



Hospitalist perspectives on buprenorphine treatment for inpatients with opioid use disorder

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ABSTRACT

Background: Patients with opioid use disorder (OUD) have high hospital admission rates. Hospitalists, clinicians that work in inpatient medical settings, may have a unique opportunity to intervene on behalf of these patients, yet their experience with and attitudes towards treating patients with OUD need further exploration.

Methods: We conducted qualitative analysis of 22 semi-structured interviews with hospitalists between January and April 2021 in Philadelphia, PA. Participants were hospitalists in one major metropolitan university hospital and one urban community hospital in a city with a high prevalence of OUD and overdose deaths. Participants were asked about their experiences, successes, and difficulties in treating hospitalized patients with OUD.

Results: Twenty-two hospitalists were interviewed. Participants were majority female (14, 64%) and White (16, 73%). We identified the following common themes: lack of training/experience with OUD, a lack of community OUD treatment infrastructure, a lack of inpatient OUD/withdrawal treatment resources, the “X-waiver” as a barrier to prescribing buprenorphine, the “ideal” patient to start on buprenorphine, and the hospital as an ideal intervention setting.

Conclusions: Hospitalization due to acute illness or complication of drug use represents a potential intervention point to initiate treatment for patients with OUD. While hospitalists exhibit willingness to prescribe medications, provide harm reduction education, and link patients to outpatient addiction treatment, they identify training and infrastructure barriers that must first be addressed.

1. Introduction

Overdose deaths due to synthetic opioids other than methadone (e.g., fentanyl, carfentanil, sufentanil) increased 1040% from 2013 to 2019 (Mattson et al., 2021). In a study looking at the National Hospital Ambulatory Medical Care Survey and the National Ambulatory Medical Care Survey, opioid-related visits were 41.8% higher in 2016 when compared to 2011 (Shastry et al., 2020). The changing drug supply and increased hospitalization rates due to opioid use disorder (OUD) require the integration of evidence-based OUD treatment into routine hospital practice (i.e. medication initiation, linkage to longitudinal outpatient addiction treatment, and naloxone prescribing at discharge) (Mattick et al., 2014; Theisen-Toupal et al., 2017).

Medications for opioid use disorder (MOUD) are the standard of care for the chronic management of OUD to decrease opioid withdrawal symptoms, dampen the euphoria associated with opioids, and reduce cravings (Hinde et al., 2018). Treatment with MOUD is endorsed by the National Institutes of Health, the World Health Organization, and the American Society for Addiction Medicine, among others, as an effective strategy in increasing treatment retention, reducing illicit opioid use, and reducing overdose deaths (Hinde et al., 2018; Sordo et al., 2017). One of the medications approved by the Food and Drug Administration for OUD is buprenorphine (American Society of Addiction Medicine, 2020). For some patients, buprenorphine may be more desirable compared to other MOUD because of its convenience in dosing and

Abbreviations: MOUD, Medications for Opioid Use Disorder; OUD, Opioid Use Disorder; SUD, Substance Use Disorder.

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dispensing and its overall safety profile (American Society of Addiction Medicine, 2020; Gregory et al., 2021; Lee et al., 2018; Morgan et al., 2019). Buprenorphine is successful when offered with or without the addition of psychosocial treatment; however, psychosocial treatment for OUD is more successful when medication is added (et al., 2019).

Despite buprenorphine being a gold-standard treatment for OUD, barriers such as obtaining a buprenorphine waiver and inadequate addiction training hinder clinicians from prescribing buprenorphine. Among American physicians, only 2.2% have their buprenorphine waiver and only half of those physicians prescribe the medication in their practice (Christian et al., 2021; Duncan et al., 2020; Huhn & Dunn, 2017; Rosenblatt et al., 2015; Substance Abuse and Mental Health Services Administration, 2021). The demand for OUD treatment is high, with 96% of all US states having rates of OUD that surpass treatment capacity (Jones et al., 2015) and 46% of US counties without a single buprenorphine prescriber in 2017 (Haffajee et al., 2019).

Patients with OUD and those who inject drugs often seek acute medical care and are hospitalized for complications of their substance use disorder (SUD), acute illnesses, or trauma (D'Onofrio et al., 2015; Liebschutz et al., 2014). Hospitalization can serve as a pivotal time for people who use drugs as they may be motivated to start MOUD in the face of acute illness (D'Onofrio et al., 2015). Yet while hospitalist clinicians have the unique opportunity to screen and initiate treatment for inpatients with OUD during times of crisis (Liebschutz et al., 2014), inpatient initiation of MOUD is underutilized (Christian et al., 2021; Green et al., 2014; Mospan & Chaplin, 2022; Patel et al., 2021).

Previous studies on providers' attitudes towards treating inpatients with OUD are sparse and often oversampled addiction specialists (Green et al., 2014; Huhn & Dunn, 2017). In this work, we sought to understand hospitalists' perceptions of and experiences in treating patients with OUD, including attitudes towards prescribing MOUD. Interviews with hospitalists (including physicians and advanced practice providers) can provide insights into barriers, organizational supports, attitudes, costs, and benefits associated with providing adequate care to patients with OUD.

2. Material and methods

We conducted a content analysis of 22 semi-structured interviews with clinical hospitalists to assess their practices and attitudes towards inpatients with OUD from January to April 2021.

2.1. Study sample

We recruited hospitalists from two sites (1) a major metropolitan academic university hospital and (2) an urban university-affiliated community hospital in a city with high rates of OUD and overdose deaths. This study was approved by the Thomas Jefferson University Institutional Review Board (IRB).

2.2. Research team

The research team consisted of a multidisciplinary team of one PhD in Public Health (M.K.R.), three physicians (K.L.R., J.K.H., J.H.Z), and two MD/MPH students (V.M., N.S.).

