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Emergency Department–Initiated Buprenorphine for Opioid Use Disorder
A Randomized Clinical Trial

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IMPORTANCE Extended-release injectable buprenorphine may expand the reach of initiating medications for opioid use disorder in high-risk and hard-to-reach individuals who visit the emergency department (ED) and can be administered in low levels of withdrawal.

OBJECTIVE To compare the effect of ED-initiated 7-day extended-release injectable buprenorphine vs sublingual buprenorphine on treatment engagement at 7 days.

DESIGN, SETTING, AND PARTICIPANTS Multicenter randomized clinical trial enrolling adult patients presenting to the ED with untreated opioid use disorder and a Clinical Opiate Withdrawal Scale (COWS) score of 4 or higher across 29 EDs in the US from July 12, 2020, to August 21, 2024. Final follow-up was completed on October 24, 2024.

INTERVENTIONS Patients were randomized to receive a 24-mg injection of extended-release buprenorphine (equivalent to 16 mg/d) or sublingual buprenorphine, which included either self-administration instructions if the COWS score was less than 8 or administration of 8 mg of sublingual buprenorphine in the ED if the COWS score was 8 or higher. All sublingual buprenorphine group patients received a 7-day prescription for 16 mg/d. Both groups were provided referral for ongoing medication with a scheduled appointment within 7 days.

MAIN OUTCOMES AND MEASURES Engagement in opioid use disorder treatment on day 7 was the primary outcome. Secondary outcomes included engagement at 30 days, precipitated withdrawal and overdose events, craving scores, days of illicit opioid use, and patient satisfaction with treatment.

RESULTS Among 2000 patients randomized, 6 who were enrolled twice were excluded, resulting in 991 in the extended-release group and 1003 in the sublingual group. The median age was 37 (IQR, 30-47) years, 68% were male, 31% had an initial COWS score of 4 to 7, and 76% tested positive for fentanyl. The adjusted proportion of engagement in opioid use disorder treatment at 7 days was 40.5% with extended-release buprenorphine vs 38.5% with sublingual buprenorphine (adjusted difference, 1.6%; 95% CI, −2.8% to 6.0%). Engagement at 30 days was similar, with adjusted proportions of 43.8% with extended-release buprenorphine vs 44.9% with sublingual buprenorphine (adjusted difference, −1.5%; 95% CI, −6.2% to 3.2%). Precipitated withdrawal was rare: 6 (0.6%) with extended-release buprenorphine and 8 (0.8%) with sublingual buprenorphine. Overdose events within 30 days occurred in 18 participants (2.3%) in each group. Patients receiving extended-release buprenorphine reported lower mean craving scores at 7 days vs those receiving sublingual buprenorphine (scale, 0-100; mean score, 26.5 vs 30.2, respectively; adjusted mean difference, −3.85; 95% CI, −7.08 to −0.63), fewer days of illicit opioid use in the past 7 days (adjusted ratio of means, 0.77; 95% CI, 0.68-0.95), and better treatment satisfaction scores (scale, 1-5; adjusted mean difference, 0.13; 95% CI, 0.01-0.25).

CONCLUSIONS AND RELEVANCE No difference was detected in opioid use disorder treatment engagement on day 7 between the 7-day extended-release and sublingual buprenorphine groups. Both buprenorphine formulations were well tolerated; precipitated withdrawal was rare despite a high prevalence of fentanyl.

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Approximately 5.7 million individuals in the US have an opioid use disorder.[1] Opioid overdose deaths, while recently declining,[2] continue to be the leading cause of death in people younger than 45 years despite the availability of effective medications.[3] Each overdose death results in 38 years of potential life lost.[4] Emergency department (ED)-initiated buprenorphine has increased treatment engagement in multiple trials[5,6] and is cost-effective,[7,8] yet adoption has lagged.[9]

Nationally, there have been minimal improvements in ED provision of buprenorphine,[10] despite removal of some regulatory barriers to buprenorphine treatment access, such as the X-waiver, and national consensus recommendations from the American College of Emergency Physicians supporting ED provision of medication for opioid use disorder.[11] Specific state-level investments, such as California's expansive ED resources and technical assistance, have paid off, leading to an increase in the number of ED-initiated buprenorphine prescriptions from 0.1% (2017) to 5% (2022).[12] Nonetheless, significant clinician-level barriers to broader adoption exist, including reticence to prescribe, lack of prompt access to community clinicians or treatment programs, and concerns regarding risk of precipitated withdrawal.[13] Patients also face numerous challenges. The proliferation of fentanyl in the illicit drug supply has complicated buprenorphine initiation, as its bioaccumulation and prolonged metabolism often delays the onset of withdrawal, resulting in individuals with opioid use disorder presenting with minimal to mild withdrawal symptoms that preclude sublingual buprenorphine administration under existing guidelines.[14] Additional logistical barriers—such as timely access to outpatient follow-up, insurance coverage, lack of photo identification, preauthorization requirements, transportation, and limited pharmacy availability—can complicate access to continuation of treatment after ED initiation.

Innovative strategies including use of a 7-day extended-release injectable formulation of buprenorphine,[15] administered during an ED visit, may overcome many of these barriers. This study aimed to compare the effectiveness of extended-release buprenorphine vs sublingual buprenorphine initiation in patients presenting to the ED with untreated opioid use disorder on engagement in formal opioid use disorder treatment at 7 days. We hypothesized that use of extended-release buprenorphine would result in more patients engaged in formal opioid use disorder treatment at 7 days.

Key Points

Question Does 7-day extended-release injectable buprenorphine compared with sublingual buprenorphine improve treatment engagement at 7 days?

Findings In this multicenter randomized trial of 1994 adult patients presenting to the emergency department with untreated opioid use disorder and a Clinical Opiate Withdrawal Scale (COWS) score of 4 or higher, 40.5% in the extended-release group and 38.5% in the sublingual buprenorphine group were in treatment at 7 days, demonstrating no significant difference between groups.

Meaning A 7-day extended-release injectable preparation of buprenorphine does not improve treatment engagement.

Methods

Study Design and Oversight

The ED-Initiated Buprenorphine Validation Network Trial (ED INNOVATION) was a parallel, 2-group, open-label, individually randomized trial conducted at 29 geographically diverse EDs in academic and community sites in the US. The trial protocol and statistical analysis plan (Supplement 1) were previously published[16] and were approved by WCG, which served as the single institutional review board. The trial was funded by the National Institutes of Health through the Helping to End Addiction Long-Term (HEAL) Initiative. All patients provided written informed consent, including contacting any referral treatment source.

The trial was conducted under a US Food and Drug Administration investigational new drug application supervised by the National Institute on Drug Abuse (NIDA) Center for Clinical Trials Network. A data and safety monitoring board chartered by NIDA monitored the trial. NIDA's contractor for the clinical coordinating center and data and statistics center, the Emmes Company LLC, managed the data and provided statistical analyses. This trial followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials.

Study Population

All patients presenting to the ED during rotating screening hours were assessed for eligibility. Patients aged 18 years or older were eligible if they met *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*) criteria for moderate to severe opioid use disorder[17] and had urine toxicology results demonstrating presence of an opioid. Patients with methadone detected in urine were excluded. Eligibility also required a Clinical Opiate Withdrawal Scale (COWS) score[18] of 8 or higher, which was lowered to 4 or higher on April 5, 2021. This change occurred as a result of a parallel ancillary nonrandomized study that demonstrated the feasibility and safety of directly initiating the 7-day extended-release buprenorphine formulation, CAM2038, for patients with COWS scores of 4 to 7 without necessitating a lead-in dose of sublingual buprenorphine.[19] In addition, patients were excluded if they were pregnant, received medications for opioid use disorder within the past 14 days, required ongoing opioid medication for pain, had active suicidal ideation or a medical or psychiatric condition requiring hospitalization, were non-English speaking, were unable to provide locator information, were unwilling to follow study procedures, or were incarcerated or in police custody.

