

Opioid Use Disorder Treatment Initiation and Continuation: a Qualitative Study of Patients Who Received Addiction Consultation and Hospital-Based Providers



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ABSTRACT:

BACKGROUND: Hospitalizations related to opioid use disorder (OUD) are rising. Addiction consultation services (ACS) increasingly provide OUD treatment to hospitalized patients, but barriers to initiating and continuing medications for OUD remain. We examined facilitators and barriers to hospital-based OUD treatment initiation and continuation from the perspective of patients and healthcare workers in the context of an ACS.

METHODS: In this qualitative study, we sought input using key informant interviews and focus groups from patients who received care from an ACS during their hospitalization and from hospitalists, pharmacists, social workers, and nurses who work in the hospital setting. A multidisciplinary team coded and analyzed transcripts using a directed content analysis.

FINDINGS: We conducted 20 key informant interviews with patients, nine of whom were interviewed following hospital discharge and 12 of whom were interviewed during a rehospitalization. We completed six focus groups and eight key informant interviews with hospitalists and hospital-based medical staff ($n = 62$). Emergent themes related to hospital-based OUD treatment included the following: the benefit of an ACS to facilitate OUD treatment engagement; expanded use of methadone or buprenorphine to treat opioid withdrawal; the triad of hospitalization, self-efficacy, and easily accessible, patient-centered treatment motivates change in opioid use; adequate pain control and stabilization of mental health conditions among patients with OUD contributed to opioid agonist therapy (OAT) continuation; and stable housing and social support are prerequisites for OAT uptake and continuation.

CONCLUSION: Modifiable factors which facilitate hospital-based OUD treatment initiation and continuation include availability of in-hospital addiction expertise to offer easily accessible, patient-centered treatment and the use of methadone or buprenorphine to manage opioid withdrawal. Further research and public policy efforts are urgently needed to address reported barriers to hospital-based OUD treatment initiation and continuation which

include unstable housing, poorly controlled chronic medical and mental illness, and lack of social support.

KEY WORDS: qualitative; addiction; opioid use disorder; opioid agonist; buprenorphine; methadone.

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INTRODUCTION

Hospitalizations related to opioid use and opioid overdose quadrupled in the past three decades.¹ Medical complications of injection drug use, including solid organ infections, may require weeks of intravenous antibiotics to ensure bacterial clearance.² People who inject drugs often remain hospitalized to complete antibiotic treatment which may be challenging for those who lack social support or coping skills.^{3,4} Consequently, patients with substance use disorders and healthcare providers report difficult interactions related to in-hospital substance use, poorly controlled withdrawal, patients leaving prior to treatment completion, and in-hospital overdose deaths.^{5–8} To address increasing opioid-related hospitalizations, some hospitals have implemented addiction consultation services (ACS).⁹ ACS meet with hospitalized patients to discuss their substance use, offer treatment, and link patients to post-discharge addiction treatment.^{10–13} Provision of hospital-based addiction treatment is associated with reduced rehospitalization and increased post-discharge treatment engagement.^{14,15}

Population-level data has demonstrated that receipt of opioid agonist therapy (OAT), including buprenorphine or methadone, following an overdose event was associated with a 50% mortality reduction over 12 months compared to no treatment receipt.¹⁶ In the outpatient setting, patient-reported barriers to OAT initiation and continuation include negative perceptions of treatment by family, friends, or healthcare providers, difficulty accessing treatment, and lack of

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motivation to remain in treatment.¹⁷ The ACS is a novel intervention that is becoming increasingly implemented in hospitals in North America.^{9, 10, 18, 19} As hospitals expand access to ACS, we identified facilitators and barriers to hospital-based opioid use disorder (OUD) treatment initiation and continuation. We included the perspective of patients who received care from an ACS during hospitalization and from hospitalists and hospital-based nurses, social workers, and pharmacists who cared for hospitalized patients with OUD. This study was conducted to inform efforts to expand patient-centered, hospital-based OUD treatment, with a focus on treatment uptake and retention.