2.3. Interview procedures

A list of 60 hospitalist providers was obtained from the division and department heads in both hospitals. A general recruitment email was sent out to these hospitalists with information regarding the study, including that participation was voluntary and confidential. Personalized emails were sent to respondents to schedule interview times. Providers were interviewed either by telephone or Zoom video conferencing, with verbal informed consent obtained prior to interview initiation. Interviews were conducted by two trained research assistants with experience in qualitative research (N.S., V.M.). Participants were not provided

with any incentives for participation. Interviews were audio recorded in accordance with IRB-approved protocols. Interviewers used a semi-structured interview guide with general and specific questions about treating patients with OUD. This guide was informed by a comprehensive literature search and by subject matter experts. Recruitment was continued until all hospitalists who indicated interest had been interviewed.

2.4. Qualitative analyses

Recorded interviews were transcribed verbatim and cleaned to ensure removal of all identifying information. Using NVivo (International Pty, 2020), three coders trained in qualitative analysis performed thematic content analysis using a constant comparative approach, with the purpose of classifying text into distinct categories representing similar meanings (Hsieh & Shannon, 2005). Coders began by immersing themselves in transcribed interviews to gain an understanding of the content. Coders re-read interviews to identify major themes related to the research questions. Codes were identified, and a codebook was developed via iterative coding and discussion with the research team. The codebook was refined at team meetings until no further modifications were needed. Data from each interview were coded with use of the final codebook, with frequent checks to ensure interrater reliability across coders ($\kappa=0.94$). Codes were grouped into themes and subthemes of provider attitudes towards buprenorphine prescribing. Results are reported as a summary of key themes with supportive quotes and examples from interviews.

3. Results

Twenty-two hospitalists were interviewed. Twenty-one were physicians and one was a nurse practitioner. Among these, 14 identified as female (63.6%), sixteen identified as White (72.7%), one identified as Black/African American (4.5%), and four identified as Asian (18.2%). The mean age was 37 years (range 29–54). Sixteen hospitalists practiced at the academic university hospital and six practiced at the urban community hospital. Fourteen participants reported having a personal connection to addiction. Out of the 22 hospitalists, nine were X-waivered to prescribe buprenorphine (Table 1).

Six interview themes were identified: lack of training/experience with OUD, a lack of community OUD treatment infrastructure, a lack of inpatient OUD/withdrawal treatment resources, the "X-waiver" as a barrier to prescribing buprenorphine, the "ideal" patient to start on buprenorphine, and the hospital as an ideal intervention setting (Table 2).

3.1. Theme 1: lack of training/experience with OUD

Ten hospitalists cited lack of comfort and experience as former or current barriers to prescribing buprenorphine to inpatients with OUD. Some noted having far more experience with methadone, with less knowledge and education on the pharmacology of buprenorphine. Four participants reported that their fear of precipitating withdrawal in patients who use opioids was a barrier to initiating buprenorphine. Many cited that education had helped overcome these barriers or identified a need to receive this education.

3.2. Theme 2: lack of community OUD treatment infrastructure

A lack of community infrastructure made inpatient buprenorphine initiation seem futile for many hospitalists. They felt that patients would have nowhere to seek care post-discharge, especially those who were uninsured or underinsured. Hospitalists communicated a critical need for a chronic care structure in addiction treatment with appropriate community-based case management. Resources that participants cited

Table 1
Demographics of hospitalists interviewed about MOUD attitudes and prescribing.

	Participants (n = 22)
Age – M (range)	37.2 (29-54)
Gender – n (%)	
Men	14 (63.6)
Women	8 (36.4)
Hispanic or Latinx – n (%)	0 (0)
Yes	
Race – n (%)	
White	16 (72.7)
Asian	4 (18.2)
Black	1 (4.5)
Other	1 (4.5)
Have you, a family member, or a friend struggled with addiction? – n (%)	
Yes	14 (63.6)
No	8 (36.4)
Level of Training – n (%)	
MD/DO	21 (95.5)
PA	0 (0)
NP	1 (4.5)
Practice in years – M (range)	11 (4-21)
X-waivered – n (%)	
Yes	9 (40.9)
No	13 (59.1)

*X-waiver – a certification that allows clinicians to prescribe buprenorphine in qualified practice settings.

included social services like accessible insurance marketplaces or affordable housing and access to outpatient buprenorphine prescribers or mental health professionals.

Some hospitalists mentioned the lack of local skilled nursing or subacute rehabilitation facilities that accepted patients on MOUD. Patients with OUD may require physical rehabilitation after acute illness, trauma, or surgery. Patients with injection-drug related bloodstream, bone, or heart valve infections may require skilled nursing for supervision of long-term vascular access and weeks-long courses of intravenous antibiotics. Patients with OUD requiring antibiotic infusions or other long-term rehabilitation had limited care facilities to choose from.

3.3. Theme 3: (lack of) inpatient OUD/withdrawal treatment resources

Hospitalists were asked to comment on what resources were available to help manage inpatients with OUD and what additional resources were needed. Broadly, participants mentioned consultation by psychiatry/addiction medicine, anesthesia/acute pain management, and social work. Hospitalists reported that anesthesia/pain management consultants assisted with ketamine-assisted rapid buprenorphine titrations and with withdrawal management in patients with severe pain or withdrawal. Some hospitalists hoped for increased availability of these consultants around the clock because they did not feel comfortable doing ketamine-assisted buprenorphine titrations themselves.

Ten hospitalists reported consulting psychiatry for assistance with uncontrolled opioid withdrawal, polysubstance use, and for methadone dosing. Some hospitalists used the terms ‘psychiatrist’ and ‘addiction specialist’ interchangeably, but six hospitalists mentioned that no addiction medicine-trained psychiatrists were available for consultation across both hospital sites. Some participants suggested that having access to an addiction medicine-trained clinician or more psychiatrists would be helpful to keep up with the volume of inpatients with OUD.

Nine participants mentioned that social workers and Certified Recovery Specialists, who are people with lived experiences of substance use, were available to link patients to appropriate OUD services (inpatient rehab, outpatient rehab, opioid treatment programs for methadone, and buprenorphine prescribers). Hospitalists hoped for more of such re-

sources to meet increasing demand. Many hospitalists expressed a need for more social workers to manage this patient population.