Randomization and Treatment Conditions

After screening, eligible patients were randomly assigned in a 1:1 ratio to receive extended-release buprenorphine or sublingual buprenorphine. The randomization sequence was generated using a permuted-block procedure with random block

sizes and stratification by site and insurance status. The randomization process was performed by the data statistical center with the allocation sequence concealed.

Patients randomized to the extended-release buprenorphine group received a 24-mg subcutaneous injection approximately equivalent to 16 mg/d of sublingual buprenorphine. Patients randomized to the sublingual buprenorphine group with an initial COWS score of 8 or higher received a total of 8 mg. Patients randomized to sublingual buprenorphine with an initial COWS score of 4 to 7 were provided with instructions, in the form of an infographic, for unobserved buprenorphine initiation, allowing self-administration of up to 12 mg within the first 24 hours. All patients randomized to sublingual buprenorphine were discharged with a prescription for 16 mg/d until their follow-up appointment. All randomized patients were monitored and observed for 2 hours after study medication administration, provided with a scheduled follow-up appointment including date and time frames for ongoing treatment within 7 days, and received either dispensed or prescribed naloxone.

Additional doses of buprenorphine and ancillary medications such as antiemetics, α-agonists, and nonsteroidal anti-inflammatory drugs were administered as needed during the ED encounter for withdrawal symptoms. COWS scores were documented prior to initial buprenorphine administration, at the end of the observation period, and any time that a patient or ED clinician observed an increase in withdrawal symptoms or ancillary medications were administered. Records of the entire ED course of any patient with an increase of 5 or more points in their COWS score were reviewed by independent investigators (M.R.L. and S.L.W.) to adjudicate a diagnosis of precipitated withdrawal.[20,21]

Training and Supervision

All site investigators and research associates underwent extensive training in person initially and with continuous support throughout the trial. The study psychologist (M.V.P.) trained the research associates on all of the assessments, including the *DSM-5*, COWS scores, and timeline follow-back methods, and met biweekly for discussion. Lead coinvestigators (A.A.H., K.F.H., J.P., E.C., and R.P.M.) were assigned geographic regions and were available in real time for any study or clinical issues. Regulatory monitors visited each site multiple times to ensure compliance with all study procedures. All site principal investigators and coinvestigators met weekly to discuss screening, enrollment, and shared experiences. The study lead investigators (G.D. and D.A.F.) met weekly to discuss enrollments, adverse events, protocol deviations, and follow-up rates, to monitor fidelity to all interventions.

Outcomes

The primary outcome was engagement in formal opioid use disorder treatment at 7 days. Patient report of engagement was verified by the treatment source, including clinician, clinic, or opioid treatment program. We were not able to verify self-reports of no treatment engagement. Formal opioid use disorder treatment was defined per the American Society of Addiction Medicine levels of care 1 through 4.[22] Secondary outcomes included (1) engagement in treatment at 30 days; (2) self-reported nonfatal overdose events at 30 days; (3) craving scores at 7 days on a scale ranging from 0 to 100, with higher scores indicating more craving; (4) self-reported past-7-day illicit opioid use at 7 days and 30 days as measured by the timeline follow-back method[23]; (5) treatment satisfaction at 7 days on a scale from 1 (completely ineffective) to 5 (completely effective); (6) engagement specifically in treatment with medications for opioid use disorder at 7 days and 30 days, verified by the treatment source; (7) self-reported ED visits and hospitalizations; and (8) the Treatment Effectiveness Assessment, evaluating progress in treatment from patients' perspectives.[24] Adverse events included precipitated withdrawal, and serious adverse events included hospitalizations and death.

Race and ethnicity were self-reported according to prespecified categories and were included in the analysis because outcomes can differ across racial and ethnic groups.

Statistical Analysis

A sample size of 850 participants per treatment group was required to ensure 90% power at the 2-sided α = .05 significance level to detect a difference of 8% in the proportion engaged in formal opioid use disorder treatment on day 7 (ie, 53% engaged in the extended-release buprenorphine group vs 45% engaged in the sublingual buprenorphine group). Anticipated engagement was based on prior research[5,19] and a meaningful difference. We targeted 2000 randomizations to accommodate up to 15% loss to follow-up.

Analyses were conducted according to the intention-to-treat principle, analyzing participants within the group to which they were randomized, using SAS version 9.4 (SAS Institute Inc). Where specified, analyses were adjusted for prespecified covariates of age, sex, ethnicity, race, insurance status, housing status, and site. The primary outcome was tested at the 2-sided α = .05 significance level. Treatment effects and 95% confidence intervals are presented for secondary outcomes. Confidence interval widths for secondary outcomes were not adjusted for multiplicity and should not be used to infer definitive effects.

Treatment differences (extended-release vs sublingual buprenorphine) for treatment engagement at 7 days (primary outcome) and 30 days were examined using a weighted generalized estimating equation.[25] Imputation was not used in the primary analysis for those without the primary outcome observed (ie, those lost to follow-up or death). Inverse probability weights were estimated by a logistic regression of observed vs not observed at a particular measurement occasion. The logistic model included the baseline demographic and clinical characteristics of site, treatment group, insurance status, and time and outcomes at previous time points. From this model, the inverse of the predicted cumulative probability of being observed was estimated for each participant at each postrandomization time point and used as a weight for the generalized estimating equation. The weighted generalized estimating equation model included effects for intervention (extended-release vs sublingual

buprenorphine), time (7 days and 30 days), and their interaction, as well as the prespecified covariates described above. An exchangeable working correlation was used to account for clustering of responses from the same participants (ie, 7 days and 30 days). Linear contrasts were used to estimate odds ratios, treatment differences, and 95% confidence intervals for the proportions of participants engaged in opioid use disorder treatment in the extended-release buprenorphine vs sublingual buprenorphine groups at 7 days and 30 days. The model weighted the observed outcomes to estimate the marginal treatment effect (ie, odds ratio for engagement) in the target population had all participants completed outcome assessments without loss to follow-up. As such, for this treatment policy estimand, it is implied that those lost to follow-up may have had a nonzero probability of engagement.

The primary analysis is unbiased under the missing at random (MAR) assumption, meaning that missingness could be associated with observed variables in the loss to follow-up model but not associated with unobserved outcomes. Unadjusted/unweighted treatment differences (including only those with the primary outcome observed) and treatment differences imputed as not engaged in treatment for those without primary outcome data are presented as sensitivity analyses.

Self-reported craving and treatment satisfaction scores at 7 days were analyzed using analysis of covariance. The self-reported number of days of illicit opioid use at 7 days and 30 days was evaluated using a generalized linear mixed model with a negative binomial distribution. Engagement in treatment with medications for opioid use disorder at 7 days and 30 days was analyzed as described for the primary outcome.

Results

Patients

Between July 12, 2020, and August 21, 2024, 2000 patients were enrolled across 29 sites in the US, representing 1994 unique patients (**Figure 1**). Six patients were enrolled twice; only their first enrollment was included in the intention-to-treat analysis. The baseline characteristics of the randomized participants were similar in the 2 treatment groups (**Table 1**). A total of 68% of patients were male; 31% were Black, 15% Hispanic, and 55% White. Most (75%) had public insurance, 51% reported unstable housing in the past year, 37% reported current unstable housing, and 76% had urine toxicology results demonstrating the presence of fentanyl, with 77% having at least 1 other substance detected in addition to an opioid. Buprenorphine was detected in the urine of 40% of participants at baseline, with 10% of patients having received a dose earlier in their ED course, prior to enrollment. Psychiatric comorbidities were common, with 20% of participants receiving a psychiatric evaluation during their index ED visit. Treatment exposure among randomized patients was 94.7% for extended-release buprenorphine and 98.4% for sublingual buprenorphine.

