Initiating Buprenorphine in Patients Hospitalized with Intravenous Drug-Use-Related Endocarditis

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INITIATING BUPRENORPHINE IN PATIENTS HOSPITALIZED WITH INTRAVENOUS DRUG-USE-RELATED ENDOCARDITIS

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

April 2019

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Class of 2019  Professor of General Medicine
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Abstract

During the current opioid crisis, hospitalizations for the treatment of intravenous drug use-related infective endocarditis have increased. Despite this, opioid use disorder is inadequately treated resulting in continued drug use, higher surgical intervention, recurrence and mortality rates relative to non-drug use-related endocarditis. Buprenorphine* is a safe and effective medication-assisted addiction treatment in outpatient settings; however, buprenorphine remains underutilized, particularly among patients hospitalized for infective endocarditis. Emergency department-initiated buprenorphine combined with referral to ongoing treatment is associated with improved rates of addiction treatment engagement. Therefore, our objective is to investigate whether hospital-initiated buprenorphine combined with referral in patients with opioid use disorder admitted for infective endocarditis is more effective than referral alone for treatment engagement 30 days post-hospital discharge. These results may optimize our standard of care for patients with intravenous drug use-associated infective endocarditis to enhance enrollment in treatment for opioid use disorder.
Chapter 1 Introduction:

1.1 Background

Intravenous drug use (IVDU) rates in the United States have doubled between 2006 and 2013.\textsuperscript{20} People who inject drugs (PWID) are at increased risk for serious infections such as infective endocarditis (IE) through the direct injection of bacteria or the spread of injection site abscesses into the bloodstream.\textsuperscript{2,6,14,16,20,21} Among various institutions, the increasing prevalence of IVDU is accompanied by more than a sevenfold increase in IE diagnoses and up to a fivefold increase in surgical tricuspid valve interventions.\textsuperscript{6,20} Nationally, up to 20\% of PWID are reported to have had IE.\textsuperscript{21} Moreover, data from the National Inpatient Sample, which represents 20\% of U.S. non-federal, community hospitals, indicates that the incidence of hospitalizations between 2009 and 2013 for IE in persons with substance use disorder increased from 12.3\% to 23.2\%, \textit{p}<0.0001.\textsuperscript{2}

Recurrence and readmission rates of IE are as high as 50\% and are directly proportional to the 50\% prevalence of active drug use among patients hospitalized with IVDU-related conditions.\textsuperscript{10,14,21} These recurrences come with high costs. IE has a 5-year mortality rate of 50\% and up to 26\% inpatient mortality rate.\textsuperscript{21} The cost of hospitalization for IE increased between 2009 and 2013 from $49,669 to $57,389, \textit{p}<0.0001 with length of hospital stays averaging from 17 days to 31 days across the literature.\textsuperscript{2,6,7,10} Treatment strategies for these patients are typically focused on infection management but not the causative underlying addiction.\textsuperscript{5,14}

Medication-assisted treatment (MAT) for opioid use disorder (OUD), which is commonly seen in association with IVDU improves morbidity and mortality.\textsuperscript{5,9} Buprenorphine has proven safety and efficacy for treating withdrawal symptoms,
decreasing craving for opioids and improving substance use-related outcomes including
treatment engagement, substance use, and substance use-related complications in both
inpatient and outpatient settings. Emergency department (ED) initiated
buprenorphine treatment for OUD combined with referral to ongoing addiction
treatment is associated with enhanced treatment engagement following discharge from
the ED. ED-initiated buprenorphine coupled with referral is also proven to be more
cost-effective for the healthcare system than referral strategies alone ($97 versus $283-
322, p<0.001). In spite of this, substance abuse treatment is woefully underutilized.

Looking beyond ED visits, hospitalizations may also provide a golden opportunity for
interventions to be introduced. 15% of all hospitalized patients have a
substance use disorder and intervention approaches are inadequately focused solely on
referral to addiction treatment after discharge. In one retrospective case study, 62%
of patients with OUD who were admitted for intravenous drug use-related infective
endocarditis (IVDU-related IE) accepted MAT, and half of these accepted hospital-
initiated buprenorphine. In another retrospective case study, 46.8% of hospitalized
patients identified with opioid dependence whom accepted buprenorphine induction,
initiated addiction treatment within 2 months of discharge.

1.2  Statement of the Problem

The incidence of IVDU-related IE is increasing in the context of a national opioid-use
epidemic. Addiction treatment during hospitalizations for IVDU-related IE is often
overlooked, and if it occurs at all, is largely focused on post-discharge referral to
subsequent addiction treatment rather than a hospital-initiated addiction treatment
intervention. As a result, transition and adherence to addiction treatment after IVDU-related IE hospitalization is low, while IVDU-related IE hospital readmissions and associated morbidity, mortality, and recurrence rates are on the rise, despite the availability of effective medication-assisted treatment options like buprenorphine. To date, research on hospital-initiated buprenorphine for the treatment of opioid use disorder is severely limited. The data that does exist suggests the utility of hospital-initiated buprenorphine but has mostly come from small studies that were insufficiently powered to demonstrate effectiveness and has not focused on patients with IE. This warrants further research to investigate whether incorporation of buprenorphine in the treatment of patients hospitalized for IVDU-related IE facilitates addiction treatment engagement after discharge, in support of IVDU-related IE recurrence prevention.

1.3 Goals and Objectives

We propose a multicenter, randomized clinical trial to optimize addiction treatment in patients with OUD who are hospitalized for IVDU-related IE. This study aims to compare the efficacy of hospital-initiated buprenorphine alongside an Addiction Medicine referral for ongoing buprenorphine treatment versus referral only, for opioid use disorder addiction treatment engagement after hospital discharge.

