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ORIGINAL ARTICLE

Methadone vs. Buprenorphine for In-Hospital Initiation: Which Is Better for Outpatient Care Retention in Patients with Opioid Use Disorder?

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Abstract

Introduction Currently, few hospitals provide medications for opioid use disorder (MOUD) to admitted patients with opioid use disorder (OUD). Data are needed to inform whether the choice of medication during hospitalization influences probability of retention in outpatient OUD treatment.

Methods This was a retrospective cohort analysis of patients who received a medical toxicology consult for OUD. Medical records were reviewed to determine if patients received MOUD and were referred to Engaging Patients in Care Coordination (EPICC), a service that connects hospitalized patients with OUD to outpatient care. Patients were stratified by the last form of MOUD they received in the hospital (methadone verses buprenorphine); retention in outpatient treatment was measured at 2 weeks, 30 days, and 12 weeks. The log-rank test was used to determine the difference in probabilities of retention in the methadone and buprenorphine groups. An event was defined as drop-out from outpatient treatment.

Results Of 267 total patients with medical toxicology consults for OUD, 155 received MOUD and referral to EPICC. One hundred six patients received buprenorphine and 46 received methadone. Three additional patients were excluded. The rate of retention in outpatient treatment for patients who received buprenorphine was 37%, 26%, and 13% and for patients who received methadone was 43%, 39%, and 35% at 2 weeks, 30 days, and 12 weeks, respectively. Methadone was associated with a statistically significant increased probability of retention in outpatient treatment as compared to buprenorphine ($P < 0.01$).

Conclusion Despite the limitations of this retrospective study, in hospitalized patients who received MOUD, the probability of retention in outpatient treatment was higher in patients receiving methadone compared to buprenorphine.

Keywords Medication for addiction treatment · Opioid use disorder · Methadone · Buprenorphine · Outpatient addiction treatment

Introduction

In 2018, almost 47,000 Americans died from an overdose involving an opioid, a number that has increased almost six-fold since 1999 [1]. This crisis has reached epidemic proportions, with drug overdose becoming a leading cause of death in recent years [2]. However, the opioid epidemic extends well beyond the roughly 50,000 Americans who died from an opioid-related overdose in 2018, as that statistic does not account for the additional significant morbidity related to harmful opioid use. For instance, an estimated 2.1 million Americans aged 12 or older suffered from opioid use disorder (OUD) in 2018 [3]. There are a variety of treatment options for OUD including three forms of medication for opioid use disorder (MOUD): methadone, a full m-opioid agonist; buprenorphine, a partial m-opioid agonist; and

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naltrexone, an m-opioid antagonist. Unfortunately, adoption of hospital-initiated MOUD has been slow. While patients who receive ED-initiated buprenorphine are significantly more likely to be engaged in formal OUD treatment at 30 days post discharge, a survey of academic emergency physicians from 2019 found that only 27% feel comfortable initiating buprenorphine [4, 5].

Public health campaigns to combat the crisis have focused extensively on the distribution of naloxone to prevent overdose deaths. This measure is important and has the potential to reduce morbidity and mortality from opioid misuse. In fact, there was a 2.0% decrease in the rate of opioid overdose deaths in the USA between 2017 and 2018, the first year-to-year decrease since 1990 [6]. Though these data are promising, the crisis is not over. In Philadelphia, where a statewide standing order allows pharmacies to dispense naloxone without a prescription, only one-third of pharmacies carried intranasal naloxone. Communities with the highest rates of overdose deaths in that city were found to have the greatest barriers in access to naloxone [7]. In Missouri, there was a 19.0% increase in opioid overdose deaths between 2017 and 2018 [8]. In 2017 in St. Louis, the city where the study was conducted, there was the highest incidence of opioid overdose deaths and emergency department visits related to opioid misuse in the state of Missouri [9]. Data recently published by Weiner et al. demonstrate that greater than 5% of patients who present to the emergency department (ED) with a nonfatal opioid overdose die within 1 year [10]. These tragic findings underscore the importance of implementing treatment for those who suffer from OUD in addition to risk reduction public health campaigns.