Engagement in Treatment at 7 Days and 30 Days

The primary outcome, engagement in formal opioid use disorder treatment at 7 days, was assessed among 854 participants (86%) and 870 participants (87%) in the extended-release and sublingual groups, respectively. In the extended-release buprenorphine group, an adjusted 40.5% (95% CI, 31.3%-50.3%) of participants were engaged in treatment compared with an adjusted 38.5% (95% CI, 29.5%-48.5%) in the sublingual buprenorphine group (adjusted treatment difference, 1.6%; 95% CI, −2.8% to 6.0%) (**Table 2**). In those with COWS scores of 4 to 7, the proportion of patients engaged was an adjusted 40.1% in the extended-release group compared with an adjusted 34.7% in the sublingual group, a difference that was not statistically significant.

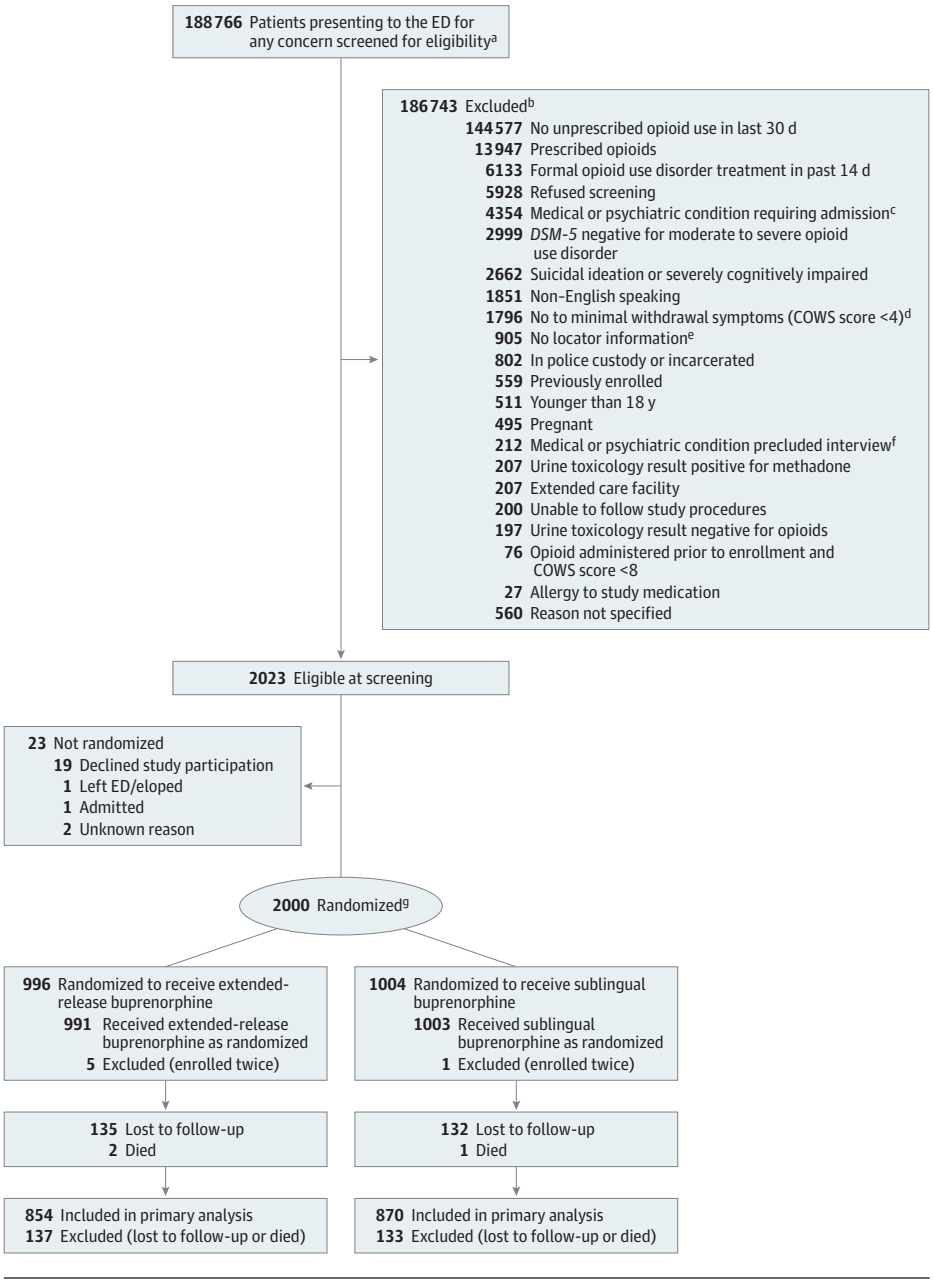
The odds ratios for engagement in opioid use disorder treatment at 7 days by subgroup comparing extended-release buprenorphine vs sublingual buprenorphine revealed no significant differences among a variety of demographic and clinical characteristics (**Figure 2**). Engagement in treatment at 30 days, a secondary outcome, was overall higher than engagement at 7 days, although similar in both groups (an adjusted 43.8% in the extended-released group vs an adjusted 44.9% in the sublingual group).

If all patients lost to follow-up at 7 days were counted as not engaged in treatment, the results regarding engagement in treatment were similar (extended-release buprenorphine, 385/991 [38.9%]; sublingual buprenorphine, 373/1003 [37.2%]; odds ratio, 1.07; 95% CI, 0.90-1.29). There were similar results at 30 days (extended-release buprenorphine, 384/991 [38.8%]; sublingual buprenorphine, 389/1003 [38.8%]; odds ratio, 1.00; 95% CI, 0.83-1.20).

Additional Secondary Outcomes

Because the primary end point was null, all findings for the secondary end points should be considered hypothesis-generating (**Table 3**). There were no differences in the proportion of patients (2.3% in both groups) self-reporting nonfatal overdose events within 30 days. Craving scores at 7 days (scale, 0-100) were lower in the extended-release buprenorphine group compared with the sublingual buprenorphine group (mean score, 26.5 vs 30.3, respectively; difference between means, −3.85; 95% CI, −7.08 to −0.63). The mean number of days with illicit opioid use was also lower in the extended-release buprenorphine group compared with the sublingual buprenorphine group at 7 days. The extended-release buprenorphine group reported higher mean treatment satisfaction scores than the sublingual buprenorphine group (mean score, 4.12 vs 3.99, respectively; difference in means, 0.13; 95% CI, 0.01-0.25). There were no differences in patient engagement specifically in treatment with medications for opioid use disorder at 7 days or 30 days. There were 388 ED visits in the sublingual buprenorphine group vs 291 in the extended-release buprenorphine group, driven by a small number of individuals with multiple visits. The proportion of participants with at least 1 ED visit was similar in both groups. Treatment Effectiveness Assessment scores were higher in the extended-release buprenorphine group in all domains compared with the sublingual buprenorphine group.

Figure 1. Flow Diagram of the ED-Initiated Buprenorphine Validation Network Trial (ED INNOVATION)



COWS indicates Clinical Opiate Withdrawal Scale; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); and ED, emergency department.

[a]All patients in the ED during enrollment periods and able to communicate were screened by a research associate with a general health quiz (eg, smoking and drinking history, opioid use prescribed and unprescribed). Patients unable to be screened due to conditions such as medical illness or known pregnancy were listed as ineligible. Further ineligibility was determined after initial screening due to various reasons (eg, no to minimal withdrawal symptoms [COWS score <4], not meeting opioid use disorder criteria, positive results for methadone on urine screening).

[b]Patients may have been ineligible for multiple reasons.

[c]Knowledge of or anticipated admission.

[d]The COWS is a 10-item, point-based scale of withdrawal symptoms. Each item denotes a different withdrawal symptom (scores of 5-12 indicate mild withdrawal; 13-24, moderate withdrawal; 25-36, moderately severe withdrawal; and ≥37, severe withdrawal).