1.4 Hypothesis

Among patients hospitalized for IVDU-related IE, we predict that compared to referral-only patients there will be a statistically significant higher proportion of patients engaged in addiction treatment among hospital-initiated buprenorphine patients,
measured as the absolute difference in between-group proportions at 30 days after discharge.

1.5 Definitions

Abbreviation: IVDU-related IE = intravenous drug use-related infective endocarditis
*Buprenorphine = refers to combination drug buprenorphine/naloxone.

1.6 References


Chapter 2  Review of the Literature:

2.1  Introduction

The databases used for this literature review include PubMed, Cochrane Library, ScienceDirect, Web of Science, EMBASE Ovid, and Scopus. All publications were searched using the keywords and phrases endocarditides, infective endocarditides, infective endocarditis, drug abuse, drug addiction, drug dependence, drug use disorder, substance abuse, substance addiction, substance dependence, substance use disorder, intravenous drug abuse, intravenous substance abuse, parenteral drug abuse, medication assisted treatment of opioid, opiate medication assisted treatment, opiate replacement therapy, opiate substitution treatment, opioid medication assisted treatment, opioid replacement therapy, opioid substitution therapy, buprenorphine, RX6029M, and 6029M. The resulting set of references were examined to include relevant reports, reviews, meta-analyses, and clinical trials.

2.2  Drug Use Disorder Epidemiology

Opioid use disorder is a brain disorder provoked by recurrent opioid use that causes gamma-aminobutyric acid (GABA) inhibition thru mu receptor interaction, followed by increased dopamine release.$^{1,26}$ The ultimate result is neuronal remodeling at the nucleus accumbens, amygdala, and prefrontal cortex within the mesocorticolimbic dopamine systems, or the “reward systems,” of the brain.$^1$ Long-term opioid use also desensitizes and increases the number of opioid receptors such that tolerance levels rise.$^1$ Discontinuation of opioids precipitates a “noradrenergic storm” we refer to as withdrawal.$^1$ Symptoms of withdrawal include: yawning, lacrimation, rhinorrhea,
nausea, emesis, diarrhea, hypertension, chills, piloerection, myalgias, abdominal pain, tremor, anxiety, agitation, delirium, and seizures.¹

According to the United Nations Office on Drugs and Crime (UNODC) and the World Health Organization (WHO), there are 15.6 million people with opioid use disorder worldwide, 71% of whom use heroin.¹ The economic burden of opioid use disorder ranges from 0.2 to 2% of a country’s gross domestic product secondary to healthcare costs, social welfare services, criminal justice demands, and unemployment.¹

Throughout the United States, the rate of heroin use doubled between 2006 and 2013.²⁵ Approximately 3% of the American population (n=9.8 million) has injected drugs.⁶,¹³  In Virginia, a retrospective chart review identified an 89% increase in emergency room visits for heroin overdose in 2015 compared to 2014.¹⁰,²⁰ Another retrospective chart review in Kentucky identified 335 hospitalizations associated with intravenous drug use (IVDU) between 2012 and 2015; 108 were included in the study.¹³ 95.4% of these hospitalizations had explicit documentation of illicit opioid use during admission, however, only 57.4% were formally diagnosed with a substance use disorder, a mere 2.8% received medication-assisted addiction treatment, and a lamentable 16.7% received an addiction treatment referral at discharge.¹³

These studies offer small representations of the United States that complement national analyses reporting an opioid epidemic. Overall, the data suggest a recent and under-addressed, rapid increase in IVDU and overdose rates.¹⁰
2.3 **Intravenous Drug Use-Related Infective Endocarditis**

Persons who inject drugs are at an increased risk for death and IVDU-related infections.\(^5,10,11,19,27\) Intravenous drug use-related infective endocarditis (IVDU-related IE) typically presents as right-sided heart disease involving endothelial damage to the tricuspid valve.\(^10,11,25,27\) The tricuspid valve is the first heart valve to interact with the returning venous circulation.\(^10,11,25,27\) In patients with history of IVDU, this blood often carries microorganisms and particulate matter introduced during injection or from the hematogenous spread of soft tissue infections caused by injection.\(^10,11,25,27\) Up to 20% of persons who inject drugs have had infective endocarditis (IE), at an incidence rate 100 times greater than in the general population.\(^3,10,27\)

In 2013 at the Hospital of the University of Pennsylvania (HUP), IVDU-related IE hospitalizations accounted for 12% of total hospitalizations.\(^25\) In a retrospective descriptive review of all surgical tricuspid IE cases at HUP (n=783), surgical IVDU-related IE cases exhibited a 5-fold increase between 2011 and 2017 from 7 cases to 32 cases per year, respectively.\(^25\) Additionally, a history of illicit drug use in patients with IE rose from 14.3% to 81.8% during this same time period.\(^25\) Of note, the median patient age decreased from 52.85 years to 39.2 years and overall 30-day post-operative mortality in this population was 11.11%.\(^25\) These results are in agreement with the current opioid epidemic within the U.S., as well as the increased risk of IE associated with IVDU.

The National Inpatient Sample (NIS) database includes approximately 20% of all non-federal, community hospital discharges in the U.S.\(^5,27\) A cross-sectional study used NIS to identify IVDU-related IE discharges from 2000 to 2013.\(^27\) Wurcel et al. found that the proportion of IVDU-associated IE discharges among total IE hospitalizations
increased significantly from 7% to 12.1%, and a parallel significant increase in IVDU-related IE among patients 15 to 34 years old from 27.7% to 42%, p<0.001.27 A reciprocal significant decrease in IVDU-related IE rates occurred in patients 35 to 54 years old from 67.2% to 39.9%, p<0.001.27 Of note, rate changes were most significant between 2008 and 2013, which corresponds with the significant increases in heroin use of the period.

