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Hospital-Based Methadone and Buprenorphine Initiation Practices by Addiction Consult Services

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Abstract

IMPORTANCE The emergence of fentanyl and other high-potency synthetic opioids (HPSOs) has not only been underlying overdose deaths, but has complicated initiation of methadone and buprenorphine for opioid use disorder (OUD) treatment, including in the hospital. In response, clinicians with addiction expertise have developed novel initiation practices, yet no studies have characterized initiation practices nationally.

OBJECTIVE To assess the use of novel hospital-based practices for initiating methadone and buprenorphine.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional survey study of directors of hospital-based addiction consult services (ACS) associated with addiction medicine and addiction psychiatry fellowships in hospitals in the US was conducted using a REDcap anonymous survey from October 2023 to April 2024.

EXPOSURE Predefined methadone and buprenorphine initiation practices. Standard methadone initiation was defined as 40 mg oral maximum on day 1 with up-titration of 5 to 10 mg every 3 days. Rapid methadone initiation was defined as any initiation regimen more rapid than standard. Buprenorphine initiation practices included low dose, high dose, traditional, and rescue.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of ACS directors using predefined methadone and buprenorphine initiation practices. Perceived impact of the drug supply on methadone and buprenorphine initiation was assessed through a 5-point Likert scale ranging from strongly disagree to strongly agree. Typical selection of buprenorphine initiation practices was assessed using 7 case-based scenarios intended to represent common hospital scenarios.

RESULTS Among 80 consult services, 58 directors (72.5%; median [IQR] age, 41 [38-50] years; 27 of 57 [47.3%] women) completed surveys, one of which was partially completed. Of 57 ACS directors, specialties included addiction medicine (41 respondents [71.9%]), addiction psychiatry (11 respondents [19.3%]), general or consult liaison psychiatry (11 respondents [19.3%]), and toxicology (2 respondents [3.5%]). Among those who reported initiating methadone (47 of 58 respondents [81.0%]), 33 (70.2%) agreed that HPSOs changed their methadone initiation practices. Of 46 respondents, 40 (87.0%) reported rapid initiation of methadone, and of those, 26 (65.0%) reported using rapid initiation for more than 50% of initiations. Full-agonist opioids were used by 31 of 46 ACS directors (67.4%) to treat withdrawal during methadone initiation. Of 58 respondents, 54 (93.1%) agreed that HPSOs changed their buprenorphine initiation practices. All 58 ACS directors reported that their initiation practices offered buprenorphine initiation, including 53 of 57 (92.9%) offering low dose, 50 of 57 (87.7%) offering traditional, 43 of 57 (75.4%) offering high dose , and 20 of 57

(continued)

Key Points

Question How commonly are hospital-based addiction clinicians using novel methadone and buprenorphine initiation practices to address challenges brought by fentanyl and high-potency synthetic opioid use?

Findings In this national, cross-sectional survey study of 58 addiction fellowship–associated hospital consult service directors, practices including rapid methadone initiation, use of full-agonist opioids for opioid withdrawal, and use of low- and high-dose buprenorphine initiation were widespread.

Meaning These findings suggest that among hospital-based academic addiction consult directors, methadone and buprenorphine initiation in the hospital setting is adapting to a shifting opioid supply, often outpacing advances in research and clinical guidelines.

+ Invited Commentary

+ Supplemental content

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Abstract (continued)

(35.1%) offering rescue. For 7 clinical cases provided, low-dose initiation was the most commonly endorsed method of buprenorphine initiation, except in the case of a person presenting in significant withdrawal 2 days after last fentanyl use.

CONCLUSIONS AND RELEVANCE The findings of this survey study of hospital-based academic ACS directors suggest that methadone and buprenorphine initiation has adapted to a shifting opioid supply, often outpacing research and changes in clinical guidelines.

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Introduction

The emergence of high-potency synthetic opioids (HPSO), such as fentanyl and fentanyl analogues, has led to an overdose crisis in the US. Methadone and buprenorphine are the most effective medications for opioid use disorder (MOUD), reducing overdoses and opioid-related mortality by up to 50%.[1] To reduce overdose deaths, timely initiation and retention of methadone and buprenorphine are critical.

While the drug supply has changed, clinical guidelines about methadone and buprenorphine initiation were based on research when heroin and prescription opioids dominated the opioid supply.[2,3] Standard guidance about methadone initiation begins with 30 to 40 mg taken orally followed by up-titration every 3 to 5 days.[2] Guidance for the initiation of the partial opioid agonist buprenorphine begins with repeated doses of 2 to 4 mg; this begins only after opioid withdrawal symptoms emerge to decrease the risk of precipitated opioid withdrawal, an abrupt worsening of withdrawal symptoms due to buprenorphine displacing full opioid agonists on the opioid receptors.

However, evidence suggests HPSOs complicate methadone and buprenorphine initiation due to their high affinity at the μ-opioid receptor, prolonged clearance due to lipophilicity, and creation of high tolerance.[4-8] For methadone initiation, the high tolerance induced by HPSOs means the standard methadone approach may inadequately treat withdrawal, reducing retention early in treatment.[9] For buprenorphine initiation, HPSOs are thought to lead to more challenging initiations and risk for precipitated opioid withdrawal.[7,10-12]

Initiation of methadone and buprenorphine in the hospital setting has proven benefits.[13,14] With the ability to closely monitor patients and adequately address symptoms and complications, hospital-based addiction consult services (ACS) are at the forefront of innovations seeking to overcome methadone and buprenorphine initiation barriers fueled by HPSOs. ACS have described rapid (ie, faster dose escalation compared with standard initiation) methadone initiation protocols, and have found them to be feasible and effective.[15-18] Hospital ACS adapted buprenorphine initiations through several novel approaches,[19] namely, the use of higher initiation doses (high-dose initiation)[20] and the use of initially low but gradually increasing buprenorphine doses while overlapping full opioid agonists (low-dose initiation).[21] Evidence, including the data synthetized by ACS, led to the American Society of Addiction Medicine (ASAM) releasing an expert-based guidance document addressing the adaptation of buprenorphine initiations to HPSOs.[19]

Despite reports of novel methadone and buprenorphine initiation practices, there remains a dearth of evidence describing the practices that ACS are using. We examined academic ACS directors' self-report of perceptions of HPSOs and hospital-based methadone and buprenorphine initiation practices nationally.

Methods

Study Setting and Data Sources

This survey study was deemed exempt from full review by the Yale University institutional review board. Reporting follows the American Association for Public Opinion Research (AAPOR) reporting guideline.[22] From October 2023 to April 2024, we surveyed ACS directors associated with addiction fellowships about their current practices for hospital-based methadone and buprenorphine initiation from the 50 US states; Washington, DC; and Puerto Rico.

We used public databases[23,24] to identify Accreditation Council of Graduate Medical Education (ACGME)–accredited addiction medicine fellowships (96 fellowships) and addiction psychiatry fellowships (54 fellowships) and lists of fellowship directors from the American College of Academic Addiction Medicine and the American Academy of Addiction Psychiatry. We emailed program directors to identify the directors of the ACS associated with their fellowship program.

Study Sample and Recruitment

Potential respondents were directors of hospital-based ACS affiliated with ACGME-accredited addiction medicine and addiction psychiatry fellowship programs. We chose this group because it is geographically diverse and likely to lead in methadone and buprenorphine initiation practice and educating addiction specialists. If more than 1 ACS was associated with a program, each service was included that provided services at distinct sites.

Eligible respondents received a unique link to a self-administered online survey. Codirectors were sent a joint email with a unique survey link that could only be completed once to ensure no single ACS was overrepresented. We sent potential respondents up to 3 reminders. Respondents received a $50 electronic gift card for participation. Informed consent was obtained electronically prior to the start of the survey.

Survey Development

The survey (eAppendix in Supplement 1) was based on a prior study assessing practice variation in low-dose buprenorphine initiation,[25] literature and recent ASAM Clinical Consensus Statement,[19] and the research team's expert opinion. We examined the face validity of the survey through pilot testing with addiction medicine and addiction psychiatry clinicians. Case-based scenarios were refined using one-on-one cognitive interviews,[26] a structured interview method used for eliciting understanding of the questions and thought process to ensure consistent interpretation. Cognitive interviews were conducted over video conference with a geographically diverse group of 3 addiction medicine and 3 addiction psychiatry specialists; after each interview, the cases were iteratively refined.

The survey included definitions for each methadone and buprenorphine initiation method. We defined standard methadone initiation based on 2021 Substance Abuse and Mental Health Services Administration guidance[2] as 40 mg maximum on day 1 with up-titration of 5 to 10 mg every 3 days. Rapid methadone initiation was defined as any initiation regimen more rapid than the standard initiation (using higher doses or shorter duration between dose escalations).

We defined 3 buprenorphine initiation practices based on ASAM Clinical Considerations.[19] (1) Traditional initiation starts with a first dose of 2 to 4 mg of buprenorphine after reaching moderate withdrawal. (2) High-dose initiation (ie, macrodosing) starts with the first dose (8-16 mg) of buprenorphine after reaching moderate withdrawal. (3) Low-dose initiation (ie, overlapping or microdosing) starts with low doses of buprenorphine (eg, 0.5 mg sublingual), which gradually increases while continuing full opioid agonists. We defined a fourth option, buprenorphine rescue (ie, buprenorphine administration after intentional naloxone-precipitated withdrawal) based on recent case reports.[27,28]

Survey Variables

Study data were collected and managed using REDCap.[29,30] We assessed perceived impact of the drug supply on methadone and buprenorphine initiation through a 5-point Likert scale ranging from strongly disagree to strongly agree.

We assessed if methadone and buprenorphine initiation were offered. If buprenorphine initiation was offered, we assessed use of long-acting injectable formulations prior to discharge.

Regarding methadone initiation, we assessed the use of rapid initiation, additional use of full-agonist opioids to treat continued withdrawal, and other adjunctive medications to treat withdrawal (eg, clonidine). For services that used rapid methadone initiation, we assessed the proportion of initiations using rapid initiation in the last 2 weeks (1%-100% in 10% increments) as well as the clinical situations in which rapid initiation was used (ie, regular fentanyl use, pregnancy, prior premature discharge against medical advice, concomitant acute pain and OUD, recently discontinued methadone within last month, persistent withdrawal despite standard protocol, or other). We asked about the typical dose of methadone on days 1 to 5 of a rapid initiation through free-text response. For services that did not initiate methadone, we queried their approach to management of methadone prescribed as an outpatient.

Regarding buprenorphine initiation, we used multiple choice questions assessing use of each of the buprenorphine initiation practices defined previously and the proportion of initiations using each practice in the last 2 weeks (1%-100% in 10% increments). Low-dose initiation was further characterized by the formulations of buprenorphine used (split films or tabs, buccal, transdermal, intravenous, and other) and the length of a typical low-dose initiation.

We assessed typical selection of buprenorphine initiations practices using 7 case-based scenarios intended to represent common hospital scenarios. All cases pertained to hospitalized patients with severe OUD not interested in in other forms of MOUD. In brief the cases included: (1) a person using fentanyl with last use hours ago and short expected hospital length of stay, (2) a person using fentanyl with last use hours ago and long expected hospital length of stay, (3) a person using fentanyl in acute opioid withdrawal with last use days ago, (4) a person taking long-term opioids for pain now with severe OUD, (5) a person using fentanyl now with prolonged hospitalization taking opioids for pain, (6) a person with OUD in remission treated methadone with a relative contraindication to continuing methadone (loss of transportation access), and (7) a person with OUD in remission treated methadone with an absolute contraindication to continuing methadone (Torsades de Pointes and prolonged corrected QT interval).

Participants self-reported their demographic information and consult service characteristics. Race and ethnicity were self-identified and collected as required by the funder. Race categories were defined by Office of Management and Budget 1997 Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity, including American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, other (free-text response), and prefer not to answer. Ethnicity categories included Hispanic or Latino, not Hispanic or Latino, and prefer not to answer. Respondents could identify as more than 1 category.

Statistical Analysis

For categorical variables, we used frequencies to describe the data. For continuous variables, we used median and IQR. Analyses were conducted in STATA 18 (StataCorp).[31]

Results

We identified 83 ACS directors from 80 unique ACS associated with 77 ACGME-accredited addiction medicine and addiction psychiatry fellowships. Three ACS with 2 codirectors were sent a joint invitation. Of the 80 survey invitations, 58 directors responded (72.5% response rate). One survey was partially completed and was included in perceptions analysis; this survey provided partial information about medication initiation (only whether they initiated methadone, buprenorphine,

and/or naltrexone but not specific practices used) and was not included in analysis of respondent characteristics.

Respondent Characteristics

Of 57 ACS respondents (median [IQR] age, 41 [38-50] years), 41 (71.9%) were in addiction medicine, 11 (19.3%) were in addiction psychiatry, 11 (19.3%) were in general or consult liaison psychiatry, and 2 (3.5%) were in toxicology (**Table**). The services were associated with addiction medicine fellowships (48 respondents [84.2%]), followed by general or consult liaison psychiatry fellowships (14 respondents [24.6%]), addiction psychiatry fellowships (13 respondents [22.8%]), medical toxicology fellowships (6 respondents [10.5%]), and pain fellowships (2 respondents [3.5%]). The services saw a median (IQR) of 11 (7-20) new consults for patients with OUD per week. ACS were predominantly in urban hospitals (47 respondents [82.5%]) and located in the Northeast (24 respondents [42.1%]) and West (18 respondents [31.6%]), South (8 respondents [14.0%]), and Midwest (7 respondents [12.3%]).

Of 57 respondents, 47 (82.5%) self-identified their ethnicity as not Hispanic or Latino, and 6 (10.5%) identified as Hispanic or Latino; for self-reported race, 7 respondents (12.3%) identified as Asian, 3 (5.3%) as Black or African American, 38 (66.7%) as White, and 10 (17.5) as another race, with 6 (10.5%) preferring not to answer. Respondents were split between women (27 respondents [47.3%]) and men (26 respondents [45.6%]), with 1 respondent (1.8%) identifying as nonbinary. Most were physicians (56 respondents [98.2%]), of whom 50 (89.3%) were board certified in addiction medicine and/or psychiatry. Respondents practiced addiction medicine or psychiatry for a median (IQR) of 6 (5-10) years. Nearly two-thirds (37 respondents [64.9%]) had experience working at an opioid treatment program (OTP).

Perceptions of the Drug Supply

Of 58 respondents, nearly all agreed (57 respondents [98.3%]) that HPSOs were common in the opioid supply, and 34 (58.6%) agreed xylazine was common (**Figure 1**). Of the 34 respondents who thought xylazine was common in the opioid supply, 11 (32.4%) agreed it impacted MOUD initiation.

Methadone Initiation

For people with OUD not currently taking MOUD, 47 of 58 ACS directors (81.0%) offered methadone initiation. Of those, 33 (70.2%) agreed fentanyl changed methadone initiation.

Rapid methadone initiation was used by 40 of 46 ACS directors (87.0%) that initiated methadone. A majority of those who used rapid initiation (26 of 40 ACS [65.0%]), reported using it for more than 50% of their methadone initiations, with 14 (35.0%) using rapid initiation for more than 90% of their methadone initiations. Typical reported methadone doses by day of rapid initiation regimen are displayed in **Figure 2**. Of the clinical situations provided, 76.1% of services that initiated methadone (35 of 46 ACS) reported using rapid initiation for persistent withdrawal, 67.4% (31 of 46 ACS) for regular fentanyl use, 58.7% (27 of 46 ACS) for pregnancy, 58.7% (27 of 46 ACS) for prior premature discharge, 58.7% (27 of 46 ACS) for concomitant pain and OUD, and 56.5% (26 of 46 ACS) for methadone discontinued within last month.