[e]Patient had no ability to be contacted (ie, housing instability, no telephone, no alternative contacts).

[f]Conditions such as dementia or altered mental status, regardless of admission status.

[g]The randomization sequence was generated in a 1:1 ratio using a permuted-block procedure with random block sizes and stratification by site and insurance status.

Safety Analysis

A total of 22 patients had an increase of 5 points or more in their COWS scores during the course of the trial, triggering a detailed ED record review by study investigators. Overall, the rates of precipitated withdrawal were low at less than 1.0%: 6 (0.6%) in the extended-release buprenorphine group and 8 (0.8%) in the sublingual buprenorphine group. Only 2 of 14 patients with precipitated withdrawal presented with low COWS scores (4-7). Serious adverse events attributable to buprenorphine administration were rare (Table 3).

Additional Medications

Additional buprenorphine during the ED encounter was administered to 86 patients (8.6%) in the extended-release buprenorphine group and to 100 (10%) in the sublingual buprenorphine group. The median doses were 4 mg and 8 mg, respectively, with IQRs of 4 mg to 8 mg in both groups. Ancillary medications were rarely administered (listed in the eTable in Supplement 2). The most common medications were infrequent: antiemetics (8.0%), α_2-agonists (clonidine; 3.8%), nonsteroidal anti-inflammatory drugs (ibuprofen or ketorolac; 3.4%), and acetaminophen (2.9%).

Table 1. Baseline Participant Characteristics

Characteristics	Extended-release buprenorphine (n = 991)	Sublingual buprenorphine (n = 1003)
Sex, No. (%)		
Female	327 (33.0)	319 (31.8)
Male	664 (67.0)	684 (68.2)
Age, median (IQR), y	37 (30-46)	37 (30-48)
Ethnicity, No. (%)		
Hispanic or Latino	150 (15.1)	156 (15.6)
Not Hispanic or Latino	826 (83.4)	840 (83.7)
Other[a]	15 (2.0)	7 (0.6)
Race, No.(%)[b]		
American Indian or Alaska Native	18 (1.8)	18 (1.8)
Asian	9 (0.9)	7 (0.7)
Black or African American	304 (30.7)	308 (30.7)
Multiracial	19 (1.9)	29 (2.9)
Native Hawaiian or Pacific Islander	6 (0.6)	4 (0.4)
White	541 (54.6)	547 (54.5)
Other[c]	94 (9.4)	90 (8.9)
Housing stability, No. (%)[d]		
Unstable in past 12 mo	495 (49.9)	525 (52.3)
Currently in unstable housing	371 (37.4)	370 (36.9)
Insurance status, No./total No. (%)		
None	166/990 (16.8)	162 (16.2)
Public	739/990 (74.6)	753 (75.1)
Private	85/990 (8.6)	88 (8.8)
Education, No./total No. (%)		
Less than high school	231/959 (24)	215/961 (22)
High school graduate or equivalent	509/959 (53)	494/961 (51)
Some college or advanced degrees	219/959 (23)	252/961 (26)
Employment, No./total No. (%)		
Employed	201/980 (20)	212/988 (21)
Unemployed	633/980 (65)	640/988 (65)
Permanent or temporary disability	76/980 (8)	60/988 (6)
Other[e]	70/980 (7)	76/988 (8)
Psychiatric history, No. (%)		
Lifetime psychiatric treatment		
Outpatient	357 (36.0)	383 (38.1)
Inpatient	255 (25.7)	304 (30.3)
Psychiatric evaluation at index emergency department visit	219 (22.0)	218 (21.7)
Treated for any psychological/emotional problems with counseling or medication in past 30 d	124 (12.5)	142 (14.1)
Self-reported overdose in past 30 d, No. (%)		
≥1 Overdose	145 (15)	166 (17)
Opioid overdose, No. of events	232	239
Naloxone reversal[f]	162 (78)	170 (74)
Treated in emergency department	117 (57)	121 (53)
Resulted in hospital admission	21 (10)	18 (8)
Days with opioid use in the past 7 d, median (IQR)	7 (5-7)	7 (5-7)
Days since last reported opioid use, median (IQR)	0 (0-1)	0 (0-1)
Route of opioid use, No./total No. (%)[g]		
Nasal	316/989 (31.9)	292/1002 (29.1)
Intravenous injection	232/989 (23.5)	259/1002 (25.8)
Smoking	227/989 (22.9)	236/1002 (23.6)
Oral	117/989 (11.8)	131/1002 (13.1)
Nonintravenous injection	11/989 (1.1)	13/1002 (1.3)
Emergency department presentation, No. (%)		
Seeking opioid use disorder treatment	211 (21.3)	231 (23.0)
Overdose	73 (7.4)	69 (6.9)
COWS score at enrollment, No. (%)[h]		
4-7	297 (30.0)	312 (31.1)
≥8	694 (70.0)	691 (68.9)
Median (IQR)	10 (7-13)	9 (7-13)
Positive result for substance on point-of-care urine screening, No. (%)		
Fentanyl	747 (75.5)	761 (76.1)
Marijuana	448 (45.2)	453 (45.2)
Buprenorphine	414 (41.8)	386 (38.5)
Methamphetamine	360 (36.3)	372 (37.1)
Cocaine	358 (36.1)	354 (35.3)
Opiates	355 (35.8)	348 (34.7)
Amphetamine	335 (33.8)	340 (33.9)
Benzodiazepines	144 (14.5)	156 (15.6)
Methylenedioxymethamphetamine	92 (9.3)	82 (8.2)
Oxycodone	67 (6.8)	61 (6.1)
Phencyclidine	21 (2.1)	14 (1.4)
Barbiturate	14 (1.4)	11 (1.1)
Opioids plus ≥1 other substance[i]	760 (77)	767 (77)

[a] Other included categories selected by participants including "don't know" or refusal to answer.

[b] Race was reported by participants according to the closed categories specified in this table. Participants could select 1 option.

[c] Other included categories selected by participants including "other" and "don't know" or refusal to answer.

[d] Housing stability information was collected by a research associate as part of the in-person interview in the baseline demographics assessments. Unstable housing refers to living conditions lacking permanence, security, or adequacy and may include frequent moves, eviction risk, homelessness, temporary arrangements (eg, shelters, motels, couch surfing), severe cost burden, overcrowding, or substandard housing quality. Commonly, it is operationalized as lacking a fixed, regular, and adequate nighttime residence.

[e] Other included on leave (sick/maternity), retired, or student.

[f] Percentages are based on the number of self-reported overdoses for which additional information was available: 207 for extended-release buprenorphine and 229 for sublingual buprenorphine.

[g] Highest-risk route of use across any opioid use reported on any day in the 7-day period prior to providing informed consent, in descending frequency.

[h] The Clinical Opiate Withdrawal Scale (COWS) is a 10-item, point-based scale of withdrawal symptoms. Each item denotes a different withdrawal symptom (scores of 5-12 indicate mild withdrawal; 13-24, moderate withdrawal; 25-36, moderately severe withdrawal; and ≥37, severe withdrawal).

[i] Opioids included fentanyl, buprenorphine, opiates, and oxycodone.

