Original Investigation

Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence
A Randomized Clinical Trial

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IMPORTANCE Opioid-dependent patients often use the emergency department (ED) for medical care.

OBJECTIVE To test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine).

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial involving 329 opioid-dependent patients who were treated at an urban teaching hospital ED from April 7, 2009, through June 25, 2013.

INTERVENTIONS After screening, 104 patients were randomized to the referral group, 111 to the brief intervention group, and 114 to the buprenorphine treatment group.

MAIN OUTCOMES AND MEASURES Enrollment in and receiving addiction treatment 30 days after randomization was the primary outcome. Self-reported days of illicit opioid use, urine testing for illicit opioids, human immunodeficiency virus (HIV) risk, and use of addiction treatment services were the secondary outcomes.

RESULTS Seventy-eight percent of patients in the buprenorphine group (89 of 114 [95% CI, 70%-85%]) vs 37% in the referral group (38 of 102 [95% CI, 28%-47%]) and 45% in the brief intervention group (50 of 111 [95% CI, 36%-54%]) were engaged in addiction treatment on the 30th day after randomization ($P < .001$). The buprenorphine group reduced the number of days of illicit opioid use per week from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) vs a reduction from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) in the referral group and from 5.6 days (95% CI, 5.3-5.9) to 2.4 days (95% CI, 1.8-3.0) in the brief intervention group ($P < .001$ for both time and intervention effects; $P = .02$ for the interaction effect). The rates of urine samples that tested negative for opioids did not differ statistically across groups, with 53.8% (95% CI, 42%-65%) in the referral group, 42.9% (95% CI, 31%-55%) in the brief intervention group, and 57.6% (95% CI, 47%-68%) in the buprenorphine group ($P = .17$). There were no statistically significant differences in HIV risk across groups ($P = .66$). Eleven percent of patients in the buprenorphine group (95% CI, 6%-19%) used inpatient addiction treatment services, whereas 37% in the referral group (95% CI, 27%-48%) and 35% in the brief intervention group (95% CI, 25%-37%) used inpatient addiction treatment services ($P < .001$).

CONCLUSIONS AND RELEVANCE Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk. These findings require replication in other centers before widespread adoption.

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Dependence on prescription opioids and heroin is a major public health problem that is increasing in the United States and internationally.[1,2] Opioid agonist treatment, including methadone and buprenorphine, is the most effective treatment and is associated with individual and societal benefits.[3,4] Patients with opioid dependence are at increased risk of adverse health consequences and often seek medical care in emergency departments (EDs). This may include seeking treatment for their substance use disorder, comorbid medical and psychiatric conditions, or acute illnesses and trauma. Currently, the primary option available to the ED for opioid dependence is referral to addiction treatment services. The introduction of buprenorphine/naloxone (hereinafter referred to as buprenorphine), a partial opioid agonist combined with an antagonist, may provide ED physicians the opportunity to initiate effective medication treatment in conjunction with a brief intervention and referral. Buprenorphine is a treatment for opioid use disorder that decreases withdrawal, craving, and opioid use and that can be prescribed by appropriately trained physicians.[5]

Emergency department and primary care screening, brief intervention, and referral to treatment (SBIRT) can reduce unhealthy alcohol use[6,7] and tobacco use.[8] To date, the evidence supporting the efficacy of SBIRT for drug use in ED and primary care settings is limited.[9,10] Three recent trials failed to demonstrate that patients benefited from the method.[11-13] However, no study has focused exclusively on opioid dependence. Due to the profound neurobiological and behavioral changes that characterize opioid dependence, it is likely that a more potent intervention, such as ED-initiated treatment including buprenorphine, will be needed to produce optimal outcomes. This model is similar to other chronic medical conditions such as hypertension, diabetes, and asthma in which ED clinicians initiate or restart treatment. Thus, our study was designed to test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention and facilitated referral (brief intervention), and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care (buprenorphine).

Methods

Setting and Participants

The study was conducted in a large urban teaching hospital. We attempted to screen all patients 18 years or older during select times when research associates were present, using a health quiz that contained questions on prescription opioid and heroin use embedded in a 20-item health questionnaire. Patients were not screened with the health quiz if they were non-English speaking, critically ill, unable to communicate due to dementia or psychosis, suicidal, or in police custody. Patients who indicated that they had nonmedical use of prescription opioids or any heroin use in the past 30 days were further evaluated and excluded if enrolled in formal addiction treatment, had a medical or psychiatric condition that required hospitalization, or required opioid medication for a pain condition. The Mini-International Neuropsychiatric Interview (MINI) was administered to evaluate for opioid dependence using *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) criteria. Patients with a urine sample that tested positive for opioids (opiates or oxycodone) and a MINI score 3 or higher were considered to have met criteria for opioid dependence and were eligible for inclusion. Research associates reviewed the study procedures and protocol and obtained signed informed consent from those interested in participation. Race and ethnicity were collected by self-report. The study sample was enrolled between April 7, 2009, and June 25, 2013. The study was approved by the Human Investigation Committee of Yale School of Medicine.

Treatment Conditions

After screening, enrolled patients were randomized to the referral group, the brief intervention group or the buprenorphine group (**Figure**). Patients in the referral and brief intervention groups did not receive treatment for withdrawal symptoms as part of their participation in the study. The management of withdrawal symptoms for these patients was at the discretion of the treating ED physician.

