |
|---|---|---|---|
| Variable | No./Total (%) | No./Total (%) | p-value* |
| Age, mean (SD) | 47 (15.3) | 39 (13.6) | 0.08 |
| Sex Male Female | 12/15 (80) 3/15 (20) | 19/26 (73) 7/26 (27) | 0.62 |
| Race White Black Other/Unknown | 3/15 (20) 2/15 (13) 10/15 (67) | 6/26 (23) 7/26 (27) 13/26 (50) | |
| Ethnicity Hispanic or Latino Not Hispanic or Latino | 5/15 (33) 10/15 (67) | 3/26 (12) 23/26 (88) | 0.09 |
| Hepatitis C Status† Positive Negative/Unknown | 14/15 (93) 1/15 (7) | 23/26 (88) 3/26 (12) | 0.61 |
| Homelessness Yes No | 8/15 (53) 7/15 (47) | 23/26 (88) 3/26 (12) | 0.01 |
| Methamphetamine Use Yes No/unknown | 10/15 (67) 5/15 (33) | 17/26 (65) 9/26 (35) | 0.93 |
| Cocaine Use Yes No/unknown | 5/15 (33) 10/15 (67) | 5/26 (19) 21/26 (81) | 0.31 |
| Phencyclidine Use Yes No/unknown | 2/15 (13) 13/15 (87) | 2/26 (8) 24/26 (92) | 0.56 |

SD – standard deviation. MAT – Medication assisted treatment.
* Chi-squared used for categorical variables and t-test for means
† Documented hepatitis C antibody positive or reported history of infection.



**Figure 1** Figure 1: Chart Showing the Admission for infective endocarditis and opioid use.
*Three patients had multiple admissions with final admission resulting in inpatient death (n=3)

**Table 2.** Endocarditis Characteristics

| Variable | No./Total* (%) |
|---|---|
| Modified Duke Criteria | |
| Microorganism in vegetation | 3/49 (6) |
| Pathologic lesion | 6/49 (12) |
| Blood cultures positive for infective endocarditis | 45/49 (92) |
| Predisposing heart conditions or injection drug use | 49/49 (100) |
| Fever | 36/49 (74) |
| Vascular phenomenon | 16/49 (33) |
| Immunologic phenomenon | 1/49 (2) |
| Microbiological evidence | 0/49 (0) |
| Definite | 41/49 (84) |
| Possible | 8/49 (16) |
| Vegetation seen on TTE | |
| Yes | 28/49 (57) |
| No | 21/49 (43) |
| Vegetations seen on TEE | |
| Yes | 13/49 (27) |
| No | 5/49 (10) |
| Not complete | 31/49 (63) |
| Valve involved (if known) | |
| Tricuspid | 18/35 (51) |
| Pulmonic | 1/35 (3) |
| Mitral | 10/35 (29) |
| Aortic | 10/35 (29) |
| Organism | |
| Methicillin-sensitive Staphylococcus aureus | 10/49 (20) |
| Methicillin-resistant Staphylococcus aureus | 18/49 (16) |
| Coagulase-negative staphylococci | 4/49 (8) |
| Viridians group streptococci | 13/49 (27) |
| Streptococci (non-viridians group) | 4/49 (8) |
| Enterococci | 2/49 (4) |
| Finegoldia magna | 1/49 (2) |
| Culture negative | 3/49 (6) |
| Infective Endocarditis Complication | |
| Septic Arthritis | 4/49 (8) |
| Spinal Epidural Abscess | 5/49 (10) |
| Brain Abscess | 2/49 (4) |
| Septic Pulmonary Emboli | 17/49 (35) |
| Stroke | 3/49 (6) |
| Splenic Infarction | 3/49 (6) |
| Septic Shock | 13/49 (27) |
| Renal Infarct | 2/49 (4) |
| Heart Failure | 7/49 (14) |
| Cardiac Abscess | 3/49 (6) |
| Cardiac Conduction Abnormality | 6/49 (12) |
| Cardiac Valvular Surgery | 10/49 (20) |
| Inpatient Death | 11/49 (22) |

TTE – transthoracic echocardiogram. TEE – Transesophageal echocardiogram.
*Includes patients (n=8) who died on admission and were excluded from group comparisons