Another cross-sectional study utilized NIS to analyze IVDU-related IE hospital discharges between 2009 and 2013.5 During this period, overall IE hospitalization rates remained stable, but the prevalence of substance use disorder significantly increased from 12.3% to 23.2%, p<0.0001.5 The percentage of IE in patients ≥65 years significantly decreased from 40.6% to 32.9%, p<0.0001, while the percentage of IE in patients ≤39 years reflected a significant rise.5 More specifically, in patients <18 years old IVDU-IE rates rose from 1.1% to 2.1%, p=0.0261 and in patients 18 to 39 years old IVDU-IE rates increased from 17% to 24.2%, p<0.0001.5

Both studies using NIS presumed a diagnosis of IVDU-related IE through the inclusion of discharges with ICD-9 codes for IE and substance use disorder, and concurrent exclusion of discharge codes for other IE risk factors like history of rheumatic disease. These data strongly suggest a correlation between substance use disorder and IE in the hospitalizations, but due to the retrospective design of the studies a direct association could not be established.5

At Wake Forest Baptist Medical Center, a retrospective chart review compared IVDU-related IE hospitalizations to non-IVDU-related IE hospitalizations between 2009 and 2014.11 During this time the proportion of IVDU-IE increased from 14% to 56%.11 The median age for patients with IVDU-related IE was 32.6 years, as opposed to 54.4
years in patients with non-IVDU-related IE, p<0.0001. Similarly, a retrospective cohort study in Virginia identified a 7.54-fold increase in IVDU-related IE from 2000 to 2016 at the University of Virginia Medical Center. As with previous studies, this study also indicated that IVDU-related IE is more likely in younger adults with a mean age of 35 years in contrast to a mean age of 61 years among non-IVDU-related IE, p<0.001. Of note, the average cost of admission was almost double for IVDU-related IE than for non-IVDU-related IE at $47,899 versus $26,460 (p=0.001), respectively.

The reproducibility of results in the literature strongly supports a correlation between IVDU and IE, the increasing rates of IVDU-related IE in the United States, and the higher financial burden that IVDU-related IE represents relative to non-IVDU-related IE. Causation could not be determined in these studies secondary to their retrospective design. The retrospective designs also pose a risk for selection bias that threatens underrepresentation of IVDU and associated IE, secondary to improper ICD-9 coding in the hospitalizations that were screened. Finally, with the exception of the NIS studies, these were single-center studies that offered limited generalizability.

2.4 Medication-Assisted Addiction Treatment: Buprenorphine/Naloxone

WHO defines the goals of medication-assisted treatment (MAT) of opioid use disorder as: “reduction or cessation of illicit opioid use, injection, and associated risk of bloodborne virus transmission; reduction of overdose risk and criminal activity; and improvement of psychological and physical health.” Available options for MAT include naltrexone, buprenorphine, and methadone.
In a study comparing the efficacy of extended-release naltrexone injections and sublingual buprenorphine therapy, 94% of patients successfully inducted to buprenorphine versus 72% in naltrexone patients (HR 1.36, 95% CI 1.1 – 1.68, p<0.0001).\textsuperscript{15} Relapse rates were significantly greater in the naltrexone group than the buprenorphine group at 65% and 57% (p=0.036), respectively.\textsuperscript{15} Buprenorphine patients also provided a significantly higher average of opioid-negative urine samples (buprenorphine: 10 negative samples vs. naltrexone: 4 negative samples, p<0.0001).\textsuperscript{15} These results concur with WHO recommendations for MAT with an opioid agonist.\textsuperscript{1}

Opioid-agonist maintenance treatment, with methadone or buprenorphine, alongside psychosocial assistance is the most effective treatment option for opioid dependence when compared to detoxification or no treatment.\textsuperscript{1,6,8,9,12,21,24} Buprenorphine significantly decreases drug use and increases addiction treatment engagement.\textsuperscript{1} Buprenorphine is also associated with fewer side effects and drug-drug interactions than methadone.\textsuperscript{1,6}

Of note, buprenorphine use can be diverted for injection to produce strong effects. Buprenorphine/naloxone combination products at a 4:1 ratio were developed in an effort to minimize diversion.\textsuperscript{1} Sublingually, buprenorphine affinity supersedes naloxone affinity.\textsuperscript{1} However, with injection of the combination product naloxone induces withdrawal in opioid-dependent individuals.\textsuperscript{1,6}

Buprenorphine dosing is patient-specific based on their opioid use and tolerance level.\textsuperscript{1} It should be initiated at a low dose and quickly increased over days, typically to a dose between 8-24 mg.\textsuperscript{1} Fixed buprenorphine doses > 6 mg are as equally effective as fixed methadone doses > 40 mg in addiction treatment retention and illicit opioid use
Buprenorphine doses of 16 mg are superior to placebo for addiction treatment retention (RR 1.52, 95% CI 1.23 to 1.88) and greater opioid-negative urinalyses (SMD –0.65, 95% CI –0.86 to –0.44). Buprenorphine doses > 16 mg are also superior to placebo for addiction treatment retention (RR 1.82, 95% CI 1.15 to 2.9) and greater opioid-negative urinalyses (SMD –1.17, 95% CI –1.85 to –0.49).

In a retrospective study at the University of Virginia Medical Center, of 76 patients with IVDU-related IE only 13% received medication-assisted addiction treatment (MAT). 63% had a prescribed opioid documented on their discharge medication list, and only 53% had IVDU or a substance use disorder diagnosis documented on their discharge summary.

In another similar study out of Beth Israel Deaconess Medical Center in Boston, of 102 patients hospitalized for IVDU-related IE, addiction was only mentioned in 55.9% of discharge plans, only 7.8% had MAT plans, and none were prescribed naloxone for harm reduction. Of note, 13.7% had recurrent IVDU-related IE and 49% were “ever readmitted,” with a 32.1% rate of readmission IVDU documentation.