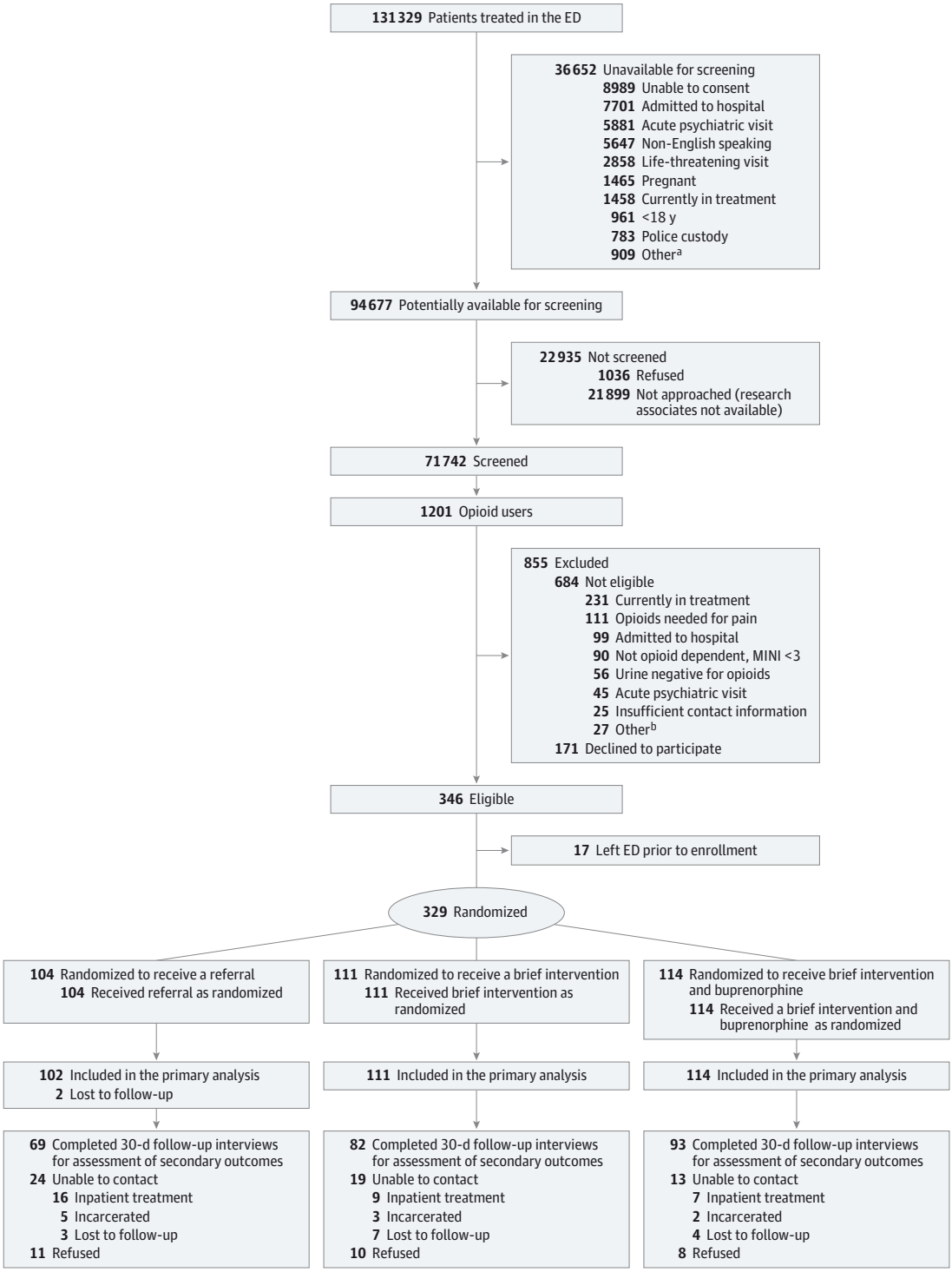
Screening and Referral to Treatment

After undergoing screening, referral patients received a handout from a trained research associate providing names, locations, and telephone numbers of addiction treatment services in the area and telephone access to call a clinician or facility of their choice, which were categorized according to the insurance plans in which they participated. These addiction services included a range of treatments with varying intensity and duration, including opioid treatment programs, inpatient or residential treatment, and outpatient services including intensive outpatient programs and office-based physicians who prescribe buprenorphine or other forms of medication-assisted treatment. The research associate was trained not to use any motivating statements in this simple referral. The conversation was audiotaped to assess for critical actions (fidelity).

Screening, Brief Intervention, and Referral to Treatment

Patients received a 10- to 15-minute manual-driven, audiotaped brief negotiation interview (BNI) from a research associate.[7,14] The Brief Negotiation Interview, previously described,[15] was modified for opioid dependence. It contained 4 components: raise the subject, provide feedback, enhance motivation, and negotiate and advise with a total of 27 critical actions, eg, asking the patient permission to discuss opioid use. The research associate discussed a variety of treatment options in a similar format as what was provided patients in the referral group, based on patient insurance, residence, and preferences. The research associate directly linked the patient with the referral. This included reviewing the patient's eligibility for services, insurance clearance, and arranging transportation.