METHODS

Study Design

We conducted key informant interviews and focus groups to understand facilitators and barriers to hospital-based OUD treatment initiation and continuation from the perspective of patients with OUD and from hospital-based providers (hospitalists, nurses, social workers, and pharmacists). The University of Colorado Institutional Review Board determined this project to be exempt and not human subject research because we did not collect any participant identifiers (Protocol # 19-0336). Three theoretical frameworks informed study design and analysis: the Health Belief Model^{20, 21}; the Knowledge, Attitudes, and Practices Framework²²; and the Donabedian Framework.²³ The analysis was not pre-registered and the results should be considered exploratory. Data collection, coding, and analysis closely followed the consolidated criteria for qualitative research (COREQ) (checklist available upon request).²⁴

Study Settings and Participants

We recruited patients who received care from a hospital-based ACS at a university hospital. ACS team members (SLC and CC) recruited patients for study inclusion by calling them to inquire about their interest in study participation with a brief description of the study purpose. At the time of the interview, participants either were discharged from their initial hospitalization or had been re-hospitalized. We interviewed participants one-on-one over the telephone or in their private hospital room. Interviews lasted approximately 1 h, and we provided a gift card as compensation for participation.

We recruited providers from two locations, a large public hospital and a university hospital in Denver, Colorado. Both hospitals employ a weekday ACS. We used a purposeful sampling strategy for recruitment. We contacted the Director of Services for Hospital Medicine and team leaders for nursing, social workers, and pharmacy staff who distributed an email solicitation for focus group participation with a brief description of the study purpose. Focus group participants were segmented into practice type: hospitalists, pharmacists,

and nurses with social workers because we anticipated that homogenous groups would allow for more free-flowing conversations.²⁵ One-hour focus group sessions were held in a hospital conference room at noontime with lunch provided as compensation for participation. Due to low focus-group participation by nurses based on COVID-19-related scheduling conflicts, we also conducted one-on-one key-informant interviews with nurses over the telephone at their convenience. These interviews lasted approximately 45 min, and gift cards were provided for compensation. Recruitment for both groups continued until it appeared that data saturation was reached.²⁶ Study participants were informed that interviews were confidential and provided verbal consent prior to data collection.

Study Team and Key Informant Interview and Focus Group Guide Content and Structure

Our multidisciplinary team was comprised of two addiction-trained clinician researchers (SLC, IAB), a hospitalist physician (CC), a trained qualitative analyst (SL), and a master's student in clinical science (KH).

Patient Key Informant Interviews

SLC and SL developed a patient interview guide to elicit information regarding their hospitalization experience and whether it impacted their substance use, their experiences with the medical team and the ACS, their perceptions of the hospital discharge process, and the ease of linkage to addiction treatment post-discharge. Among rehospitalized patients, we inquired if the ACS could have provided services to prevent rehospitalization. The interview guide was informed by the authors' experience in clinical practice (SLC and CC) and by a literature review of patients' perspectives regarding addiction treatment (Appendix A).^{6, 17, 27, 28} Interviews were conducted by two physicians (SLC and CC), both of whom work on their institution's ACS. SLC and CC previously provided medical treatment to some study participants, but not during the study period.

Hospital-Based Provider Focus Groups and Key Informant Interviews

SLC and SL developed three provider-specific focus group guides (hospitalists, pharmacists, and nurses plus social workers; Appendix B–D) informed by two theoretical frameworks: the Knowledge, Attitudes, and Practices Framework, which identifies barriers to physician adherence to practice guidelines in relation to behavior change, and the Donabedian Framework for the Evaluation of the Quality of Care, which includes measures to identify structures, process, and outcome measures of care provided by healthcare organizations.^{22, 23} The primary facilitator of each focus group was trained in qualitative research methods (SL) and was joined by KH. JH, SC, and CC participated as co-facilitators and recorded field notes. Additional key informant interviews with nurses were conducted by SLC and SL using a modified focus group guide.