**Table 3.** Outcomes among 78 unique hospital admissions involving 41 unique patients

| | Inpatient MAT n=18 admissions | No Inpatient MAT n=60 admissions | p Value | OR (95% CI) |
|---|---|---|---|---|
| Variable | No./Total (%) | No./Total (%) | | |
| Adhered to IE treatment | 14/18 (78) | 21/60 (35) | 0.001 | 6.5 (1.9, 22.27) |
| Left AMA | 4/18 (22) | 39/60 (65) | 0.001 | 6.5 (1.9, 22.27) |
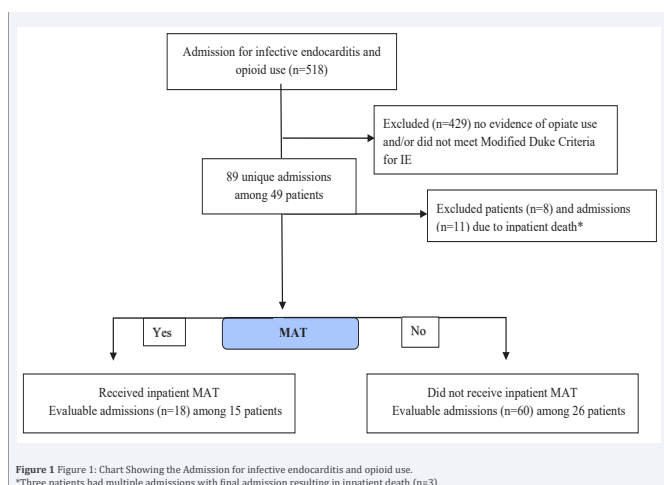
(65%) when no MAT was given (p=0.001). Those who received inpatient MAT had significantly greater odds of adhering to treatment (OR=6.5; 95% CI=1.9, 22.27) compared to those who did not. Conversely, those who did not receive inpatient MAT had significantly greater odds of leaving AMA (OR=6.5; 95% CI=1.9, 22.27) compared to those who did not.

Two patients accounted for 19 of the 81 admissions, with 17 of those resulting in leaving AMA and not being started on MAT. To address this, we excluded all 19 admissions from a sensitivity analysis, and still found statistically significant differences (p<0.05) in treatment adherence between the MAT and no-MAT group (OR=4.2, 95% CI=1.19, 14.8), as well as AMA outcomes between MAT and no-MAT groups (OR=3.85, 95% CI 1.09, 13.65).

## DISCUSSION

This retrospective cohort study demonstrated that inpatient initiation of MAT with buprenorphine or methadone is associated with improved adherence to treatment of infective endocarditis in patients with OUD-IE. Furthermore, those with OUD-IE who receive inpatient MAT are less likely to leave against medical advice prior to completion of treatment. This is an important finding as inadequately treated infective endocarditis is associated with significant complications and is almost always universally fatal.

Our study confirms a significant high mortality rate in those with OUD-IE within an already vulnerable patient population, with the majority co-infected with hepatitis C (HCV) as well as experiencing homelessness and poly substance use. Additionally, the majority of individuals with OUD-IE in our study did not receive inpatient MAT, which identifies a significant need for improvement. This is consistent with a large retrospective cohort study that showed the majority of individuals who were treated for an opioid overdose were not started on MOUD [17].

Devising institutional screening tools for OUD and withdrawal, as well ensuring prescribing capabilities for inpatient MAT with methadone or buprenorphine, would likely improve outcomes in those with OUD-IE. Furthermore, OUD educational programs would be expected to improve provider management of OUD. Developing discharge protocols for linkage to outpatient clinics with MAT prescribing capabilities may further improve patient outcomes. One randomized controlled trial found that individuals with OUD who were initiated on inpatient buprenorphine were more likely to remain on buprenorphine treatment and less likely to use illicit drugs if they were linked to an outpatient clinic for further management compared to those who were not linked to an outpatient clinic [18].

Limitations of our study include the retrospective nature of our analyses, which relied heavily on chart review and accurate documentation. We were also limited by our small sample size of individuals with OUD-IE. Due to our inability to assess outcomes in those patients who were transferred to outside facilities to complete treatment, we used inpatient treatment adherence and leaving against medical advice as surrogates to clinical outcomes.

As a result, we were unable to assess full duration of treatment and long-term outcomes beyond discharge. Instead, we focused on short-term outcomes of each individual admission.

## CONCLUSION

We conclude that inpatient MAT during admissions for OUD-IE is associated with improved short-term outcomes. Prompt evaluation and offering of MAT should be routinely considered for all patients admitted with OUD-IE.

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