Discussion

In this multicenter randomized trial, no difference was detected between groups in the primary outcome of opioid use disorder treatment engagement on day 7 (40.5% in the extended-release buprenorphine group vs 38.5% in the sublingual buprenorphine group). Although more patients overall were engaged in treatment at 30 days, a difference between groups was not detected (43.8% vs 44.9%). ED INNOVATION

Table 2. Treatment Engagement Outcomes

Outcome	Extended-release buprenorphine		Sublingual buprenorphine		Treatment difference, % (95% CI)		Odds ratio (95% CI)		P value
	Unadjusted No./total No. (%)[a]	Adjusted % (95% CI)[b]	Unadjusted No./total No. (%)[a]	Adjusted % (95% CI)[b]	Unadjusted[a]	Adjusted[b]	Unadjusted[a]	Adjusted[b]	
Primary outcome									
Treatment engagement at 7 d (as randomized)[c]	385/854 (45.1)	40.5 (31.3-50.3) [n = 854]	373/870 (42.9)	38.5 (29.5-48.5) [n = 870]	2.2 (−2.5 to 6.9)	1.6 (−2.8 to 6.0)	1.09 (0.9-1.32)	1.08 (0.89-1.32)	.44[d]
Primary outcome by COWS score[e]									
Treatment engagement at 7 d									
COWS score ≥8	252/588 (42.9)	40.9 (31.5-50.9) [n = 588]	259/607 (42.7)	40.5 (31.1-50.7) [n = 607]	0.2 (−5.4 to 5.8)	−0.1 (−5.5 to 5.3)	1.01 (0.80-1.27)	1.02 (0.80-1.30)	.27[f]
COWS score 4-7	133/266 (50)	40.1 (29.6-51.6) [n = 266]	114/263 (43.3)	34.7 (25.0-45.0) [n = 263]	6.7 (−1.8 to 15.0)	5.4 (−2.5 to 13.3)	1.31 (0.93-1.84)	1.26 (0.88-1.81)	
Secondary outcome									
Treatment engagement at 30 d	384/792 (48.5)	43.8 (34.3-53.7) [n = 854]	389/796 (48.9)	44.9 (35.2-55.0) [n = 870]	−0.4 (−5.3 to 4.5)	−1.5 (−6.2 to 3.2)	0.98 (08.1-1.20)	0.96 (0.78-1.18)	.68[d]

[a] Unadjusted analysis including individuals with primary outcome observed.

[b] Model estimates of proportions, treatment differences in proportions, and odds ratios with 95% CIs for those engaged at either 7 days or 30 days were obtained using a repeated-measures generalized estimating equation model weighted by the inverse probability of being observed (ie, not lost to follow-up). Models included treatment, visit, treatment × visit subgroup interaction, site, age, sex, ethnicity, race, housing status, and insurance status. Treatment differences greater than 0 and odds ratios less than 1 indicate greater benefit for extended-release vs sublingual buprenorphine.

[c] Formal treatment engagement corresponded to American Society of Addiction Medicine levels of care 1-4.

[d] P value estimated from the generalized estimating equation model for the adjusted odds ratio.

[e] The Clinical Opiate Withdrawal Scale (COWS) is a 10-item, point-based scale of withdrawal symptoms. Each item denotes a different withdrawal symptom (scores of 5-12 indicate mild withdrawal; 13-24, moderate withdrawal; 25-36, moderately severe withdrawal; and ≥37, severe withdrawal). COWS scores were assessed at the time of enrollment.

[f] P value for interaction comparing treatment odds ratios for COWS scores of 4-7 vs ≥8.

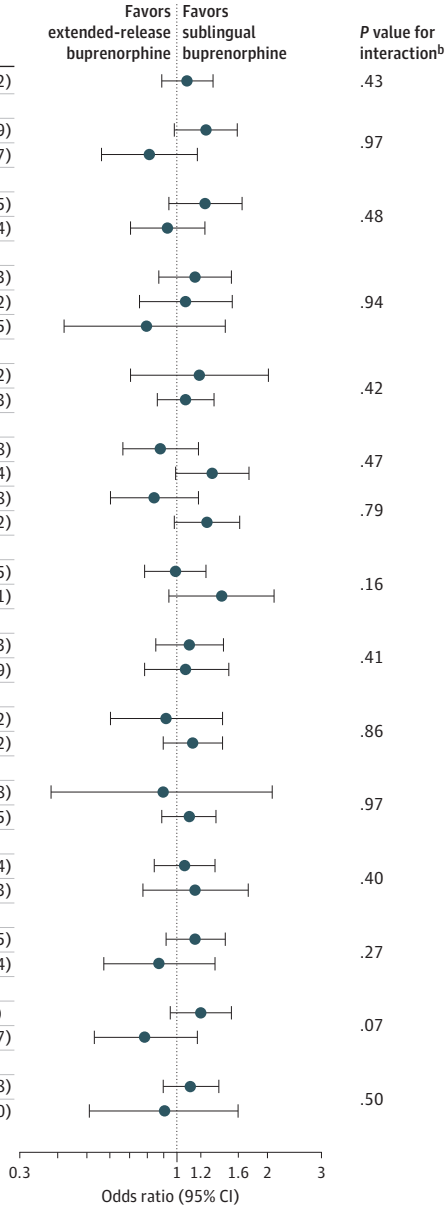
demonstrates that both preparations of buprenorphine can be safely and successfully initiated in a large, geographically diverse sample of US EDs, serving patients with opioid use disorder from varied racial, ethnic, and socioeconomic backgrounds, amid a high prevalence of fentanyl use. The finding that more patients overall were engaged in treatment at 30 days than at 7 days may reflect ongoing lack of timely, open-access follow-up care for opioid use disorder after ED initiation in many communities.

This study highlights the potential for expansion of ED-initiated buprenorphine in high-risk and hard-to-reach patients with fentanyl use, even among those presenting with low levels of withdrawal. Half of the patients in this study reported experiencing unstable housing in the past 12 months, the majority had fentanyl use (76%), and approximately one-third were enrolled below the currently established clinical threshold for buprenorphine initiation, with COWS scores of 4 to 7. Unfortunately, despite evidenced-based care established more than a decade ago,[5] in many EDs where buprenorphine is regularly initiated, patients with low levels of withdrawal (COWS score <8) would receive a referral only, without immediate ED treatment initiation. Although a difference in rate of treatment engagement at 7 days was observed (40.1% vs 34.7% in the extended-release and sublingual groups, respectively), the study may have been underpowered to detect heterogeneity of treatment differences. However, a direct-to-inject option, allowing safe ED administration of a 7-day extended-release buprenorphine treatment to patients with fentanyl use who are having minimal to mild withdrawal symptoms, has the potential to greatly expand the capacity of ED clinicians to start buprenorphine in high-risk patients, who frequently have no other site for medical care. The necessity for immediate treatment was emphasized in a recent retrospective study using encounter-level data from the Epic Cosmos database on buprenorphine administered and/or prescribed in the ED from 2013 to 2022. Of the 745 289 opioid-related encounters in the most recent 3 years, buprenorphine was administered in 16.1% but prescribed in only 5.7%.[9]

The low rate of precipitated withdrawal observed in this study indicates that the protocols for ED-initiated extended-release and sublingual buprenorphine were safe. With 2000 buprenorphine initiations, less than 1% (6 in the extended-release group and 8 in the sublingual group, inclusive of only 2 with COWS scores of 4-7) experienced precipitated withdrawal. The low rate of precipitated withdrawal in the extended-release buprenorphine group may be partially explained by the pharmacokinetics of the 7-day formulation, which allow for a gradual and sustained rise in plasma concentrations over time[15,19] and eliminate the lead-in dose of sublingual buprenorphine that results in a rapid rise in serum plasma levels that may increase the risk of precipitating withdrawal during early abstinence.[21] In addition, clinical and research staff were trained to administer the COWS and practiced together throughout the duration of the study. The COWS[18] was originally developed as a research tool and is imperfect when applied to

Figure 2. Dot Plot of Subgroup Analysis of 7-Day Extended-Release Injectable Buprenorphine vs Sublingual Buprenorphine for the Primary Outcome of Engagement in Opioid Use Disorder Treatment on Day 7