3.4. Theme 4: X-waiver as a barrier to prescribing buprenorphine

Several hospitalists (16/22) in both hospitals reported that their hospital division supported starting buprenorphine for inpatients with OUD. Seven participants mentioned that their hospital division or physician group incentivized prescribers to obtain the X-waiver to prescribe buprenorphine. Some hospitalists reported that even if they were not X-waivered, they could message other waivered colleagues in their division to prescribe buprenorphine for their patients with OUD. When asked how the division/hospital could be more supportive of hospitalists initiating buprenorphine for inpatients, some participants responded that more education for treating OUD would be helpful. Two hospitalists mentioned incorporating X-waiver training into in-service or division meetings.

While the departmental message on obtaining the X-waiver was well-received by hospitalists, several reported that obtaining the X-waiver was still a barrier to offering and prescribing buprenorphine to inpatients with OUD. Six hospitalists stated that the 8 h X-waiver training was too long. One participant found the 24 h X-waiver training for nurse practitioners and physician assistants to be an even more significant barrier to getting more hospitalists waivered. Four participants wanted more opportunities for X-waiver training to be provided by the hospital. Some hoped that the training was incorporated in the work schedule, rather than completing it outside of work.

3.5. Theme 5: the ideal patient to start on buprenorphine versus methadone

Hospitalists were asked to describe patient characteristics that could influence their OUD treatment as inpatients. The majority (16) stated that a good candidate for buprenorphine was a patient who was motivated and willing to take the medication. Hospitalists explained that many inpatients may not be willing to endure mild to moderate opioid withdrawal to start buprenorphine safely. They found that these patients were often more receptive to and successful on methadone. Hospitalists reported that some patients with concomitant OUD and acute pain required a ketamine-assisted buprenorphine initiation. Five hospitalists mentioned that patients with serious medical comorbidities (i.e., acute myocardial infarction) would be poor candidates for buprenorphine initiation because the acute withdrawal might worsen their medical condition.

Eleven participants mentioned that patients’ past experiences or fears of precipitated withdrawal were barriers to accepting buprenorphine in the hospital. They mentioned that many patients may have previously suffered precipitated withdrawal due to inappropriate use of the medication.

Many hospitalists (7) mentioned that patients who required the structure and accountability of presenting to an outpatient treatment program may be better candidates for methadone and felt that those who could remain engaged in treatment without going to a clinic might be better suited to buprenorphine.

Seven hospitalists considered the patient’s social situation when recommending buprenorphine. Six hospitalists stated that patients taking other opioids (methadone, fentanyl, etc.) or who required opioids for pain control would be poor candidates for inpatient initiation of buprenorphine due to its partial antagonist properties. Some hospitalists felt buprenorphine did not provide adequate analgesia for pain control. One hospitalist mentioned that, in her opinion, benzodiazepine use was a contraindication to buprenorphine initiation. Two participants stated that younger patients earlier in the OUD disease course may respond better to buprenorphine than a patient with chronic, long-standing OUD would.

While nine hospitalists considered the possibility of racial differences in MOUD prescribing, almost all (20/22) reported they had not person-

Table 2
Themes and quotes from hospitalists in Philadelphia, PA (n = 22).

Theme	Illustrative Quotes
Lack of training/experience with OUD	<i>I am an internist, not an addiction psychiatrist, and I feel like I'm out of my league sometimes. It's not something that I was trained on in medical school of how – or residency for that matter – of how to prescribe it ... once I became more educated about the pharmacokinetics of buprenorphine and how to appropriately start it and uptitrate it, then I felt much more comfortable trying it on patients that were interested in the hospital.</i> <i>I've only learned about [buprenorphine] and like really learned about it in the last year or so. Because of that, I personally feel less comfortable with it. And I find, just as a culture, a lot of us feel less comfortable with that as opposed to methadone..</i>
Lack of community OUD treatment infrastructure	<i>I think for me getting people hooked up with the clinics is the hardest thing. Because you are presented, typically, with a patient population that has already got like a bunch going against them. They do not have the financial support. They do not have the social support. They typically have a lot of psychiatric barriers, as well. And you are tasked with the almost-impossible task of getting them essentially to a primary care physician and having somebody take ownership of this medication that has a lot that goes with it.</i> <i>I had to discharge a person who wanted to be on [buprenorphine] who had been on [buprenorphine], I had no follow up for her. But she's like, I can get [buprenorphine] on the street and that was our discharge plan ... We will give her 10 to 14 days. She needs to like follow up and get health insurance through the state and hopefully she does that, and if she does not, she will get it through the street.</i> <i>They may need six weeks of IV antibiotics to continue to treat whatever medically is going on. There are only a few facilities within the Philadelphia area that will agree to take patients that are on [MOUD] therapy or have a history of opioid use disorder that we see in our patient population.</i>
(Lack of) inpatient OUD/withdrawal treatment resources	<i>I think managing pain in the context of withdrawal is very challenging.</i> <i>[Access to people trained in addiction medicine] would help tremendously. We do not. We only have a psychiatrist, and he handles everything - addiction, as well as psych issues, and it's very overwhelming. So we really could use someone because of the volume that we see here at [Hospital 2]. The hospital in general could have more social workers, more case managers to help with a lot of these other issues that patients with substance use disorder are facing in their lives that are contributing a lot to their continued use of narcotics. So, like helping people get set up with a psychiatrist or a psychologist or housing or like all of those things I think would be – are root causes a lot of times of people's opiate use disorder to start with. We throw 30 milligrams of methadone at a patient who uses three to four bundles of fentanyl a day and it's almost - it's funny.</i>
X-waiver as a barrier to prescribing buprenorphine	<i>There's a push to get everybody their X-waiver. I can not speak to individual providers, but the stated culture is to have – to be all-in on helping this particular population to be as successful as possible.</i> <i>I need my X-waiver...I would love for my department to give me a day to get my X-waiver.</i>
The ideal patient to start on buprenorphine versus methadone	<i>Overall I think most people should be starting on buprenorphine if I think they're fairly high functioning.</i> <i>I think that there are times where it makes sense to do methadone over buprenorphine. Like, for instance, homeless, where they're likely to have their meds stolen living in a shelter or somebody that might benefit from having a regular place to go and get their meds and checking in with a methadone clinic. I think there are times where that scenario sort of makes more sense for the patient. That being said, it's their choice.</i> <i>I think there are people where they're still working and have a life to live and want to get back to that. I met a woman who was a college student or college grad and had a job and was taking pills. And I'm like, for you, it's probably worth it to [take buprenorphine] because you'll be able to live more of a normal life. And it's not gonna be as like prohibitive to you.</i> <i>It does seem like there is a race issue with that, but I never thought about that. But thinking of some patients in my mind, it seems like for whatever reason methadone is suggested more for nonwhite people.</i>
The hospital as an ideal intervention setting	<i>The hospital takes everybody. You do not have to be insured. You do not have to be someone who has it together enough to make it to a 9 a.m. primary care appointment, right? We – everyone comes to the hospital, gets admitted – who needs to be – and I think it can be a really important intervention point for people who may not be able to seek healthcare elsewhere who come in in sort of crisis situations as a result of that.</i> <i>Another thing that we've been doing more recently is providing people with [naloxone] on discharge as well that are high risk of continued opioid use disorder or that are leaving on with controlled substances. Educating people about overdosing, giving them the [naloxone], is a way to try to prevent that. They're also outside of the environment that is often pressuring them to relapse.</i>