Figure. Enrollment and Follow-up Flow Diagram for Trial of Interventions for Opioid Dependence



ED indicates emergency department; MINI, Mini-International Neuropsychiatric Interview

[a] Miscellaneous reasons (eg, isolation, sexual assault, deceased).

[b] Miscellaneous reasons (eg, unable to consent, non-English speaking, pregnant, deceased, isolation, age <18 years, police custody).

Screening, Brief Intervention, ED initiated Treatment With Buprenorphine, and Referral

Patients in the buprenorphine group received a Brief Negotiation Interview and ED-initiated treatment with buprenorphine if they exhibited moderate to severe opioid withdrawal.[16] Sufficient take-home daily doses were provided to ensure they had adequate medication until a scheduled appointment in the hospital's primary care center, within 72 hours. Buprenorphine doses were 8 mg on day 1 and 16 mg on days 2 and 3. In the 65 patients (57%) not manifesting opioid withdrawal in the ED, buprenorphine was provided for unobserved (eg, home) induction, with a detailed self-medication guide.[17] Office-based buprenorphine treatment was provided for 10 weeks by physicians and nurses using established procedures with visits ranging from weekly to twice monthly based on clinical stability.[18,19] After 10 weeks, patients were transferred for ongoing opioid agonist maintenance treatment to either a community program or a clinician or were offered detoxification over a 2-week period, based on their stability, insurance, and preference.

Assignment of Treatment

After written consent was obtained, patients completed the baseline assessments and were randomly assigned in a 1:1:1 ratio to 1 of the 3 groups. A computerized stratified randomization procedure[20] under the control of an investigator (M.C.C.) who was not involved with enrollment or assessment for eligibility was used to ensure that the groups were balanced with regard to sex, cocaine use in the last 30 days, and primarily prescription opioid or heroin use. A research associate not involved with assessments or randomization then facilitated the assigned treatment and performed the Brief Negotiation Interview if indicated.

Intervention Fidelity

The referral conversation with patients in the referral group and the Brief Negotiation Interview with patients in either the brief intervention group or the buprenorphine group were audiotaped and reviewed by independent trained raters who were blind to the study design and hypothesis to assess for critical actions that were prescribed and proscribed for each condition.

Outcomes

The primary outcome, *engagement in treatment*, is defined as enrollment and receiving formal addiction treatment on the 30th day following randomization, assessed by direct contact with the facility, clinician, or both. Formal addiction treatment included any of a range of clinical settings including an opioid treatment program, inpatient or residential treatment, and outpatient services including intensive outpatient programs and office-based physicians who prescribe buprenorphine or other forms of medication-assisted treatment. Secondary outcomes collected at 30 days included self-reported number of days of illicit opioid use in the past 7 days, urine toxicology for illicit opioid use, HIV risk-taking behavior using an 11-item validated scale for drug use and sexual behavior,[21] and the use of addiction treatment services.[22] Urine samples collected at 30 days were analyzed using a rapid qualitative immunoassay. Addiction services included inpatient, outpatient, and ED-based services used at any point between study enrollment and the 30th day following randomization. Data on all outcomes were collected by research associates not involved in the patients' ED care.

Sample Size Calculation and Statistical Analysis

Power calculations regarding the adequacy of the sample size were based on data from published reports and reviews of studies investigating the efficacy of SBIRT[9,23] as well as on our previous studies of buprenorphine in primary care.[19] In general, these reports suggest a medium effect size of brief interventions (average effect size of $f = 0.5$) for improving rates of treatment engagement and a small- to moderate-range effect size for reducing drug- or sex-related HIV risk behaviors or for reducing medical consequences ($f = 0.2$ to $f = 0.4$). The sample size of 360 provided power of 0.80 or greater to detect significant differences of this magnitude[24] while taking into consideration potential attrition. This corresponds to a statistical power of 0.80 to detect a difference of 35% or greater between the buprenorphine group and the referral group and a difference of 18% or more between the buprenorphine group and brief intervention group for the primary outcome of engagement in treatment at 30 days. Due to time and financial constraints, we enrolled 329 of the planned 360 patients.

We used χ^2 tests or analysis of variance procedures to examine the baseline comparability of the 3 treatment groups. The χ^2 tests were used to evaluate statistical significance of the differences in engagement in treatment on the 30th day following randomization, rates of opioid-negative urine samples, and rates of use of inpatient addiction treatment, and ED visits. We used the mixed-models procedure repeated measures linear models to evaluate the differences between baseline and 30-day follow-up in the number of days per week of illicit opioid use, HIV risk behaviors, and inpatient addiction services across the study groups. This analytical approach uses all available data on each randomized patient; therefore, all study patients, including those with missing data, were included in the analyses; no imputations were required.[25] All analyses involved 2-tailed tests of significance and were performed using SPSS software, version 21. *P* values less than .05 were considered statistically significant. No interim data examination or analyses were performed.