MOUD is an effective therapy for opioid addiction [11–15]. Buprenorphine-naloxone (hereafter referred to as buprenorphine) and methadone are the two most commonly used medications for OUD. Many studies have demonstrated increased retention in outpatient treatment programs and decreased hazardous use of opioids with methadone as compared to buprenorphine maintenance therapy [16–18]. Despite studies demonstrating better outcomes with methadone in the outpatient setting, there is no clear evidence that methadone is superior to buprenorphine for in-hospital treatment of OUD. While buprenorphine can be prescribed for the outpatient treatment of OUD, methadone cannot; it must be dispensed through a registered opioid treatment program (OTP). Therefore, if methadone treatment is initiated during a hospitalization, a bridge prescription cannot be written. Efforts are made to connect patients with OTPs as soon as possible following discharge, but there is the possibility of a gap between discharge and receiving the next dose of methadone at follow-up. To our knowledge, only Trowbridge et al. have compared in-hospital initiation of buprenorphine and methadone for OUD. They found increased linkage to, and retention in, outpatient treatment programs with methadone as compared to buprenorphine; however, no statistical comparison was performed [19]. Additionally, the office-based addiction treatment clinic, discharge clinic, and the three methadone clinics were staffed by the inpatient addiction faculty or addiction medicine fellows. Our study relies on community outpatient treatment centers available outside of an academic medical center and includes statistical analysis.

At Barnes-Jewish Hospital in St. Louis, Missouri, physicians in the Division of Medical Toxicology provide consultation for patients with OUD. The toxicology team engages in diagnostic services, manages administration of MOUD, and helps link patients to outpatient addiction treatment through the Engaging Patients in Care Coordination (EPICC) program. Prior to this, addiction medicine consultation was unavailable at the medical center. EPICC, which is an initiative of the Behavioral Health Network of St. Louis, is intended to connect patients being treated in-hospital for OUD with outpatient care. The initiative began on December 1, 2016, and has improved access to MOUD, recovery coaches, and outpatient addiction treatment for patients with OUD. The EPICC referral process involves an initial consult with a peer counselor that usually takes place in-person (in the emergency department or inpatient floor). The peer counselor helps the patient schedule an appointment at an outpatient treatment center, which provides a variety of addiction resources (therapy, additional peer counseling, etc.) in addition to licensed providers who prescribe MOUD. The aim of this study is twofold: to describe the Division of Medical Toxicology's experience in providing consults for OUD and determine whether there is a difference in the probability of retention in outpatient treatment between those who initiate buprenorphine therapy compared to methadone while hospitalized. The null hypothesis is that there is no difference in probability of retention in outpatient treatment based on type of MOUD administered in-hospital.

Methods

This was a retrospective cohort study approved by the Washington University Institutional Review Board. Participants were selected by identifying patients who had received a medical toxicology/addiction medicine consult from the medical toxicology service at Barnes-Jewish Hospital for a condition related to opioid use. Patients in this study were admitted with a variety of primary diagnoses including but not limited to opioid use disorder (often secondary to overdose), abscess, endocarditis, and osteomyelitis. A database of patients who received consults from a medical toxicologist between December 1, 2016, and December 31, 2019, was reviewed for patients diagnosed with OUD. The start date of December 1, 2016, was selected because this was the date that EPICC began accepting patients.

Patients who were identified as receiving an in-hospital toxicology consult for OUD were included in the analysis. A review of each patient's electronic medical record was conducted by an author (S.H.K.) to determine whether the patient received MOUD. Those who received MOUD were grouped by choice of medication: buprenorphine, methadone, or naltrexone. Patients who received MOUD chose between methadone, buprenorphine, and naltrexone after an informed consultation with a medical toxicologist, which considers known barriers as well as the patient's beliefs and opinions. Patients with OUD who received methadone for pain were not included in this study. Some patients switched medications during their inpatient stay; these patients were grouped based on the last MOUD they received prior to discharge.