Data Analysis

Focus groups and key informant interviews were recorded, transcribed, and entered into ATLAS.ti data management software. No identifiers were collected or recorded. We employed both a deductive and inductive approach, based on a directed content analysis, to analyze our data.^{29–31} A deductive approach was used to transcript text to predefined codes and categories informed by the literature,^{28, 32, 33} prior knowledge, our interview guides, and explanatory frameworks. Explanatory frameworks used to inform *a priori code* development included the Health Belief Model,²⁰ a model developed to explain and predict health-related behaviors, used with the patient transcripts, and the Knowledge, Attitudes, and Practices Framework²² and the Donabedian Framework²³ used with the hospital-based provider transcripts. An inductive approach was used to identify emergent codes or categories which included new ideas relevant to our research question.³⁴ Two separate codebooks were created for patient and hospital-based provider transcripts.

The coding team (SLC, SL, KH, CC) independently coded three patient transcripts and three focus group transcripts by assigning the predefined codes to the text and by creating new codes that emerged from the data. The team met to review code agreement and reconcile any differences until consensus was reached. Next, the team coded the remaining transcripts while meeting frequently to iteratively refine the codes and definitions. All transcripts were double coded. Individual codes were categorized into larger codes to facilitate analysis. The team met regularly to discuss emerging themes and relevancy to hospital-based OUD treatment uptake and continuation. Themes were subsequently presented and discussed with experienced researchers and hospital-based providers who work closely with the OUD patient population. Once we reached consensus on themes for the patient and provider datasets, we used a constant comparative method and reflexive team-based analysis to examine commonalities and differences across each dataset. We highlighted themes reflective of the patient experience and themes that overlapped between the patient and hospital-based provider experience.

RESULTS

Between February 2020 and June 2021, we recruited and conducted 20 interviews with patients who interacted with the ACS during hospitalization. Of these, nine patients were interviewed over the telephone and 11 were in-hospital interviews. Seventy-five percent of patients reported their ethnicity as non-Hispanic White ($n = 15$). All patients reported opioid use, 11 (55%) reported opioid and methamphetamine use, and two (10%) reported opioid and alcohol use (Table 1). Between November 2019 and February 2020, we recruited

Table 1 Participant Characteristics ($n = 82$)

Patient data ($n = 20$)	n (%)
Gender	
Female	7 (35)
Male	13 (65)
Ethnicity	
White, non-Hispanic	15 (75)
Hispanic	5 (25)
Interviewed outpatient	9 (45)
Interviewed in-hospital*	11 (55)
Reported substance(s) used†	
Opioids alone	7 (35)
Opioids and methamphetamine	11 (55)
Opioids and alcohol	2 (10)
Healthcare provider data ($n = 62$)‡	n (%)
Gender	
Female	46 (75)
Male	16 (25)
Professional role	
Hospitalist physician	19 (31)
Pharmacist	18 (30)
Nurse§	13 (21)
Social worker	11 (18)
Years working in current job type	
≤ 5	20 (33)
6–10	17 (28)
11–15	16 (26)
≥ 15	8 (13)

*Re-hospitalized at time of interview

†No reported regular use of cocaine or benzodiazepines

‡ $n = 62$ participants; one participant did not complete a survey

§8/13 nurses participated in individual interviews due to COVID-19-related scheduling conflicts

and conducted six in-person focus groups with hospital-based providers for an average of nine participants per group. Hospitalists ($n = 19$, 31%), pharmacists ($n = 18$, 30%), nurses ($n = 13$, 21%), and social workers ($n = 11$, 18%) were represented. We conducted telephone interviews with nurses at both hospitals ($n = 8$). The majority of participants were women ($n = 46$, 75%) (Table 1). From this broad range of perspectives, we identified five emergent themes as they pertained to hospital-based OUD treatment initiation and continuation including: (1) the role of an ACS to address OUD and facilitate treatment engagement; (2) expanded use of OAT to treat opioid withdrawal and to improve patient-provider interactions; (3) the triad of hospitalization, self-efficacy, and patient-centered treatment (defined as low-threshold treatment) motivated opioid use behavior change³⁵; (4) the necessity of pain control and mental health stability for OAT continuation; and (5) the significance of stable housing and social support for OAT initiation and continuation. Themes 1, 2, and 5 included perspectives from patients and hospital-based providers. Themes 3 and 4 were limited to patient perspectives (Fig. 1).