Results

Demographic and Clinical Characteristics

Baseline characteristic of the 3 groups are shown in **Table 1**. Overall, 34% were seeking treatment for opioid dependence at the index visit and 8.8% presented to the ED with an overdose. The remaining patients were identified through screening. Twenty-five percent reported using only prescription opioids and 53% of the total sample reported intravenous drug use. Other substance use during the 30 days prior to the ED visit was prevalent with 88% reporting using cigarettes, 55% cocaine, 53% cannabis, and 47% sedatives. Drinking alcohol to intoxication was reported in a third of the sample. More than 70% reported a lifetime history of prior drug treatment and 14%

Table 1. Baseline Demographic and Clinical Characteristics of Patients

	No. (%) of Patients[a]			
	Overall (n = 329)	Referral (n = 104)	Brief Intervention (n = 111)	Buprenorphine (n = 114)
Demographic Characteristics				
Men	251 (76.3)	81 (77.9)	84 (75.7)	86 (75.4)
Race/ethnicity				
White	248 (75.4)	78 (75.0)	82 (73.9)	88 (77.2)
Black	23 (7.0)	7 (6.7)	8 (7.2)	8 (7.0)
Hispanic	54 (16.4)	16 (15.4)	21 (18.9)	17 (15.0)
Other	4 (1.2)	3 (2.9)	0	1 (0.9)
Age, mean (SD), y	31.4 (10.6)	31.4 (10.6)	31.9 (9.7)	31 (9.8)
Education				
High school graduate or equivalent	136 (41.3)	40 (38.5)	51 (45.9)	45 (39.5)
Some college	113 (34.4)	33 (31.7)	35 (31.5)	45 (39.5)
≥College degree	20 (6.1)	9 (8.7)	8 (7.2)	3 (2.6)
Usual employment, past 3 y				
Full	172 (52.3)	59 (56.7)	57 (51.4)	56 (49.1)
Part time	84 (25.5)	26 (25.0)	28 (25.2)	30 (26.3)
Married	36 (10.9)	12 (11.5)	10 (9.0)	14 (12.3)
No stable living arrangement, past 30 d	30 (9.1)	8 (7.7)	10 (9.0)	12 (10.5)
Health insurance				
Private/commercial	104 (31.6)	33 (31.7)	33 (29.7)	38 (33.3)
Medicare	6 (1.8)	1 (1.0)	3 (2.7)	2 (1.8)
Medicaid	142 (43.2)	48 (46.2)	46 (41.4)	48 (42.0)
None	71 (21.6)	21 (20.2)	26 (23.4)	24 (21.1)
Primary care physician	138 (41.9)	42 (40.4)	46 (41.4)	50 (43.9)
Usual source of care				
Private physician's office	92 (27.9)	30 (28.8)	26 (23.4)	36 (31.6)
Clinic	88 (26.7)	26 (25.0)	35 (31.5)	27 (23.7)
Emergency department or none	149 (45.3)	48 (46.2)	50 (45.0)	51 (44.7)
Clinical Characteristics				
ED identification of participants				
Seeking treatment for opioid dependence	112 (34.0)	32 (30.8)	34 (30.6)	46 (40.4)
Identified via screening	217 (66.0)	72 (69.2)	77 (69.4)	68 (59.6)
Overdose	29 (8.8)	7 (6.7)	10 (9.0)	12 (10.5)
Primary type of opioid drug used and route of administration				
Prescription	82 (24.9)	31 (29.8)	24 (21.6)	27 (23.7)
Heroin	247 (75.1)	73 (70.2)	87 (78.4)	87 (76.3)
Intravenous use	174 (52.9)	46 (44.2)	66 (59.5)	62 (54.4)
Nonopioid substance use, past mo				
Alcohol to intoxication	113 (34.3)	32 (30.8)	47 (42.3)	34 (29.8)
Sedative	156 (47.4)	56 (53.8)	50 (45.0)	50 (43.9)
Cannabis	174 (52.9)	61 (58.7)	54 (48.6)	59 (51.8)
Cocaine	182 (55.3)	57 (54.8)	66 (59.5)	59 (51.8)
Cigarette	290 (88.1)	91 (87.5)	97 (87.4)	102 (89.4)
Mental health history				
Lifetime psychiatric treatment	168 (51.1)	54 (51.9)	59 (53.2)	55 (48.2)
Inpatient	86 (26.1)	28 (26.9)	29 (26.1)	29 (25.4)
Outpatient	138 (41.9)	49 (47.1)	45 (40.5)	44 (38.6)
Any psychiatric symptom, past 30 d[b]	290 (88.1)	93 (89.4)	96 (86.5)	101 (88.6)
Received treatment for depression, past 30 d	40 (12.2)	9 (8.7)	17 (15.3)	14 (12.3)
PHQ9 score, mean (SD)[c]	12.46 (6.5)	12.72 (6.3)	12.26 (6.5)	12.41 (6.6)

(continued)

Table 1. Baseline Demographic and Clinical Characteristics of Patients (continued)

	No. (%) of Patients[a]			
	Overall (n = 329)	Referral (n = 104)	Brief Intervention (n = 111)	Buprenorphine (n = 114)
Acute psychiatry ED evaluation	77 (23.4)	23 (22.1)	30 (27.0)	24 (21.1)
Lifetime treatment for addiction				
Alcohol	46 (14.0)	17 (16.3)	20 (18.0)	9 (7.9)
Drugs	240 (72.9)	73 (70.2)	88 (79.3)	79 (69.3)

Abbreviations: ED, emergency department; PHQ9, Patient Health Questionnaire.