Adjunctive medications for the treatment of opioid withdrawal symptoms during methadone initiation were almost universally used (44 of 46 ACS [95.7%]). The most common were clonidine (36 of 46 ACS [78.3%]), hydroxyzine (34 of 46 ACS [73.9%]), full-agonist opioids such as oxycodone (31 of 46 ACS [67.4%]), loperamide (31 of 46 ACS [67.4%]), gabapentin (24 of 46 ACS [52.2%]), benzodiazepines (18 of 46 ACS [39.1%]), and ondansetron (5 of 46 ACS [10.9%]). Of 11 services that did not initiate methadone, all continued methadone if a patient was receiving methadone prior to hospitalization at the OTP-confirmed dose, and 5 (45.5%) offered to up-titrate the dose if clinically indicated.

Table. Respondent Characteristics

Characteristics	Respondents, No. (%) (N = 57)[a]
Addiction consult service characteristics	
Primary specialty of consult service[b]	
Addiction medicine	41 (71.9)
Addiction psychiatry	11 (19.3)
General or consult liaison psychiatry	11 (19.3)
Pain	0
Toxicology	2 (3.5)
Specialty of associated fellowship[b]	
Addiction medicine	48 (84.2)
Addiction psychiatry	13 (22.8)
General or consult liaison psychiatry	14 (24.6)
Pain	2 (3.5)
Toxicology	6 (10.5)
Hospital type	
Private, for profit	3 (5.2)
Private, not for profit	26 (44.8)
Public	23 (39.7)
US Department of Veterans Affairs	3 (5.2)
Other[c]	2 (3.5)
Hospital setting	
Rural	3 (5.3)
Suburban	7 (12.1)
Urban	47 (81.0)
Hospital size	
No. of hospitals with with data	56
No. of beds, median (IQR)[d]	588 (399-800)
New consults for OUD per wk	
No. with data	56
Median (IQR)	11 (7-20)
Hospital region	
Northeast	24 (41.3)
Midwest	7 (12.3)
South	8 (14.0)
West	18 (31.6)
Consult director characteristics	
Age, median (IQR), y	41 (38-50)
Race[b]	
American Indian or Alaska Native	0
Asian	7 (12.3)
Black	3 (5.3)
Native Hawaiian and other Pacific Islander	0
White	38 (66.7)
Prefer not to answer	6 (10.5)
Other[e]	10 (17.5)
Ethnicity	
Hispanic or Latino(a)	6 (10.5)
Not Hispanic or Latino(a)	47 (82.5)
Prefer not to answer	4 (7.0)
Gender	
Woman	27 (47.4)
Man	26 (45.6)
Nonbinary	1 (1.8)
Prefer not to answer	3 (5.3)

(continued)

Table. Respondent Characteristics (continued)

Characteristics	Respondents, No. (%) (N = 57)[a]
Clinician type	
MD or DO	56 (98.2)
Advanced practice provider (APRN or PA)	1 (1.8)
Residency completed[b]	
Emergency medicine	7 (12.3)
Family medicine	5 (8.6)
Internal medicine	25 (43.1)
Obstetrics and gynecology	0
Pediatrics	1 (1.8)
Preventative medicine	1 (1.8)
Psychiatry	21 (36.2)
Toxicology	1 (1.8)
Addiction board certifications, No./total No. (%)[f]	
Addiction medicine	42/56 (75.0)
Addiction psychiatry	5/56 (9.0)
Both	3/56 (5.4)
Neither	6/56 (10.7)
Years of medical practice, median (IQR)	10 (5-15)
Years of addiction practice, median (IQR)	6 (5-10)
Experience working at an opioid treatment program	37 (63.8)
Days on consult service per mo, median (IQR)	10 (5-20)

Abbreviations: APRN, advanced practice registered nurse; DO, doctor of osteopathic medicine; MD, medical doctor; PA, physician associate.

[a] One of 58 respondents did not complete the characteristic question; all percentages were calculated out of 57.

[b] More than 1 option could be selected.

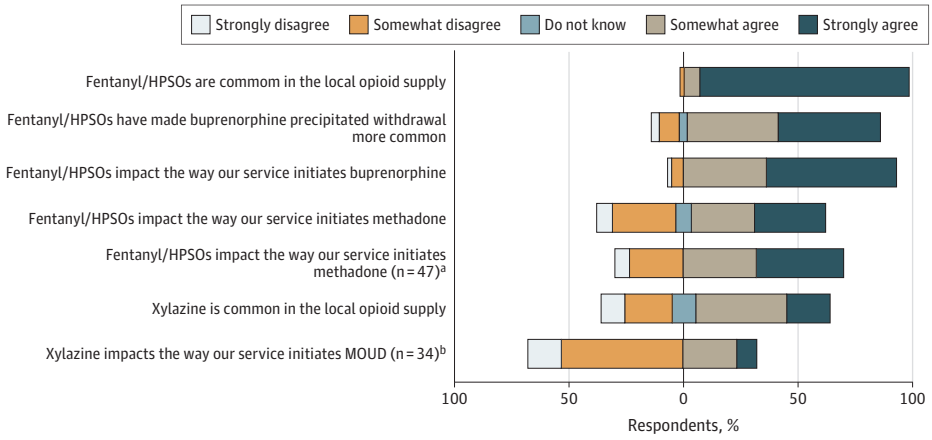
[c] Included state university–affiliated academic medical center and teaching hospital.

[d] One answer of greater than 700 was calculated as 700 for analyses.

[e] Other race allowed free-text responses and included Hispanic, Hispanic or Latino, Latine, Latino, Human, Middle Eastern, and 4 blank responses.

[f] Only asked to MD and DOs.

Figure 1. Hospital-Based Addiction Consult Service Directors' Perception of the Impact of Opioid Supply on Methadone and Buprenorphine Initiation (n = 58 Directors)



HPSO, High-potency synthetic opioids; MOUD, medication for opioid use disorder.

[a] Only including services that initiate methadone.

[b] Only including services that answer agree or strongly agree that xylazine is common.

Buprenorphine Initiation

For people with OUD not currently taking MOUD, all 58 ACS offered buprenorphine initiation, including 21 (36.2%) additionally offering long-acting injectable buprenorphine during hospitalization. The majority of ACS directors (54 of 58 ACS directors [93.1%]) agreed that HPSOs changed the way they initiate buprenorphine, with 49 (84.5%) agreeing that HPSOs made precipitated opioid withdrawal with buprenorphine more common.

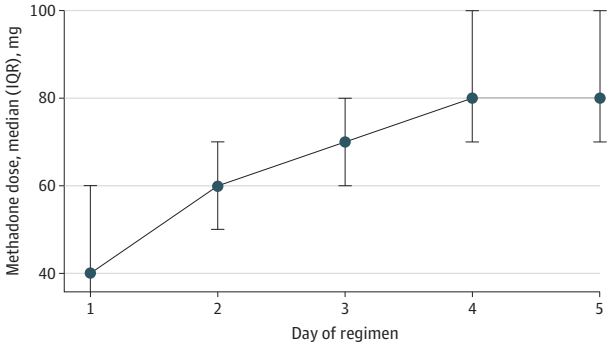
Low-dose buprenorphine initiation was offered by the highest proportion of ACS (53 of 57 ACS [92.9%]), followed by traditional (50 of 57 ACS [87.7%]), high dose (43 of 57 ACS [75.4%]), and buprenorphine rescue (20 of 57 ACS [35.1%]) (**Figure 3**). Of the 53 ACS that used low-dose initiation, the median (IQR) length of their initiation regimen was 5 (3-5) days. To administer doses of buprenorphine less than 2 mg, 28 (52.8%) used split films or tabs, 21 (39.6%) used buccal administration, 16 (30.2%) used transdermal administration, 8 (15.1%) used intravenous administration, 1 (1.9%) used the intravenous formulation of buprenorphine sublingually, and 1 (1.9%) used a formulation of buprenorphine-naloxone tablets available in the equivalent of 1-mg doses. Of these services, 14 (26.4%) used more than 1 of these formulations.

In the clinical cases presented (**Figure 4**), low-dose initiation was reported as the most frequently offered method of buprenorphine initiation in all cases other than one. A person presenting with significant opioid withdrawal (Clinical Opiate Withdrawal Scale score >12) with last fentanyl use 2 days prior was more commonly offered traditional or high-dose initiation.

Discussion

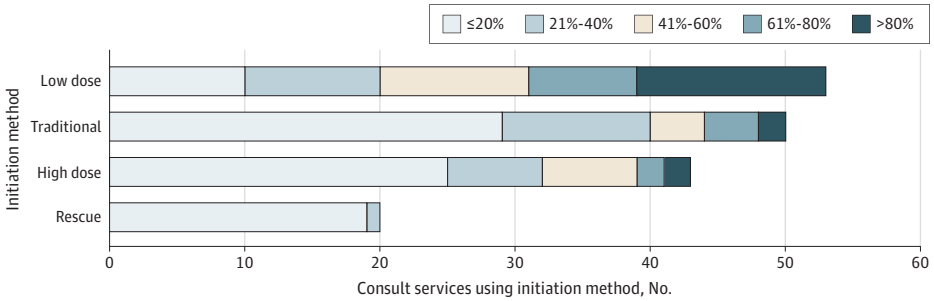
To our knowledge, this is the first survey study to systematically characterize hospital methadone and buprenorphine initiation practices for OUD in a national sample. Our study generated several key findings. First, we found widespread agreement that HPSOs had changed their practices of initiating methadone and buprenorphine. Second, of those that initiated methadone, most (81%) offered rapid methadone initiation with variable maximum daily doses. When opioid withdrawal symptoms continued during methadone initiation, nearly all services (96%) offered ancillary medications, with a majority (67%) utilizing full-agonist opioids. Third, all services initiated buprenorphine, most

Figure 2. Rapid Methadone Up-Titration, Median Dose by Day of Regimen Among 39 Addiction Consult Services



Of the 40 addiction consult services that used rapid methadone up titration, 1 respondent dropped because they listed 0 mg for all days of the rapid methadone up-titration regimen.

Figure 3. Frequency of Buprenorphine Initiation Practices Used by Addiction Consult Services (n = 57 Services)



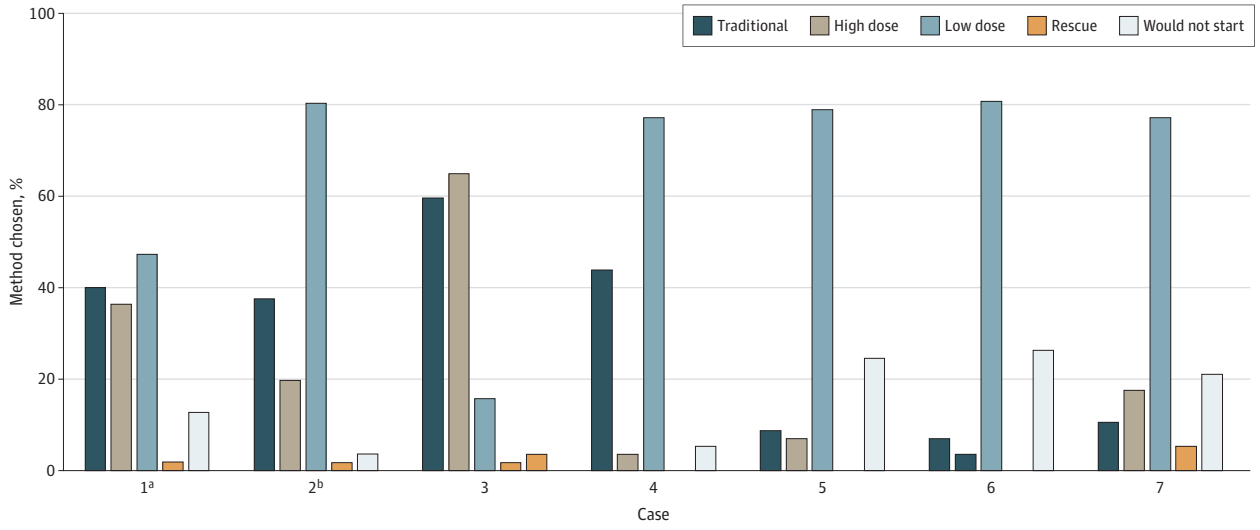
The frequency of the buprenorphine initiation practice used by addiction consult services (ACS) for each practice (low dose, traditional, high dose, and rescue) are displayed. Each bar represents the total number of ACS using that initiation practice and within each bar the frequency of use is stratified into quintiles. For example, for low dose initiation, a total of 53 of 57 ACS used this method and among those, 14 used it for more than 80% of their initiations, 8 used it for 61% to 80% of their initiations, 11 used it for 41% to 60% of their initiations, 10 used it for 21% to 40% of their initiations, and 10 used it for 1% to 20% of their initiations.

commonly with low-dose initiation, followed closely by traditional and high-dose initiation. Across 7 clinical scenarios, low-dose buprenorphine initiation remained the most frequently offered practice except in the scenario of a patient presenting in significant opioid withdrawal 2 days after last fentanyl use in which traditional or high-dose initiation were preferred.

To our knowledge, this is the first study assessing hospital-based methadone initiation practices across different institutions. In the setting of higher opioid tolerances due to HPSOs and undertreated opioid withdrawal contributing to poor outcomes like premature hospital discharges,[32,33] adequate dosing of methadone and control of withdrawal is critical. Hospitalization is an opportunity to quickly achieve an effective methadone dose in a monitored setting to maximize the potential for improved treatment retention[15-18] and offers a setting to utilize short-acting opioids for withdrawal management.[34] We found widespread and frequent use of rapid methadone initiations with short-acting opioids for continued withdrawal symptoms. Together, these results show that practice changes, in response to an evolving drug supply, have outpaced clinical guidelines and rigorous research in this area, and that research is needed to fully elucidate risks and benefits of each novel initiation practice. Despite this research gap, our results suggest collective consensus among ACS directors of the benefits of more assertive approaches in the hospital setting that outweigh concerns about the risks.

The impact of HPSOs on buprenorphine initiation is an area of ongoing research. There is widespread perception that buprenorphine-precipitated opioid withdrawal is increasingly common and that this is an underlying factor of buprenorphine initiation adaptations, which this study confirmed,[4,10,11] yet hospital- and emergency department–based observational data has found widely variable rates of buprenorphine-precipitated opioid withdrawal ranging from 1%[6,35] to more than 10%.[6,7,36] Regardless of the true incidence, our study suggests that ACS are adopting novel buprenorphine initiation practices such as low-dose initiation. For hospitalized patients for whom

Figure 4. Buprenorphine Initiation Practice Chosen by Clinical Scenario (n = 57 Directors)



Case 1: fentanyl use multiple times per day, last use being hours prior to admission, no current opioid withdrawal, and expected hospital discharge in 1 to 2 days. Case 2: fentanyl use multiple times per day, last use being hours prior to admission, no current opioid withdrawal, and expected hospital discharge in 1 week. Case 3: fentanyl use multiple times per day, last use being 2 days before admission, and Clinical Opiate Withdrawal Scale score of 12 with mydriasis and piloerection. Case 4: chronically prescribed 30 mg of immediate-release oxycodone every 6 hours for chronic pain from physician and currently diagnosed with severe opioid use disorder (OUD) in setting of using additional nonprescribed pharmaceutical oxycodone. Case 5: fentanyl use multiple times per day prior to admission, now admitted for 1 week with endocarditis and severe pain, and currently requiring opioid analgesics for acute pain. Case 6: OUD stable without substance use for years, receiving 100 mg of methadone in an outpatient setting, no longer can get to daily opioid treatment program, and last methadone dose was this morning. Case 7: OUD stable without substance use for years, receiving 100 mg of methadone, admitted to intensive care unit with Torsades, corrected QT-interval of 700 ms (electrolytes normal and no other QT-interval–prolonging medications), and last methadone dose this morning.

[a] Percentage calculated out of 55 (2 additional missing answers).

[b] Percentage calculated out of 56 (1 additional missing answer).

full-agonist opioids can be administered, low-dose buprenorphine initiation offers several additional potential advantages: reducing need for opioid withdrawal, expanding clinical situations in which buprenorphine can be initiated to include those in which opioids must be continued (ie, for acute pain or for a person currently treated with methadone),[21] and being the novel method with the most robust observational hospital-based data.[37-40] Despite its common use, the specifics of low-dose initiation regimens, such as length of regimen and buprenorphine formulation, remain highly variable.[21,25,37-40] Future research should examine the comparative effectiveness of the different low-dose initiation regimens.