Key Themes

Theme 1: Benefits of an ACS to Address OUD and to Facilitate Treatment Engagement. Patients and hospital-based providers perceived the role of the ACS as reducing

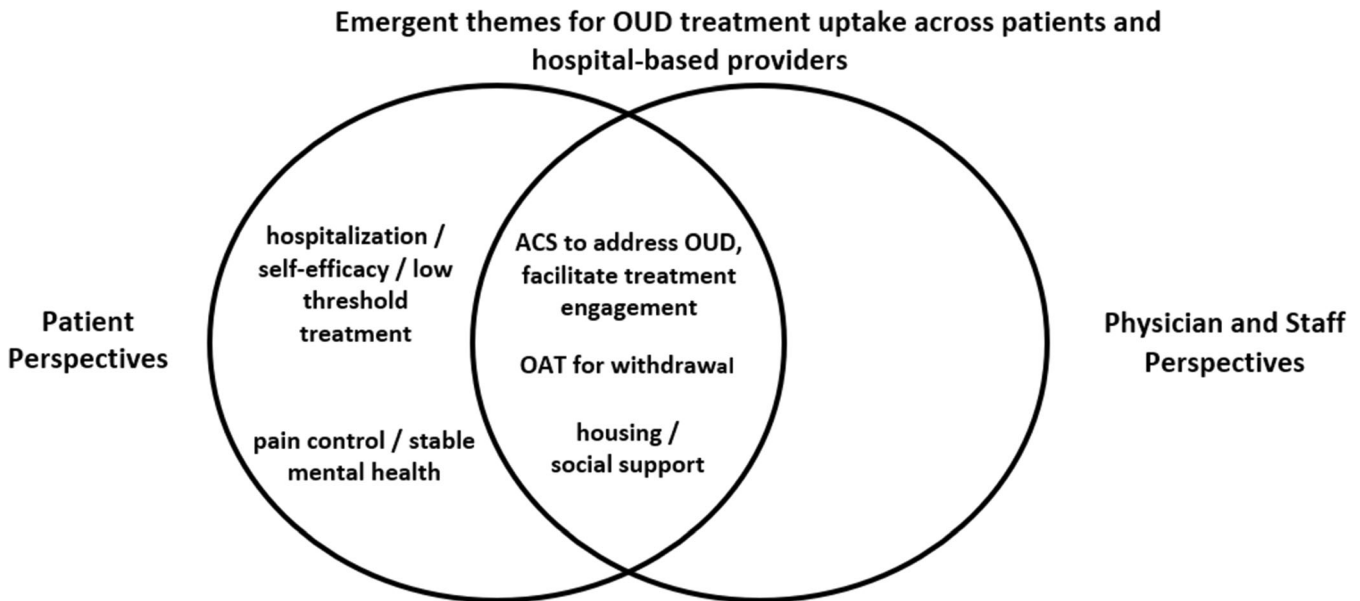


Figure 1 Emergent themes for OUD treatment uptake across patients and hospital-based providers.

shame, providing information, and supporting OUD treatment engagement and follow-up. Patients reported that their interactions with ACS contributed to feelings of greater self-worth and improved their understanding of treatment options, including medications to treat OUD. One patient described their experiences meeting with the ACS:

“They [ACS] made me feel like I am a good person. I am not a criminal. I am worth having a life. I am worth them taking their time to work on me. That made me feel so good.” (Patient 7)

Another person discussed their shame and concerns with using buprenorphine with the ACS:

“I have a lot more positive take on it. Before, I felt really ashamed taking buprenorphine ‘cause, people always assume you’re a heroin addict, so people made me feel ashamed to take it. When I talked to them, they were really understanding, so it made me feel a lot better. They were very informative, very nice, very caring.” (Patient 2)

Hospital-based providers identified that the ACS allowed for dedicated time and resources to spend with patients to discuss personal goals as a way to provide patient-centered care:

“I definitely think, with addiction medicine being able address the addiction piece and what kind of treatment that they might want after, and what other factors might come after that, just having the resources and someone that’s able to focus in and help the patient in whatever way they want, that they see themselves succeeding, it has been helpful.” (Focus group 6, social worker)

Patients and hospital-based providers appreciated that the ACS linked patients to addiction treatment following discharge. Patients appreciated the removal of barriers to obtain treatment following hospitalization:

“They [ACS] didn’t just hand me a packet and say, “All right, here’s your information, good luck.” They [ACS] actually followed through. That helps because it takes some of the pressure off ‘cause, sometimes it’s overwhelming. It’s like, “Okay, I’ve got all these phone calls to make. I’ve got all this stuff to do.” Having me already set up with something when I got out [of the hospital] was immensely helpful.” (Patient 6)

Hospital-based providers reported that treatment initiation with care linkage contributed to a sense of providing high-quality care to support patients in recovery, even following discharge:

“I think they’re [the ACS] are able to hook them up with our methadone services easily so that, as they leave the hospital, they can follow up directly with our methadone clinic.” (Nurse interview 3)

Theme 2: Expanded Use of Opioid Agonists to Treat Opioid Withdrawal Improved Patient-Provider Interactions.. Patients and hospital-based providers appreciated the use of OAT in the hospital to reduce opioid withdrawal symptoms and improve patient-provider interactions. One patient described feeling greater relief from opioid withdrawal when prescribed OAT, in contrast to short-acting opioids, traditionally used to manage opioid withdrawal.

The use of methadone allowed him to remain in the hospital to receive necessary medical treatment.

“Methadone helped. Dilaudid and oxycodone just don’t work [for treating opioid withdrawal]. It’s gotta be heroin or methadone. I stayed longer than I would have had I not been on [methadone] because the withdrawals were really bad.” (Patient 20)

Hospitalists noted that when they prescribed OAT to manage withdrawal, their interactions with patients improved.

“They’re just so challenging [patients experiencing opioid withdrawal]. Once you get them on Suboxone, they’re much more engaged and receptive. And I go, “Oh, this is who you are.” But when you are withdrawing, you’re not yourself.” (Focus group 4, hospitalist)

Some pharmacists noted that as physicians used more methadone and buprenorphine, they could benefit from a better understanding of the medications, the legality of their use, and indications for their use.

“As their use is increasing [methadone and buprenorphine], I think the education on the pharmacist side needs to match up to that of the physicians. We need a better understanding of these medications because we are seeing it more in practice.” (Focus group 2, pharmacist)

Theme 3: The Triad of Hospitalization, Self-Efficacy, and Low-Threshold Treatment Motivated Change in Opioid Use Behaviors.. Some patients described hospitalization as a motivator to make a change in their opioid use, especially when accompanied by a preexisting desire to make a change in their lifestyle or use behaviors.

“I thought I was dying, not giving life. It turns out I was growing a human being inside of me. They [the ACS] gave me the correct dose of Suboxone, they found me programs and resources. I didn’t want my baby being born on heroin going through withdrawal.” (Patient 6)

For some patients, hospitalization removed barriers to make changes in their opioid use.

“When this opportunity came up about Suboxone when I was in the hospital, I was a little hesitant, but I said, ‘I’m gonna take the leap and start takin’ this. Maybe it will change things.’” (Patient 4)

For others, the thought of changing their opioid use was inconceivable, often expressing hopelessness and helplessness over their addiction.

“The methadone clinic didn’t matter to me. Once I put the heroin in me, I don’t care about that. I’m gonna use when I get out ‘cause I don’t wanna be sick.” (Patient 17)

Theme 4: Adequate Pain Control and Stabilization of Mental Health Conditions Among Patients with OUD Contributed to OAT Continuation.. Chronic pain and mental illness were closely linked with substance use behaviors. Some patients used alcohol and opioid pills to manage chronic pain, while others used heroin. For these patients, the end result contributed to their hospitalization. For one patient, in-hospital buprenorphine initiation allowed for improved pain control and stabilization of substance use.