A database of EPICC participants was obtained from the Behavioral Health Network. The patients who received a toxicology consult for the evaluation of OUD were cross-referenced with the database provided by the Behavioral Health Network to determine whether each patient had been referred to the EPICC program. Linkage with EPICC entails a consultation between the patient and a peer recovery coach, during which the peer coach provides counseling and take-home naloxone, and assists the patient in scheduling an outpatient appointment. Referral to EPICC does not guarantee that a patient attends an appointment at an outpatient treatment center. The EPICC program records attendance at 2 weeks, 30 days, and 12 weeks following date of referral to the program. The EPICC dataset was the only database with information regarding retention in outpatient treatment for our study participants. Therefore, we were unable to monitor retention in outpatient treatment for anyone who was not referred to EPICC. A second reviewer (D.B.L) conducted a chart review on 30 out of 267 (11%) study participants. All data abstracted were in agreement; Cohen's kappa = 1.0.

Statistical Analysis

In order to test the null hypothesis that there is no difference in probably of retention in outpatient treatment based on type of MOUD administered in-hospital, a survival analysis curve was created and the log-rank test was performed. An event was defined as drop-out from attendance at outpatient treatment sessions. Since EPICC records attendance at 2 weeks, 30 days, and 3 months, an event could only be reported at these time points. Once a patient dropped out, they were considered absent at all future time points. Statistical significance was assigned for a P value < 0.05. Demographic data on type of MOUD selected were compared with the t-test for continuous variables (age) and the chi-squared test for categorical data (all other demographic variables). All statistical analyses were performed using GraphPad Prism 9.

Results

Between December 1, 2016, and December 31, 2019, the Division of Medical Toxicology received 267 consults for patients with OUD in the emergency department or admitted to the hospital ward. Of these 267 consults, 230 occurred on an inpatient floor and 37 occurred in the emergency department. Medical toxicologists managed the administration of MOUD in 88% (234/267) of these patients. No patients received methadone or naltrexone while in the ED.

Of all the patients who received a consult while in the emergency department or on an inpatient floor, 58% (155/267) received MOUD and connection with EPICC. An additional 30% (79/267) received MOUD but were not connected with EPICC. Four percent (10/267) were linked with EPICC but did not receive MOUD, and 9% (23/267) received neither MOUD nor linkage with EPICC (Fig. 1). One of the patients who received both in-hospital MOUD and linkage to EPICC discontinued MOUD 10 days prior to discharge after disposition planning changed, and there was no longer intention for this patient to continue MOUD as an outpatient. This patient is reflected in Fig. 1 but was excluded from further analysis.

Of the remaining 154 patients in the MOUD + EPICC group, 106 (69%) received buprenorphine, 46 (30%) received methadone, and 2 (1%) received naltrexone as their last form of MOUD prior to discharge (Fig. 1). Given the clinically insignificant sample size for the naltrexone group, these two patients were excluded from statistical analysis. We monitored retention in outpatient treatment for the 152 patients who received buprenorphine or methadone along with referral to EPICC (Fig. 1). Background demographic data are also reported for these patients (Table 1). At 2 weeks, 38 of 106 (36%) patients who received buprenorphine were enrolled in EPICC. At 30 days, 26 (25%) patients remained enrolled. At 12 weeks, 13 (12%) patients remained enrolled (Fig. 2). Of the 46 patients who received methadone, 20 (43%) were enrolled at 2 weeks. At 30 days, 18 (39%) remained enrolled, and at 12 weeks, 16 (35%) remained enrolled (Fig. 2). Using the log-rank test, methadone was associated with a statistically significant increase in the probability of retention in outpatient treatment as compared to buprenorphine ($P < 0.01$).