The data from these efficacy trials strongly supports the utility of buprenorphine in addressing opioid use disorder. However, the descriptive studies are reflective of the problem of unaddressed addiction treatment in patients with substance use disorder, despite its potential to improve patient outcomes, decrease hospital visits and thereby decrease healthcare costs.
2.5 Hospital-Initiated Medication-Assisted Treatment

Since 2000 IVDU-related infections have increased more than 70%, leading to more frequent healthcare utilization.\textsuperscript{14,16,22,24,27} Opioid-related emergency department visits have increased by 183% between 2004 and 2011, a quarter of who are admitted.\textsuperscript{2,14,16} Approximately 15% of hospitalized patients have an active substance use disorder.\textsuperscript{24} Healthcare providers have a unique opportunity to identify and treat substance use disorder.\textsuperscript{13,21,23}

In a randomized clinical study performed at Boston Medical Center (BMC), 337 hospitalized patients were referred for inpatient addiction consultation services.\textsuperscript{24} 78\% of the patients were diagnosed with opioid use disorder.\textsuperscript{24} 110 patients received opioid-agonist treatment with methadone or buprenorphine. 67\% of these patients transitioned to outpatient addiction treatment after discharge, 50\% remained engaged in treatment at 30 days, 35\% remained engaged at 90 days, and 25\% at 180 days.\textsuperscript{24} Of the buprenorphine patients, 49\% transitioned to outpatient addiction treatment after discharge, 39\% remained engaged in treatment at 30 days, 27\% remained engaged at 90 days, and 18\% at 180 days.\textsuperscript{24}

The addiction consultation services at BMC are a model for optimized addiction treatment in an inpatient setting. This serves as a limitation for the generalizability of this study, because it is a highly specialized team comprised of an attending physician and fellows specializing in Addiction Medicine, Internal Medicine and Family Medicine residents, a social worker, and a psychiatrist with case management collaboration.\textsuperscript{24} This type of coordinated care for inpatient substance use disorder identification and intervention is not yet ubiquitous throughout the healthcare system. This specialty
service, along with the single-center setting for the study, negatively affect the generalizability of its results. Moreover, no control group was included in this study for comparison.

A randomized clinical trial at Butler Hospital screened patients hospitalized for any reason for opioid dependence.\textsuperscript{16} Identified patients were offered the choice to start methadone treatment or participate in the study comparing buprenorphine and detoxification.\textsuperscript{16} Of the 72 patients that initiated hospital-buprenorphine, 72.2\% engaged in outpatient addiction treatment within 6 months of discharge compared to the 11.9\% randomized to detoxification, $p<0.001$.\textsuperscript{16} Addiction treatment engagement at 6 months after discharge was 16.7\% in the buprenorphine group in contrast to 3\% in the detoxification group, $p<0.007$.\textsuperscript{16} These data reinforce the superiority of opioid agonist MAT in addiction treatment and the opportunity hospitalizations provide for MAT initiation for effective transition to outpatient addiction treatment. This study is limited by its single-center setting that compromises generalizability and high attrition rates. It is also threatened by information bias secondary to research interviewers being privy to treatment group assignments at follow-up appointments.

A retrospective study at a Partners hospital in Boston, MA identified 47 cases of patients diagnosed and treated for DSM-IV opioid dependence between 2013 and 2014.\textsuperscript{22} Addiction treatment consisted of Clinical Opioid Withdrawal Scale-driven buprenorphine induction and maintenance, followed by referral to addiction treatment services at discharge.\textsuperscript{22} 46.8\% of these patients engaged in outpatient treatment.\textsuperscript{22} This study is limited by a small sample size and a retrospective design that only suggests a correlation between hospital-initiated and engagement in outpatient addiction treatment.\textsuperscript{22} However,
these findings are consistent with the results from the aforementioned prospective studies.16,22,24

D’Onofrio et al. investigated emergency department initiated-buprenorphine at Yale New Haven Hospital.8 Between 2009 and 2013, all patients 18 years or older were screened for opioid use disorder.8 329 patients were identified with DSM-IV opioid use disorder diagnoses and were randomized to receive either (1) referral to outpatient addiction treatment, (2) brief intervention via motivational interviewing alongside referral to outpatient addiction treatment, or (3) brief intervention alongside buprenorphine and referral to outpatient addiction treatment.8 Engagement in addiction treatment at 30 days following randomization was significantly higher in the buprenorphine group (78%, 95% CI, 70% – 85%) compared to the referral group (37%, 95% CI, 36% – 54%) or brief intervention group (45%, 95% CI, 36% – 54%), p<0.001.8 The buprenorphine group also reported a significant reduction in weekly illicit opioid use from an average of 5.4 days to 0.9 days, p<0.001.8 Long term assessments of the D’Onofrio study were performed to find that 74% in the buprenorphine group were engaged in addiction treatment at 2 months compared to 53% in referral group or 47% in the brief intervention group, p<0.001.7 At the 2 month follow-up, self-reported illicit opioid use in the past 7 days was also significantly lower in the buprenorphine group with an average of 1.1 days in contrast to 1.8 days in the referral group and 2 days in the brief intervention group, p=0.040.7 Secondary analyses comparing costs between the interventions indicate that ED-initiated buprenorphine is most cost-effective, when considering only healthcare system costs.4 These results support the general superiority of hospital-initiated buprenorphine for engagement to outpatient addiction treatment compared to referral
with or without motivational interviewing. This study’s outcome analyses were limited by insufficient power and attrition rate. Information bias in self-reports for opioid use poses a threat to validity. And, the context of a single-center affects generalizability.