While there was widespread use of novel initiation practices, there remained variability in details of these practices. Some variability in initiation should be expected given that ACS individualize care to adapt to the local drug supply[41] and patient preference, yet, the amount of variability may reflect inconsistent dissemination and implementation of new practices, variable clinician comfort with practices prior to incorporation into guidelines, contradictory hospital and pharmacy guidance, and lack of comparative effectiveness data. As the drug supply continues to shift, as evidenced by new adulterants such as xylazine,[42] guidelines are often not able adapt or be implemented quickly enough due to a lack of established evidence base and the known time lag in implementation of guidelines.[43] Learning about health care systems and community-participatory research and leveraging the experience of the community of people who use drugs and community-based clinicians to understand and adapt to changes in the drug supply, such as through the Delphi Method,[44] offers potential avenues to respond more quickly.[5]

An additional finding was the lack of self-identified racial and ethnic diversity among ACS directors. Despite overdose rates rising more quickly in racially and ethnically minoritized populations, particularly among Black, Hispanic, and American Indian or Alaska Native people,[45-47] only 5% of our sample self-identified as Black, 10% identified as Hispanic, and none identified as American Indian or Alaska Native; this highlights the need to develop and invest in strategies to diversify and retain a workforce that reflects the communities they serve.[48]

Limitations

This study has limitations. First, our study was limited to academic addiction fellowship–associated ACS in predominantly urban settings, and results may not generalize to services in other settings. Second, the study captured self-report of current practice, which may differ from actual practice. Third, we surveyed about adaptation in methadone and buprenorphine initiation based on published practices and thus may not have captured unpublished practices. Fourth, although our definitions (ie, rapid methadone initiation and low-dose buprenorphine initiation) were based on the literature and were provided throughout the survey, respondents may use different definitions to describe their practice, which may not have been adequately captured.

Conclusions

In this survey study of hospital-based ACS directors, we found widespread agreement that HPSOs impact methadone and buprenorphine initiation and widespread use of novel initiation practices in response. Rapid methadone initiation and adjunctive use of full-agonist opioids to treat additional withdrawal were common. Low-dose initiation of buprenorphine was the most common buprenorphine initiation method used. Future research should assess the safety and effectiveness of these adaptations on patient outcomes and use community-partnered research to aid in implementation of new adaptations in response to a continuously shifting drug supply. Leveraging community expertise to generate time-sensitive guidance, such as through the Delphi Method, may serve as an important bridge to adapt clinical care more rapidly.

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SUPPLEMENT 1.
eAppendix. Hospital-Based Opioid Agonist Treatment Initiation Survey

SUPPLEMENT 2.
Data Sharing Statement

JAMA Network Open

Original Investigation | Substance Use and Addiction

Injectable-Only Overlapping Buprenorphine Starting Protocol in a Low-Threshold Setting

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Abstract

IMPORTANCE Initiating buprenorphine for opioid use disorder (OUD) in outpatient settings has become more difficult for individuals using fentanyl. Novel buprenorphine starting strategies are needed, especially for people experiencing homelessness.

OBJECTIVE To evaluate the short-term outcomes of the implementation of an injectable-only overlapping buprenorphine starting protocol in a low-threshold clinic and field-based setting serving individuals with OUD and active fentanyl use.

DESIGN, SETTING, AND PARTICIPANTS This retrospective observational cohort study was based on electronic health record data from September 2024 to January 2025 of an urban low-threshold voluntary OUD treatment program embedded in a drop-in center that offered care in the clinic and at various outreach sites, including shelters, supportive housing buildings, and encampments. Patients with moderate to severe OUD using fentanyl were included if they chose to have initial medications ordered for the injectable-only overlapping buprenorphine starting protocol between September 1 and November 30, 2024. Follow-up data were collected through January 15, 2025. Exclusion criteria were consumption of sublingual buprenorphine in the week prior, current methadone use, or lack of active fentanyl use.

EXPOSURE The injectable-only overlapping buprenorphine starting protocol, which does not require the cessation of fentanyl use before or during the process, includes the following steps: day 1 involves a weekly 8-mg injection without preceding sublingual buprenorphine, day 2 involves a weekly 16-mg injection, and day 3 involves a monthly 128-mg or 300-mg injection.

MAIN OUTCOMES AND MEASURES The outcomes and cascade of care were rates of protocol initiation (receipt of the initial 8-mg buprenorphine injection), completion (eventual receipt of all 3 long-acting buprenorphine injections), and 2-month retention (receipt of a second monthly buprenorphine injection within 45 days of the first).

RESULTS Ninety-five individuals met the inclusion criteria. These patients had a median (IQR) age of 39 (23-69) years and included 52 men (55%), 75 (79%) of whom were experiencing homelessness or living in permanent supportive housing. Of the 95 patients included, 85 (90%) initiated the protocol, 71 (75%) eventually completed the protocol, and 61 (64%) received a second monthly long-acting buprenorphine injection.

CONCLUSIONS AND RELEVANCE This retrospective cohort study found that a novel injectable-only overlapping buprenorphine starting protocol had a relatively high rate of completion and 2-month retention in a low-threshold setting for individuals with OUD who used fentanyl, most of

(continued)

Key Points

Question What outcomes are associated with an injectable-only buprenorphine starting protocol in a low-threshold outpatient setting among individuals with opioid use disorder using fentanyl?

Findings In this cohort study of 95 patients with moderate to severe opioid use disorder using unregulated fentanyl, these patients chose a protocol that involved 3 escalating long-acting injectable buprenorphine doses over 3 days without requiring cessation of fentanyl and without sublingual buprenorphine. Most of these individuals (75%) completed the protocol and 64% received a second monthly long-acting injectable buprenorphine dose.

Meaning The findings suggest that an injectable-only buprenorphine starting protocol is a promising potential pathway for patients to start this lifesaving medication in the outpatient setting.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

whom were experiencing homelessness. These findings suggest that this protocol is a promising potential pathway for patients to start buprenorphine in the outpatient setting.

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Introduction

Unregulated fentanyl has substantially increased overdose fatalities in the community of drug users.[1] Buprenorphine has been shown to effectively treat opioid use disorder (OUD), reducing all-cause mortality and overdose mortality[2]; however, only approximately 20% of individuals who would benefit from medication for OUD receive treatment.[3]

Initiating buprenorphine for OUD has become more challenging in the context of widespread unregulated fentanyl.[4] Novel strategies for starting buprenorphine in acute care settings have shown promise.[5,6] However, implementing these approaches in outpatient settings can be challenging.

Barriers to successful buprenorphine initiation include the multistep complexity of overlapping sublingual (low dose) buprenorphine starting protocols,[7] the need to cease fentanyl use in withdrawal-first (high dose) protocols,[8] and deliberate precipitation of withdrawal in naloxone-assisted methods.[9] Such barriers can be heightened for people who experience homelessness, while the overdose risk among this population makes access to medications for OUD more crucial than ever.[10,11]

There is considerable interest in the role long-acting injectable buprenorphine may have in reducing overdose risk and supporting patients who aim to reduce or stop using unregulated fentanyl.[12,13] Implementation of long-acting injectable buprenorphine has been associated with high patient satisfaction; favorable changes in abstinence, accessibility, employment, and social relationships; and reduced fentanyl use in people with OUD.[12,14,15]

In February 2025, the US Food and Drug Administration approved label changes for a monthly long-acting injectable buprenorphine product to include a rapid initiation protocol after a single 4-mg dose of sublingual buprenorphine to lessen practical obstacles to medication initiation.[16,17] The manufacturer of the weekly long-acting injectable buprenorphine product also recommends a sublingual buprenorphine dose of at least 4 mg prior to injectable buprenorphine initiation.[18] Recent evidence suggests that long-acting injectable buprenorphine can be effectively used to initiate patients in emergency department settings with minimal risk of precipitated withdrawal, provided these patients have a Clinical Opiate Withdrawal Scale (COWS) score of 4 or higher (with higher scores indicating greater opioid withdrawal).[19]

Achieving tolerance to 4 mg of transmucosal buprenorphine or waiting to achieve a COWS score of at least 4, however, can still present a barrier to long-acting injectable buprenorphine initiation. In response to such challenges, in routine care, we initially offered a modification of the drug label recommendations for the weekly long-acting injectable buprenorphine formulation. The drug label recommends, after reaching tolerance to 4 mg of sublingual buprenorphine, a sequence of up to 3 weekly injections administered within the first week: a weekly 16-mg injection, weekly 8-mg injection, and another weekly 8-mg injection if needed. Consolidation into a higher-dose weekly or monthly formulation is recommended at the start of the second week.[18] Our initial modified protocol changed this sequencing. Patients were encouraged to achieve tolerance to a total daily dose of 2 to 3 mg of sublingual buprenorphine before receiving an initial 8-mg weekly injection, followed by a 16-mg weekly injection the next day, and a monthly injection thereafter. Some individuals declined any sublingual buprenorphine, due to prior negative experiences with the sublingual product, and, with informed consent, proceeded with a weekly 8-mg injection, without substantial subsequent withdrawal. Based on these experiences, we began offering an injectable-only overlapping buprenorphine starting protocol as an alternative method to individuals with moderate to severe OUD and active fentanyl use. This retrospective observational cohort study describes the short-term

outcomes of the implementation of an injectable-only overlapping buprenorphine starting protocol in a low-threshold clinic and field-based setting.

Methods

Design and Settings

We conducted a retrospective cohort study of individuals with OUD using unregulated fentanyl who chose an injectable-only overlapping buprenorphine starting protocol between September 1 and November 30, 2024. The University of Washington Institutional Review Board approved all study procedures and waived the informed consent requirement because of the retrospective and low-risk nature of the study. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Individuals voluntarily sought treatment at the Downtown Emergency Service Center's Opioid Treatment Network, a low-threshold outpatient OUD care program in Seattle, Washington. Individuals served at this clinic are primarily experiencing chronic homelessness and housing instability or living in permanent supportive housing. Individuals sought care in person at the clinic or were engaged through outreach by clinic staff. Patient-labeled long-acting buprenorphine injectables were provided in the clinic or at outreach sites, including at shelters or supportive housing buildings. Nearly all patients were covered by Washington State Medicaid or were dual-eligible with Medicare due to disabling conditions. Weekly and monthly forms of long-acting injectables were paid for by Washington State Medicaid without need for prior authorization.

Participants

Patients with moderate to severe OUD using unregulated fentanyl were included in the study if they had a weekly long-acting buprenorphine 8-mg injection ordered and paid for by insurance between September 1 and November 30, 2024, with an intent to start the injectable-only overlapping buprenorphine starting protocol. Follow-up data were assessed through January 15, 2025. OUD was confirmed based on patient-reported history, corroborated by medical records, prior buprenorphine prescriptions, and (if needed for diagnosis) point-of-care urine toxicology testing. We excluded individuals who reported consumption of sublingual buprenorphine in the week prior to the 8-mg injection, current methadone use, lack of active fentanyl use, or choice of another buprenorphine starting protocol.

Protocol Description

The injectable-only overlapping buprenorphine starting protocol (**Table 1**) includes the following steps, without requiring the cessation of fentanyl use before or during the process: day 1 involves a weekly 8-mg injection without preceding sublingual buprenorphine; day 2 involves a weekly 16-mg injection; and day 3 involves a monthly, long-acting 128-mg or 300-mg buprenorphine injection. These 2 monthly doses were offered to provide choice and accommodate patient preferences, paired with the counseling that the 300-mg dose would likely result in higher buprenorphine levels and a larger subcutaneous depot and that the 128-mg dose would likely result in lower buprenorphine levels and a smaller subcutaneous depot.[16,18]

Table 1. Summary of the Injectable-Only Overlapping Buprenorphine Starting Protocol[a]

Day	Long-acting injectable buprenorphine administered	Guidance for delayed buprenorphine injections[b]
1	Weekly 8-mg injection	NA
2	Weekly 16-mg injection	Offer the weekly 16-mg injection up to 2 d after the initial 8-mg injection before restarting.
3	Monthly 128-mg or 300-mg injection	Offer the monthly injection up to 3 d after the 16-mg injection before repeating a 16-mg injection. Consider restarting the full protocol if 7 d have passed since the 16-mg injection.

Abbreviation: NA, not applicable.

[a] See the **Box** for the routine patient counseling provided to patients who selected the protocol.

[b] Decisions on restarting after delayed injections are always informed by shared decision-making and patient preferences.

All patients who chose the protocol were provided with counseling that was based on prior clinical experience (Box). Standard patient counseling included a notification that, during the starting protocol, some degree of opioid withdrawal may be likely and severe opioid withdrawal remained possible. As with sublingual-based overlapping protocols, continued unregulated full agonist opioid use was assumed. Ceasing fentanyl or other full agonist opioid use during the process may result in opioid withdrawal and prompt the need to pivot to other buprenorphine starting methods. All patients were provided naloxone and counseled on safe use strategies.

If injections were not given on sequential days, the 16-mg injection was given as late as 2 days after the initial 8-mg injection before restarting. The monthly injection was given as late as 3 days after the 16-mg injection before needing to repeat a 16-mg injection. The protocol was fully restarted if a week had passed since the 16-mg injection.

Clonidine, hydroxyzine, and ondansetron were offered to treat opioid withdrawal symptoms if they occurred. Supplemental sublingual buprenorphine was provided at the time of the monthly injection, to be taken as needed for opioid cravings no earlier than 24 hours after the monthly injection.

Clinic and Pharmacy Procedures

Individuals interested in the injectable-only overlapping protocol met with a clinician to discuss their OUD and to establish individualized treatment goals. Visits with a clinician happened either in person at the low-barrier clinic on a walk-in basis or remotely via telehealth. Telehealth visits were facilitated by a care team member who accompanied the patient at an outreach site.

All medications needed for the injectable-only overlapping protocol were prescribed to a local pharmacy and were delivered to the clinic often within 1 business day. In instances where same-day medications were needed, a licensed health care professional retrieved the medication directly from the pharmacy.

Medications were securely stored at the clinic, with a documented chain of custody for all removals and additions of controlled medications. When outreached-based care was indicated, licensed health care professionals transported and administered pharmacy-dispensed, patient-labeled medications to individuals at outreach sites, including supportive housing units, emergency housing shelters, tiny house villages, and tent encampments.

Data Collection and Measures

All data were manually abstracted from the electronic health record (EHR) from September 2024 to January 2025, with discrepancies resolved by consensus between at least 2 authors. Demographic variables collected for this study included age, gender identity, race, and housing status. Race, gender identity, and housing status data were self-identified and documented in the EHR. Gender identity was defined as women, men, or transgender or nonbinary. Housing status was defined as unsheltered, shelter, permanent supportive housing, and non–permanent supportive housing. Race was categorized as American Indian or Alaska Native, Asian or Pacific Islander, Black, Middle Eastern or North African, White, multiracial, or unknown (ie, individuals who did not want to disclose race). Race data were collected to describe the population generalizability of individuals choosing the novel

Box. Routine Patient Counseling

- Expect some opioid withdrawal symptoms during the 3-day process.
- Severe opioid withdrawal still remains a possibility.
- Continued use of unregulated fentanyl is assumed. Ceasing fentanyl or other full agonist opioid use during the process may result in opioid withdrawal and prompt the need to pivot to other buprenorphine starting methods.
- When using unregulated opioids, use them as safely as possible and carry naloxone.
- Supplemental sublingual buprenorphine is recommended as needed for continued fentanyl cravings, starting at 24 hours after the monthly injection.
- Use adjunct support medications provided (typically clonidine, hydroxyzine, and ondansetron) as needed for withdrawal symptoms.

protocol. Buprenorphine injection doses and administration dates were obtained from the EHR and used to determine individuals' progression through the injectable-only overlapping protocol.