Discussion

Between December 1, 2016, and December 31, 2019, medical toxicologists at Barnes-Jewish Hospital received 267 consults for patients with OUD

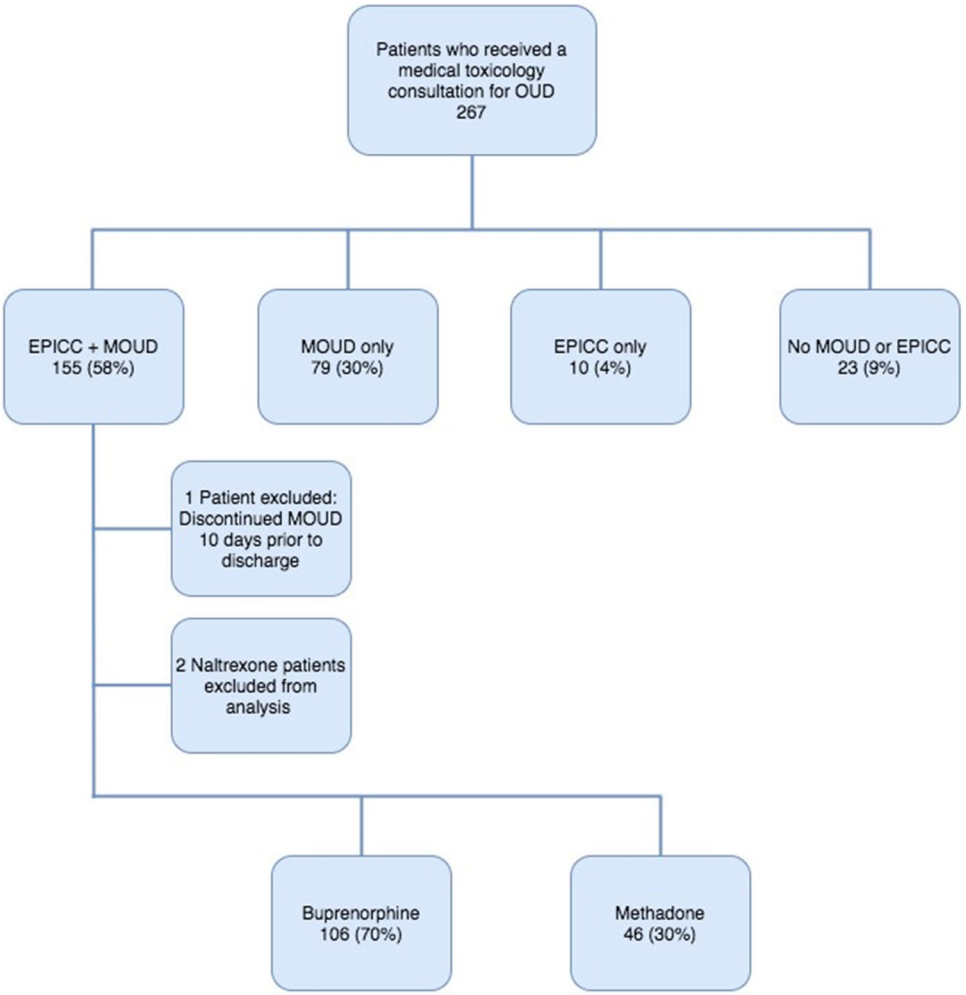

Fig. 1 Flow diagram for included and excluded patients and their respective treatment paths. EPICC, Engaging Patients in Care Coordination; MOUD, medication for opioid use disorder; OUD, opioid use disorder

Table. 1 Background demographic data for EPICC + MOUD patients

Characteristic	Total cohort ($N=152$)	Methadone ($N=46$)	Buprenorphine ($N=106$)	P value
Age, mean (SD), yrs	40.8 (10.8)	38.1 (9.6)	42.0 (11.1)	0.04
Sex				
Male	92 (61)	28 (61)	64 (60)	0.95
Female	60 (39)	18 (39)	42(40)	
Race				
Caucasian	47 (31)	13 (28)	34 (32)	0.26
African American	96 (63)	28 (61)	68 (64)	
Hispanic	3 (2)	1 (2)	2 (2)	
Other & refused	6 (4)	4 (9)	2 (2)	
Unhoused	30 (20)	10 (22)	20 (19)	0.68

Represents demographic data for participants who received MOUD and were referred to EPICC. Data are presented as number (percent) of subgroup except for age, as indicated. The *t*-test was used to compare means of continuous variables (age), whereas the chi-squared test was used to compare the other categorical variables

and facilitated administration of MOUD in 88% of these patients. Patients who received methadone as the last form of MOUD prior to discharge had an increased probability of remaining in outpatient treatment 12 weeks after discharge compared to those who received buprenorphine.