[a] All patients were screened and referred to a treatment program. Patients in the brief intervention group received a 10- to 15-min manual-driven, audiotaped Brief Negotiation Interview and facilitated referral to a treatment program. Patients in the buprenorphine group received a Brief Negotiation Interview and ED-initiated treatment with buprenorphine if they exhibited moderate to severe opioid withdrawal until a scheduled appointment within 72 h in the hospital's primary care center could be arranged.

[b] From the addiction severity index.

[c] The range of possible scores for the PHQ9[26] is 0 to 27. A score of 5 to 14 suggests the patient may need treatment based on the patient's duration of symptoms and functional impairment. A score of more than 15 warrants treatment for depression, using antidepressant, psychotherapy, or a combination of treatment.

with prior alcohol treatment. Coexisting mental health problems were prevalent with more than half reporting prior psychiatric treatment and 23% of patients requiring a psychiatric evaluation at the index ED visit.

Intervention Participation and Fidelity

A total of 225 patients (100%) in the brief intervention and the buprenorphine groups received a Brief Negotiation Interview at the index ED visit. The mean (SD) Brief Negotiation Interview duration was 10.6 minutes (4.3). The rate of Brief Negotiation Interview critical actions performed was 21.5 of 27 (80%) in the brief intervention group and 20.5 of 27 (76%) in the buprenorphine group. The mean (SD) referral duration was 2.0 minutes (1.3) and the rate of referral critical actions performed was 2.5 of 4 (62%).

Primary Outcome

Engagement in Treatment

Data on enrollment and receiving formal addiction treatment on the 30th day following randomization was obtained by program or by clinician report and was available for 327 of 329 participants (99%). Incarcerated patients were considered not in treatment. Eighty-nine of 114 patients (78%; 95% CI, 70%-85%) in the buprenorphine group were engaged in treatment at significantly higher rates than the 38 of 102 patients (37%; 95% CI, 28%-47%) in the referral group or 50 of 111 patients (45%; 95% CI, 36%-54%) in the brief intervention group ($P < .001$).

Secondary Outcomes

Illicit Opioid Use

Self-report data on illicit opioid use in the past 7 days were collected on 244 of 329 patients (74%), 69 of 104 in the referral group, 82 of 111 in the brief intervention group, and 93 of 114 in the buprenorphine group. This was primarily due to the inability to contact (n = 56); including those who were incarcerated (n = 10), receiving inpatient treatment (n = 22), or lost to follow-up (n = 14). Twenty-nine patients declined the 30-day assessment. The buprenorphine group reported greater reductions in the mean number of days of illicit opioid use per week—from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) than did the referral group, which decreased from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) and the brief intervention group, which decreased from 5.6 days (95% CI, 5.3-5.9) to 2.4 (95% CI, 1.8-3.0). Patients in all groups reduced their illicit opioid use over time ($P < .001$), the between group ($P < .001$), and the group by time interaction ($P = .02$) effects were also statistically significant (**Table 2**).

The overall rate of urine sample collection was 220 of 329 (66.9%): 65 of 104 (63%) in the referral group, 70 of 111 (63%) in brief intervention group, and 85 of 114 (74.6%) in buprenorphine group. The rates of opioid negative urine toxicology test results did not differ statistically across the treatment groups with 53.8% (95% CI, 42%-65%) in the referral group, 42.9% (95% CI, 31%-55%) in the brief intervention group, and 57.6% (95% CI, 47%-68%) in the buprenorphine group having tested negative for opioid use ($P = .17$).

HIV Risk Behaviors

Patients in all 3 groups reported significantly reduced HIV risks from baseline to 30 days ($P < .001$). However, the differences in these reductions were not statistically significant across groups. The risk decreased in the referral group from 8.5 (95% CI, 7.0-9.9) to 5.7 (95% CI, 4.2-7.1); in the brief intervention group from 9.2 (95% CI, 7.8-10.7) to 6.2 (95% CI, 4.9-7.6); and in the buprenorphine group from 9.1 (95% CI, 7.7-10.5) to 5.8 (95% CI, 4.5-7.1) ($P = .66$). The interaction between the time and group effects was not statistically significant ($P = .95$).

Addiction Treatment Service Use

There was no difference in the mean number of outpatient visits across the 3 groups (Table 2). Patients in the referral and brief intervention groups used inpatient addiction treatment services at a higher rate than did those in the buprenorphine group: 37% (95% CI, 27%-48%) in the referral group; 35% (95% CI, 25%-37%) in the brief intervention group; and 11% (95% CI, 6%-19%) in the buprenorphine group ($P < .001$). There were no statistically significant differences in ED use for addiction treatment across the 3 groups ($P = .51$).

Post Hoc Analysis

A post hoc analysis of a subgroup of patients who presented to the ED specifically seeking treatment for opioid depen-

Table 2. Baseline and 30-Day Secondary Outcome Measures Among Opioid-Dependent Patients Treated in the Emergency Department[a]

