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Effects of access barriers and medication acceptability on buprenorphine-naloxone treatment utilization over 2 years: Results from a multisite randomized trial of adults with opioid use disorder

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Abstract

Background: Nationwide efforts seek to address the opioid epidemic by increasing access to medications for opioid use disorder (OUD), particularly with buprenorphine. A poorly understood challenge is that among individuals with OUD who do receive buprenorphine, many do not adhere to the pharmacotherapy long enough to achieve sustained benefits. We aimed to identify factors associated with buprenorphine treatment utilization over time.

Methods: We used random-intercept modeling to identify factors associated with buprenorphine treatment utilization over 2 years after first follow-up by 789 individuals with OUD who had participated in a multi-site randomized clinical trial of buprenorphine compared to methadone. Key predictors were participants' reports of buprenorphine treatment accessibility and acceptability (assessed at first follow-up) and their interaction effects, controlling for baseline randomization status, sociodemographics, and other covariates.

Results: Approximately 9.3 – 11.2% of participants utilized buprenorphine treatment over the 2 years of follow-up. Interaction effects indicated that individuals who perceived buprenorphine to

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Contributors

EE, DH, and YH were responsible for the study design. CY and DH performed data analysis and interpreted the data. EE, AS, and YH interpreted findings. EE, CY, and DH drafted the manuscript. All authors critically reviewed content and approved the final version of the manuscript.

Declaration of Interest

Authors disclosing relevant financial interests, activities, relationships, and affiliations are:

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be both accessible and acceptable were most likely to use buprenorphine during follow-up, controlling for other factors. In contrast, individuals who perceived buprenorphine to be unacceptable were least likely to use buprenorphine, regardless the level of perceived access to the medication. Buprenorphine treatment utilization was also negatively associated with Hispanic ethnicity, West coast context, and cumulative months receiving methadone treatment and incarceration during follow-up.

Conclusions: To engage more individuals with OUD in long-term treatment with buprenorphine, interventions should target buprenorphine treatment acceptability, in addition to increasing buprenorphine access, and tailor efforts to meet the needs of vulnerable populations.

Trial registration: The START Follow-up Study on ClinicalTrials.gov ().

Keywords

buprenorphine; treatment acceptability, access, and utilization; opioid use disorder; pharmacotherapy; longitudinal

1. Introduction

The U.S. opioid epidemic has resulted in extraordinary numbers of accidental injuries, infectious diseases, and premature deaths (Hedegaard et al., 2017), contributing to a historically unprecedented shortening of American life expectancy (Hedegaard et al., 2017; Kochanek et al., 2017). Opioid use disorder (OUD) is typically a chronic condition (Evans & Hser, 2019; Hser et al., 2017, 2007; Nosyk et al., 2014) that requires long-term, or even life-long treatment with medications (e.g., methadone, buprenorphine-naloxone, hereafter referred to as buprenorphine; U.S. Department of Health and Human Services [HHS], 2016). Individuals with OUD who adhere to treatment with medications have lower mortality (Degenhardt et al., 2011; Evans et al., 2015), less opioid use (Hser et al., 2016; Thomas et al., 2014), less HIV risk, and other positive outcomes (Evans et al., 2019; Mattick et al., 2014; Woody et al., 2014). When used appropriately, methadone and buprenorphine are both effective medications for the long-term stabilization of individuals with OUD (Bart, 2012; Bell et al., 2009; Connock et al., 2007; Mattick et al., 2008). Methadone is a Schedule II, full opioid agonist that has been used in the U.S. for almost five decades in licensed specialty opioid treatment programs. In contrast, buprenorphine is a Schedule III partial agonist approved for use in the U.S. in 2002 and available in general health care settings. In addition to buprenorphine's greater ease of access, its abuse potential is lower than methadone, and it has a higher margin of safety (Bonhomme et al., 2012; Gryczynski et al., 2013; Whelan and Remski, 2012). Despite the advantages of buprenorphine, individuals remain engaged in buprenorphine treatment for less time than those who receive methadone (Burns et al., 2015; Hser et al., 2016; Proctor et al., 2014). Few studies have examined factors that influence use of buprenorphine over time; thus, why buprenorphine is underutilized despite its potential advantages is poorly understood. The present study aims to explore factors associated with utilization of buprenorphine for individuals with opioid use disorder.