Overall, these studies are suggestive of the feasibility in initiating emergency room or inpatient medication-assisted addiction treatment.\textsuperscript{16,23,24} The results support the effectiveness of hospital-initiated MAT, and buprenorphine specifically, for engaging patients in addiction treatment after discharge in a financially prudent manner.\textsuperscript{24}

### 2.6 Conclusion

At present, the role of hospitalists is not well-defined for the treatment of opioid use disorder.\textsuperscript{6,23} Current data validates opioid use disorder as a condition that is most effectively treated with opioid-agonist addiction treatment and psychosocial support. The prevalence of opioid use disorder among patients presenting to the emergency room and whom are hospitalized is well-established, particularly in those presenting with infections attributable to IVDU. Unfortunately, these studies have been limited by insufficient power, lack of generalizability, and information bias. Our study addresses some of these limitations through a prospective, randomized clinical design to establish causation in a multicenter context to support generalizability. Our study will include a referral-only control group for comparison, and it will blind its research associates involved in follow-up appointments in order to limit information bias.
2.7 References

Chapter 3  Study Methods:

3.1 Study Design

This 24-month multicenter, randomized clinical trial will recruit patients (18 years or older) with opioid use disorder hospitalized for intravenous drug use-associated infective endocarditis (IVDU-IE). The study will be conducted by Yale New Haven Hospital and Partners HealthCare, to include 17 hospitals throughout the Northeast United States. Physician and other healthcare professional members of the Addiction Medicine subspecialty will be invited to participate in this collaborative study. Protocol for this study will be submitted for review by the Institutional Review Board (IRB) at each participating center.

3.2 Study Population and Sampling

We will practice convenience sampling using electronic medical records (EMR) to identify patients hospitalized with a diagnosis of infective endocarditis. Each patient will be clinically screened using the ASSIST-Drug tool for IVDU and DSM-V diagnosis of opioid use disorder, and diagnostically screened via urine toxicology for presence of opioids (Table 1).8,9 We expect to enroll 196 adults, with 98 adults in the buprenorphine group and referral-only group, respectively.

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<th>SP (%) [95% CI]</th>
<th>LR+ [95% CI]</th>
<th>LR- [95% CI]</th>
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<td>50.3%[81.2–94.5]</td>
<td>92.4%[89.8–94.3]</td>
<td>11.8[8.8–16.6]</td>
<td>0.1[0.0–0.2]</td>
<td>92.0</td>
<td>20.6</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Note: AUC = Area Under the ROC Curve; SE = Sensitivity; SP = Specificity; LR = Likelihood Ratio; Eff = Efficiency; Test+ = Test Positive Rate; CI = Confidence Interval.

8 Using the Mini International Neuropsychiatric Interview as the criterion.
6 Using the Inventory of Drug Use Consequences as the criterion.

Table 1. ASSIST-Drug Screening Tool Validity Against the MINI Screening Tool
3.2.1 Inclusion Criteria

Patients must meet ALL of the following criteria to enroll in the study:

1. 18 years or older at the time of screening.
2. DSM-V diagnosis of opioid use disorder.
3. Urine sample positive for non-prescribed opioids on hospital admission.
4. Ability and willingness to provide written consent.

3.2.2 Exclusion Criteria

Patients who meet ANY of the following criteria will be excluded from the study:

1. Present condition compromises safety or compliance. Examples include: pre-operative, intensive care unit admission, dementia, suicidal, or homicidal.
2. Currently receiving formal addiction treatment.
3. Contraindication and/or allergy to buprenorphine.
4. Requirement of opioids for chronic pain management.
5. Currently enrolled in another study.
6. Pregnant and/or breastfeeding.
7. Patients in police custody.

3.3 Subject Protection and Confidentiality

This study will be reviewed by the Human Investigation Committee for required approval prior to performing. In compliance with Institutional Review Board (IRB) requirements (Policy 200) and current HIPAA regulations, all prospective study participants will be informed of the study’s purpose and counselled on the risks and benefits of buprenorphine in a manner and language that is understandable. Patients will
receive an invitation to participate without coercion, understanding that their participation is voluntary and may be withdrawn at any time. Written informed consent will be obtained from all study participants prior to all procedures. Interpreters and translated research document will be used, as necessary.

3.4 Recruitment

Study participants will be prospectively enrolled during the first 18 months of the study. Patients initially admitted to preoperative care or intensive care units can enroll after surgery and transfer to a medical floor. Post-operative narcotic analgesia course must be completed prior to enrollment.

3.5 Interventions

After obtaining written informed consent, study participants will be asked to complete baseline assessments, and then will be randomly assigned at a 1:1 ratio to 1 of the 2 groups using a computerized stratified randomization procedure to ensure equal distribution of post-operative patients and those solely medically-managed.\textsuperscript{3,4,7} Randomization will be under the control of an investigator not involved with enrollment or data collection.\textsuperscript{3,4,7}

3.5.1 Buprenorphine Group

Patients in the buprenorphine group will receive hospital-initiated sublingual buprenorphine alongside referral to Addiction Medicine for ongoing buprenorphine treatment of opioid use disorder.

We will provide pamphlets that include provider names, locations, and telephone numbers for addiction treatment centers that are covered by each patient’s insurance. The
addiction treatment centers we refer to will offer services that include various treatment options such as inpatient and outpatient settings, opioid-agonist treatment with methadone or buprenorphine, detoxification and naltrexone treatment, as well as psychosocial support services.

We will initiate buprenorphine when a patient exhibits moderate-to-severe opioid withdrawal using the Clinical Opiate Withdrawal Scale (COWS) (Table 2). We will administer buprenorphine 8 mg on day 1, buprenorphine 12 mg on day 2, and buprenorphine 16 mg daily thereafter. In patients who do not exhibit withdrawal prior to discharge, a prescription for buprenorphine will be provided with detailed instructions for home induction.