The outcomes evaluated reflect the cascade of care. Protocol initiation rates were defined as the number of patients who received the day-1 weekly 8-mg injection divided by the total cohort who chose the injectable-only overlapping buprenorphine starting protocol as their buprenorphine initiation method. Protocol completion was defined as receiving all 3 injections in the protocol, which included those who needed a repeated weekly 8-mg or 16-mg injection to complete the process, with distinction between those who needed vs did not need any repeated weekly 8-mg or 16-mg injections to complete the 3-injection series. Two-month retention was defined as those who received a second monthly long-acting buprenorphine injection within 45 days of the first monthly long-acting buprenorphine injection. Measures of time to protocol completion were assessed, including (1) the number of days between the initial medication pharmacy order and the administration of the initial weekly 8-mg injection as well as the first monthly long-acting buprenorphine injection and (2) the number of days between the administration of the initial weekly 8-mg injection and the administration of the first monthly long-acting buprenorphine injection. Retention rates and days between injections were treated as continuous variables.

Statistical Analysis

Descriptive statistics are reported for the cohort. The association between housing status and receipt of a second monthly buprenorphine injection—evaluated due to concerns that a 3-day injection series may be more burdensome for individuals living unhoused—was assessed using Pearson χ^2 test and logistic regression. A 2-sided $P < .05$ was considered statistically significant. All analyses were conducted in RStudio, version 2023.12.1 (RStudio).

Results

Ninety-five individuals met the inclusion criteria and chose to have medications ordered for the injectable-only overlapping buprenorphine starting protocol between September 1 and November 30, 2024. These patients had a median (IQR) age of 39 (23-69) years; included 42 women (44%), 52 men (55%), and 1 transgender or nonbinary individual (1%); and 6 (6%) self-identified as American Indian or Alaska Native, 5 (5%) as Asian or Pacific Islander, 13 (14%) as Black, 2 (2%) as Middle Eastern or North African, 48 (51%) as White, and 5 (5%) as multiracial, with 16 individuals (17%) having unknown race. Seventy-five patients (79%) were experiencing homelessness or living in permanent supportive housing. Patient characteristics are summarized in **Table 2**.

Of the 95 patients who met the inclusion criteria, 85 (90%) initiated the injectable-only overlapping buprenorphine starting protocol with a weekly 8-mg injection. Seventy-one patients (75%) completed the protocol by receiving a monthly long-acting buprenorphine injection, with 58 (61%) completing the protocol with 3 injections and 13 (14%) requiring at least 1 additional weekly 8-mg or 16-mg injection due to gaps in the injection series. Of the 71 individuals who received the first monthly injection, 67 (94%) received a monthly 300-mg injection, with 4 (6%) receiving a monthly 128-mg injection. Sixty-one patients received a second monthly long-acting buprenorphine injection, for a 2-month retention rate of 64% (61 of 95) for individuals who chose the protocol and 72% (61 of 85) for those who initiated the protocol (**Figure**).

Median (IQR) times between the medication pharmacy orders and the receipt of the initial weekly 8-mg injection as well as the first monthly injection for those who received it were 4 (1-7) days and 7 (4.5-14.5) days, respectively. Median (IQR) time between the initial weekly 8-mg injection and the first monthly injection was 2 (2-3) days.

Among all 95 individuals choosing the injectable-only buprenorphine starting protocol, housing status was not associated with receipt of a second monthly injection ($\chi^2_3 = 3.67$; $P = .30$). Compared with housed individuals other than those in permanent supportive housing, those living unsheltered (odds ratio [OR], 0.72; 95% CI, 0.22-2.36; $P = .59$), in temporary shelter (OR, 2.22; 95% CI, 0.63-8.31;

P = .22), and in permanent supportive housing (OR, 1.33; 95% CI, 0.39-4.65; *P* = .65) did not have significantly different odds of progressing to a second monthly buprenorphine injection.

Discussion

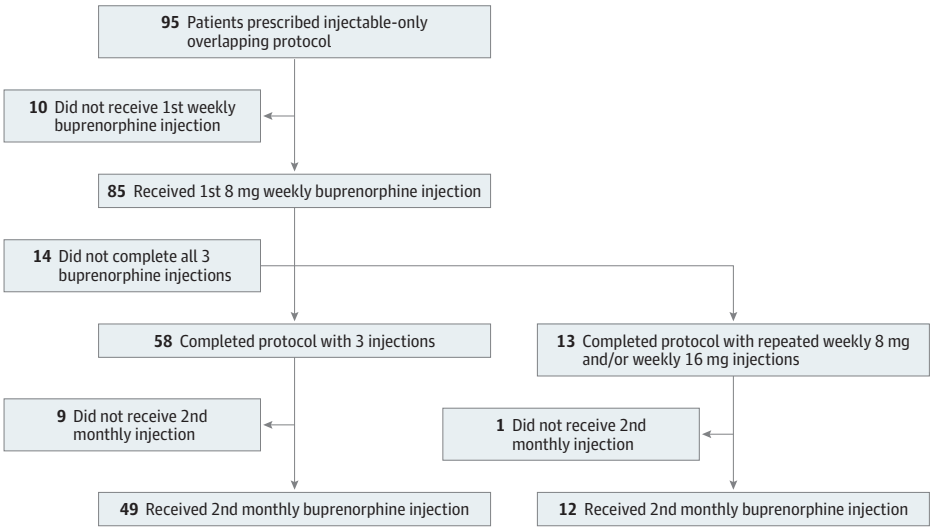
This novel injectable-only overlapping buprenorphine starting protocol is a promising alternative to existing methods for individuals, including those experiencing homelessness, with active fentanyl use who desire to start buprenorphine in an outpatient setting. With no need to stop fentanyl use before or during the protocol and using 3 serial buprenorphine injections, 64% of individuals for whom initial medications were ordered went on to receive a second monthly long-acting buprenorphine injection in this cohort.

Table 2. Patient Characteristics

Characteristic	Patients, No. (%) (N = 95)
Age, median (IQR), y	39 (23-69)
Gender identity	
Women	42 (44)
Men	52 (55)
Transgender or nonbinary	1 (1)
Race, self-identified	
American Indian or Alaska Native	6 (6)
Asian or Pacific Islander	5 (5)
Black	13 (14)
Middle Eastern or North African	2 (2)
White	48 (51)
Multiracial	5 (5)
Unknown	16 (17)
Housing status	
Unsheltered	25 (26)
Shelter	26 (27)
PSH	24 (25)
Non-PSH	20 (21)

Abbreviation: PSH, permanent supportive housing.

Figure. Cascade of Care for the Injectable-Only Overlapping Buprenorphine Starting Protocol



Our findings add to the sparse literature on rates of successful completion of existing and novel buprenorphine starting protocols outside of acute care settings for individuals using fentanyl. In the largest study of overlapping sublingual buprenorphine starts (also called low-dose initiations) in outpatient settings, 35% of individuals completed the protocol, with 22% retained at 28 days.[20] A smaller study of individuals mostly experiencing housing instability found a 37% buprenorphine retention rate at 30 days.[21] A recent scoping review on high-dose (withdrawal-first) buprenorphine starts found only 2 case studies, with a total 9 participants, that assessed this method for individuals using fentanyl in nonfacility outpatient settings, leaving uncertainty on success rates in such settings broadly.[22] Both overlapping sublingual (low-dose) and withdrawal-first (high-dose) starts have documented success in acute care settings, where process controls and supports are likely higher.[7,8,22]

In our cohort, 79% of individuals were experiencing homelessness or had a history of chronic homelessness (eg, those in permanent supportive housing). Prior to the emergence of widespread fentanyl, buprenorphine retention rates at 30 days for individuals experiencing housing instability were lower than the general population, with some studies reporting 37% to 45%.[23-25] Use of long-acting injectable buprenorphine in those experiencing homelessness has been associated with greater buprenorphine coverage compared with sublingual buprenorphine.[26] With a 75% eventual completion rate of this injectable-only buprenorphine starting protocol in our cohort and resulting in initiation of monthly long-acting buprenorphine injections, this starting method may be well suited for use in populations experiencing housing instability.

The injectable-only buprenorphine starting protocol builds on earlier work showing that a single weekly 24-mg dose without preceding buprenorphine given to patients with OUD in the emergency department carried a low risk (3.2%) of precipitated withdrawal for those with COWS scores of 4 to 7 and a higher risk (13.5%) for those with COWS scores of 0 to 3.[19]

Future studies should compare success rates across different buprenorphine initiation methods and identify factors in successful initiation, completion, and retention. Another area of future research is comparing variations of injectable-only protocols by using different numbers and doses of injections to assess if there are more optimal sequences of injections that maximize patient retention and minimize medication costs.

Limitations

Our study has several limitations. Participants engaged with members of the care team and, after that engagement, requested buprenorphine medications. Thus, the injectable-only buprenorphine starting protocol may not have similar success rates with non–treatment-seeking populations. Within the course of routine clinical care, there were no standardized assessments of the patient experience after each injection. We observed that many patients experienced mild withdrawal symptoms even after the initial 8-mg weekly injection, with patient-reported severe withdrawal occurring for some, particularly after the first monthly dose. Future research should describe the patient experience and quantify the prevalence and magnitude of patient-reported opioid withdrawal symptoms experienced during this protocol. Also, while most individuals received a monthly 300-mg, rather than 128-mg, dose, this selection may have been biased by greater patient familiarity with the brand name of the 300-mg dose and greater care team experience with using this product.

Several factors limit the generalizability of this study. The program that implemented this protocol provides pharmacy-dispensed, patient-labeled long-acting buprenorphine injections at a drop-in clinic and through field-based outreach, reaching shelters, encampments, and permanent supportive housing buildings. The low-threshold clinic and outreach-based care likely contributed to the high initiation and completion rates.[27] However, it remains unclear whether completion rates would be as high without the outreach-based component. Research assessing retention rates associated with implementation of this protocol within clinic-only settings, without an outreach component, would assist in clarifying the generalizability of this protocol to such settings. Furthermore, in our setting, the weekly and monthly injections were paid for by Medicaid insurance

without prior authorization. Implementation will likely be more difficult in settings with greater logistical or financial barriers to medication access.

Conclusions

In this retrospective cohort study of patients with moderate to severe OUD who used fentanyl and had high rates of homelessness, those who had medications ordered for an injectable-only overlapping buprenorphine starting protocol had a 75% eventual completion rate and 64% rate of receipt of the second monthly injection. These findings suggest that this protocol is a promising potential pathway for patients to start this lifesaving medication in the outpatient setting.

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Supervision: Waters, Hoog, Toland, Gerard, Klein.

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SUPPLEMENT.
Data Sharing Statement

Case Study

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Post-Overdose Extended-Release Buprenorphine Initiation Facilitated by a Partnership Between Emergency Medical Services and an Outpatient Substance Use Disorder Observation Unit

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Abstract

Background: People who experience a nonfatal opioid overdose and receive naloxone are at high risk of subsequent overdose death but experience gaps in access to medications for opioid use disorder. The immediate post-naloxone period offers an opportunity for buprenorphine initiation. Limited data indicate that buprenorphine administration by emergency medical services (EMS) after naloxone overdose reversal is safe and feasible. We describe a case in which a partnership between a low-barrier substance use disorder (SUD) observation unit and EMS allowed for buprenorphine initiation with extended-release injectable buprenorphine after naloxone overdose reversal.

Case: A man in his 40's with severe opioid use disorder and numerous prior opioid overdoses experienced overdose in the community. EMS was activated and he was successfully resuscitated with intranasal naloxone, administered by bystanders and EMS. He declined emergency department (ED) transport and consented to transport to a 24/7 SUD observation unit. The patient elected to start buprenorphine due to barriers attending opioid treatment programs daily. His largest barrier was unsheltered homelessness. His severe opioid withdrawal symptoms were successfully treated with 16/4 mg sublingual buprenorphine/naloxone and 300 mg extended-release injectable buprenorphine (XR-buprenorphine), without precipitated withdrawal. Two weeks later, he reported no interval fentanyl use.

Discussion: We describe the case of a patient successfully initiated onto XR-buprenorphine in the immediate post-naloxone period via a partnership between an outpatient low-barrier addiction programs and EMS. Such partnerships offer promise in expanding buprenorphine access and medication choice, particularly for the high-risk population of patients who decline ED transport.

Keywords

opioid overdose, opioid-related disorders, substance withdrawal syndrome, buprenorphine

Highlights

- Emergency medical services (EMS) buprenorphine administration for patients who experience opioid overdose reversed by naloxone is associated with buprenorphine treatment engagement.
- This case report describes a successful extended-release buprenorphine initiation in the post-naloxone period facilitated by a partnership between EMS and outpatient addiction program.
- Partnerships between EMS and outpatient addiction programs increase access for patients who decline emergency department transport and others who benefit from tailored addiction urgent care.

Introduction

Buprenorphine is 1 of 2 United States Food and Drug Administration-approved medications for opioid use disorder (MOUD) with evidence for opioid overdose death risk reduction. People who experience a nonfatal opioid overdose are at extraordinarily high risk of a subsequent fatal overdose and all-cause mortality. In the year after an emergency department (ED) visit for opioid overdose, more than 5% of people die and more than 19% experience another opioid overdose.[1,2] Furthermore, 20% of the fatalities that occur after an ED visit for nonfatal overdose occur within 30 days with a spike in the initial 48 hours.[3] Yet overdose survivors experience well-described gaps in access to MOUD.[4,5] Illicitly manufactured fentanyl has

also complicated buprenorphine initiation due to reports of longer required washout periods and more frequent buprenorphine-precipitated withdrawal.[6,7] Strategies that optimize care in the post-overdose period and facilitate buprenorphine initiation are urgently needed.

Naloxone is an opioid receptor antagonist that can treat opioid overdose by displacing opioids from μ-opioid receptors, resulting in reversal of respiratory depression. The immediate post-naloxone period offers a window of opportunity with lower risk of buprenorphine-precipitated withdrawal.[8] At least 2 case reports describe patients who have undergone elective naloxone administration to start buprenorphine.[8,9] Data from EDs, where therapeutic use of buprenorphine is increasingly common,[10] indicate that administration of buprenorphine after prehospital naloxone overdose reversal effectively treats opioid withdrawal symptoms.[11] In addition, a case series (n = 19) of extended-release injectable buprenorphine (XR-buprenorphine) initiation within 7 days of an ED visit for opioid overdose was associated with no precipitated withdrawal events and no subsequent overdose or death within 6 months.[12]

However, many patients who experience naloxone overdose reversal, including 36% during the COVID-19 pandemic, according to one study,[13] decline ED transport, for reasons including opioid withdrawal symptoms, low confidence in hospital care, and stigmatizing treatment by medical providers.[14] This group is at particularly high risk of subsequent overdose fatality.[13-17] Amid crisis rates of ED crowding,[18] there are also individual- and systems-level benefits to reducing ED visits after uncomplicated emergency medical services (EMS) overdose reversals. These factors have spurred interest in increasing access to buprenorphine via EMS to facilitate buprenorphine initiation and treat opioid withdrawal in the post-naloxone period.[19,20]

Post-naloxone EMS-administered buprenorphine has been found to be feasible, safe, and associated with a higher likelihood of subsequent opioid use disorder (OUD) treatment. A California program trained paramedics to administer 16 to 24 mg of sublingual (SL) buprenorphine for naloxone-precipitated or other opioid withdrawal symptoms after on-call physician consultation.[21] Among 36 patients treated with buprenorphine in the first year, 50% were retained in treatment at 7 days and 36% at 30 days.

A healthcare system in New Jersey evaluated the impact of EMS-administered SL buprenorphine (16-24 mg) after naloxone reversal on withdrawal symptoms, care retention, and subsequent opioid overdose.[19] Those cared for by a buprenorphine-equipped ambulance experienced a two-thirds reduction in opioid withdrawal symptoms, and those who received buprenorphine were 6 times more likely to engage in OUD treatment at 30 days. However, reductions in subsequent opioid overdose were not observed in the following 24 hours or 7 days.

Low-barrier addiction care settings are accessible, provide same-day treatment, incorporate principles of harm reduction, and offer flexibility[22]; as such, they are well-positioned to partner with EMS to deliver rapid post-naloxone buprenorphine induction during their hours of operation or to provide aftercare for patients who have received post-naloxone EMS-administered buprenorphine. These settings can also offer on-demand access to XR-buprenorphine, which provides MOUD coverage of the critical 30-day post-overdose period in a single administration.