Subgroup	Engagement in opioid use disorder treatment on day 7, No./total No. (%)		Risk difference, % (95% CI)[a]	Odds ratio (95% CI)[a]	*P* value for interaction[b]
	Extended-release buprenorphine	Sublingual buprenorphine			
Overall	385/854 (45)	373/870 (43)	1.6 (-2.8 to 6.0)	1.08 (0.89 to 1.32)	.43
Sex					
Male	274/579 (47)	255/601 (42)	4.8 (-0.5 to 10.0)	1.25 (0.98 to 1.59)	.97
Female	111/275 (40)	118/269 (44)	-4.8 (-12.9 to 3.3)	0.81 (0.56 to 1.17)	
Age, y					
≤37	198/443 (45)	177/451 (39)	4.6 (-1.6 to 10.7)	1.24 (0.94 to 1.65)	.48
>37	187/411 (46)	196/419 (47)	-1.9 (-8.4 to 4.5)	0.93 (0.70 to 1.24)	
Race					
Black	125/273 (46)	113/264 (43)	1.3 (-6.3 to 8.9)	1.07 (0.75 to 1.53)	.94
White	202/455 (44)	198/476 (42)	2.9 (-3.3 to 9.1)	1.15 (0.87 to 1.52)	
Other	34/81 (42)	46/102 (45)	-5.8 (-19.4 to 7.8)	0.79 (0.42 to 1.45)	
Ethnicity					
Hispanic or Latino	54/127 (43)	52/135 (39)	3.8 (-7.8 to 15.3)	1.19 (0.70 to 2.02)	.42
Not Hispanic or Latino	327/714 (46)	318/728 (44)	1.2 (-3.6 to 6.1)	1.07 (0.86 to 1.33)	
Housing stability[c]					
Unstable in prior 12 mo	161/419 (38)	182/444 (41)	-3.0 (-9.4 to 3.3)	0.88 (0.66 to 1.18)	.47
Stable in prior 12 mo	220/425 (52)	190/423 (45)	6.1 (-0.1 to 12.2)	1.31 (0.99 to 1.74)	
Currently unstable	123/315 (39)	131/310 (42)	-4.1 (-11.6 to 3.4)	0.84 (0.60 to 1.18)	.79
Currently stable	258/530 (49)	241/557 (43)	5.2 (-0.3 to 10.7)	1.26 (0.98 to 1.62)	
Urine screening for fentanyl[d]					
Positive	254/633 (40)	256/651 (39)	-0.6 (-5.7 to 4.5)	0.99 (0.78 to 1.25)	.16
Negative	130/220 (59)	115/215 (54)	7.1 (-1.9 to 16.2)	1.41 (0.94 to 2.11)	
Urine screening for stimulants[d]					
Positive	226/534 (42)	207/523 (40)	2.2 (-3.4 to 7.8)	1.10 (0.85 to 1.43)	.41
Negative	159/320 (50)	166/347 (48)	0.8 (-6.4 to 8.0)	1.07 (0.78 to 1.49)	
Seeking referral for opioid use disorder treatment at ED index visit					
Yes	81/190 (43)	91/204 (45)	-2.1 (-11.7 to 7.5)	0.92 (0.60 to 1.42)	.86
No	304/664 (46)	282/666 (43)	2.5 (-2.4 to 7.5)	1.13 (0.90 to 1.42)	
Overdose at ED index visit					
Yes	15/56 (27)	16/58 (28)	-5.8 (-21.3 to 9.7)	0.90 (0.38 to 2.08)	.97
No	370/798 (46)	357/812 (44)	1.9 (-2.7 to 6.5)	1.10 (0.89 to 1.35)	
Injection opioid use					
No	303/635 (48)	282/625 (45)	1.1 (-4.1 to 6.3)	1.06 (0.84 to 1.34)	.40
Yes	78/205 (38)	87/237 (37)	2.8 (-5.8 to 11.4)	1.15 (0.77 to 1.73)	
Psychiatric evaluation at ED index visit					
No	304/670 (45)	283/682 (42)	3.1 (-1.8 to 8.0)	1.15 (0.92 to 1.45)	.27
Yes	81/184 (44)	90/188 (47)	-3.3 (-13.3 to 6.8)	0.87 (0.57 to 1.34)	
Lifetime inpatient psychiatric history					
No	308/632 (49)	268/608 (44)	4.2 (-0.1 to 12.9)	1.2 (0.95 to 1.52)	.07
Yes	77/222 (35)	105/262 (40)	-5.7 (-13.7 to 2.3)	0.78 (0.53 to 1.17)	
History of psychiatric medications/counseling in past 30 d					
No	339/745 (46)	316/748 (42)	2.2 (-2.5 to 6.9)	1.11 (0.90 to 1.38)	.50
Yes	46/109 (42)	57/122 (46)	2.1 (-14.6 to 10.8)	0.91 (0.51 to 1.60)	



ED indicates emergency department. See Table 2 for primary outcome results by baseline Clinical Opiate Withdrawal Scale scores.

[a]Odds ratios and risk differences (with 95% CIs) are based on a repeated-measures generalized estimating equations model assessing engagement at day 7, weighted by the inverse probability of being observed. Models included treatment, visit, treatment × visit × subgroup interaction, site, age, sex, ethnicity, race, housing status, and insurance status. Odds ratios less than 1 and treatment differences greater than 0 indicate greater benefit for extended-release buprenorphine compared with sublingual buprenorphine.

[b]*P* values for interaction testing homogeneity of odds ratios across subgroup levels, with the exception of the overall *P* value, which tests the main effect treatment difference.

[c]Housing stability information was collected by a research associate as part of the in-person interview in the baseline demographics assessments. Unstable housing refers to living conditions lacking permanence, security, or adequacy and may include frequent moves, eviction risk, homelessness, temporary arrangements (eg, shelters, motels, couch surfing), severe cost burden, overcrowding, or substandard housing quality. Commonly, it is operationalized as lacking a fixed, regular, and adequate nighttime residence.

[d]Collected as part of point-of care urine screening during the baseline ED visit.

clinical practice. The study team prioritized the presence of objective signs of withdrawal to determine readiness for buprenorphine initiation. Patient reporting of symptom severity is subjective, which may affect COWS scoring; additionally, opioid withdrawal mimics are common in the ED setting from co-occurring illness or other substances. Given that most patients present with polysubstance use, accurately distinguishing the signs and symptoms specific to opioid withdrawal