<table>
<thead>
<tr>
<th>Clinical Opiate Withdrawal Scale (COWS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For each item, circle the number that best describes the patient’s signs or symptoms. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.</td>
</tr>
<tr>
<td>Reason for this assessment:</td>
</tr>
<tr>
<td>Patient’s Name: ____________________________ Date and Time: ____________________________</td>
</tr>
</tbody>
</table>

**Resting Pulse Rate:**
- 0: pulse rate 80 or below
- 1: pulse rate 81-100
- 2: pulse rate 101-120
- 3: pulse rate greater than 120

**GI Upset:**
- 0: no GI symptoms
- 1: stomach cramps
- 2: nausea or loose stool
- 3: vomiting or diarrhea
- 5: Multiple episodes of diarrhea or vomiting

**Sweating:**
- 0: no report of chills or flushing
- 1: subjective report of chills or flushing
- 2: flushed or observable moistness on face
- 3: beads of sweat on brow or face
- 4: sweat streaming off face

**Tremor:**
- 0: No tremor
- 1: tremor can be felt, but not observed
- 2: slight tremor observable
- 4: gross tremor or muscle twitching

**Restlessness Observation during assessment:**
- 0: able to sit still
- 1: reports difficulty sitting still, but is able to do so
- 3: frequent shifting or extraneous movements of legs/arms
- 5: unable to sit still for more than a few seconds

**Yawning Observation during assessment:**
- 0: no yawning
- 1: yawning once or twice during assessment
- 2: yawning three or more times during assessment
- 4: yawning several times/minute

**Pupil size:**
- 0: pupils pinned or normal size for room light
- 1: pupils possibly larger than normal for room light
- 2: pupils moderately dilated
- 5: pupils so dilated that only the rim of the iris is visible

**Anxiety or Irritability:**
- 0: none
- 1: patient reports increasing irritability or anxiety
- 2: patient obviously irritable or anxious
- 4: patient so irritable or anxious that participation in the assessment is difficult

**Bone or Joint aches:**
- If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored
- 0: not present
- 1: mild diffuse discomfort
- 2: patient reports severe diffuse aching of joints/muscles
- 4: patient is rubbing joints or muscles and is unable to sit still because of discomfort

**Rumey nose or tearing:**
- Not accounted for by cold symptoms or allergies
- 0: not present
- 1: nasal stuffiness or unusually moist eyes
- 2: nose running or tearing
- 4: nose constantly running or tears streaming down cheeks

**Total Score:**
- The total score is the sum of all 11 items

<table>
<thead>
<tr>
<th>Table 2. Clinical Opiate Withdrawal Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score: 1-12 is mild, 13-24 is moderate, 25-38 is moderately severe, more than 38 is severe withdrawal</td>
</tr>
</tbody>
</table>

*Source: Winsten and Ling 2003*
3.5.2 Referral-Only Group

Patients in the referral-only group will receive an Addiction Medicine referral and information for addiction treatment providers in the same manner as our patients in the buprenorphine group.

3.6 Outcomes and Covariates

3.6.1 Covariates

Sociodemographic data and clinical characteristics will be recorded in the baseline assessments.

3.6.2 Sociodemographic Data

Patients’ sex, race/ethnicity, age, highest level of education, employment status, relationship status, stable housing, health insurance status, primary care provider (PCP) status, and usual source of care.²,³ Race includes: White, Black, Hispanic, and other. Highest level of education includes: high school graduate/equivalent, some college, and college degree. Health insurance status includes: private/commercial, Medicare, Medicaid, and none. Usual source of care includes: PCP office, clinic, and emergency department/none.

3.6.3 Clinical Characteristics

Clinical characteristics data to be collected will include patients’ primary type of opioid used and route of administration, nonopioid substance use in the past month, mental health history, occurrence of any psychiatric symptom in the past month, depression treatment receipt in the past month, and any lifetime treatment for addiction.²,³ Primary type of opioid drug and route of administration includes: prescription, heroin,
and IV use. Nonopioid substance use in the past month includes: alcohol to intoxication, benzodiazepines, cannabis, cocaine, and cigarettes. Mental health history includes: lifetime psychiatric diagnoses and treatment, both inpatient and outpatient. Any lifetime substance use disorder diagnoses and past treatment for addiction to alcohol and/or other drugs.

3.6.4 Primary Outcome

The primary outcome is engagement in addiction treatment 30 days after discharge. A patient is considered engaged in addiction treatment if they are confirmed to be enrolled in ongoing formal addiction treatment through direct contact with the programs.

3.6.5 Secondary Outcomes

Secondary outcomes are engagement in addiction treatment 3 months after discharge, and urine toxicology screening for opioids at 30 days and 3 months after discharge.

3.7 Blinding of Outcome

Research associates collecting data after discharge will be blinded to each study participant’s intervention assignment and corresponding inpatient course.

3.8 Data Collection and Statistical Considerations

3.8.1 Data Collection

Engagement in addiction treatment will be assessed by direct contact with the addiction treatment facility, clinician, or both for verification of enrollment in ongoing
formal addiction treatment at 30 days and 3 months after hospital discharge. Urine samples will be collected by research associates and analyzed using rapid qualitative immunoassay.\(^3\)

### 3.8.2 Sample Size Calculation

Sample size calculations were based on data from published studies investigating the efficacy of buprenorphine initiated in emergency department (ED) and inpatient settings.\(^3,11\) These reports support addiction treatment engagement 30 days post-randomization in 78% of ED-initiated buprenorphine patients and 37% of ED-referral patients, with an effect size of 0.41.\(^3\) Moreover in another study, 39% of hospital-initiated buprenorphine patients were engaged in addiction treatment 30 days post-discharge.\(^11\) This suggests a half-fold difference in positive outcomes between these acute care settings. Under this assumption, we inferred 18% of hospitalized patient referrals would engage in addiction treatment and an anticipated effect size of 0.21.