ally witnessed a patient's race influence the choice of treatment for OUD. Three participants stated they were not aware of racial differences because they treated mostly White patients with OUD.

Some interviews contained stigma-related biases and negative moral views on people who use drugs and addiction that were expressed both implicitly and explicitly. This stigma against patients with OUD also played a role in preventing buprenorphine prescribing to patients. For example, one hospitalist worried that if they obtained the X-waiver, more patients would divert buprenorphine.

3.6. Theme 6: the hospital as an ideal intervention setting

Several hospitalists mentioned that inpatient hospitalization was a critical time and place to intervene and treat OUD. They cited the availability of resources available to inpatients during hospitalization (medications, specialists, social work, counseling, education, and linkage to outpatient facilities). One hospitalist mentioned harm reduction and overdose prevention education for inpatients with OUD. Others mentioned that being in a new environment surrounded by those who were willing to help was vital to gaining a patient's trust or buy-in for a treatment plan.

Hospitalists reported anecdotally that many patients with OUD, when faced with a life-threatening illness, were more motivated to start treatment. One hospitalist said that inpatients with OUD who were uninsured or who had psychosocial barriers to accessing outpatient care benefited from the increased access to care in the hospital setting compared to the community.

Another hospitalist mentioned that inpatient hospitalization was an ideal time to continue interventions for OUD initiated in the emergency department because patients and hospitalists may have more time to develop a solid treatment plan. One hospitalist mentioned that a potential downside to the inpatient setting as an intervention point was that patients who leave before treatment completion risk having poor outcomes.

4. Discussion

In this study with hospitalists, we identified six themes related to hospitalist care for inpatients with OUD. First, several clinicians disclosed their lack of experience and training with OUD management and with buprenorphine specifically. Hospitalists expressed difficulties in establishing a safe discharge plan due to a lack of community infrastructure to manage chronic opioid use disorder. Many hospitalists mentioned the lack of inpatient OUD and withdrawal treatment resources such as the availability of addiction medicine-trained clinicians. Several hospitalists cited the X-waiver as a barrier to initiating and prescribing buprenorphine upon discharge. Hospitalists described specific patient characteristics that could influence their approach to OUD/withdrawal management (American Society of Addiction Medicine, 2020). They also uniformly agreed that the inpatient setting was an important intervention point for patients with OUD to initiate buprenorphine and link to outpatient addiction care.

Hospitalists who cited a lack of formal training in OUD and addiction found the hospital's protocol on buprenorphine induction helpful

to bridge the gap between their expertise and patient needs. Hospitalists indicated that they struggled with initiating/continuing MOUD for patients with acute pain or during pre- and post-operative periods.

An unarticulated but observed gap in hospitalists' knowledge of MOUD had to do with co-prescription of buprenorphine to patients on illicit or prescription benzodiazepines. Practice guidelines indicate that MOUD need not be discontinued prior to surgery. These guidelines also state that the harm caused by untreated OUD outweighs the risks of serious interactions between MOUD and benzodiazepines, though this varies by benzodiazepine type (*American Society of Addiction Medicine, 2020; Wolf & Griffiths, 1991*). Most hospitalists indicated that though they had little specialized training or experience, they were open to learning and becoming more competent with this patient population. Hospitalists in this study were interviewed at the beginning of a certified recovery specialist program with consults available to inpatients and those in the Emergency Department. Expanded use of certified recovery specialists, or peers with lived experiences of substance use disorders, can assist hospitalists achieve this goal. (*Liebling et al., 2021*). Other initiatives, such as a clinical pathway for universal screening to identify patients at risk of opioid withdrawal, may help identify and treat additional patients (*Williams et al., 2022*). Implementation of this pathway has increased nurse confidence working with this patient population (*Williams et al., 2022*). Results may be applicable to hospitalists, as well.

Hospitalists cited difficulties with linking patients to an outpatient buprenorphine prescriber, accessibility of community mental health and addiction resources, and placement of patients on MOUD in skilled nursing or rehabilitation facilities. Hospitalists reported that these facilities perceived an increased liability among patients with OUD, and this was cited as a barrier to timely placement in outpatient skilled nursing or rehabilitation facilities. Food security, access to stable housing, and other basic human needs were mentioned as critical predictors of OUD treatment outcomes. Without these basic resources, patients may not reach their full potential on MOUD. Policymakers and public health officials should consider increasing community social services in areas especially affected by the opioid crisis. Hospital-based multidisciplinary teams (e.g., hospitalists, certified recovery specialists, social workers, psychiatrists) can help address these issues and facilitate community-based MOUD continuation (*Christian et al., 2021; Englander et al., 2019*). Programs such as the B-Team at Dell Seton Medical Center (a hospitalist-led consult service for patients with OUD) and the Boston Medical Center Addiction Consult Service (with dedicated staff with addiction expertise) have achieved high rates of MOUD induction and continuation on medication after discharge (*Christian et al., 2021; Trowbridge et al., 2017*).