The Roundhouse Stabilization Care Center, operated by Boston Medical Center, was a 24/7 outpatient substance use disorder (SUD) observation and urgent care center (hereafter, the "SUD observation unit") in Boston, MA, offering walk-in access to care including MOUD; withdrawal management; management of over-intoxication; post-overdose observation; wound care; infection screening, treatment, and prevention services; behavioral health evaluation; and harm reduction services.[23] This SUD observation unit partnered with Boston EMS to develop a protocol to allow specific patients, including those post-opioid overdose, to elect ambulance transport to the SUD observation unit instead of transport to the ED or no transport (Table 1).

We describe the case of a patient who experienced opioid overdose in the community, was resuscitated with 12 mg intranasal naloxone, and elected EMS transport to the SUD observation unit. His acute withdrawal symptoms were successfully treated with SL buprenorphine/naloxone and XR-buprenorphine. The patient provided written informed consent for case publication.

Case

A man in his 40s experiencing homelessness with a history of methamphetamine use disorder, benzodiazepine use disorder, and OUD complicated by prior overdoses

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Table 1. Clinical Eligibility for EMS Transport to SUD Observation Unit.

	Y	N
General eligibility (must meet all)		
Not suffering from an acute emergency	☐	
Age ≥18	☐	
Able to communicate	☐	
Able to consent	☐	
Most recent vital signs (must meet all)		
SpO2 ≥92%	☐	
HR 50-120 bpm	☐	
SBP >100	☐	
Clinical contraindications (must have none)		
Reporting chest pain, shortness of breath, or syncope		☐
Pregnant >20 weeks		☐
Suicidal, homicidal, exhibiting violent behavior, or restrained		☐
Actively seizing		☐
Evidence of acute trauma or fracture		☐
Ineligible to return to SUD observation unit		☐

Abbreviations: EMS, emergency medical services; SUD, substance use disorder; SpO2, oxygen saturation; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure.

struggled with ongoing fentanyl use on up to 120 mg daily methadone in opioid treatment programs (OTP). Over the course of 7 months, he attended numerous inpatient medically-managed withdrawal programs. Each time, he returned to fentanyl use after discharge to the community. He attributed ongoing use to difficulty attending the OTP daily while experiencing unsheltered homelessness and frequent benzodiazepine intoxication.

The patient experienced opioid overdose in a fast-food establishment and was treated with 8 mg intranasal naloxone, transported to the ED, and referred again to an inpatient medically-managed withdrawal program. For 7 days, his withdrawal symptoms were treated with methadone, including 15 mg methadone on day of discharge. Due to the subtherapeutic dose, he returned to use that day and experienced opioid overdose after injecting 0.5 mg fentanyl. EMS was activated. He received a total of 12 mg intranasal naloxone from a combination of bystander and then EMS administration, with return of spontaneous respirations and clear mentation. He consented to transport to the SUD observation unit.

On arrival, he reported severe opioid withdrawal symptoms including nausea, vomiting, headache, and abdominal pain (Table 2). Triage vital signs were blood pressure 140/76, heart rate 102, oxygen saturation 97%, and respiratory rate 16. An initial Clinical Opioid Withdrawal Scale (COWS) score was not recorded due to symptom severity. Acetaminophen, clonidine, dicyclomine, and hydroxyzine and later lorazepam were administered to reduce symptoms and allow clarification of MOUD goals.

Given his difficulties stabilizing on methadone, the patient was interested in a trial of buprenorphine and motivated for XR-buprenorphine to mitigate medication storage and adherence challenges. He received 16/4 mg SL buprenorphine/naloxone with improvement in symptoms followed by 300 mg XR-buprenorphine administered subcutaneously. He tolerated the injection well and was monitored overnight, with no recurrence of opioid withdrawal symptoms. He was discharged with a prescription for SL buprenorphine/naloxone 8/2 mg with instructions to take up to 16 mg daily as needed for opioid withdrawal or cravings, since the full effect of XR-buprenorphine may take days-to-weeks following the initial injection.[24] The following evening, he returned to the SUD observation unit with a COWS score of 9, treated with 8/2 mg SL buprenorphine/naloxone from his own prescription. He required an additional 8/2 mg that evening.

One week later, he reported no interval fentanyl use. He endorsed readiness to address his benzodiazepine use disorder and was transported to an inpatient medically-managed withdrawal program for benzodiazepine withdrawal. Two weeks after his initial XR-buprenorphine injection, he continued to report no return to opioid use and high satisfaction with his buprenorphine initiation. Twenty-six days after his first buprenorphine injection, he received a second dose of 300 mg XR-buprenorphine. Thirty-three days after his second injection, he returned, reporting no interval fentanyl use and resolution of cravings. He had obtained housing in another city. He received a third dose of XR-buprenorphine, 100 mg. He did not return for his scheduled fourth dose of XR-buprenorphine. He returned to an affiliated program 4 months later reporting a return to fentanyl use and was prescribed buprenorphine.

Discussion

The period immediately after opioid overdose reversal with naloxone offers a critical window of opportunity for buprenorphine initiation. However, many patients decline transport to the ED, necessitating novel pathways for buprenorphine administration in the community. We describe a case in which a partnership between a low-barrier SUD observation unit and EMS allowed for buprenorphine initiation with XR-buprenorphine on the same day as a naloxone-reversed opioid overdose.

Although XR-buprenorphine for OUD treatment was initially studied in patients who had been therapeutic on SL buprenorphine for 7 days, more rapid transition from SL to XR formulations has been described[24] and is common in our practice. Our case of same-day post-naloxone XR-buprenorphine initiation builds on prior work evaluating XR-buprenorphine initiation within 7 days of opioid overdose and XR-buprenorphine administration on the

Table 2. Timeline of Post-Overdose Extended-Release Buprenorphine Initiation.

Day	Time*	Event	Vitals	Medication
0	Unknown	• Received final dose of methadone at inpatient medically-managed withdrawal program		Methadone 15 mg PO
0	Unknown	• Discharged from inpatient medically-managed withdrawal program		
0	Unknown	• Used 0.5 mg IV fentanyl • Opioid overdose		
0	Unknown	• Bystanders responded and activated EMS • Received a total of 12 mg IN naloxone • Spontaneous respirations and clear mentation returned • Declined ED transport • Consented to transport to SUD observation unit		Naloxone, total of 12 mg IN
0	1315	• Arrived at SUD observation unit • Symptoms: nausea, vomiting, headache, and abdominal pain^ • Undecided on preferred MOUD	BP 140/76 HR 102 SpO2 97% RR 16	
0	1358	• Symptom-directed medications administered		Acetaminophen 650 mg PO Clonidine 0.1 mg PO Dicyclomine 20 mg PO
0	1500	• GI symptoms improved but not resolved, anxious • Further discussion of post-naloxone buprenorphine	BP 127/65 HR 83 SpO2 96%	
0	1528	• Symptom-directed medication administered • Patient requesting buprenorphine		Lorazepam 2 mg PO
0	1629	• SL buprenorphine administered, tolerated well		Buprenorphine/naloxone 16/4 mg SL
0	1713	• Symptoms improving • Subcutaneous buprenorphine administered		Buprenorphine 300 mg SQ
0	1900	• Symptoms resolved		
0	2000	• Vitals check	BP 108/57 HR 85 SpO2 97% RR 16	

Abbreviations: PO, by mouth; IV, intravenous; EMS, emergency medical services; IN, intranasal; ED, emergency department; SUD, substance use disorder; BP, blood pressure; HR, heart rate; SpO2, oxygen saturation; RR, respiratory rate; MOUD, medication for opioid use disorder; SL, sublingual; SQ, subcutaneous.
*Time stamps are specific to medication administration or vital signs; other contemporaneous care summarized in event column; ^Due to acuity of presentation, a Clinical Opioid Withdrawal (COWS) score was not formally evaluated.

first day of a planned buprenorphine induction. Although clear therapeutic benefits of the extended-release injectable compared to the SL formulations of buprenorphine have not yet been established in general OUD treatment populations, a same-day XR-buprenorphine initiation after opioid overdose reversal may offer advantages, particularly for patients experiencing homelessness and others with medication storage and adherence barriers.[25]

Indeed, the Camden NJ team who utilized SL buprenorphine did not observe a decrease in opioid overdose in the week following index overdose and buprenorphine initiation, when treatment retention was 50%. Same-day XR-buprenorphine—which delivers 30 days of buprenorphine—may be more effective than SL buprenorphine in preventing subsequent opioid overdose in the very high-risk post-overdose period. This warrants further study.

The potential role of XR-buprenorphine also highlights the importance of partnerships between EMS and non-ED addiction care settings. Low-barrier outpatient programs often have the resources to manage prior authorization, medication storage, and medication administration protocols that present challenges on ambulances and in EDs. Furthermore, low-barrier addiction care programs are acceptable[26] to patients who have experienced stigma in other settings,[27,28] and may thus overcome stigma-related barriers to ED transport. While ED buprenorphine initiation remains a critical pathway, non-ED settings offer an important alternative for appropriate patients. Boston EMS applied for and received a waiver from the Massachusetts Department of Public Health[29] allowing transport of patients whose primary problem appears to be substance-induced directly to the SUD observation unit if they are otherwise medically stable. This case illustrates the type of rapid, tailored SUD care that patients can receive under these circumstances and suggests that transport to a non-ED addiction care setting may be optimal for many patients.

While SUD observation units may not be available in many regions, the care involved could be readily delivered in other, more prevalent outpatient addiction settings such as bridge clinics, allowing the model to be scaled.[30] After the July 2023 closure of the SUD observation unit, our bridge clinic set up a similar partnership with Boston EMS.

Notably, our patient was successfully initiated on buprenorphine after naloxone administration in the context of significant recent methadone exposure, though his dose of 15 mg on the day of his overdose was relatively low. This contrasts with the California and New Jersey protocols, which excluded patients recently on methadone. We discussed the risks of buprenorphine-precipitated withdrawal with the patient; however, naloxone effectively displaces methadone as well as fentanyl from opioid receptors and his initiation was uncomplicated.

Overall, we describe a case of successful buprenorphine initiation with SL and XR-buprenorphine in the immediate post-naloxone reversal period facilitated by a partnership between an outpatient, low-barrier addiction program and EMS. This case report builds on prior work on EMS buprenorphine administration for patients who experience opioid overdose and XR-buprenorphine on the same day as buprenorphine initiation. Similar partnerships between outpatient addiction programs and EMS have the potential to increase access for patients with opioid overdose who decline ED transport and offer a tailored care setting for those at very high risk of subsequent opioid overdose.

Author's Note

Paige Colicchio is now affiliated with Mount Sinai West, New York, NY, USA. Jacqueline Gott is now affiliated with the Dimock Center, Boston, MA, USA.

Author Contributions

JLT, JG, PC, and MSK were involved in the clinical care of the patient. JG obtained written informed consent from the patient. JLT drafted the initial manuscript. All authors contributed to the writing of the manuscript, provided critical feedback to the manuscript, and approved the final manuscript draft for submission.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Compliance, Ethical Standards, and Ethical Approval

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Addiction Science & Clinical Practice

STUDY PROTOCOL

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Rapid intravenous symptom-inhibiting fentanyl induction (SIFI) to optimize rotation onto oral opioid agonist therapy among individuals who use unregulated fentanyl: protocol for an open-label, single arm clinical trial

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Abstract

Background Most opioid use disorder (OUD) treatment guidelines target community medical settings, and the subsequent recommendations were established to prioritize safety and reduce diversion prior to the fentanyl era. For people with OUD who use unregulated fentanyl, slow induction onto opioid agonist therapy (OAT) with gradual dose titration is often ineffective or insufficient for reducing withdrawal symptoms and cravings, thereby hampering engagement and retention in treatment. Given the severe risks associated with continued use of the increasingly toxic unregulated drug supply, new and innovative approaches to the management of OUD are urgently needed. We have developed an alternative induction protocol, using a rapid intravenous symptom-inhibiting fentanyl induction (SIFI) to optimize rotation onto oral OAT.

Methods An open-label, single arm, prospective pilot clinical trial is being conducted in an outpatient setting to assess the safety, feasibility, and efficacy of a rapid symptom-inhibiting intravenous fentanyl induction protocol to establish starting doses of methadone or sustained-release oral morphine (SROM) based on individual opioid requirements, as a treatment strategy for individuals with OUD who use unregulated fentanyl. The primary outcome is safety, as defined by occurrence of study drug-related adverse events (including but not limited to opioid toxicity and QT interval prolongation) that require intervention during induction and the first 7 days on OAT. Secondary objectives are to determine whether the SIFI protocol will result in use of higher-than-standard starting doses of methadone and SROM, and to determine whether implementation of this protocol will be acceptable to participants and will result in reduced withdrawal symptoms, improved retention, and better long-term outcomes on OAT.

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Discussion This is the first study to rapidly and objectively estimate opioid tolerance and use it to calculate individualized starting doses of oral OAT in an outpatient setting among people who use unregulated fentanyl. We predict that starting methadone or SROM with individually-tailored doses will lead to therapeutic target concentrations being achieved quickly, safely, and with good patient satisfaction. This approach has the potential to more effectively and safely initiate OAT, to minimize opioid withdrawal and cravings, and in turn to decrease unregulated fentanyl use and increase retention on life-saving OAT.

Trial registration ClinicalTrials.gov, NCT05905367; date of registration: June 15, 2023; latest update posted July 18, 2024. https://clinicaltrials.gov/study/NCT05905367

Protocol version: 4.0, April 22, 2024.

Keywords Fentanyl, Methadone, Opioid use disorder, Opioid substitution treatment

Background

Canada is facing an escalating epidemic of unregulated drug overdoses, with fatalities in unprecedented numbers. More than 42,000 opioid toxicity deaths occurred in Canada between January 2016 and September 2023 [1]. The province of British Columbia (BC) is the most severely affected, with an annual rate of 45.3 opioid toxicity deaths per 100,000 population compared with the Canadian average of 19.4 per 100,000 population in 2022 [1].

The major driver of the ongoing crisis of drug overdoses and deaths is the increasing toxicity of the unregulated drug supply, fueled by fentanyl and its analogues. Fentanyl, a potent opioid agonist, was developed in the 1950 s to fill a need for strong and rapid analgesia. Because of these characteristics, fentanyl is commonly used to treat chronic cancer pain or in anesthesia [2]. Initially present as an adulterant in unregulated drugs, especially heroin, fentanyl is now the substance of choice for many people with opioid use disorder (OUD) [3].

The harms associated with fentanyl use are related to its high potency and short duration of action, leading to very frequent use, severe cravings, and more difficult to manage withdrawal symptoms [2, 4, 5]. Fentanyl was involved in 82% of Canadian opioid toxicity deaths in 2023 [1]. In BC, fentanyl was detected (alone or in combination with other drugs) in 86% of unregulated drug toxicity deaths in 2021, a striking increase from 5% in 2012 [6].

Opioid agonist therapy (OAT) has been shown to be safe and effective for the treatment of OUD. When prescribed in therapeutic doses, OAT decreases morbidity and mortality due to overdose and other OUD-related harms including serious acute and chronic infections including human immunodeficiency virus (HIV) and hepatitis C [7]. However, the shift to fentanyl in the unregulated drug supply has significantly complicated the management of OUD. People who use fentanyl experience severe withdrawal symptoms, often compromising OAT initiation, retention and adherence [4, 8].

Effective OAT doses are highly variable, depending on a number of factors, including the individual's opioid tolerance and interindividual variability in pharmacokinetics [9]. Unfortunately, assessment of opioid tolerance is challenging, and is typically subjective, relying on the patient's self-report of the amount and frequency of their opioid use, and is further complicated by the unpredictability of the unregulated drug supply [4]. Unknown opioid tolerance increases the risk of opioid overdose with OAT, and sequential administration of methadone without reaching steady state may cause "dose stacking" and the potential for dose accumulation [10]. In view of these risks, current North American OUD treatment guidelines (developed when heroin was the dominant opioid in the unregulated market) take a cautious approach, recommending low starting doses and slow, gradual dose increases [7, 11]. The British Columbia Centre on Substance Use (BCCSU) and Ontario's Mentoring, Education, and Clinical Tools for Addiction: Partners in Health Integration (META:PHI) initiative have updated their guidance to reflect the changing unregulated drug market, providing recommendations for more rapid, albeit still conservative methadone initiation and titration [10, 12].