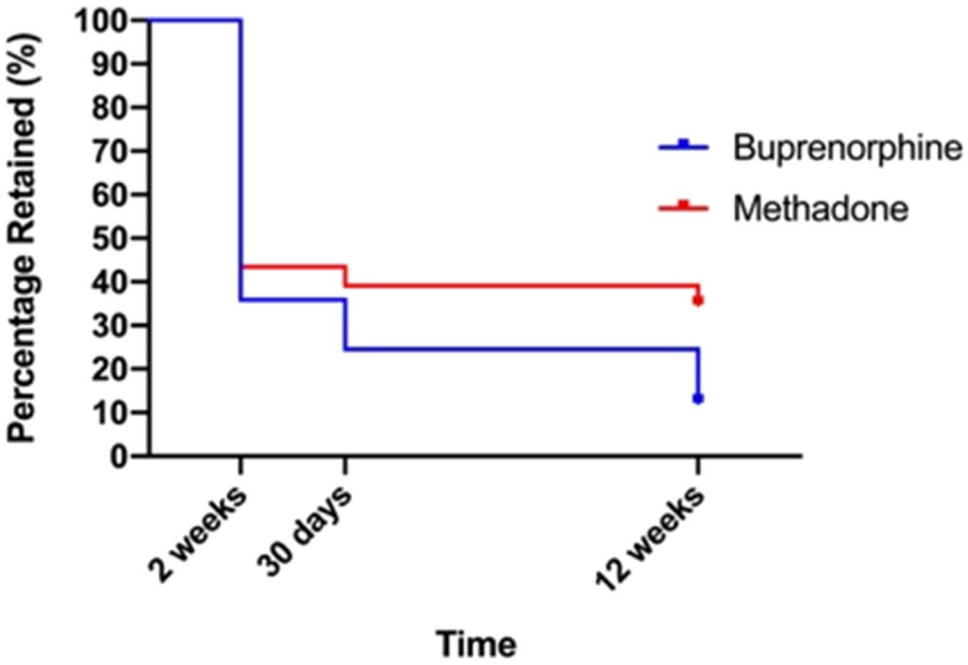

Fig. 2 Retention in outpatient treatment for patients who received MOUD and were referred to EPICC. An event is defined as drop-out from the outpatient treatment program and could occur at either 2 weeks, 30 days, or 12 weeks. As data were not recorded beyond 12 weeks, patients still enrolled at the 12-week time point were censored at that point. Statistical analysis was performed using the log-rank test, $P < 0.01$

The main goal of this study was to compare retention in outpatient treatment for OUD based on the type of MOUD administered in-hospital. There is a paucity of experimental data as to which medication is superior for in-hospital initiation. Factors that influence a patient's decision when choosing MOUD include prior MOUD experience, anticipated length of hospital visit, ability to access an outpatient clinic, anticipated costs, and the provider's own perception of the available medication options. A potential downside of prescribing methadone for in-hospital treatment of MOUD is that patients must be discharged without a bridge prescription for methadone due to legal regulations. Efforts are made to connect these patients with an outpatient methadone clinic via the EPICC program as soon as possible, but there may be a period of time during which these patients have no access to methadone. This is in addition to the other known barriers that patients face when deciding to receive care at a methadone clinic [20].

The results of this study suggest that patients who chose methadone as compared to those who chose buprenorphine for in-hospital treatment of OUD had an increased probability of remaining in outpatient treatment after hospital discharge. Our findings support studies conducted in the outpatient setting that have found methadone to be more effective than buprenorphine in retaining patients and decreasing hazardous opioid use [16–18].