Some hospitalists expressed insufficient availability of addiction specialists and felt that addiction medicine was outside their own scope of practice, calling for more addiction medicine-trained consultants and social workers to help care for increasing numbers of patients with OUD. Since addiction medicine was formally recognized in 2016 as a medical subspecialty, there has been an increase in the number of fellowship training programs. Notwithstanding, there remains a significant addiction medicine workforce shortage and a dearth in fellowship funding (*Derefinko et al., 2020*). Until this deficit in medical education is addressed, the onus to provide evidence-based addiction care will fall onto the hospitalists' shoulders. For hospitals without access to dedicated staff trained in addiction medicine, more informal consult services have been successful improving outcomes for patients with OUD (*Trowbridge et al., 2017*).

In a call to action to hospitalists in the *Journal of Hospital Medicine*, Englander et al. asserted that basic addiction care should be a core competency for all hospitalists and that hospital-initiated addiction treatment should be hospitalist-led without over-reliance on specialists. This initiative could include the development of more robust guidelines or order sets for inpatients with OUD, coordination with community OUD treatment facilities to ensure timely and efficient linkage, and training

of students, residents, and other staff in basic addiction management (*Derefinko et al., 2020; Englander et al., 2020*).

Hospitalists cited regulations on buprenorphine (X-waiver requirements) as a barrier to inpatient initiation and prescription. Several leaders and advocates of hospital-initiated OUD treatment have called for the deregulation of buprenorphine and the elimination of the X-waiver requirement (*D'Onofrio et al., 2021; Fiscella et al., 2019; Marino et al., 2019; Weimer et al., 2021*). A recent review of buprenorphine misuse and diversion revealed that illicitly obtained buprenorphine was mostly used to self-treat withdrawal rather than being used for its euphoric properties (*Jicha et al., 2019*). Areas with high amount of buprenorphine availability have lower rates of diversion (*National Academies of Sciences Engineering and Medicine, 2019*). Increased regulation designed to prevent misuse/diversion may paradoxically increase the demand for diverted buprenorphine (*Shastri et al., 2022*). Further, strict regulations for MOUD could perpetuate stigmas related to addiction and undermine addiction as a chronic relapsing and remitting disease. Deregulation in turn could decrease stigma and lead to the integration of OUD treatment into mainstream primary care.

In April of 2021, the Department of Health and Human Services released a new buprenorphine practice guideline that exempts clinicians from the federal 8- and 24 h training requirements and from the ancillary services and counselling requirements. Clinicians are still required to apply for a "Notice of Intent" in order to prescribe buprenorphine and can treat up to 30 patients without the need for further training. This change represents a step towards removing barriers to evidence-based addiction treatment to make it more accessible for patients with OUD.

Many advocates for deregulation have noted that the elimination of the X-waiver alone does not address the lack of education in OUD and addictions as a part of undergraduate or post-graduate allied health training (*American Society of Addiction Medicine, 2021*). The American Society of Addiction Medicine advocates for complementary legislation and funding for health professional schools, residency programs, and continuing education to strengthen the workforce when it comes to OUD treatment. X-waiver training and OUD treatment are becoming a mandatory part of medical school curricula (*Gorfinkel et al., 2019; Lien et al., 2021*). The "normalization" of SUD evaluation and treatment in medical education could mitigate the effects of addiction-related stigma later in clinical practice.

In addition to considering patients' motivations and preferences for treatment, hospitalists mentioned other demographic or social characteristics that could influence their treatment approach and/or patient outcomes on MOUD (*Dreifuss et al., 2013; O'Connor et al., 2020*). Associations between buprenorphine treatment retention and race/ethnicity, gender, and substance use were inconsistent across multiple studies (*O'Connor et al., 2020*). Moreover, recent literature on the topic has uncovered racial/ethnic disparities in buprenorphine treatment. Buprenorphine treatment for OUD is more common among White patients with private insurance or who self-pay (*Goedel et al., 2020; Lagisetty et al., 2019*). This phenomenon reflects the major role that structural racism and classism plays in healthcare resource allocation. Given the discordance among studies on patient-level characteristics that could predict buprenorphine treatment outcomes, clinicians should adhere to evidence-based recommendations when treating OUD. Another crucial intervention is for policymakers and researchers to keep racial, ethnic, and socioeconomic disparities in mind when devising and studying equitable and sustainable solutions to the opioid epidemic.

Hospitalists were undivided in characterizing the inpatient setting as a crucial intervention point for patients with OUD. Inpatients with OUD who received an addiction medicine consultation in a hospital where this was available were more likely to receive MOUD, more likely to complete their parenteral antibiotic treatment course, less likely to leave before treatment completion, and less likely to be readmitted within 90 days post-discharge (*Marks et al., 2019*). A recent study in *Hospital Pharmacy* and another in *The American Journal of Medicine* showed that inpatient initiation of buprenorphine was associated with decreased rates

of leaving before treatment completion and decreased rates of readmissions (Kays et al., 2022; Wang et al., 2020). Further research on the proper implementation of OUD treatment for inpatients is needed to take full advantage of this intervention opportunity. For example, the lipophilic nature of fentanyl complicates buprenorphine induction due to heightened risk of precipitated withdrawal. High fat-solubility results in storage of fentanyl and its metabolites in adipocytes leading to a protracted renal clearance. This pattern of clearance differs significantly from those of other short acting drugs like oxycodone and morphine. Fentanyl and its metabolites could remain present for weeks rather than days following abstinence. This can lead to increased rates of buprenorphine precipitated opioid withdrawal among patients who use fentanyl chronically even when clinicians follow standard induction protocols (Huhn et al., 2020; Varshneya et al., 2022). The Bernese method, in which patients are initiated in low doses of buprenorphine and titrated up while continuing to receive full opioid agonists, has some favorable results to date (Ahmed et al., 2021; Sue et al., 2022). Another emerging approach for buprenorphine inductions in monitored inpatient or emergency department settings involves the use of ketamine. Ketamine has been observed to potentiate opioid analgesia and to act as a rapid antidepressant. Subdissociative doses of the drug could help treat precipitated withdrawal and facilitate buprenorphine induction, titration, and stabilization among patients who use fentanyl (Hailozian et al., 2022).