Table 3. Additional Secondary Outcomes and Safety Outcomes

Outcomes[a]	Extended-release buprenorphine	Sublingual buprenorphine	Relative risk or difference in means or medians (95% CI)	
			Unadjusted	Adjusted
Overdose in past 30 d[b]				
Patients with opioid overdose, No./total No. (%)	18/773 (2.3)	18/780 (2.3)	1.01 (0.52 to 1.95)	
Opioid overdose, No. (rate)	26 (0.034)	26 (0.033)		
Naloxone reversal, No. (%)	20 (75)	16 (62)		
Treated in the ED, No. (%)	10 (38)	15 (58)		
Hospital admission, No. (%)	3 (12)	0		
Craving score at 7 d, mean (SD)[c]	26.5 (32.8) [n = 829]	30.2 (34.2) [n = 836]	−3.74 (−6.96 to −0.52)	−3.85 (−7.08 to −0.63)[d]
Days with illicit opioid use, mean (SD)[e]				
At 7 d	0.93 (2.04) [n = 839]	1.13 (2.28) [n = 850]	0.82 (0.63 to 1.08)	0.77 (0.68 to 0.95)[f]
At 30 d	1.21 (2.50) [n = 773]	1.37 (2.64) [n = 774]	0.88 (0.65 to 1.20)	0.84 (0.69 to 1.03)[f]
Engagement in treatment for opioid use disorder, No./total No. (%)[g]				
At 7 d	347/854 (40.6)	347/870 (39.9)	1.03 (0.85 to 1.25)	1.00 (0.82 to 1.23)[h]
At 30 d	363/793 (41.0)	369/796 (42.4)	0.98 (0.80 to 1.19)	0.94 (0.76 to 1.17)[h]
ED visits and hospitalizations in past 30 d[i]				
No. (rate) of ED visits	291 (0.31)	388 (0.39)		
Patients with ED visits, No./total No. (%)	188/938 (20.0)	209/987 (21.2)	0.93 (0.75 to 1.16)	
ED visits per patient, No. (%)				
0	750 (80.0)	778 (78.8)		
1-2	161 (17.2)	168 (17.0)		
≥3	27 (2.8)	41 (4.2)		
No. (rate) of hospitalizations	62 (0.066)	76 (0.077)		
Patients with hospitalizations, No./total No. (%)	58/938 (6.2)	72/987 (7.3)	0.84 (0.59 to 1.20)	
Hospitalizations per patient, No. (%)				
0	880 (93.8)	915 (92.7)		
1	55 (5.9)	68 (6.9)		
2-3	3 (0.3)	4 (0.4)		
Patient treatment satisfaction score, mean (SD)[j]	4.12 (1.21) [n = 800]	3.99 (1.27) [n = 829]	0.13 (0.01 to 0.25)	0.13 (0.01 to 0.25)[d]
Treatment Effectiveness Assessment score, median (IQR)[k]				
How much better are you with your drug use?	9.0 (6-10) [n = 829]	8.0 (5-10) [n = 836]	1.0 (0.54 to 1.46)	
Has your health improved?	8.0 (6-9) [n = 828]	7.0 (5-9) [n = 836]	1.0 (0.71 to 1.29)	
How much better are you at taking care of personal responsibilities?	8.0 (5-10) [n = 828]	7.0 (5-10) [n = 836]	1.0 (0.71 to 1.29)	
Are you a better member of the community?	9.0 (7-10) [n = 827]	8.0 (5-10) [n = 836]	1.0 (0.54 to 1.46)	

(continued)

Table 3. Additional Secondary Outcomes and Safety Outcomes (continued)

Outcomes[a]	Extended-release buprenorphine	Sublingual buprenorphine	Relative risk or difference in means or medians (95% CI)	
			Unadjusted	Adjusted
Serious adverse events				
Patients with ≥1 treatment-emergent serious adverse event, No. (%)[l]				
Hospitalization	49 (76.6)	71 (79.8)		
Life-threatening	12 (18.8)	12 (13.5)		
Death	4 (6.3)	3 (3.4)		
Other important medical event[m]	0	5 (5.6)		
Persistent or significant disability or incapacity	0	1 (1.1)		
Relationship of treatment-emergent serious adverse event to study medication, No. (%)[n]				
No	70 (98.6)	99 (98.0)		
Yes	1 (1.4)	2 (2.0)		

Abbreviation: ED, emergency department.

[a] Because of variation in the number of participants providing data, sample sizes used for analysis are reported for each outcome.

[b] Overdose data were collected by self-report.

[c] Craving was assessed using a visual analog scale: "On a scale from 0 to 100 where 0 is definitely not and 100 is definitely so, do you desire opioids at this moment?"

[d] Estimated mean differences were obtained from analysis of covariance adjusted for age, sex, site, race, ethnicity, insurance, and housing status.

[e] Illicit opioid use information was collected by self-report using the timeline follow-back method.

[f] Estimated rate ratios were obtained from a repeated-measures negative binomial mixed model conditioned on baseline number of days of opioid use and adjusted for age, sex, site, race, ethnicity, insurance, and housing status.

[g] Treatment with medications for opioid use disorder, including buprenorphine, methadone, or naltrexone, as opposed to formal opioid use disorder treatment defined per the American Society of Addiction Medicine levels of care 1-4. Patients self-report was verified by the treatment source.

[h] Estimated odds ratios from a repeated-measures weighted generalized estimating equation model adjusted for age, sex, site, race, ethnicity, insurance, and housing status.

[i] The ED Visits and Hospitalizations form collects information about the index ED visit and any visits or hospitalizations between the index visit and 30-day follow-up. Data are acquired for this form by patient self-report and electronic health record query.

[j] Patient treatment satisfaction was collected by self-report of overall experience with medication on a scale from 1 to 5, where 1 is completely ineffective and 5 is completely effective.

[k] The Treatment Effectiveness Assessment is based on self-reported data across 4 domains (substance use, health, lifestyle, and community) on a scale ranging from 1 to 10, where 1 is "none"/"no" and 10 is "much better," collected on day 7.

[l] Treatment-emergent serious adverse events refer to any expected or unexpected adverse events, related or unrelated to the medication studied, occurring at any phase of the study that resulted in any of the listed categories.

[m] Other important medical events included auditory hallucinations, suicidal ideation, exacerbation of schizoaffective disorder, unintentional overdose, and hepatitis B virus infection.

[n] Serious adverse events related to the study medication included 3 episodes of precipitated withdrawal; 2 patients were admitted to the hospital and 1 was discharged after a prolonged ED stay (9 hours) after the initial study dose.

is important for safe and effective buprenorphine initiation. If, after initial buprenorphine administration, patients did not improve or felt worse, they were given additional buprenorphine and ancillary medications to prevent escalation in withdrawal symptoms. Buprenorphine was detected in 40% of baseline urine samples. This may partially be explained by 10% of patients receiving a dose earlier in their ED course (eTable in Supplement 2) or by the availability of buprenorphine in the illicit drug supply.

Craving scores and the number of days with illicit opioid use were lower in the extended-release buprenorphine group, potentially due to the advantage of sustained concentration of buprenorphine over time. However, this did not result in differences in self-reported nonfatal overdoses between groups. The number of repeat ED visits was substantially less in the extended-release buprenorphine group. Emergency departments are strained by growing demand and decreasing compensation, and without sustained funding earmarked for opioid use disorder care, many EDs remain ill-equipped to manage the many common issues that arise after discharge for prescribed sublingual buprenorphine. Thus, reduced returning ED visits with extended-release buprenorphine could be an important advantage for many health systems that justifies the added cost.

Finally, patients in the extended-release buprenorphine group were more satisfied with their overall experience with treatment and responded more positively on all 4 domains of the Treatment Effectiveness Assessment. This assessment acknowledges the complexity of opioid use disorder and captures patient-centered progress across domains ranging among improvement in drug use, health, personal responsibilities, and engagement with the community. Because most patients have difficulty sustaining engagement and continuing their medication use during their first attempt with opioid use disorder treatment, a positive experience with buprenorphine, even if ultimately not resulting in short-term medication continuation, is important, as it may motivate subsequent treatment initiation attempts.

In the context of ongoing ED boarding challenges, it is noteworthy that the protocol developed for ED-initiated buprenorphine did not necessitate prolonged ED stays. Emergency department pathways incorporating both extended-release and sublingual buprenorphine preparations have been developed and are currently available in some electronic health records.[26,27] This study's results further support these ongoing implementation efforts to improve the adoption of ED-initiated buprenorphine.

Limitations

This trial has several limitations. First, all sites were required to develop implementation strategies to initiate buprenorphine and establish partnerships with community clinicians and opioid treatment programs. As a result, scheduled follow-up appointments to bridge clinics and treatment programs may have been more accessible to study participants than would be typical in routine care. Second, COVID-19 interrupted the normal referral processes in many EDs and communities. Third, some data are limited by self-report; however, the primary outcome was verified by the treatment source.[28,29] Conversely, we were not able to verify reports by patients that they were not in treatment, as it would not have been feasible to conduct surveillance at all clinics and programs offering formal opioid use disorder treatment in the surrounding areas. In addition, the self-reported surveys (for example, the timeline follow-back method[23]) are validated measurements in the field of substance use disorders. Fourth, it is possible that episodes of precipitated withdrawal were missed. Patients with low withdrawal in the sublingual group, who received instructions for unobserved self-administration, may have had episodes of precipitated withdrawal that were undetected, or episodes that occurred after the observation period may have been missed. However, it is unlikely that substantial numbers were missed, as follow-up interviews were conducted with 87% of participants and return ED visits were monitored. Also, ED visits often extended beyond the 2-hour observation period to complete study-related activities. Fifth, this study did not have the power to detect a difference between groups in patients presenting with COWS scores of 4 to 7. The direct injection of the 7-day extended-release buprenorphine option may be a valuable strategy to expand access to buprenorphine for high-risk, hard-to-reach patients, particularly in rural or underserved areas. Sixth, the study did not test ED-initiated 30-day extended-release buprenorphine. There is a need for high-quality research regarding these topics.