However, as previously noted, fentanyl is highly potent and is being used in large doses. As a result, currently recommended oral OAT induction protocols provide an inadequate speed of OAT titration for a large proportion of individuals with OUD who use unregulated fentanyl. Prescribing OAT according to current recommendations is frequently associated with persistence of severe and recurrent cravings and withdrawal symptoms over the weeks to months before therapeutic target levels of OAT can be reached, with ongoing unregulated substance use during the lengthy titration period [4, 8]. Indeed, a recent analysis of BC health administrative datasets including more than 55,000 people with OUD showed that, while OAT engagement and retention were protective against hospitalization and death, methadone initiation in compliance with current clinical guidelines was associated

with increased risk of death or hospitalization within the first 6 months [13]. Even maximum recommended OAT doses are often inadequate to meet the opioid requirements of people who use fentanyl, leading to poor retention in OAT programs and continued use of unregulated drugs, with their attendant risks of overdose and death, even among those who remain on OAT [4, 13, 14].

In an attempt to address this issue in the context of managing hospitalized individuals who use fentanyl, we pioneered a novel alternative induction protocol using a rapid intravenous symptom-inhibiting fentanyl induction (SIFI) for objectively determining opioid tolerance using medically-administered intravenous (IV) fentanyl [3]. Implementation of the SIFI protocol in hospitalized patients with OUD has proven feasible, safe, and effective in meeting the patients' opioid requirements, and thereby effectively managing opioid withdrawal and averting patient-initiated discharge from hospital against medical advice. Herein we propose to conduct the first evaluation of the safety, efficacy, and acceptability of the SIFI protocol in an outpatient setting.

To this end, we will implement and evaluate our rapid IV fentanyl induction protocol among patients who use fentanyl and who are receiving services at Hope to Health, a community primary care clinic located in the Downtown Eastside neighborhood of Vancouver, the epicenter of the unregulated drug use epidemic in Canada.

In brief, we will use each individual's calculated opioid tolerance to guide their transition onto OAT with oral methadone or sustained-release oral morphine (SROM), with the choice of agent based on a shared decision-making process between the patient and their clinician. Methadone or SROM starting doses will be individualized based on an objective assessment of the patient's opioid requirements (with defined upper dose limits in the interests of safety), thus achieving therapeutic target levels more quickly than with standard OAT dosing according to current OUD treatment guidelines. We anticipate that opioid withdrawal and cravings will thus be more effectively managed, leading in turn to improved acceptability and retention on OAT.

Study design

Overview of study design

To assess the safety, feasibility, and efficacy of a rapid symptom-inhibiting IV fentanyl induction (SIFI) protocol, we plan to conduct an open-label, single arm, prospective clinical trial with a planned sample size of 50. The primary goal of this pilot study is to identify unforeseen problems with the SIFI procedures that would impact participant safety. If such a problem exists with a prevalence of 5% (i.e. potential to affect 1 out of 20 participants), it will be identified with 92% confidence in a pilot study including 50 participants [15].

Results of this pilot study will be used to inform a subsequent larger and more comprehensive investigation of the SIFI protocol as a treatment strategy for individuals with OUD who intentionally use unregulated fentanyl.

Study objectives

The primary objective is to assess the safety and feasibility of an outpatient SIFI protocol for determining individualized starting doses of oral OAT with methadone or SROM. Safety will be assessed in the first instance by a descriptive analysis of adverse events (e.g. sedation, respiratory depression, hypoxia, QT prolongation) requiring intervention during the induction/maintenance period (study days 1 through 7).

Secondary outcomes include starting OAT doses, participant satisfaction, and presence of withdrawal symptoms, OAT retention, overdose, hospitalization, and death at 1 and 3 months. Longer term impact of the strategy will be assessed at 6 and 12 months post-induction. Secondary outcomes will be reported using descriptive and summary statistics. Participants' responses to the treatment satisfaction questions will be reported qualitatively, and used to refine the SIFI procedure for future investigation.

Study setting

The opioid overdose crisis has disproportionately affected under-served communities, including those with low socioeconomic status and complex medical and mental health issues. This study will be conducted at the Hope to Health Research and Innovation Complex in Vancouver's Downtown Eastside (DTES), a neighborhood of approximately 18,000 residents with high rates of poverty, homelessness, mental illness, and drug use [16]. Residents of the DTES are disproportionately impacted by the ongoing opioid overdose crisis: in 2023, the rate of overdose deaths per 100,000 population in the DTES was 560.9, which was ten times higher than in the rest of the city of Vancouver (56.7) or in the province of BC as a whole (46.5) [17].

Hope to Health is an integrated facility that includes a low-barrier interdisciplinary Primary Care Clinic which currently supports 2800 active clients, and a co-located Supervised Consumption Site. The Supervised Consumption Site handles approximately 1000 visits per month, of which 90% involve use of opioids with or without other substances. This is a nurse- and peer-led service offering safe spaces to use unregulated or prescribed substances, as well as distributing harm reduction supplies and offering nursing care and referrals to the Primary Care Clinic or other services, as needed. Both the Primary Care

Clinic and the Supervised Consumption Site support a safer drug supply program that offers clients the possibility of replacing their unregulated drug supply with prescribed pharmaceutical grade alternatives, including hydromorphone tablets or fentanyl patches.

Recruitment

Study participants will be recruited from the Hope to Health Primary Care Clinic and the adjacent Supervised Consumption Site. The planned sample size of 50 should be feasible based on the number of clients who are currently registered in the Hope to Health Primary Care Clinic who have a diagnosis of OUD and who do not have an active OAT prescription or who are receiving a suboptimal OAT dose (based on their continued use of unregulated fentanyl). In addition, the clinic continues to register new clients from the DTES population where OUD and fentanyl use are highly prevalent, including referrals from the adjoining Supervised Consumption Site where over 90% of visits involve use of opioids with or without other substances.

The clinic medical team will identify clients who are potential candidates for OAT, based on a diagnosis of OUD, ongoing active use of unregulated street drugs, and the client's goal to decrease their opioid use. With the client's approval, the clinic team member will introduce the client to the study coordinator, who will explain the study and seek their informed consent to participate. Written informed consent will be obtained from each prospective participant prior to their undergoing any study-related procedures. A research team member who is not directly involved in the client's care will review and explain the study protocol and informed consent form with the prospective participant. It will be made clear that their participation is voluntary and that they are free to choose not to participate, or to withdraw from the study at any time, without affecting their access to clinic services or the quality care they receive at the Hope to Health Primary Care Clinic. The study procedures and reasonably foreseeable risks and potential benefits will be explained in detail. After the client has had adequate time to read the REB-approved consent form (or have it read and explained to them) and has had any questions answered to their satisfaction, if they agree to participate they will sign the consent form in a private office in the presence of the person who discussed the study with them.

After informed consent has been obtained and screening evaluations (Table 1) have been completed, research staff will review the inclusion/exclusion criteria and determine the potential participant's eligibility for the study.

Study population

Inclusion criteria

- Age 19 years or older
- OUD of any severity by DSM-5 Clinical Diagnostic criteria [18]
- Intentional use of unregulated fentanyl by any route (e.g. injection, inhalation) by participant self-report

Table 1 Schedule of assessments during screening and IV fentanyl induction phase on Day 1

	Screening	Day 1 before start of induction	5 min after each IV fentanyl dose	5, 10, and 15 min after last IV fentanyl dose
Informed consent	x			
Medical history	x			
Medication review	x			
UDT	x			
Pregnancy test[a]	x	(x)[b]		
Height, weight		x		
Record time of last opioid use		x		
ECG		x		
POSS		x	x	x
COWS		x	x	
HR, BP, RR, SpO2		x	x	x
Participant-readiness threshold		x		
MSQ for OUD meds	x	(x)[b]		

IV intravenous, *UDT* urine drug test, *ECG* electrocardiogram, *POSS* Pasero opioid-induced sedation scale, *COWS* clinical opiate withdrawal scale, *HR* heart rate, *BP* blood pressure, *RR* respiratory rate, *SpO2* oxygen saturation, *MSQ* Medication Satisfaction Questionnaire, *OUD* opioid use disorder

[a] For individuals of child-bearing potential

[b] If screening and baseline not on same day

- Urine drug test (UDT) positive for fentanyl at screening or within 7 days prior to date of screening visit, to confirm the presence of fentanyl
- Clinical indication to start OAT with methadone or SROM, or recently started OAT and receiving daily doses of methadone ≤ 150 mg or SROM ≤ 1300 mg (demonstrated to be subtherapeutic for the individual as they are continuing to use unregulated fentanyl)
- If taking prescribed opioids for safer supply, willing to discontinue them starting on study Day 1 and for at least the first 7 days of the study
- Willing and able to provide written informed consent for study participation

Exclusion criteria

- Individuals who are pregnant or breast-feeding
- Currently receiving prescribed fentanyl in any form, e.g. fentanyl patch
- Previous participation in this study (previous receipt of SIFI in an in-hospital clinical setting is not exclusionary)
- Current use of buprenorphine extended-release (Sublocade®) in any dose
- Use of buprenorphine-naloxone (Suboxone®) within the previous 3 days

Potential participants will not be excluded based on presence of substances other than fentanyl in the screening UDT, nor on the basis of alcohol use disorder or any other substance use disorder. The intent is to make the protocol applicable in a real-world setting where the majority of individuals who have OUD use multiple other substances in addition to opioids.

Study treatment

Induction phase

Once the participant has provided informed consent and is found to be eligible based on results of the screening assessments (Table 1), the participant-readiness threshold will be used to determine the appropriate time to start the induction procedure according to the participant's level of cravings (Fig. 1)[19].

When the participant reaches their readiness threshold, fentanyl 400 mcg will be administered intravenously (IV) by a study nurse or physician, with repeat doses every 5 min following assessment of sedation, withdrawal symptoms, and vital signs (Table 1) until the participant indicates comfort or has a Pasero Opioid-induced Sedation Scale (POSS) score of 2 (slightly drowsy, easily roused) [20]. After initial dosing with fentanyl 400 mcg per dose, stepwise increases to 800 mcg, 1000 mcg, and 1200 mcg per dose will be considered once tolerance and safety are established at each dose level. Sedation and vital signs will be reassessed at 5, 10, and 15 min after the final IV fentanyl dose, or until stable.

The total amount of fentanyl administered during the induction phase is the loading dose, to be used in the calculation of the individualized starting dose of methadone or SROM (Figs. 2 and 3)[21, 22].

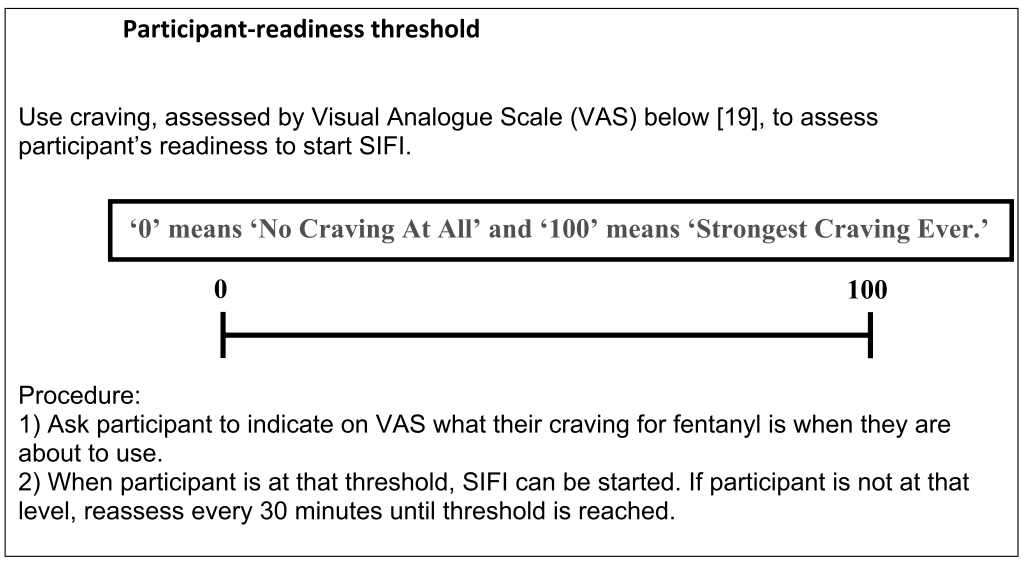

Fig. 1 Participant-readiness threshold

Conversion from Opioid Tolerance to Oral Methadone starting dose for OAT

Total cumulative dose of IV fentanyl administered during the induction phase = the loading dose

100% of the loading dose of fentanyl (in mg) x 8 = a proxy for opioid tolerance (OT) over 24 hours

$$\text{OT in mg} \times 100 = \text{"X" IV morphine equivalents (ME)}$$

$$\text{"X" IV morphine equivalents} \times 2 = \text{"2X" mg oral morphine equivalents (OME)}$$

$$\frac{\text{"2X" mg OME}}{\text{CR}} = \text{"A" mg Oral Methadone}$$

CR= the conversion ratio from OME to oral methadone, which depends on the fentanyl dose. The following table will be used to determine the CR [21]:

Daily OME (mg)	Conversion ratio from oral morphine: oral methadone
30-100	3:1
101-300	5:1
301-600	10:1
601-800	12:1
801-1000	15:1
>1000	20:1

$$\downarrow 30\% \text{ for incomplete cross tolerance: A} \times 0.7 \approx \text{"B" mg Oral Methadone}$$

The maximum total daily dose of methadone to be administered in the protocol will be 200 mg; i.e. if B >=200mg, the participant will receive methadone 200 mg daily.

Fig. 2 Conversion from Opioid Tolerance to Oral Methadone starting dose for OAT

The participant will remain under observation in the clinic while awaiting their first on-study dose of oral OAT.

Early OAT phase

The specific OAT agent will be chosen prior to study enrolment by the clinic medical team in conjunction with the participant. To determine the first post-induction dose of OAT, the loading dose of fentanyl will be multiplied by 8 and used as a proxy for the participant's opioid tolerance over 24 h. The multiplier of 8 in this calculation is based in part on anecdotal patterns of unregulated opioid use from the investigators' experience—approximately 8 times per day. Since the protocol assessment of opioid tolerance reflects a single use, the multiplier of × 8 estimates total daily use. In addition, this approach aligns with the known duration of analgesia and respiratory depression from IV fentanyl boluses, which potentially last 1.5 to 4 h [23]. The calculated opioid tolerance will then be converted to the starting dose for methadone or SROM (Figs. 2 and 3), up to a maximum daily dose of 200 mg or 2000 mg, respectively. From the investigators' clinical experience utilizing the SIFI protocol in an inpatient setting, participants are generally comfortable for approximately 1–3 h following induction [3], allowing adequate time for calculation, preparation, and dispensing of the individualized starting dose of OAT.

Conversion from Opioid Tolerance to Sustained-release Oral Morphine (SROM) starting dose for OAT

Total cumulative dose of IV fentanyl administered during the induction phase = the loading dose

100% of the loading dose of fentanyl (in mg) x 8 = a proxy for opioid tolerance (OT) over 24 hours

OT in mg × 100 = "X" IV morphine equivalents (ME)

"X" IV morphine equivalents × 2
= "2X" mg oral morphine equivalents (OME) = "C" mg SROM

↓30% for incomplete cross tolerance: C x 0.7 ~ "D" mg SROM

The maximum total daily dose of SROM to be administered in the protocol will be 2000 mg; i.e. if D >=2000mg, the participant will receive SROM 2000 mg daily.