4.1. Limitations

There are several limitations to our study. We purposely limited our recruitment to hospitalist clinicians. The perspectives and attitudes described may not be generalizable to other specialties or hospital services that care for inpatients with OUD. Our study took place in two hospitals within the same hospital system in the same city, and results are to be interpreted in this context. We enrolled a convenience sample, and participants who agreed to be interviewed may have strong views about treating inpatients with OUD or a special interest in the subject matter. The study results captured participants' perspectives during a snapshot in time. Regulations, access to MOUD, and practice guidelines may have changed during the study period.

5. Conclusion

In this qualitative study, hospitalist clinicians characterized the inpatient setting as a crucial intervention point for patients with OUD. Hospitalists expressed willingness to screen, educate, treat, and link patients with OUD to addiction treatment post-discharge. Yet they also identified knowledge gaps, institutional/community/legal barriers, and patient psychosocial factors that may contribute to the nonuniform treatment of OUD on the hospital floors. Removing regulatory barriers to prescribing buprenorphine, investing in greater community-based care for patients with OUD, and providing comprehensive training to medical students and clinical staff will improve opportunities to treat OUD among hospitalized patients.

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CRedit authorship contribution statement

Megan K Reed: Visualization, Formal analysis, Data curation, Writing – review & editing. **Vignesh Murali:** Resources, Formal analysis, Data curation, Writing – review & editing. **Nazanin Sarpoulaki:**

Resources, Formal analysis, Data curation, Writing – review & editing. **Jillian H. Zavodnick:** Writing – review & editing, Visualization. **Jeffrey K. Hom:** Writing – review & editing, Visualization. **Kristin L Rising:** Writing – review & editing, Visualization.

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References

- Ahmed, S., Bhivandkar, S., Lonergan, B.B., Suzuki, J., 2021. Microinduction of buprenorphine/naloxone: a review of the literature. *Am. J. Addict.* 30 (4), 305–315. doi:10.1111/AJAD.13135.
- American Society of Addiction Medicine. 2020 *National Practice Guideline – OUD*. Rockville, MD; 2020. <https://www.asam.org/Quality-Science/quality/2020-national-practice-guideline>. Accessed November 9, 2021.
- American Society of Addiction Medicine. (2021). ASAM Applauds Re-Introduction of Mainstreaming Addiction Treatment (MAT) Act. Retrieved from https://www.asam.org/docs/default-source/advocacy/letters-and-comments/21-02-24-x-waiver-press-release_final1f9b3a9472bc604ca5b7ff000030b21a.pdf?Status=Temp&sfvrsn=92275ac2_2
- Christian, N., Bottner, R., Baysinger, A., Boulton, A., Walker, B., Valencia, V., Moriates, C., 2021. Hospital buprenorphine program for opioid use disorder is associated with increased inpatient and outpatient addiction treatment. *J. Hosp. Med.* 16 (6), 345–348. doi:10.12788/JHM.3591.
- D'Onofrio, G., Melnick, E.R., Hawk, K.F., 2021. Improve access to care for opioid use disorder: a call to eliminate the X-waiver requirement now. *Ann. Emerg. Med.* 78 (2), 220–222. doi:10.1016/j.annemergmed.2021.03.023.
- D'Onofrio, G., O'Connor, P.G., Pantalon, M.V., Chawarski, M.C., Busch, S.H., Owens, P.H., Fiellin, D.A., 2015. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: A randomized clinical trial. *JAMA J. Am. Med. Assoc.* 313 (16), 1636–1644. doi:10.1001/jama.2015.3474.
- Derefinco, K.J., Brown, R., Danzo, A., Foster, S., Brennan, T., Hand, S., Kunz, K., 2020. Addiction medicine training fellowships in North America: a recent assessment of progress and needs. *J. Addict. Med.* 14 (4), e103–e109. doi:10.1097/ADM.0000000000000595.
- Dreifuss, J.A., Griffin, M.L., Frost, K., Fitzmaurice, G.M., Potter, J.S., Fiellin, D.A., Weiss, R.D., 2013. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. *Drug Alcohol Depend.* 131 (1–2), 112–118. doi:10.1016/j.drugalcdep.2012.12.010.
- Duncan, A., Anderman, J., Deseran, T., Reynolds, I., Stein, B.D., 2020. Monthly patient volumes of buprenorphine-waivered clinicians in the US. *JAMA Netw. Open* 3 (8), e2014045. doi:10.1001/jamanetworkopen.2020.14045.
- Englander, H., Dobbertin, K., Lind, B.K., Nicolaidis, C., Graven, P., Dorfman, C., Korthis, P.T., 2019. Inpatient addiction medicine consultation and post-hospital substance use disorder treatment engagement: a propensity-matched analysis. *J. Gen. Intern. Med.* 34 (12), 2796–2803. doi:10.1007/S11606-019-05251-9.
- Englander, H., Priest, K.C., Snyder, H., Martin, M., Calcaterra, S., Gregg, J., 2020. A call to action: hospitalists' role in addressing substance use disorder. *J. Hosp. Med.* 15 (3), 184. doi:10.12788/JHM.3311.
- Fiscella, K., Wakeman, S.E., Beletsky, L., 2019. Buprenorphine deregulation and mainstreaming treatment for opioid use disorder: X the X waiver. *JAMA Psychiatry* 76 (3), 229–230. doi:10.1001/JAMAPSYCHIATRY.2018.3685.
- Goedel, W.C., Shapiro, A., Cerdá, M., Tsai, J.W., Hadland, S.E., Marshall, B.D.L., 2020. Association of racial/ethnic segregation with treatment capacity for opioid use disorder in counties in the United States. *JAMA Netw. Open* 3 (4). doi:10.1001/JAMANETWORKOPEN.2020.3711, e203711–e203711.
- Gorfinkel, L., Klimas, J., Reel, B., Dong, H., Ahamad, K., Fairgrieve, C., Fairbairn, N., 2019. In-hospital training in addiction medicine: a mixed-methods study of health care provider benefits and differences. *Subst. Abus.* 40 (2), 207–213. doi:10.1080/0897077.2018.1561596.
- Green, C.A., McCarty, D., Mertens, J., Lynch, F.L., Hilde, A., Firemark, A., Anderson, B.M., 2014. A qualitative study of the adoption of buprenorphine for opioid addiction treatment. *J. Subst. Abus. Treat.* 46 (3), 390–401. doi:10.1016/j.jsat.2013.09.002.
- Gregory, H.M., Hill, V.M., Parker, R.W., 2021. Implications of increased access to buprenorphine for medical providers in rural areas: a review of the literature and future directions. *Cureus* 13 (11). doi:10.7759/CUREUS.19870.
- Haffajee, R.L., Lin, L.A., Bohnert, A.S.B., Goldstick, J.E., 2019. Characteristics of US counties with high opioid overdose mortality and low capacity to deliver medications for opioid use disorder. *JAMA Netw. Open* 2 (6), e196373. doi:10.1001/JAMANETWORKOPEN.2019.6373, –e196373.
- Hailozian, C., Luftig, J., Liang, A., Outhay, M., Ullal, M., Anderson, E.S., Herring, A.A., 2022. Synergistic effect of ketamine and buprenorphine observed in the treatment of buprenorphine precipitated opioid withdrawal in a patient with fentanyl use. *J. Addict. Med.* 16 (4), 483–487. doi:10.1097/ADM.0000000000000929.