Studies of buprenorphine utilization have mostly identified individual-level factors associated with use. For example, one study that compared patients treated with

buprenorphine or methadone reported that individuals receiving buprenorphine are more likely than those receiving methadone to be male, have health insurance, be employed, abuse prescription opioids, and have HIV (Fingerhood et al., 2014). Furthermore, studies focused on buprenorphine report that retention in buprenorphine treatment is positively associated with female gender, older age, psychiatric diagnosis, and receipt of prescribed psychiatric medications, and it has been negatively associated with unemployment, Hepatitis C, Black and Hispanic race/ethnicity, and cocaine use (Haddad et al., 2013; Weinstein et al., 2017). A few studies have solicited patient-reported reasons for choosing buprenorphine over methadone. Within this literature, Gryczynski and colleagues found that some individuals perceive buprenorphine to have less severe withdrawal than methadone and fewer unpleasant physical effects (Gryczynski et al., 2013). Individuals have attributed discontinuation of buprenorphine to lack of knowledge, opioid craving and withdrawal symptoms, poor social support, and the experience that buprenorphine works “too well” such that euphoric effects of illicit opioid use cannot be felt (Teruya et al., 2014).

Much less is known about contextual forces that influence access to buprenorphine for individuals with OUD. This gap in knowledge is striking given that individuals’ ability to access buprenorphine is thought to be impacted by several external forces. These include the slow adoption of buprenorphine by U.S. office-based treatment settings (Li et al., 2014), the limited number of health care providers who are willing or able to prescribe buprenorphine (DeFlavio et al., 2015; Netherland et al., 2009; Rosenblatt et al., 2015; Stein et al., 2015), negative perceptions of buprenorphine by treatment payers and regulators (Molfenter et al., 2015), gaps in treatment need versus capacity (Jones et al., 2015), and restrictive policies, such as mandatory counseling, that may function as access barriers (Walley et al., 2008).

Findings suggest that, in addition to sociodemographic characteristics, there are ways in which buprenorphine treatment utilization may be influenced by individual knowledge and attitudes and also contextual forces that shape real or perceived opportunity to access buprenorphine. Here we investigate the extent to which individual knowledge and attitudes toward buprenorphine and access barriers to care are associated with use of buprenorphine over time, while controlling for the effect of sociodemographics, medication received at baseline, and other covariates.

2. Materials and Methods

2.1. Study design

Data were provided by a large multisite prospective study that examined the long-term outcomes of participants who had been randomized to buprenorphine (as buprenorphine/naloxone) (BUP) or methadone (MET). The parent study “Starting Treatment with Agonist Replacement Therapy” (START) was a phase IV, post-marketing study designed to examine the comparative effects of buprenorphine and methadone on indices of liver health in participants with DSM-IV opioid dependence (Saxon et al., 2013). START involved nine federally licensed opioid treatment programs (located in five states: California, Oregon, Washington, Pennsylvania, and Connecticut) that together randomized 1,269 individuals to receive either buprenorphine (n=740) or methadone (n=529) during 2006-2009. Participants were offered medication for 24 weeks and then were tapered off over ≤8 weeks or referred

for ongoing clinical treatment. Midway through the study, the randomization scheme was switched from 1:1 buprenorphine:methadone to 2:1 because of higher drop out in the buprenorphine arm. This change accounts for more participants in the follow-up sample having been randomized to buprenorphine.

Using an intent-to-treat design, a follow-up study of all randomized participants was conducted during 2011-2014, consisting of 3 follow-up interviews completed approximately 2 to 8 years (mean 4.5) post-randomization (Hser et al., 2016). The findings reported here utilize data on START participants who completed the first follow-up and one additional follow-up. Of the 1,080 participants who were targeted for follow-up, 89.4% (n=965) were located with 797 interviewed (73.7% of subjects randomized to buprenorphine; 73.6% of subjects randomized to methadone); among the 168 participants located but not interviewed, 49 were deceased, 54 refused, 29 were incarcerated, and 36 were too mentally ill or otherwise unable to be interviewed. Eight of those interviewed were omitted from the present analysis because of missing data, yielding an analytic sample of 789. There were no differences in the demographic characteristics of participants included and omitted from analysis.