“When I went in the hospital, I was out of it [alcohol withdrawal seizure], and then when I came outta the hospital, he [primary care provider] didn’t prescribe oxycodone to me for a month. I was just miserable in pain so I went back to drinkin’. Ever since they prescribed Suboxone to me, it’s just been more of an even, steady little bit pain, very livable, very manageable, like it’s just a different world.” (Patient 4)

For some patients, initiation of methadone or buprenorphine was insufficient to continue OAT following discharge. One barrier to OAT continuation was persistent pain which was only controlled by heroin use.

“The heroin was cheaper [than buprenorphine]. I didn’t get high or anything, but I felt the pain go away. It’s not about getting high. It’s about getting the pain gone so I can function normally.” (Patient 18)

While the ACS initiated medications for OUD, prescribed antidepressant or anxiolytic medications, and made referrals to behavioral health clinics, this was not sufficient for treatment continuation among some patients with serious mental illness. One patient stated:

“I’m screwed up in the head so I’m gonna end up in the hospital all the time anyway.” (Patient 11)

Another said:

“I have PTSD. My drug abuse helps cover that pain, emotional and physical pain.” (Patient 19)

There was little the ACS could do during hospitalization to support these patients following hospital discharge beyond linking them to community resources.

Theme 5: Stable Housing and Social Support Are Prerequisites for Continued OAT Engagement.. Patients described the importance of stable housing and social

support to continue OAT following hospital discharge, which included daily visits to an opioid treatment program or regular visits to a buprenorphine-waivered prescriber. A lack of resources was often cited as a barrier for OAT continuation.

“I would go back [to substance use] 'cause I have nobody, no resources, no help, no housing. I'm disabled. I have nobody helping me.” (Patient 10)

Patients described the importance of housing and social support for their change in opioid use:

“Having a place to go home to, and a bed. You're not gonna have to think about, 'Where's the next place I'm gonna sleep tonight?', I think that's such a key part in sobriety.” (Patient 6)

Hospital-based providers recognized the importance of stable housing and social support for OUD treatment continuation which could be facilitated by programs offering housing and support services.

“Hooking them up with a program that could lead to housing [could reduce opioid use]. Homelessness is a great contributor to alcohol and drug use. You can't really start to focus on quitting drugs if you don't have anywhere to live.” (Focus group 3, social worker)

DISCUSSION

Patients with OUD and hospital-based providers identified several facilitators and barriers to hospital-based OUD treatment uptake and continuation. Perceived facilitators included the presence of an ACS to discuss and initiate OUD treatment, increased use of OAT to improve opioid withdrawal and to improve patient-provider interactions, and provision of easily accessible, patient-centered OAT in the hospital. Perceived barriers to OUD treatment continuation included uncontrolled pain, active mental illness, and a lack of stable housing and social support.

Patients with substance use disorders report experiencing stigma in the healthcare system, which is a barrier to OUD treatment uptake.^{17, 36} In our study, several patients described respectful and informative interactions with the ACS. For some patients, discussing treatment options with the ACS reduced their own personal stigma with OAT. Hospital-based providers appreciated having the ACS available to discuss treatment options for their patients and to facilitate addiction treatment linkage following discharge. With the presence of an ACS, non-addiction providers are exposed to effective medications and behavioral interventions for OUD, thus normalizing OUD and the medications used to manage it. Previous work demonstrated that “treatment works” messaging may mitigate addiction-related stigma.^{37, 38} As more

hospitals implement ACS to provide evidenced-based treatment, the stigma experienced by hospitalized patients with OUD may diminish. In the meantime, hospitals should support training and education of hospital-based providers to extend their knowledge, skills, and self-efficacy to best care for hospitalized patients with OUD.³⁹