Given the significant morbidity and mortality associated with opioid use disorder, it is important that hospitalized patients—both in the ED and on inpatient floors—receive appropriate treatment. Wakeman et al. found that not only are methadone and buprenorphine effective for OUD, but they are the *only* form of treatment associated with reduced risk of overdose and serious opioid-related acute care use. The authors found that only 12.5% of their cohort of patients with OUD received either methadone or buprenorphine, leaving room for improvement [14].

Even hospitalized patients admitted with a diagnosis of opioid use disorder receive suboptimal addiction treatment during the admission. Rosenthal et al. found that less than 8% of patients admitted for infective endocarditis from injection drug use were discharged with a plan for MOUD, and none were discharged with naloxone [21]. Given the setting of the opioid epidemic and the high rates of substance use among hospitalized patients, however, there is increased interest in beginning treatment for OUD in-hospital [4, 19, 22, 23]. The combination of MOUD and linkage to outpatient addiction clinics is suggested to be the most effective in reducing opioid use [22]. In our cohort, patients were offered connection with a recovery coach and MOUD; however, inpatients did not receive other psychosocial interventions while they were hospitalized. Retention may have been improved if patients had been offered these resources, particularly in those with prolonged hospitalizations.

The gap in access to MOUD further underscores the importance of increasing its use in the hospital setting. However, there is great variation among practitioners with respect to treatment protocol [24]. Presently, addiction medicine consultations are not mandated and are at the discretion of the primary team. While knowledge of this new service increased from 2016 to 2019, we cannot say why some patients received consults and some did not. Furthermore, there is minimal research comparing the efficacy

of methadone and buprenorphine for use in the ED and inpatient setting. Our observational data are in agreement with those published by Trowbridge et al., which showed increased retention in outpatient treatment following in-hospital treatment with methadone [19].

It is possible that the better outcomes observed in the methadone group are due to the strict requirements associated with outpatient methadone treatment (i.e., daily visits to a methadone clinic), which may result in increased patient engagement. Though initiating methadone in-hospital can result in a gap between discharge and continuing outpatient therapy, patients in our cohort who received methadone were usually scheduled for an appointment at an OTP the day following discharge. This was not necessarily the case for those patients who were prescribed buprenorphine at discharge as they were given bridge prescriptions to take home. Another possible explanation for the increased probability of retention associated with methadone group is a pharmacological one: methadone is a full opioid agonist, whereas buprenorphine is a partial agonist. It is possible that for some patients, only methadone is able to alleviate opioid craving symptoms. Finally, patients that received methadone may have been more motivated knowing they had to go to a clinic daily to receive their medication.

Another goal of our study was to characterize the prescribing patterns and treatment plans of medical toxicologists. At Barnes-Jewish Hospital, we found that the overwhelming majority of consults during the two-and-a-half-year time frame of this study occurred on inpatient floors. This is likely because most of the ED faculty have Drug Enforcement Administration waivers to prescribe buprenorphine for OUD, and the ED has protocols for induction of these patients that were developed by the medical toxicology service.

The goal treatment plan for patients with OUD in our study was administration of MOUD and linkage to outpatient treatment via EPICC. While the majority (58%) of our patients received this treatment pathway, some received only MOUD or EPICC consultations, and a smaller percentage received neither. The reasons for not receiving MOUD varied but included personal preference, leaving against medical advice prior to administration of MOUD, and requirement of parenteral opioids for acute pain control. The primary reason that patients did not receive linkage with EPICC was because only patients living in St. Louis City or County were eligible for this program at the time. Many of our patients resided in Illinois and were thus not eligible to participate. Additionally, lack of linkage to care does not equate to treatment failure. Prior research has shown that patients who received MOUD during their admission have decreased odds of leaving against medical advice [25].

The rates of retention in outpatient care for patients in our cohort were lower than those observed in similar studies [4, 19, 22, 26]. We believe the reasons for this are numerous and include the high rate of unhoused patients and lack of adequate transportation (both private and public) in St. Louis. Both of these issues make it more difficult for patients to attend their outpatient appointments. Additionally, unlike many other states, Missouri has not yet adopted Medicaid expansion increasing the burden for patients without health insurance. We have also found certain communities in the area that are still not proponents of MOUD nor accept that addiction is a medical disease.