For participants with known chronic kidney disease and estimated glomerular filtration rate (eGFR) between 15 and 60 mL/min, SROM doses ("C") will be adjusted according to current recommendations [22]; if eGFR<15 mL/min, the participant will not be eligible to receive SROM.

Fig. 3 Conversion from Opioid Tolerance to Sustained-release Oral Morphine (SROM) starting dose for OAT

The first on-study oral OAT dose will be administered on the same day as the induction procedure and at least 15 min after the final IV fentanyl dose. On Day 1, participants will receive a maximum total methadone dose of 200 mg or a maximum total SROM dose of 2000 mg, adjusting for any previously prescribed methadone or SROM they received on Day 1 prior to arrival at the clinic. After the post-induction OAT dose is administered, the participant will remain in the clinic for 3 h under observation for ongoing monitoring of safety and vital signs (Table 2), and will receive a cash honorarium for their participation and for the time spent at the clinic. Thereafter, the participant will be offered honoraria for attendance at daily study visits for 7 days for assessment and OAT dispensing (Table 2). If the participant is found to be over sedated (POSS 3 or 4), reports sleeping more than usual, or exhibits any other signs or symptoms of excessive opioid levels, they will be referred to the clinical team for immediate assessment and management, including adjustment of OAT dose if deemed clinically necessary.

Methadone recipients who have QT prolongation at their follow-up ECG on Day 3 or Day 7 will be referred to the clinic team for assessment and management. For participants with a stable QTc and without evidence of opioid toxicity, methadone will be maintained at the same dose for the first 7 days.

For participants receiving SROM who meet all the following criteria, SROM doses may be increased by 100 mg every 24 to 48 h as clinically indicated, consistent with current local clinical guidelines [12].

- Presence of cravings and/or withdrawal symptoms
- No evidence of opioid toxicity (e.g. excessive sedation/lethargy, respiratory depression, bradycardia)
- No evidence of SROM adverse events (e.g. constipation, nausea, vomiting, dyspepsia, abdominal pain, urinary retention, headache, dizziness, hypotension, diaphoresis, xerostomia, dental pain, dysphoria, insomnia) [24]

Table 2 Schedule of assessments during early OAT phase (Day 1 through Day 7)

	Before first OAT dose	1 h after first dose	2 h after first dose	3 h after first dose	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
HR, BP, RR, SpO2	x	x	x	x	x	x	x	x	x	x
POSS	x	x	x	x	x	x	x	x	x	x
COWS	x	x	x	x	x	x	x	x	x	x
Self-reported activity during previous 24 h					x	x	x	x	x	x
ECG	X[a]					X[b]				X[b]
MSQ for OUD meds	X[c]									x
MSQ + 3 questions re: SIFI				x						
Self-reported use of illicit opioids/other substances										x
UDT	X[c]									x
Overdose events req. intervention										x
Hospitalizations/death										x

OAT opioid agonist therapy, *UDT* urine drug test, *ECG* electrocardiogram, *POSS* Pasero opioid-induced sedation scale, *COWS* clinical opiate withdrawal scale, *HR* heart rate, *BP* blood pressure, *RR* respiratory rate, *SpO2* oxygen saturation, *MSQ* Medication Satisfaction Questionnaire, *SIFI* symptom-inhibiting fentanyl induction, *OUD* opioid use disorder

[a] For all participants, before start of IV fentanyl induction

[b] Only for participants receiving methadone

[c] At study screening

The magnitude of the SROM dose increase will be based on clinical judgement, taking into account the starting dose and severity of ongoing cravings or withdrawal symptoms.

OAT follow-up phase

After the first 7 days, OAT will be prescribed at intervals and doses adjusted as indicated according to the standard clinic protocols, and dispensed by a community pharmacy of the participant's choosing.

Participants will be asked to refrain from using prescribed opioids for safer supply during the first 7 days of the study, but thereafter concomitant care and interventions will be provided as clinically indicated.

Outcomes and assessments

Timeline of assessments

Tables 1, 2, 3

Primary outcome

The primary outcome of this study is safety, as defined by occurrence of study drug-related adverse events (including but not limited to sedation, respiratory depression, hypoxia, QT interval prolongation) requiring intervention during the induction and early OAT phases (study days 1 through 7).

The participant's level of sedation (POSS) and vital signs (heart rate and oxygen saturation by pulse oximetry, blood pressure, and respiratory rate) will be monitored before starting induction, throughout the induction phase, at 5, 10, and 15 min (or until stable) after the final IV fentanyl dose, before the starting dose of OAT is administered, and hourly during the initial 3 h following oral OAT administration. In addition, sedation and vital signs will be assessed once daily for the first 7 days after the initial OAT dose, and during OAT follow-up at 1 month, 3 months, 6 months, and 12 months (Table 3).

In case of suspected opioid overdose (excessive sedation [POSS 3 or 4], respiratory rate below 8 breaths per minute, oxygen saturation below 92% or the participant's baseline, and/or other signs or symptoms) at any time during the induction or OAT phases or during OAT follow-up, no further IV fentanyl doses will be administered and management will commence immediately according to the clinic overdose response protocol, consistent with established local and provincial guidelines [25].

Oral methadone can cause prolongation of the QTc (heart rate-corrected QT interval), which in turn is a risk factor for a rare but potentially fatal arrhythmia, Torsades de Pointes (TdP) [26]. An electrocardiogram (ECG) will be performed before commencing the induction and the results will be considered, along with other TdP risk factors, in the clinical decision-making process of selecting methadone or SROM as the appropriate OAT option for that individual [26, 27]. Participants who will receive methadone in this study will be advised during the informed consent process that the risk of arrhythmia is increased with higher doses of methadone. The first 7 days after starting methadone is the time of maximum risk of clinical adverse events, with a peak risk on Day 3 [28]; therefore, an ECG will be repeated on OAT Days 3 and 7 for participants receiving methadone. Any occurrence of QTc prolongation (>500 ms, or ≥ 60 ms increase from baseline) and/or symptoms consistent with TdP will be managed promptly, consistent with recommendations in national OUD treatment guidelines [27].

Secondary outcomes

The secondary outcomes are related to efficacy and acceptability, specifically:

- Starting doses of oral OAT (methadone or SROM)
- Participant satisfaction with the SIFI procedure
- Participant satisfaction with their current OUD treatment

Table 3 Schedule of assessments during OAT follow-up phase (months 1–12)

	1 month	3 months	6 months	12 months
Currently on oral OAT? (Yes/no)	x	x	x	x
Current OAT type and dose	x	x	x	x
Participant satisfaction (MSQ for OUD meds)	x	x	x	x
Self-reported use of illicit opioids/other substances	x	x	x	x
Clinic attendance	x	x	x	x
COWS	x	x	x	x
UDT	x	x	x	x
Overdose events req. intervention	x	x	x	x
Hospitalizations/death	x	x	x	x

OAT opioid agonist therapy, *UDT* urine drug test, *COWS* clinical opiate withdrawal scale, *MSQ* Medication Satisfaction Questionnaire, *OUD* opioid use disorder

- Proportion of participants who are retained on OAT after 1, 3, 6, and 12 months
- Withdrawal symptoms before and during induction phase, during early OAT phase, and during OAT follow-up
- Overdose, hospitalization, death at 1, 3, 6, and 12 months

Participant satisfaction with the SIFI procedure will be assessed during the immediate post-induction observation period, both quantitatively, using the single-item Medication Satisfaction Questionnaire [29, 30], and qualitatively, using three open-ended questions [31].

Participant satisfaction with their current OUD treatment (including safe supply, and recognizing that their current OUD treatment may be "none") will be assessed before starting induction and during OAT follow-up visits using the single-item Medication Satisfaction Questionnaire [29, 30].

Withdrawal symptoms will be measured by the Clinical Opiate Withdrawal Scale (COWS) [32] before and during induction phase, during the early OAT phase, and during OAT follow-up.

Retention on OAT will be collected by participant self-report during the OAT follow-up visits and from the participant's medical record. Any occurrence of overdose, hospitalization, and death during follow-up will be obtained from the participant's medical record in the clinic electronic medical record (EMR) database.

Treatment discontinuation and study discontinuation

Participants are free to withdraw from the study at any time without having to provide a reason for their decision. This will not affect their future medical care or other services that they receive at the clinic. If a participant decides to withdraw from the study, the research staff will not collect any further data from them, including data from the clinic EMR.

Discontinuation from study treatment may occur at the participant's request or in the case of clinically significant adverse reactions and/or other safety reasons. If the participant experiences signs or symptoms consistent with opioid overdose during the induction procedure, the induction will be stopped and the clinic overdose response protocol will be implemented immediately. Ongoing management of the participant following an overdose event, including starting doses of OAT if appropriate, will be at the discretion of the clinic medical staff.

If a suspected opioid overdose occurs during the observation period after the first OAT dose or during a daily visit during the first week on OAT, the participant will be immediately referred to the clinic medical team for assessment and management, including adjustment of the OAT dose if deemed clinically necessary.

Participants receiving methadone who are found to have QTc prolongation (>500 ms, or ≥60 ms increase from baseline) on their ECG on Day 3 or 7 and/or symptoms of possible TdP will be referred to the clinic medical team for prompt evaluation and management. Adjustment of methadone dose or transition to SROM may be offered as appropriate, based on clinical judgement and current Canadian OAT guidelines [27].

Data analysis and management

The primary safety outcome will be assessed in the first instance by a descriptive analysis of adverse events requiring intervention during the induction and early OAT phases of the study. Secondary outcomes will be reported using descriptive and summary statistics. Participants' responses to the treatment satisfaction questions will be summarized, and the results used to refine the SIFI procedure for future investigation.

Participants are assigned unique study codes that are not derived from or related to their personal information. Study-related documents, biological specimens, and ECG reports will be labelled only with the participant's unique study code, and not with their name, initials, or other identifying information. All study documentation will be kept in a secure area in locked cabinets.

Files that contain personal identifying information are kept securely in locked offices in electronic form, and access to these files are password restricted to the principal investigator and a limited number of designated research team members. Identifying information collected on the questionnaires will be removed and stored separately from the questionnaire responses. Participant consents and contact information for follow-up will also be stored separately in a secure area in locked cabinets.

Electronic data will be stored on a secure server. For this study, clinical and sociodemographic information will be drawn from routinely collected clinic and administrative data in the clinic electronic medical record (EMR). Clinicians and research staff access the EMR via a roles-based, credentialed, secure portal to the EMR system.

Data in the clinic EMR database is under the custody of the British Columbia Centre for Excellence in HIV/AIDS (608-1081 Burrard Street, Vancouver, British Columbia, Canada) and its Director, Dr. Julio Montaner (a co-investigator on this study). The EMR database is stored on a secure server on the Centre's network, protected by a defense-in-depth system including an industry-standard firewall prohibiting unauthorized entry. Strict measures are in place to protect the privacy of individuals in the database. The Centre also utilizes a suite of privacy

and security policies to ensure the proper protection, management and integrity of all data. All data will be de-identified for study analyses to limit the potential for disclosure of identifying information.

Monitoring

This pilot study will not have an independent Data and Safety Monitoring Board. Investigators will keep track of adverse events as they occur, and will revise the protocol and informed consent if an excess of adverse events is observed. Specifically, the trial will be put on hold (no new enrollments), revised, and resubmitted to the REB for approval before resuming, in any of the following circumstances:

1. Two serious adverse events that are possibly related to study participation and that occur during the participant's first week of the study, as serious adverse events are unlikely to be related to the study drugs after methadone or SROM have reached steady-state levels.
2. Study drug-related adverse events requiring intervention (including but not limited to those meeting the criteria for serious adverse events) in 5 or more of the first 10 participants; 10 or more of the first 20 participants; 15 or more of the first 30 participants; or 20 or more of the first 40 participants.

Current status of the study

The study protocol and informed consent form have received approval from the University of British Columbia/Providence Health Care Research Ethics Board (UBC/PHC REB Number H23-00111). The use of safe drug supply, opioid agonist therapy (OAT), and experimental approaches such as IV fentanyl for the treatment of severe opioid use disorder at the Hope to Health Research and Innovation Centre have been approved by Health Canada as part of its Substance Use and Addictions Program. Study recruitment is ongoing.

Discussion

This is the first study to objectively estimate opioid tolerance and use it to determine individualized starting doses of oral OAT for use in an outpatient setting among people who use unregulated fentanyl. This study was initiated in response the inadequacy of current OAT dosing recommendations to address the increasing contamination of the unregulated drug supply with high-potency opioids, mainly fentanyl and its analogues, resulting in an ongoing crisis of opioid overdose and death in BC and elsewhere.

The SIFI procedure involves an IV induction with medical fentanyl, guided by pharmacological principles [33, 34], and has been implemented successfully in an in-hospital setting [3]. To optimize participant safety in this outpatient study, participants will be closely supervised in the clinic during and after the IV fentanyl induction procedure.

A limitation of the SIFI protocol is that sedation observed during the induction procedure may be due to other factors in addition to medically-administered IV fentanyl. In a setting where multi-substance use is common, other contributing factors may include prescription, non-prescription, or unregulated sedating substances (e.g. benzodiazepines, alcohol), and/or catecholamine depletion as a consequence of chronic use of methamphetamine or other stimulants. Operationally, any somnolence or lethargy observed during the induction procedure is attributed to the administered IV fentanyl. If additional sedating factors are present, the consequence would be to underestimate the participant's opioid tolerance and administer too low a dose of methadone or SROM to fully meet their opioid requirements. This limitation is unavoidable in the interests of participant safety in a setting where the potential effects of concomitant sedating substances cannot be determined or quantified.

Another potentially confounding factor in the calculation of opioid tolerance could be the presence of buprenorphine, an opioid partial agonist that is sometimes prescribed for the treatment of OUD. While current use of either buprenorphine extended-release (Sublocade®) or buprenorphine-naloxone (Suboxone®) is exclusionary in our protocol, it should be noted that buprenorphine extended-release (Sublocade®) has a long terminal half-life and relevant plasma concentrations can be maintained for up to 5 months after the last administration [35, 36]. If the SIFI protocol were to be implemented in a setting where these agents are in regular use, it may be prudent to ensure a 5-month interval has passed since the last Sublocade® dose or to ensure buprenorphine is absent during urine drug testing, to mitigate the confounding effects of residual buprenorphine on the assessment of opioid tolerance using IV fentanyl.

We expect that application of the SIFI protocol will result in higher-than-standard starting doses of oral OAT. Accordingly, in the interests of participant safety and to prevent early withdrawal after OAT initiation, every effort will be made to ensure the protocol-planned assessments are completed during the 3 h after the first dose of OAT and the first 7 days thereafter. Participants will be offered an honorarium for remaining in the clinic for a full day including participation in the induction

and 3 h of assessment time following the first OAT dose. Honoraria will also be provided for participants returning to the study clinic for daily assessments during the first week on OAT.

We expect that the potential harms associated with IV fentanyl induction and high-dose methadone or SROM in this protocol will thus be minimized, especially when compared to the known harms associated with OAT dropout and continued use of the unregulated drug supply. We predict that tailored starting OAT doses will lead to therapeutic target levels being achieved more quickly, thereby more effectively managing opioid withdrawal and cravings, and in turn leading to increased retention on life-saving OAT and decreased reliance on the toxic street drug supply. We believe the findings of this study will be generalizable to other clinical settings, particularly in jurisdictions where fentanyl use is widespread.

Abbreviations

BC	British Columbia
COWS	Clinical Opiate Withdrawal Scale
ECG	Electrocardiogram
EMR	Electronic medical record
IV	Intravenous
MSQ	Medication Satisfaction Questionnaire
OAT	Opioid agonist therapy
OT	Opioid tolerance
OUD	Opioid use disorder
POSS	Pasero Opioid-induced Sedation Scale
SIFI	Symptom-inhibiting fentanyl induction
SROM	Sustained-release oral morphine
TdP	Torsades de Pointes
UDT	Urine drug test

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13722-025-00586-7.