Patients and hospital-based providers identified uncontrolled pain, active mental illness, and a lack of housing and social support as barriers to OUD treatment continuation following hospital discharge. Chronic pain management in the setting of OUD is complicated by opioid-induced hyperalgesia, high rates of co-occurring psychiatric disorders, and increased risk of relapse compared to patients with OUD alone.^{40–42} Chronic mental illness is challenging to manage when people are actively using substances, when they lack stable housing, and when they are unable to access routine mental health care.^{43–48} Hospitals are increasingly partnering with community organizations to provide housing to people with severe, chronic health problems.⁴⁹ Additionally, many hospitals provide medical respite to people experiencing homelessness who are too ill to recover on the streets, but are not ill enough to remain in the hospital.⁵⁰ Hospitalized patients with severe OUD often experience many of these barriers, leading to frequent re-hospitalizations and increased mortality.^{51, 52} For people experiencing severe mental illness, an assertive community treatment model, which offers around-the-clock, customized, community-based services to people in their homes, has been associated with a reduction in homelessness⁵³ and in substance use compared to standard case management.^{54, 55} A combination of assertive community treatment, low-threshold OAT, and stable housing may improve utilization of healthcare services and mortality among this vulnerable group of people.^{16, 53, 56}

The use of OAT to manage opioid withdrawal combined with readily accessible OUD treatment, provision of patient-centered care, and care linkage were identified as facilitators of OUD treatment uptake. The presence of an ACS facilitates education and awareness of these evidence-based practices for OUD treatment; however, an ACS is not absolutely necessary for clinical practice uptake, implementation, and dissemination. In hospitals where ACS implementation may not be feasible or necessary, successful models targeted at OUD treatment exist. Key aspects of these programs include a project champion to advocate for hospitalized patients by correctly diagnosing OUD, in-hospital buprenorphine initiation with continuation at discharge, co-prescribing of naloxone for overdose reversal, and linkage to addiction treatment upon discharge.^{57–60} Hospital-based clinicians and academic societies advocate for their colleagues to incorporate OUD treatment into their daily practice to “drive societal change by removing barriers for patients and mitigating the stigma against being an X-waivered clinician.”^{60, 61} Calls to remove restrictions on buprenorphine prescribing led to an exemption from the X-waiver training requirements and certification to psychosocial services for clinicians who prescribe

buprenorphine to 30 or less patients at any given time.^{62–65} Hospitals should support their staff to develop innovative education and training strategies to expand hospital-based OUD treatment initiation and care linkage. Insurers should provide higher reimbursement for provision of OUD services to incentive providers to incorporate this work into their clinical practice. Future work should evaluate if such programs reduce growing costs associated with opioid-related hospitalizations and help patients achieve their personal goals related to opioid use, including incorporating harm reduction strategies into their opioid use, initiating OAT when indicated, and/or engaging patients in behavioral health treatment.⁶⁶

LIMITATIONS

Our qualitative findings may not reflect the experiences of all hospitalized patients with OUD and hospital-based providers outside of these hospital settings.⁶⁷ Patient interviews were conducted at one hospital. Additional patient perspectives are needed for greater generalizability and to extend these findings. Patient participants may have previously received care from a study team member which could have influenced their study participation or responses. We attempted to mitigate this by ensuring that team members conducting the interviews were not part of the patient's medical team and by reassuring participants that their interviews were anonymous and voluntary. It is likely that our past relationships with some participants improved recruitment due to mutual appreciation, trust, and respect. Findings may be influenced by the perspectives of investigators during the collection and data analysis. We assembled a multidisciplinary team and used a team-based, iterative process with triangulation and reflexivity to employ a rigorous approach to our study questions.

CONCLUSION

Our study identified important facilitators of OUD treatment uptake and continuation that can be implemented in hospitals, including expanded access to in-hospital addiction expertise, greater use of OAT to manage opioid withdrawal, and provision of low-threshold OUD treatment. While various models exist to expand hospital-based addiction treatment, many require a project champion with knowledge and clinical experience managing OUD.^{14, 57} Currently, multisite studies are underway to measure the effectiveness and reach of hospital-based ACS on post-discharge treatment initiation and engagement.⁶⁸ Further research and public policy efforts are needed to address barriers to OUD treatment uptake raised by study participants regarding lack of stable housing, chronic mental and medical illness, and lack of social support.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11606-021-07305-3>.

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Declarations:

Conflict of Interest: The authors declare no competing interests.

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