	Referral	Brief Intervention	Buprenorphine	*P* Value[b]
Days of Self-reported Illicit Opioid Use in the Past 7 Days, Mean (95% CI)				
Baseline	5.4 (5.1-5.7)	5.6 (5.3-5.9)	5.4 (5.1-5.7)	<.001, Treatment effect <.001, Time effect .02, Interaction effect
30 d	2.3 (1.7-3.0)	2.4 (1.8-3.0)	0.9 (0.5-1.3)	
Outpatient Addiction Treatment in the Past 30 Days, Mean (95% CI)[c]				
No. of outpatient visits				
Baseline	0.38 (0.0-1.0)	1.16 (0.6-1.7)	0.20 (0.0-0.8)	.07, Treatment effect <.001, Time effect .63, Interaction effect
30 d	4.99 (3.1-6.8)	5.67 (4.0-7.4)	3.71 (2.1-5.3)	
ED-Based Addiction Treatment in the Past 30 Days, No./Total (%)				
Any addiction-related ED visit				
Baseline	8/104 (7.7)	6/111 (5.4)	5/114 (4.4)	.57
30 d	15/69 (21.7)	12/82 (14.6)	18/93 (19.4)	.51
Inpatient Addiction Treatment in the Past 30 Days, No./Total (%)[d]				
Any inpatient addiction treatment				
Baseline	10/104 (9.6)	7/111 (6.3)	7/114 (6.1)	.55
30 d	31/84 (36.9)	32/91 (35.2)	11/100 (11.0)	<.001

Abbreviation: ED, emergency department.

[a] All patients were screened and referred to a community-based treatment service. Patients in the brief intervention group received a 10- to 15-min manual-driven, audiotaped Brief Negotiation Interview and facilitated referral to treatment services. Patients in the buprenorphine group received a Brief Negotiation Interview and ED-initiated treatment with buprenorphine if they exhibited moderate to severe opioid withdrawal until a scheduled appointment within 72 hours in the hospital's primary care center could be arranged.

[b] χ^2 Test with 2 degrees of freedom used to test for differences in inpatient and ED treatment. Mixed-model procedures used to test for differences in days of self-reported illicit opioid use and outpatient addiction treatment; thus, all patients in the sample were included. Treatment × time effect = interaction effect.

[c] Includes both office-based and addiction treatment center visits.

[d] Includes residential and hospital-based treatment.

dence found that rates of treatment engagement at 30 days across the groups were not significantly different from the entire sample: 32 of 46 (70%; 95% CI, 55%-81%) in the buprenorphine; 20 of 34 (59%; 95% CI, 42%-74%) in the brief intervention group; and 13 of 31 (42%; 95% CI, 26%-59%) in the referral group (P = .054).

Discussion

In a diverse group of opioid-dependent patients with substantial psychiatric and substance use-related comorbidity, ED-initiated buprenorphine with primary care office-based follow-up for ongoing treatment resulted in a greater percentage of individuals engaged in treatment and fewer days of self-reported illicit opioid use than did referral or SBIRT. The majority of patients who were provided a referral, with or without facilitation, were not engaged in addiction treatment at 30 days.

Our findings demonstrate that ED-initiated buprenorphine with coordinated follow-up for ongoing treatment was more effective than referral with or without brief intervention. To our knowledge, this is the first randomized controlled trial comparing outcomes across these treatment strategies. An earlier observational study helped establish the feasibility of ED-initiated buprenorphine, yet there was no follow-up comparing alternative referral options or evaluating buprenorphine's effect on treatment engagement, drug use, or addiction treatment service use.[27] Few studies have examined the efficacy of SBIRT for drug use.[9,10,28,29] Recent studies in primary care and ED settings[11-13] addressing a broad spectrum of drug type and intensity of drug use found no benefit to SBIRT. The US Preventive Services Task Force[30] has determined that there is insufficient evidence to recommend this practice. However, none of these earlier studies focused exclusively on opioid-dependent ED patients, and none included ED-initiated treatment.

Both of our referral treatments had some success in engaging patients in treatment. Of note, however, the referral group received detailed referral information about community services tailored to their insurance status and the brief intervention group received a psychosocial intervention with a facilitated referral. Both of these interventions go beyond the current standard of ED care and the level of intervention in the referral group may have diminished our ability to detect a difference between the referral and brief intervention groups. The rates of negative urine toxicology test results for illicit opioids were not significantly different across groups. Because opioids can be detected in the urine for approximately 72 hours, collection at a single time point may not accurately reflect the frequency or intensity of opioid use. This decrease in urine sensitivity for drug use may account for the discrepancy between the self-reported number of days of opioid use per week and the urine test results.

Detection and initiation of treatment for chronic and relapsing medical conditions (eg, hypertension, diabetes, and asthma) is standard ED practice. There are promising results on the initiation of smoking cessation treatment.[31,32] The current study extends this work to opioid use disorders, a chronic and relapsing

medical condition that EDs are increasingly encountering.[1] It also extends the literature on "interim" opioid agonist treatment whereby medication treatment is initiated while the patient is awaiting more comprehensive treatment services.[33] The increasing prevalence of opioid use disorders and the increasing toll of overdose deaths due to opioids[2] amplifies the urgency to decrease barriers, such as the delays that can occur with treatment referrals to accessing treatment.

Patients in the buprenorphine group were less likely to use inpatient addiction treatment, suggesting more efficient, less costly resource use. In addition the buprenorphine group was more likely to be engaged in treatment on the 30th day following randomization. While the costs of implementing this intervention need to be considered, including screening costs, these findings are likely to be of interest to individuals or organizations responsible for downstream service costs through episode-based or capitated payment.