We will need a sample size of 144 to detect a between-group difference of at least 54% for the primary outcome of engagement in addiction treatment at 30 days post-discharge, with 80% power and Type I error probability 0.05. We also considered losses in follow-up from published studies to anticipate a 35% attrition rate.\(^3,6,11\) Under this assumption, we will require a sample size of 196 to adequately power our investigation.

### 3.8.3 Analysis

Patients’ sociodemographic data and clinical considerations will be presented using descriptive statistics. Primary and secondary outcomes will be described as proportions. Chi-square tests will evaluate the statistical significance of between-group
differences in outcomes. If necessary, multivariate analyses will be performed using multiple logistic regression to control for confounding. Intention to treat analyses will be employed to include every enrolled study participant. Missing urine samples will be reported as opioid-positive. 2-tailed tests of significance will be performed with IBM SPSS software. A p-value less than 0.05 will be considered statistically significant.

3.9 Timeline

This study will be divided into 2 stages. Stage 1 will be for patient recruitment and data collection to be completed in 24 months (Figure 1). Buprenorphine-initiation protocol and referral information delivery will start immediately after randomization. Recruitment will conclude 6 months prior to the end of Stage 1, to accommodate 3 months of post-discharge data collection for each individual. Data collection will occur throughout Stage 1. Stage 2 will be for data analysis.

![Figure 1. Stage 1 Timeline: Recruitment and Data Collection](image)
3.10 References


Chapter 4 Conclusion

4.1 Advantages and Disadvantages

Intravenous drug-use related infective endocarditis (IVDU-IE) therapy employing medication-assisted addiction treatment addresses the causative factor of infection recurrence. However, our current standard of care approach solely emphasizes infectious disease management. Overall, limited data exists for opportunistic hospital-initiated addiction treatment, and to our knowledge, no study has focused on hospital-initiated buprenorphine in patients hospitalized with IVDU-IE. It is imperative that we provide evidence-based recommendations to the medical community for optimization of IVDU-IE treatment.

We elected a randomized clinical trial study design and intention to treat analysis to best address treatment comparison. Study participants cannot be blinded to their intervention, however, research associates will be blinded to inpatient course to minimize information bias. To further limit information bias, urinalysis will be used for screening of opioid use after hospital discharge. A bedside diagnosis and pharmacologic management are feasible interventions. Access to 196 patients to sufficiently power the study is also feasible across 17 sites in 18 months. Additionally, our study addresses generalizability issues of previous studies through its geographic expansion to multiple sites within the Northeast United States, and by including non-English speaking patients.

This study has several limitations. First, IVDU-IE is a highly specific diagnosis. In a real-world setting, patients with active IVDU that are hospitalized for any reason may be eligible for hospital-initiated buprenorphine. Second, we have chosen to exclude patients requiring opioid management for chronic pain due to ethical and pharmacologic
considerations. Chronic opioid regimens are a risk factor for IVDU and IVDU-IE, however, use of a partial opioid agonist like buprenorphine in these patients would either precipitate withdrawal or render their pain management regimen ineffective. Methadone may be a better option for medication-assisted addiction treatment in these patients.\footnote{1} Third, sociodemographic variables present potential sources of confounding. Lack of engagement in addiction treatment and attrition may not be entirely contingent on buprenorphine efficacy but on factors such as unstable living arrangements, unemployment, and uninsured status. This warrants further research and optimization of psychosocial interventions for this patient population. Next, 3 months for data collection may be considered too brief because IVDU is a chronic brain condition. However, patient outcomes following effective transition to addiction treatment programs are more reflective of ongoing treatment strategies in said programs. Finally, initiation of buprenorphine may be viewed as burdensome as it necessitates that prescribers comply with the Comprehensive Addiction Recovery Act (CARA) by completing 8 to 24 hours of federally-mandated office-based opioid addiction treatment training and certification.\footnote{6} However, outpatient buprenorphine is more accessible in contrast to stringent, federally-regulated methadone clinics.\footnote{1,3,6,8}

4.2 **Clinical and Public Health Significance**

If hospital-initiated buprenorphine in IVDU-IE patients proves to be more effective than referral alone for engagement in addiction treatment after discharge, we may optimize recurrence prevention of IE. Continued work to reconcile social barriers and the stigma surrounding medication-assisted addiction treatment is still required, but this study proposes an interdisciplinary approach with currently available options sans
costly, innovative therapies to reduce IVDU-related morbidity and mortality.\textsuperscript{4,5,9}
Moreover, it offers an effective addiction treatment strategy amidst a national opioid epidemic.

4.3 References

Appendices:

Appendix I Sample Consent Form

WRITTEN CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR.3 (2014-1)

FOR SUBJECTS WHO DO NOT SPEAK OR ARE UNABLE TO READ ENGLISH
THIS DOCUMENT MUST BE WRITTEN IN A LANGUAGE UNDERSTANDBABLE
TO THE SUBJECT