- Hinde, J., Hayes, J., Mark, T., Bernstein, S., Karon, S., 2018. State and local policy levers for increasing treatment and recovery capacity to address the opioid epidemic: final report. ASPE. Retrieved from <https://aspe.hhs.gov/basic-report/state-and-local-policy-levers-increasing-treatment-and-recovery-capacity-address-opioid-epidemic-final-report>.
- Hsieh, H.F., Shannon, S.E., 2005. Three approaches to qualitative content analysis. *Qual. Health Res.* 15 (9), 1277–1288. doi:10.1177/1049732305276687.
- Huhn, A.S., Dunn, K.E., 2017. Why aren't physicians prescribing more buprenorphine? *J. Subst. Abuse Treat.* 78, 1–7. doi:10.1016/j.jsat.2017.04.005.
- Huhn, A.S., Hobelmann, J.G., Oyler, G.A., Strain, E.C., 2020. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug Alcohol Depend.* 214. doi:10.1016/J.DRUGALCDEP.2020.108147.
- Jicha, C., Saxon, D., Lofwall, M.R., Fanucchi, L.C., 2019. Substance use disorder assessment, diagnosis, and management for patients hospitalized with severe infections due to injection drug use. *J. Addict. Med.* 13 (1), 69–74. doi:10.1097/ADM.0000000000000454.
- Jones, C.M., Campopiano, M., Baldwin, G., McCance-Katz, E., 2015. National and state treatment need and capacity for opioid agonist medication-assisted treatment. *Am. J. Public Health* 105 (8), e55–e63. doi:10.2105/AJPH.2015.302664.
- Kays, LB, Steltenpohl, ED, McPheeters, CM, Frederick, EK, Bishop, LB, 2022. Initiation of buprenorphine/naloxone on rates of discharge against Medical advice. *Hosp Pharm.* 57 (1), 88–92. doi:10.1177/00185787209854393.
- Lagisetty, P.A., Ross, B., Bohnert, A., Clay, M., Maust, D.T., 2019. Buprenorphine treatment divide by race/ethnicity and payment. *JAMA Psychiatry* 76 (9), 979–981. doi:10.1001/JAMAPSYCHIATRY.2019.0876.
- Lee, J.D., Nunes, E.V., Novo, P., Bachrach, K., Bailey, G.L., Bhatt, S., Rotrosen, J., 2018. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet* 391 (10118), 309–318. doi:10.1016/S0140-6736(17)32812-X/ATTACHMENT/077E5E72-7964-4784-9D08-7BD54E4D5F6D/MMC1.PDF.
- Liebling, EJ, Perez, JJS, Litterer, MM, Greene, C, 2021. Implementing hospital-based peer recovery support services for substance use disorder. *Am J Drug Alcohol Abuse* 47 (2), 229–237. doi:10.1080/00952990.2020.18412184.
- Liebschutz, J.M., Crooks, D., Herman, D., Anderson, B., Tsui, J., Meshesha, L.Z., Stein, M., 2014. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. *JAMA Intern. Med.* 174 (8), 1369–1376. doi:10.1001/jamainternmed.2014.2556.
- Lien, I.C., Seaton, R., Szpytman, A., Chou, J., Webber, V., Waineo, E., Levine, D.L., 2021. Eight-hour medication-assisted treatment waiver training for opioid use disorder: integration into medical school curriculum. *Med. Educ. Online* 26 (1). doi:10.1080/10872981.2020.1847755.
- Marino, R., Perrone, J., Nelson, L.S., Wiegand, T.J., Schwarz, E.S., Wax, P.M., Stolbach, A.I., 2019. ACMT position statement: remove the waiver requirement for prescribing buprenorphine for opioid use disorder. *J. Med. Toxicol.* 15 (4), 307–309. doi:10.1007/s13181-019-00728-9.
- Marks, L.R., Munigala, S., Warren, D.K., Liang, S.Y., Schwarz, E.S., Durkin, M.J., 2019. Addiction medicine consultations reduce readmission rates for patients with serious infections from opioid use disorder. *Clin. Infect. Dis.* 68 (11), 1935–1937. doi:10.1093/CID/CY924, An Official Publication of the Infectious Diseases Society of America.
- Mattick, R.P., Breen, C., Kimber, J., Davoli, M., 2014. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst. Rev.* 2014 (2). doi:10.1002/14651858.CD002207.PUB4.
- Mattson, C.L., Tanz, L.J., Quinn, K., Kariisa, M., Patel, P., Davis, N.L., 2021. Trends and geographic patterns in drug and synthetic opioid overdose deaths - United States, 2013–2019. *MMWR Morb. Mortal. Wkly. Rep.* 70 (6), 202–207. doi:10.15585/mmwr.mm7006a4.
- Morgan, J.R., Schackman, B.R., Weinstein, Z.M., Walley, A.Y., Linas, B.P., 2019. Overdose following initiation of naltrexone and buprenorphine medication treatment for opioid use disorder in a United States commercially insured cohort. *Drug Alcohol Depend.* 200, 34–39. doi:10.1016/J.DRUGALCDEP.2019.02.031.