Our findings should be considered in light of study design features and limitations. The ED physicians who participated in this study underwent the required training to allow them to prescribe buprenorphine.[5,34] Such training has been incorporated into some residencies,[35] and more than 40 000 physicians have completed it as of 2014. In addition, specific exemptions do exist that currently allow physicians to administer buprenorphine or methadone for the purpose of relieving acute withdrawal symptoms while arranging for referral for ongoing treatment.[36] Prior to implementation, an ED would need to develop a system to correctly diagnose opioid use disorder among those who are misusing opioids. Research staff provided the referrals and performed the Brief Negotiation Interview. In our prior work addressing unhealthy alcohol use, we trained ED practitioners to provide brief interventions[7,14,37] and used health promotion advocates to provide referrals for individuals with substance use disorders.[38] The buprenorphine and the counseling care provided in the study were provided at no expense to the patients. This design feature could potentially bias our results because financial barriers could impact treatment outcomes. We believe this is unlikely because 80% of study patients had health insurance. The study design and its implementation were selected to ensure that costs, insurance coverage, or policies such as prior authorizations would not present barriers to patients accessing the unique services in the buprenorphine group. In light of our findings, future research could be conducted to determine the extent to which reimbursement and coverage barriers impact treatment outcomes.

Although we assessed the use of addiction treatment services, a full-scale cost-effectiveness evaluation is beyond the scope of this article. The buprenorphine group received both ED-initiated buprenorphine and a specific model of follow-up care. It is not possible to disentangle these 2 components in our study and future research should evaluate ED-initiated buprenorphine and referral to a variety of treatment settings. We did not achieve our anticipated sample size but our findings are robust. We were underpowered to perform subgroup analyses. We screened a large number of patients to achieve our sample size; however, in a real-world setting, some excluded patients would be eligible for ED-initiated treatment, such as non–English speakers, patients who were hospitalized, and patients who refused study participation. Finally, 30 days is a short time horizon for a chronic and relapsing condition such as opioid dependence. However, it is unlikely that care provided in the ED will influence results beyond 30 days.

Emergency department–initiated buprenorphine is feasible based on the results of our study, a previous report,[27] and the published research supporting the use of unobserved buprenorphine induction.[17,39] Emergency department clinicians who are interested in providing this treatment should work to identify a network of community-based treatment services for follow-up care. Now that the feasibility and efficacy have been established, future research should focus on assessing the effectiveness and implementation of buprenorphine. In addition, research is needed to improve the efficacy of using a brief intervention for drug use disorders, particularly promoting short-term treatment engagement. The American College of Emergency Physicians should consider broadening the scope of its position statement that indicates that emergency physicians "are positioned and qualified to mitigate the consequences of alcohol abuse through screening programs, brief intervention, and referral to treatment" to include opioid use disorders. Expanded use of ED-initiated buprenorphine with community follow-up should help increase access to treatment options for this chronic and relapsing medical condition that has substantial morbidity and mortality and that affects health care use and costs.

Conclusions

Among opioid-dependent patients presenting for emergency care, ED-initiated buprenorphine, compared with brief intervention and referral, significantly increased engagement in formal addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of positive urine testing for opioids or HIV risk. Although this single-site study supports this ED-initiated treatment strategy, these findings require replication in other centers before widespread adoption.

ARTICLE INFORMATION

Author Contributions: Drs D'Onofrio, Fiellin, and Chawarski had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: D'Onofrio, O'Connor, Pantalon, Chawarski, Busch, Fiellin.
Acquisition, analysis, or interpretation of data: D'Onofrio, O'Connor, Pantalon, Chawarski, Busch, Owens, Bernstein, Fiellin.
Drafting of the manuscript: D'Onofrio, O'Connor, Pantalon, Chawarski, Fiellin.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Chawarski.
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Study supervision: D'Onofrio, O'Connor, Pantalon, Bernstein, Fiellin.

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Disclosure of Potential Conflicts of Interest. Dr Fiellin reported that he has received honoraria from Pinney Associates for serving on an external advisory board monitoring the diversion and abuse of buprenorphine. No other disclosures were reported.

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REFERENCES

1. Centers for Disease Control and Prevention (CDC). Emergency department visits involving nonmedical use of selected prescription drugs—United States, 2004-2008. *MMWR Morb Mortal Wkly Rep*. 2010;59(23):705-709.

2. Centers for Disease Control and Prevention (CDC). CDC grand rounds: prescription drug overdoses—a US epidemic. *MMWR Morb Mortal Wkly Rep*. 2012;61(1):10-13.

3. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database Syst Rev*. 2011;8(8):CD004145.

4. *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*. Geneva, Switzerland: World Health Organization; 2009.

5. Sullivan LE, Fiellin DA. Narrative review: buprenorphine for opioid-dependent patients in office practice. *Ann Intern Med*. 2008;148(9):662-670.

6. Jonas DE, Garbutt JC, Amick HR, et al. Behavioral counseling after screening for alcohol misuse in primary care: a systematic review and meta-analysis for the US Preventive Services Task Force. *Ann Intern Med*. 2012;157(9):645-654.

7. D'Onofrio G, Fiellin DA, Pantalon MV, et al. A brief intervention reduces hazardous and harmful drinking in emergency department patients. *Ann Emerg Med*. 2012;60(2):181-192.

8. Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz N, Curry SJ; 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update US Public Health Service Clinical Practice Guideline executive summary. *Respir Care*. 2008;53(9):1217-1222.