Hospitalization—whether for a condition related to opioid use disorder or not—is an opportune time for providers to address OUD and begin medication-based treatment. A major barrier, as identified by the National Academies of Science, Engineering, and Medicine report, is regulations on the use of methadone and buprenorphine [27]. Currently, the Drug Addiction Treatment Act of 2000 requires that physicians possess a waiver (x-waiver) from the Drug Enforcement Administration in order to write outpatient buprenorphine prescriptions for the treatment of OUD. Until May 2021, obtaining a waiver required additional training. Additional training is still required for practitioners who intend to treat greater than 30 patients. There is also a misconception that a waiver is required to order MOUD for patients admitted to the ED or hospital, resulting in increased confusion among potential providers [24]. Deregulating buprenorphine and easing provider ability to prescribe could help lower the gap in patients who need but do not receive MOUD as well as eliminate the stigma surrounding the disease and its treatment [28]. The Mainstreaming Addiction Treatment Act of 2019, a bill introduced to the United States House of Representatives in 2019, aims to address this issue by loosening restrictions around prescribing MOUD [29]. Additionally, the Easy Medication and Treatment (Easy MAT) for Opioid Addiction Act was passed in December 2020, which eliminates the requirement of an x-waiver to write for up to three days of buprenorphine [30].

Limitations

The major limitation of this study is its design as a retrospective cohort analysis. Because we were unable to randomly assign patients to receive either methadone or buprenorphine, there may be confounding variables for which our analysis cannot account. For example, the severity of OUD (mild, moderate, severe) which may differ between treatment groups was not explicitly stated in the medical records. We were also unable to ask patients about consequences of continued opioid use such as job loss, relationship termination, or suspension of child custody. The legal status of a patient such as whether they are on parole, probation, currently in custody, or participating in a court-ordered drug rehabilitation program was not abstracted. As a retrospective

study, the sample size was inherent with the timeframe of analysis and could not be increased. An additional limitation of this study is that some patients switched between buprenorphine and methadone (and vice versa) during their hospital visit. As previously noted, patients were grouped based on the last MOUD administered in the hospital. In outpatient treatment, they could again change type of MOUD or discontinue MOUD and receive only non-pharmacological therapy. Additionally, the treatment centers associated with EPICC are independent of the hospital, and we are unaware of the specific programs that each facility offers or requires to remain in treatment. Furthermore, we did not have access to the specific programs in which each patient participated (pharmacotherapy, peer support, formal counseling, etc.) as part of their outpatient treatment course, which may impact retention. Our primary outcome measure, retention in outpatient addiction treatment, may not correlate with hazardous opioid use and is multifactorial. Finally, we were only able to report retention in outpatient treatment for patients who were referred to EPICC as this was the only database with outpatient addiction treatment information available. This limitation prevented us from monitoring patients who received MOUD but were not referred to EPICC. The results of this study should be considered preliminary, and we hope that they will guide future research and be used to inform clinical decision-making. Future research should be designed in a prospective fashion that allows for direct follow-up with study participants. Outcomes should include hazardous opioid use in addition to retention in outpatient treatment.

Conclusion

Our findings demonstrate that medication-based treatment for OUD can be initiated in hospitalized patients. Our data suggest an increased probability of retention in outpatient treatment at 12 weeks following hospital discharge among patients who receive methadone for in-hospital treatment of OUD compared to those who receive buprenorphine. These data are limited by the retrospective observational study design which cannot account for differences in the patients who choose one medication over the other, including the severity of their OUD and their motivations for seeking treatment.

Abbreviations OUD: Opioid use disorder; MOUD: Medication for opioid use disorder; ED: Emergency department; OTP: Opioid treatment program; EPICC: Engaging Patients in Care Coordination

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Author Contribution All authors contributed to study design. SHK and DBL collected and analyzed the data. SHK drafted the manuscript, and all authors edited and approved the final manuscript.

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Declarations

Conflicts of Interest None.

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