YALE-NEW HAVEN HOSPITAL
YALE-NEW HAVEN HOSPITAL: SAINT RAPHAEL CAMPUS
YALE-NEW HAVEN HOSPITAL: BRIDGEPORT HOSPITAL
YALE-NEW HAVEN HOSPITAL: LAWRENCE + MEMORIAL HOSPITAL
YALE-NEW HAVEN HOSPITAL: WESTERLY HOSPITAL
YALE-NEW HAVEN HOSPITAL: NORTHEAST MEDICAL GROUP
PARTNERS HEALTHCARE: BRIGHAM AND WOMEN’S HOSPITAL
PARTNERS HEALTHCARE: MASSACHUSETTS GENERAL HOSPITAL
PARTNERS HEALTHCARE: FAULKNER HOSPITAL
PARTNERS HEALTHCARE: COOLEY DICKINSON HOSPITAL
PARTNERS HEALTHCARE: MARTHA’S VINEYARD HOSPITAL
PARTNERS HEALTHCARE: MCLEAN HOSPITAL
PARTNERS HEALTHCARE: NANTUCKET COTTAGE HOSPITAL
PARTNERS HEALTHCARE: NEWTON-WELLESLEY HOSPITAL
PARTNERS HEALTHCARE: NORTH SHORE MEDICAL CENTER
PARTNERS HEALTHCARE: PARTNERS COMMUNITY PHYSICIANS
PARTNERS HEALTHCARE: WENTWORTH-DOUGLASS HOSPITAL

Study Title: INITIATING BUPRENORPHINE IN PATIENTS HOSPITALIZED WITH
INTRAVENOUS DRUG-USE-RELATED ENDOCARDITIS

Principal Investigator: Naiska Y. Cheung, PA-SII; Patrick O’Connor, MD, MPH, FACP

Funding Source: Pending

Consent to Participate in Research

You are being invited to participate in a research study designed to investigate the
efficacy of different treatment strategies for secondary prevention of intravenous drug
use-related infective endocarditis. You have been asked to participate because you are 18
years or older; have a DSM-V diagnosis of substance use disorder; and provided a urine
sample positive for opioids. We expect to enroll 196 adults across all study sites.
In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent for gives you detailed information about the research study, which a member of the research team will discuss with you. Before you agree, a member of the research team must tell you about (i) the procedures and duration of the research; (ii) any reasonably foreseeable risks, discomforts, and benefits of the research; (iii) any potentially beneficial alternative procedures or treatments; and (iv) how confidentiality will be maintained. Once you understand the study, you will be asked if you wish to participate.

If you agree to participate, you must be given a signed copy of this document and a written summary of the research.

**Description of Procedures**

Once enrolled in this study, you will be asked to fill out a form for us to better know you.

You will be randomly chosen to receive one of two treatment options offered. The two treatment options include sublingual buprenorphine combined with referral and referral alone.

If you are chosen to receive buprenorphine, your care team will independently evaluate your opioid withdrawal severity using the Clinical Opiate Withdrawal Scale (COWS) as a guide for opioid use disorder treatment initiation. Buprenorphine treatment is clinically indicated for moderate-to-severe opioid withdrawal symptoms. If buprenorphine treatment is not indicated during your hospitalization, we will provide you with a prescription for buprenorphine and detailed instructions on when and how to take the medication at home. Referral to ongoing treatment will be provided to you, along with information pamphlets of facilities covered by your insurance.

If you are chosen to receive referral alone, your care team will provide you with a referral to an opioid use disorder treatment provider and information pamphlets for facilities covered by your insurance.

Regardless of the treatment course you are chose for, we highly encourage you to enroll in opioid use disorder treatment after you have been discharged. You will return for follow-up with our research team in one (1) month and three (3) months after discharge.

At each follow-up visit you will be asked to provide a urine sample for opioid screening. These results will only be made available to members of our research team.
Risks and Inconveniences

Sublingual buprenorphine adverse reactions include headache (29%), insomnia (21%), sweating (13%), nausea (14%), abdominal pain (12%), constipation (8%), and vomiting (8%). This medication may impair your ability to drive or operate machinery. Less common complications include allergy/anaphylaxis, hypotension, arrhythmia, and respiratory depression. This medication should not be taken with other depressants or sedatives such as benzodiazepines or alcohol due to risk of overdose, coma or death.

Benefits

Potential benefits from treatments include opioid use abstinence and treatment of withdrawal symptoms that include: yawning, lacrimation, rhinorrhea, nausea, emesis, diarrhea, hypertension, chills, piloerection, myalgias, abdominal pain, tremor, anxiety, agitation, delirium, and seizures.

Economic Considerations

The cost of treatment involves several charges, including fees charged by your care team, the cost of buprenorphine (if applicable), and opioid use disorder treatment provider charges after discharge.

Your health insurance will partially or completely cover these costs. If you do not have health insurance, your case manager will direct you to the appropriate resources for potential financial assistance.

Treatment Alternatives/Alternatives

The most common treatment medical alternatives to buprenorphine maintenance therapy include methadone, naltrexone, and detoxification/non-medication treatment.

Confidentiality

Research materials will be stored in locked cabinets and shredded before discarding. Digital data will be stored and analyzed only on properly encrypted devices. All identifiable information will be deidentified prior to analysis to ensure confidentiality. When the results of the research are published or discussed in conferences, no
information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Participating in this study is voluntary. You are free to refuse your participation in this study. Refusing to participate will involve no penalty or loss of benefits to which you would otherwise be entitled. However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow the use of your information as part of this study.

You do agree to become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw you from participating in the research if necessary. Conditions under which a subject might be withdrawn from the research include, but are not limited to, when the subject is no longer a suitable candidate due to health, or the subject develops serious side effects or complications to treatment.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your doctors or with the affiliated institute.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you do not understand and to consider this research and consent form carefully—as long as you feel is necessary—before you make a decision.

I. ________________________________, have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature indicates that I have received a copy of this consent form.

_________________________        _________________________        ______________
Name                          Signature                          Date
Signature of Principal Investigator  
(This should not be the person obtaining consent)  

Date

or

Signature of Person Obtaining Consent  

Date

You may contact Naiska Y. Cheung, PA-SII at (123) 456-7890 any time you have questions about the research or what to do if you are injured.

If you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee/Yale Human Research Protection Program (HRPP) at 203-785-4688.
Bibliography