9. Bernstein J, Bernstein E, Tassiopoulos K, Heeren T, Levenson S, Hingson R. Brief motivational intervention at a clinic visit reduces cocaine and heroin use. *Drug Alcohol Depend*. 2005;77(1):49-59.

10. Bernstein E, Edwards E, Dorfman D, Heeren T, Bliss C, Bernstein J. Screening and brief intervention to reduce marijuana use among youth and young adults in a pediatric emergency department. *Acad Emerg Med*. 2009;16(11):1174-1185.

11. Saitz R, Palfai TP, Cheng DM, et al. Screening and brief intervention for drug use in primary care: the ASPIRE randomized clinical trial. *JAMA*. 2014;312(5):502-513.

12. Roy-Byrne P, Bumgardner K, Krupski A, et al. Brief intervention for problem drug use in safety-net primary care settings: a randomized clinical trial. *JAMA*. 2014;312(5):492-501.

13. Bogenschutz MP, Donovan DM, Mandler RN, et al. Brief intervention for patients with problematic drug use presenting in emergency departments: a randomized clinical trial. *JAMA Intern Med*. 2014;174(11):1736-1745.

14. D'Onofrio G, Pantalon MV, Degutis LC, et al. Brief intervention for hazardous and harmful drinkers in the emergency department. *Ann Emerg Med*. 2008;51(6):742-750.e2.

15. D'Onofrio G, Pantalon MV, Degutis LC, Fiellin DA, O'Connor PG. Development and implementation of an emergency practitioner-performed brief intervention for hazardous and harmful drinkers in the emergency department. *Acad Emerg Med*. 2005;12(3):249-256.

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

17. Lee JD, Grossman E, DiRocco D, Gourevitch MN. Home buprenorphine/naloxone induction in primary care. *J Gen Intern Med*. 2009;24(2):226-232.

18. Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. *Am J Med*. 2013;126(1):74.e11-74.e17.

19. Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med*. 2006;355(4):365-374.

20. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet*. 2002;359(9305):515-519.

21. Darke S, Hall W, Heather N, Ward J, Wodak A. The reliability and validity of a scale to measure HIV risk-taking behaviour among intravenous drug users. *AIDS*. 1991;5(2):181-185.

22. 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.

23. Stein MD, Charuvastra A, Maksad J, Anderson BJ. A randomized trial of a brief alcohol intervention for needle exchangers (BRAINE). *Addiction*. 2002;97(6):691-700.

24. Barber J, Critis-Christoph P. Development of a therapist adherence/competence rating scale for supportive-expressive dynamic psychotherapy. *Psychother Res*. 1996;6(2):81-94.

25. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the *Archives of General Psychiatry*. *Arch Gen Psychiatry*. 2004;61(3):310-317.

26. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.

27. Berg ML, Idrees U, Ding R, Nesbit SA, Liang HK, McCarthy ML. Evaluation of the use of buprenorphine for opioid withdrawal in an emergency department. *Drug Alcohol Depend*. 2007;86(2-3):239-244.

28. Humeniuk R, Ali R, Babor T, et al. A randomized controlled trial of a brief intervention for illicit drugs linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in clients recruited from primary health-care settings in four countries. *Addiction*. 2012;107(5):957-966.

29. Madras BK, Compton WM, Avula D, Stegbauer T, Stein JB, Clark HW. Screening, brief interventions, referral to treatment (SBIRT) for illicit drug and alcohol use at multiple healthcare sites. *Drug Alcohol Depend*. 2009;99(1-3):280-295.

30. Drug use, illicit screening. US Preventive Services Task Force web page. http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/drug-use-illicit-screening. Released January 2008. Accessed November 12, 2014.

31. Bernstein SL, Bijur P, Cooperman N, et al. Efficacy of an emergency department-based multicomponent intervention for smokers with substance use disorders. *J Subst Abuse Treat*. 2013;44(1):139-142.

32. Rabe GL, Wellmann J, Bagos P, et al. Efficacy of emergency department-initiated tobacco control. *Nicotine Tob Res*. 2013;15(3):643-655.

33. Schwartz RP, Highfield DA, Jaffe JH, et al. A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry*. 2006;63(1):102-109.

34. Fiellin DA, O'Connor PG. New federal initiatives to enhance the medical treatment of opioid dependence. *Ann Intern Med*. 2002;137(8):688-692.

35. Kunins HV, Sohler NL, Giovanniello A, Thompson D, Cunningham CO. A buprenorphine education and training program for primary care residents. *Subst Abus*. 2013;34(3):242-247.

36. Prescriptions. Food and Drugs, Drug Enforcement Administration, Department of Justice. 21 *CFR* 1306.07(b), 71-72.

37. Pantalon MV, Martino S, Dziura J, et al. Development of a scale to measure practitioner adherence to a brief intervention in the emergency department. *J Subst Abuse Treat*. 2012;43(4):382-388.

38. D'Onofrio G, Degutis LC. Integrating Project ASSERT: a screening, intervention, and referral to treatment program for unhealthy alcohol and drug use into an urban emergency department. *Acad Emerg Med*. 2010;17(8):903-911.

39. Gunderson EW, Wang XQ, Fiellin DA, Bryan B, Levin FR. Unobserved versus observed office buprenorphine/naloxone induction. *Addict Behav*. 2010;35(5):537-540.