Conclusions

Among patients in the ED with untreated opioid use disorder, no difference was detected in engagement in treatment at 7 days between the 7-day extended-release injectable and sublingual formulations of buprenorphine. Both were safe and effective in a population with high rates of fentanyl use and housing instability. Precipitated withdrawal was rare.

ARTICLE INFORMATION

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REFERENCES

1. Substance Abuse and Mental Health Services Administration. *Key Substance Use and Mental Health Indicators in the United States: Results From the 2023 National Survey on Drug Use and Health*. HHS publication PEP24-07-021, NSDUH Series H-59. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2024. Accessed February 5, 2025. https://www.samhsa.gov/data/report/2023-nsduh-annual-national-report

2. Post LA, Ciccarone D, Unick GJ, et al. Decline in US drug overdose deaths by region, substance, and demographics. *JAMA Netw Open*. 2025;8(6):e2514997. doi:10.1001/jamanetworkopen.2025.14997

3. Ahmad FB, Cisewski JA, Rossen LM, et al. *Provisional Drug Overdose Death Counts*. National Center for Health Statistics; 2025. Accessed February 5, 2025. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

4. Hébert AH, Hill AL. Impact of opioid overdoses on US life expectancy and years of life lost, by demographic group and stimulant co-involvement: a mortality data analysis from 2019 to 2022. *Lancet Reg Health Am*. 2024;36:100813. doi:10.1016/j.lana.2024.100813

5. D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department–initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. *JAMA*. 2015;313(16):1636-1644. doi:10.1001/jama.2015.3474

6. Herring AA, Rosen AD, Samuels EA, et al. Emergency department access to buprenorphine for opioid use disorder. *JAMA Netw Open*. 2024;7(1):e2353771. doi:10.1001/jamanetworkopen.2023.53771

7. Busch SH, Fiellin DA, Chawarski MC, et al. Cost-effectiveness of emergency department-initiated treatment for opioid dependence. *Addiction*. 2017;112(11):2002-2010. doi:10.1111/add.13900

8. Lu T, Ryan D, Cadet T, et al. Cost-effectiveness of implementation facilitation to promote emergency department-initiated buprenorphine for opioid use disorder. *Ann Emerg Med*. 2025;85(3):205-213. doi:10.1016/j.annemergmed.2024.10.001

9. Chhabra N, Smith D, Dickinson G, et al. Trends and disparities in initiation of buprenorphine in US emergency departments, 2013-2022. *JAMA Netw Open*. 2024;7(9):e2435603. doi:10.1001/jamanetworkopen.2024.35603

10. Hawk KF, Weiner SG, Rothenberg C, et al. Leveraging a learning collaborative model to develop and pilot quality measures to improve opioid prescribing in the emergency department. *Ann Emerg Med*. 2024;83(3):225-234. doi:10.1016/j.annemergmed.2023.08.490

11. Hawk K, Hoppe J, Ketcham E, et al. Consensus recommendations on the treatment of opioid use disorder in the emergency department. *Ann Emerg Med*. 2021;78(3):434-442. doi:10.1016/j.annemergmed.2021.04.023

12. Dekker AM, Schriger DL, Herring AA, Samuels EA. Emergency clinician buprenorphine initiation, subsequent prescriptions, and continuous prescriptions. *JAMA*. 2025;333(14):1232-1241. doi:10.1001/jama.2024.27976

13. Hawk KF, D'Onofrio G, Chawarski MC, et al. Barriers and facilitators to clinician readiness to provide emergency department–initiated buprenorphine. *JAMA Netw Open*. 2020;3(5):e204561. doi:10.1001/jamanetworkopen.2020.4561

14. Substance Abuse and Mental Health Services Administration. *Buprenorphine Quick Start Guide*. Accessed February 5, 2025. https://www.samhsa.gov/sites/default/files/quick-start-guide.pdf

15. D'Onofrio G, Perrone J, Hawk KF, et al; ED-INNOVATION Investigators. Early emergency department experience with 7-day extended-release injectable buprenorphine for opioid use disorder. *Acad Emerg Med*. 2023;30(12):1264-1271. doi:10.1111/acem.14782

16. D'Onofrio G, Hawk KF, Herring AA, et al. The design and conduct of a randomized clinical trial comparing emergency department initiation of sublingual versus a 7-day extended-release injection formulation of buprenorphine for opioid use disorder: Project ED Innovation. *Contemp Clin Trials*. 2021;104:106359. doi:10.1016/j.cct.2021.106359

17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.

18. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35(2):253-259. doi:10.1080/02791072.2003.10400007

19. D'Onofrio G, Herring AA, Perrone J, et al. Extended-release 7-day injectable buprenorphine for patients with minimal to mild opioid withdrawal. *JAMA Netw Open*. 2024;7(7):e2420702. doi:10.1001/jamanetworkopen.2024.20702

20. Dunn KE, Strain EC. Establishing a research agenda for the study and assessment of opioid withdrawal. *Lancet Psychiatry*. 2024;11(7):566-572. doi:10.1016/S2215-0366(24)00068-3

21. Rosado J, Walsh SL, Bigelow GE, Strain EC. Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100 mg of daily methadone. *Drug Alcohol Depend*. 2007;90(2-3):261-269. doi:10.1016/j.drugalcdep.2007.04.006

22. Mee-Lee D, Shulman GD, Fishman MJ. *The ASAM Criteria*. American Society of Addiction Medicine; 2013.

23. Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen JP, eds. *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods*. Humana Press/Springer Nature; 1992:41-72. doi:10.1007/978-1-4612-0357-5_3

24. Ling W, Farabee D, Liepa D, Wu LT. The Treatment Effectiveness Assessment (TEA): an efficient, patient-centered instrument for evaluating progress in recovery from addiction. *Subst Abuse Rehabil*. 2012;3(1):129-136. doi:10.2147/SAR.S38902

25. Robins JM, Rotnitzky A, Zhao LP. Analysis of semi-parametric regression models for repeated outcomes in the presence of missing data. *J Am Stat Assoc*. 1995;90:106-121. doi:10.1080/01621459.1995.10476493

26. Melnick ER, Nath B, Dziura JD, et al. User centered clinical decision support to implement initiation of buprenorphine for opioid use disorder in the emergency department: EMBED pragmatic cluster randomized controlled trial. *BMJ*. 2022;377:e069271. doi:10.1136/bmj-2021-069271

27. Lowenstein M, Perrone J, McFadden R, et al. Impact of universal screening and automated clinical decision support for the treatment of opioid use disorder in emergency departments: a difference-in-differences analysis. *Ann Emerg Med*. 2023;82(2):131-144. doi:10.1016/j.annemergmed.2023.03.033

28. McLellan AT, Alterman AI, Cacciola J, Metzger D, O'Brien CP. A new measure of substance abuse treatment: initial studies of the treatment services review. *J Nerv Ment Dis*. 1992;180(2):101-110. doi:10.1097/00005053-199202000-00007

29. Cacciola JS, Alterman AI, Lynch KG, Martin JM, Beauchamp ML, McLellan AT. Initial reliability and validity studies of the revised Treatment Services Review (TSR-6). *Drug Alcohol Depend*. 2008;92(1-3):37-47. doi:10.1016/j.drugalcdep.2007.06.004