- Mospan, G.A., Chaplin, M., 2022. Initiation of buprenorphine for opioid use disorder in the hospital setting: practice models, challenges, and legal considerations. *Am. J. Health Syst. Pharm.* 79 (3), 140–146. doi:10.1093/AJHP/ZXAB373, AJHP : Official Journal of the American Society of Health-System Pharmacists.
- National Academies of Sciences Engineering and Medicine, 2019. Medications for opioid use disorder save lives. In: Mancher, M., Leshner, A. (Eds.), *Medications for Opioid Use Disorder Save Lives* eds.. National Academies Press, Washington (DC) doi:10.17226/25310.
- O'Connor, A.M., Cousins, G., Durand, L., Barry, J., Boland, F., 2020. Retention of patients in opioid substitution treatment: a systematic review. *PLoS ONE* doi:10.1371/journal.pone.0232086, PLoS One.
- Patel, N., Schwenk, E.S., Ferd, P., Torjman, M.C., Baratta, J.L., Viscusi, E.R., 2021. An anesthesiologist-led inpatient buprenorphine initiative. *Pain Pract.* 21 (6), 692–697. doi:10.1111/PAPR.12996, The Official Journal of World Institute of Pain.
- Presnall, N.J., Wolf, D.A.P.S., Brown, D.S., Beeler-Stinn, S., Gruzca, R.A., 2019. A comparison of buprenorphine and psychosocial treatment outcomes in psychosocial and medical settings. *J. Subst. Abuse Treat.* 104, 135–143. doi:10.1016/J.JSAT.2019.06.010.
- QSR International Pty Ltd. (2020). NVivo. Released in March 2020), <https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home>
- Rosenblatt, R.A., Andrilla, C.H.A., Catlin, M., Larson, E.H., 2015. Geographic and specialty distribution of US physicians trained to treat opioid use disorder. *Ann. Fam. Med.* 13 (1), 23–26. doi:10.1370/afm.1735.
- Shastri, S., Manini, A.F., Richardson, L.D., Lin, M.P., 2020. US ED opioid-related visits increase, while use of medication for opioid use disorder undetectable, 2011–2016. *J. Gen. Intern. Med.* 35 (3), 965. doi:10.1007/S11606-019-05249-3.
- Shastri, S., Nobel, I., Allen, L.R., Richardson, L.D., Vidal, K., Manini, A.F., 2022. Prior use of medications for opioid use disorder in ED patients with opioid overdose: prevalence, misuse and overdose severity. *Am. J. Emerg. Med.* 51, 114–118. doi:10.1016/J.AJEM.2021.10.012.
- Sordo, L., Barrio, G., Bravo, M.J., Indave, B.I., Degenhardt, L., Wiessing, L., Pastor-Barriuso, R., 2017. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ Clin. Res. Ed.* 357, j1550. doi:10.1136/bmj.j1550.
- Substance Abuse and Mental Health Services Administration. (2021, February 22). Practitioner and program data. Retrieved April 28, 2021, from <https://www.samhsa.gov/medication-assisted-treatment/practitioner-resources/DATA-program-data>
- Sue, K.L., Cohen, S., Tilley, J., Yocheved, A., 2022. A plea from people who use drugs to clinicians: new ways to initiate buprenorphine are urgently needed in the fentanyl era. *J. Addict. Med.* 16 (4), 389–391. doi:10.1097/ADM.0000000000000952.
- Theisen-Toupal, J., Ronan, M.V., Moore, A., Rosenthal, E.S., 2017. Inpatient management of opioid use disorder: a review for hospitalists. *J. Hosp. Med.* 12 (5), 369–374. doi:10.12788/JHM.2731.
- Trowbridge, P., Weinstein, Z.M., Kerensky, T., Roy, P., Regan, D., Samet, J.H., Walley, A.Y., 2017. Addiction consultation services – linking hospitalized patients to outpatient addiction treatment. *J. Subst. Abuse Treat.* 79, 1–5. doi:10.1016/j.jsat.2017.05.007.
- Varshneya, N.B., Thakrar, A.P., Hobelmann, J.G., Dunn, K.E., Huhn, A.S., 2022. Evidence of buprenorphine-precipitated withdrawal in persons who use fentanyl. *J. Addict. Med.* 16 (4), E265–E268. doi:10.1097/ADM.0000000000000922.
- Wang, S.J., Wade, E., Towle, J., Hachey, T., Rioux, J., Samuels, O., Foster, K., 2020. Effect of inpatient medication-assisted therapy on against-medical-advice discharge and readmission rates. *Am. J. Med.* 133 (11), 1343–1349. doi:10.1016/J.AMJMED.2020.04.025.
- Weimer, M.B., Wakeman, S.E., Saitz, R., 2021. Removing one barrier to opioid use disorder treatment: is it enough? *JAMA* 325 (12), 1147–1148. doi:10.1001/JAMA.2021.0958.
- Williams, KD, Wilson, BL, Jurkowitz, CT, et al., 2022. Implementation of a clinical pathway to screen and treat medical inpatients for opioid withdrawal. *Implement Res Pract* 3. doi:10.1177/26334895221096290, 263348952210962.
- Wolf, B., Griffiths, R.R., 1991. Physical dependence on benzodiazepines: differences within the class. *Drug Alcohol Depend.* 29 (2), 153–156. doi:10.1016/0376-8716(91)90044-Y.