Additional file 1

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Author contributions
PA (study sponsor) and MJI are addiction psychiatrists and co-principal investigators; they conceived and designed the study, developed the interventions, and are responsible for medical oversight of study implementation. MH is a co-investigator and contributed to the design of the study, wrote the protocol, obtained ethical approval, and wrote the manuscript. ZB is the study coordinator, and contributed to study design and implementation including the informed consent process. RD is the study nurse and JF is the Clinical Nurse Coordinator at the Hope to Health Primary Care Clinic; they contributed to study design and implementation, and performed the nursing assessments and procedures. JSHW is a research associate and ensured study activities are performed in accordance with University of British Columbia and health authority policies. AM is a co-investigator and contributed to the study design with respect to the pharmacologic principles. NM is an addiction psychiatrist and co-investigator and contributed to the study design. DH is a co-investigator and the Associate Medical Director of the Hope to Health Research and Innovation Centre (the study site). He contributed to study design and implementation. SAG is a co-investigator and the Interim Medical Director of Clinical Services at Hope to Health. She supported study implementation. RB is a co-investigator, the Senior Medical Director of the British Columbia Centre for Excellence in HIV/AIDS, and the Medical Director of Hope to Health Research and Innovation Centre. He contributed to study design and supported study implementation. JSGM is a co-investigator and Director of the British Columbia Centre for Excellence in HIV/AIDS. He contributed to study design and implementation. All authors revised draft versions of the manuscript, and read and approved the final manuscript.

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Availability of data and materials
After the study is finished, results will be published in medical journals and reports, and presented at scientific meetings and conferences. These materials will be made available on the British Columbia Centre for Excellence website at www.bccfe.ca. Results will only be reported as aggregate data. No information which could identify any individual study participant will be included in any such presentations or publications. The final study dataset will be made available on specific written request to the Principal Investigator. The required study data will be de-identified and only the unique study code will be used for individual participant data.

Declarations

Ethics approval and consent to participate
The study protocol and informed consent form were approved by the University of British Columbia/Providence Health Care Research Ethics Board (H23-00111). The investigators will inform the UBC/PHC REB about the progress of the study and any protocol amendments will be submitted for REB approval before implementation. The investigators will notify the REB of any significant protocol deviations, unanticipated problems, or serious adverse events that may occur during the course of the study.

Consent for publication
See Supplementary Materials for the approved informed consent document.

Competing interests
PA was a consultant on Indivior-led buprenorphine extended-release studies, and has received speaking honoraria for Indivior-funded buprenorphine presentations, both of which are unrelated to this study protocol. MJI has received honoraria from Indivior, unrelated to this study protocol. The other authors declare that they have have no competing interests.

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CASE SERIES

Case series: Symptom-inhibited fentanyl induction (SIFI) onto treatment-dose opioid agonist therapy in a community setting

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Abstract

Background and Objectives: Existing opioid agonist therapy (OAT) guidelines are far from sufficient to address rising opioid tolerances and potency of the unregulated opioid market in North America. Inadequate starting doses of OAT are a universally recognized barrier for people who use fentanyl. Our objectives are to present a novel induction protocol called symptom-inhibiting fentanyl induction (SIFI) that uses rapid intravenous fentanyl administration to inhibit symptoms of opioid withdrawal.

Methods: We describe two cases highlighting the potential clinical utility of SIFI.

Results: This case series demonstrates two safe and successful transitions onto higher-than-standard doses of methadone and slow-release oral morphine harnessing an emerging approach of SIFI in a community clinic setting.

Discussion and Conclusions: These results support emerging evidence that SIFI is safe and feasible to meet patients' opioid requirements and facilitate rotation onto OAT. Further studies are needed to increase the generalizability of these findings.
Scientific Significance: Safe transitions onto treatment-dose OAT are of heightened clinical importance at a time when fentanyl and high-potency synthetic opioids are now the norm. SIFI is a novel induction method that could address significant gaps in the currently available OAT options in the fentanyl era.

BACKGROUND

Canada is in the midst of an unprecedented overdose crisis, with British Columbia (BC) being one of the most severely impacted. The most recent and pronounced wave of the overdose crisis has been driven in large part by fentanyl, a synthetic opioid with potency and lethality levels far higher than heroin.[1] Between January 2023 and June 2024, fentanyl was detected in 85% of all unregulated drug deaths in BC.[2]

Opioid agonist therapy (OAT) is currently indicated as best practice for the treatment of opioid use disorder (OUD).[3] Growing evidence, however, suggests that the treatment trajectory of individuals who receive OAT may be compromised in the era of fentanyl. In BC, provincial guidelines for OUD recommend starting doses of 30–40 mg methadone and 300 mg slow-release oral morphine (SROM) for people who use fentanyl.[4] However, anecdotal evidence has found fentanyl withdrawal to have a faster onset, higher severity, and longer duration than other opioids, driving users to prematurely exit treatment.[5] Pharmacokinetic studies of fentanyl have suggested that the worsened withdrawal is likely due to its lipophilic accumulation in peripheral stores and long terminal elimination.[6]

A novel alternative induction protocol uses rapid intravenous (IV) fentanyl administration to inhibit symptoms of opioid withdrawal (thus "symptom-inhibited fentanyl induction," hereafter referred to as SIFI) and objectively determine opioid tolerance. This protocol has been described in a patient with severe OUD and unregulated fentanyl use to receive optimized doses of OAT and avoid withdrawal in an inpatient setting.[7] In brief, once patients reach their subjective readiness threshold for induction, 400 mcg of IV fentanyl is administered with repeat doses every 5 min, with each dose followed by assessments of sedation, vital signs, withdrawal symptoms, cravings, and comfort levels. Once baseline safety is established through vital measurements, doses increase stepwise up to 800 and 1200 mcg until either subjective comfort or a Pasero Opioid-Induced Sedation Scale (POSS) score of two is obtained.[8] Dose increases will occur after each time safety is established through the varied assessments. The patient is monitored for sedation levels and vital signs at 5, 10, and 15 min following the final dose, at which point induction is complete. The total cumulative dose of IV fentanyl administered from start to completion of SIFI is used as a measure of opioid tolerance, which in turn is used to calculate and transition patients to an equivalent starting dose of either methadone or SROM. Patients will receive maximum daily doses of up to 200 mg methadone or 2000 mg SROM (Figure 1). In this paper, we present two cases where SIFI has safely and successfully been completed in a community clinic with patients who use fentanyl. Written consent was obtained from both patients. The protocol and informed consent forms were approved by the University of British Columbia/Providence Health Care Research Ethics Board (H23-00111). The SIFI protocol is registered with ClinicalTrials.gov (NCT05905367).

CASE PRESENTATIONS

Case 1

The patient is a 51-year-old male with severe OUD and 30 years of illicit opioid use. He has a lifelong history of trauma, chronic pain, unstable housing, and mental health challenges. His medical history includes concurrent nicotine use disorder, stimulant use disorder, and benzodiazepine use disorder. He self-reported smoking or injecting 7 gm fentanyl daily. He had previously been treated with buprenorphine-naloxone, extended-release buprenorphine, SROM, oral hydromorphone, IV diacetylmorphine, and fentanyl patches. His most recent OAT was 175 mg methadone, canceled due to missed doses. He received a 40 mg dose the day before his clinic visit.

Before SIFI, his Clinical Opioid Withdrawal Scale (COWS)[9] score was two, and he was slightly tachycardic with a heart rate of 104 bpm. He reported smoking 0.1 g of fentanyl immediately before the clinic visit and having opioid cravings. His SIFI consisted of a total 9600 mcg of IV fentanyl administered over 79 min (Table 1a). Over induction, his COWS gradually dropped to zero and his POSS did not increase above one. Based on his opioid tolerance, his SROM dosing was calculated to be 538 mg. The patient was transitioned to 200 mg methadone, with the first dose administered in clinic with hourly assessments for 3 h thereafter. He received methadone at the clinic for a total of 8 days, with missed doses on Days 2 and 7. His COWS scores remained around 0 or 1 with the exception of a 3 on the 3rd day following a missed dose the day prior. Electrocardiogram (ECG) interval measurements were taken on Days 4 and 8, with QTc intervals of 425 and 392, respectively. One week after SIFI, his daily OAT prescription was increased to

a: Conversion from Opioid Tolerance to Oral Methadone starting dose for OAT

Total cumulative dose of IV fentanyl administered during the induction phase = the loading dose

100% of the loading dose of fentanyl (in mg) x 8 = a proxy for opioid tolerance (OT) over 24 hours

$$\text{OT in mg} \times 100 = \text{"X" IV morphine equivalents (ME)}$$

$$\text{"X" IV morphine equivalents} \times 2 = \text{"2X" mg oral morphine equivalents (OME)}$$

$$\frac{\text{"2X" mg OME}}{\text{CR}} = \text{"A" mg Oral Methadone}$$

CR= the conversion ratio from OME to oral methadone, which depends on the fentanyl dose. The following table will be used to determine the CR [20]:

Daily OME (mg)	Conversion ratio from oral morphine: oral methadone
30-100	3:1
101-300	5:1
301-600	10:1
601-800	12:1
801-1000	15:1
>1000	20:1

$$\downarrow 30\% \text{ for incomplete cross tolerance: A} \times 0.7 \approx \text{"B" mg Oral Methadone}$$

The maximum total daily dose of methadone to be administered in the protocol will be 200 mg; i.e. if B >=200mg, the participant will receive methadone 200 mg daily.

b: Conversion from Opioid Tolerance to Sustained-release Oral Morphine (SROM) starting dose for OAT

Total cumulative dose of IV fentanyl administered during the induction phase = the loading dose

100% of the loading dose of fentanyl (in mg) x 8 = a proxy for opioid tolerance (OT) over 24 hours

$$\text{OT in mg} \times 100 = \text{"X" IV morphine equivalents (ME)}$$

$$\text{"X" IV morphine equivalents} \times 2 = \text{"2X" mg oral morphine equivalents (OME)} = \text{"C" mg SROM}$$

$$\downarrow 30\% \text{ for incomplete cross tolerance: C x 0.7 ~ "D" mg SROM}$$

The maximum total daily dose of SROM to be administered in the protocol will be 2000 mg, i.e. if D >=2000mg, the participant will receive SROM 2000 mg daily.

For participants with known chronic kidney disease and estimated glomerular filtration rate (eGFR) between 15 and 60 mL/min, SROM doses ("C") will be adjusted according to current recommendations [21]; if eGFR<15 mL/min, the participant will not be eligible to receive SROM.

FIGURE 1 (a) Conversion from opioid tolerance to oral methadone starting dose for opioid agonist therapy (OAT). (b) Conversion from opioid tolerance to sustained-release oral morphine (SROM).

205 mg of methadone per the client's request and transferred to a community pharmacy. No hospital admissions, naloxone administration, or emergency department visits were required during the induction or in the next 30 days. All measured indices, including heart rate and oxygen saturation levels, remained within normal ranges at follow-up visits including on Day 30. At Day 30, he remained stable on his methadone and verbally reported satisfaction with OAT.

TABLE 1 Dosage regimens for Cases 1 and 2.

Admission timeline	Fentanyl IV	Dose (mcg)	Cumulative fentanyl dose (mcg)	COWS	POSS	Methadone daily doses (mg)
(a) Case 1						
Day 1	400–800 mcg q5 min prn (induction)	400	/	2	1	
		400	/	2	1	
		800	/	2	1	
		800	/	1	1	
		800	/	2	1	
		800	/	2	1	
		800	/	1	1	
		800	/	1	1	
		800	/	1	1	
		800	/	1	1	
		800	/	1	1	
		800	/	0	1	
		800	9600	1	1	200
Day 2: no show						
Day 3				3	1	200
Day 4				0	1	200
Day 5				1	1	200
Day 6				1	1	200
Day 7: no show						
Day 8				3	1	200
(b) Case 2						
Day 1	400–800 mcg q5 min prn (induction)	400	/	6	1	
		400	/	5	1	
		800	/	6	1	
		800	/	4	1	
		800	/	4	1	
		800	/	4	1	
		800	4800	1	2	2000
Day 2				2	1	2000
Day 3				2	1	2000
Day 4				1	1	2000
Day 5				1	2	2000
Day 6: no show						
Day 7				3	1	2000

Abbreviations: COWS, Clinical Opiate Withdrawal Score; IV, intravenous; mcg, microgram; mg, milligram; POSS: Pasero Opioid-Induced Sedation Scale; prn, as needed; q_h, every hour(s); q_min, every minute(s).

Case 2

A 36-year-old female with a longstanding history of addiction and chronic pain presented to the clinic. In addition to her severe OUD, her comorbidities include hepatitis C virus infection, asthma, gastroesophageal reflux disease, stimulant use disorder, tobacco use disorder, and two previous cerebral vascular accidents. Her illicit opioid use began 24 years previously and she self-reported smoking or injecting up to 1.75 g fentanyl daily. Due to negative experiences with side effects, the patient had remained on 50 mg of methadone for 2 years and was reluctant to increase her dose any further.

The patient's last reported use was smoking 0.05 g fentanyl and crystal methamphetamine immediately before the clinic visit. She had received her regular prescription of 50 mg methadone earlier in the day. During assessment, her baseline QTc interval was 413, POSS score was 1, and she tested negative for pregnancy. She was determined to be in a mild state of withdrawal with a COWS of six and symptoms of restlessness, join aches, nasal stuffiness, anxiety, sweating, and opioid cravings.

Her SIFI induction phase consisted of total 4800 mcg of IV fentanyl administered over 50 min, throughout which her withdrawal symptoms improved (Table 1b). Based on her opioid tolerance, her SROM dosing was calculated to be 5376 mg. Following SIFI, she was transitioned to 2000 mg of daily SROM. The first dose was administered in clinic, similar to all other doses following apart from Day 6. Her POSS scores consistently remained at 1 with the exception of a 2 on Day 5. Her COWS scores ranged from 1 to 2 and rose to a maximum of 3 on Day 7 following a missed dose on the day prior. Her subjective comfort levels and vital signs, including QTc interval, remained normal from the preinduction baseline throughout the induction week.

After 7 days, she continued to have strong cravings and withdrawal when using less illicit fentanyl. She requested a higher SROM dose and underwent a scheduled titration to 2500 mg. For 10 days thereafter, she did not encounter any complications or need for medical care. On Day 13, she reported feeling unwell with symptoms including diplopia. Following assessment, a diagnosis was made of neurosyphilis, unrelated to SIFI or OAT. Two months following the induction, she had completed antibiotic treatment, was stable and continuing to receive daily 2800 mg SROM.

DISCUSSION

This case series supports emerging evidence that SIFI is safe and feasible to meet patients' opioid requirements and facilitate rotation onto effective doses of OAT. To our knowledge, there have been no formal studies of IV fentanyl used as a means to transition to methadone or SROM in a community clinic setting. Though more research is needed, the potential implications of this are significant, from increasing the clinical utility of OAT to improving patient satisfaction and overall retention in a community setting.

Following its arrival and proliferation in North America, fentanyl has exponentially increased the number of lives lost to overdose. OAT initiations are a particular challenge for people who use fentanyl and whose opioid tolerance levels are far higher than can be immediately accommodated by current protocols.[10] An analysis of 39,456 BC patients identified that methadone initiation in compliance with current guidelines was associated with an increased risk of death or hospitalization within the next 6 months.[11] The adaptation of novel induction protocols for people who use fentanyl, including more rapid methadone titration, has been recommended by recent guidelines[12] and described in several case reports.[13–15] A recent retrospective chart review of hospitalized OUD patients also demonstrated safety with up-titrating methadone doses quicker than with traditional induction.[16] This work is critical to pursue in an era when fentanyl is omnipresent. Pragmatic approaches like SIFI are needed to reduce the risks of mortality from fentanyl overdose and OAT discontinuation.

CONCLUSION

In the wake of the ever-growing overdose crisis, there is an urgent need to innovate OAT to ensure adequacy for those who use fentanyl. Strategies that are both desirable and acceptable to the growing population of fentanyl users are a necessity for treatment systems to keep up with the evolving toxic street drug supply. This case series demonstrates a novel approach and application of SIFI that can meet the needs of the patients where they are, prevent fatal and nonfatal overdose in those who exit treatment, and improve their engagement with the care system.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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