2.2. Interview procedures

Research staff at the clinics where participants were originally recruited conducted follow-up interview 1 face-to-face approximately 2-7 years (mean 4.2) post-randomization and obtained a urine sample for drug testing. UCLA staff conducted follow-up interviews 2 and 3 over the telephone approximately 1 (mean 1.3) and 2 (mean 2.4) years, respectively, after follow-up interview 1. Participants were compensated according to local policies, which generally consisted of a $50-$70 gift card for each follow-up interview and $10 for a urine sample. All study procedures were approved by the Institutional Review Board (IRB) at UCLA and by the local site IRBs. A federal Certificate of Confidentiality was obtained to protect against disclosure of sensitive information.

2.3. Primary measures

The dependent variable is self-reported receipt of any prescribed buprenorphine-naloxone over 24 months after follow-up 1 as collected from participants using timeline follow back (TLFB) methodology (Sobell and Sobell, 1992) aided by a calendar and other memory prompts (Hser et al., 1992; Murphy et al., 2010). The TLFB was used to collect buprenorphine treatment use over time from START enrollment to follow-up 1, from follow-up 1 to follow-up 2, and from follow-up 2 to follow-up 3. Data collected at follow-up 1 included utilization of buprenorphine as provided by the original START trial. Therefore, in the present analysis we examined utilization of any buprenorphine during the 24 months after follow-up 1, when participation in the trial had already ended. Finally, given that individuals treated for OUD may have the opportunity to receive either methadone or buprenorphine, we included in analyses individuals who had been randomized by the START trial to methadone in addition to those who had been randomized to buprenorphine.

A key independent variable is buprenorphine accessibility, that is, the extent to which participants reported having experienced barriers to accessing buprenorphine treatment.

Participants were asked at follow-up 1 to indicate whether any of 5 factors affect their ability to access buprenorphine treatment when needed (shown in Table 2). Indicators were analyzed separately and then aggregated into one buprenorphine accessibility composite score. To calculate the composite score, a value was assigned to each indicator: 0 for participants who indicated on a single item having no problem accessing buprenorphine treatment when needed and −1 for responses that indicated a constrained or limited ability to access such care. Indicators included: inability to afford buprenorphine because of no health insurance or no pocket money; inability to find free buprenorphine; inability to find a nearby doctor or clinic that prescribed buprenorphine; and inability to receive buprenorphine treatment during the clinic's usual hours. Instances in which a participant did not indicate a constrained or limited ability to access such care (i.e., those with knowledge of buprenorphine or did not have problem getting it) were coded as 0. A negative value was assigned for each indicator since the questionnaire measures barriers to access. Values were summed such that a higher composite score (possible range was −5 to 0) indicated greater accessibility to buprenorphine.

Another key independent variable is buprenorphine acceptability, that is, the extent to which participants express negative attitudes towards buprenorphine medication as self-reported at follow-up 1 in response to 6 items (see Table 3). Indicators were analyzed separately and then aggregated into one composite score. To calculate the composite score, a value of −1 was assigned to each item that indicated participants' unwillingness to take buprenorphine if it were made available due to reasons that included: dislike of buprenorphine; having heard bad things about buprenorphine; negative physical reactions to buprenorphine; other unwanted side effects; reports that the effect of buprenorphine is not strong enough; and the inability to feel the effects of opioids when also taking buprenorphine. Instances in which a participant did not report such attitudes/experiences (i.e. those without knowledge of buprenorphine or currently taking buprenorphine) were coded as 0. A negative value was assigned for each indicator since the questionnaire measures negative attitudes toward buprenorphine. Values were summed such that a higher composite score (possible range was −6 to 0) indicated stronger acceptability of buprenorphine.

Covariates are conceptualized as person-level predisposing and enabling factors and were selected based on prior findings from this cohort (Hser et al., 2017, 2016). Sociodemographic baseline variables as provided by the parent study include age, gender, race/ethnicity, education level, injection drug use, a cocaine positive urine test, and site (West vs. East coast). Also, included as covariates were experiences after follow-up 1 of methadone treatment and incarceration.

The key measures, sources of data, measurement points, and time horizon of the analysis are outlined in Figure 1.

2.4. Statistical analysis

Group differences between participants randomized to buprenorphine and methadone treatments were examined using chi-square test for categorical variables and t-test for continuous variables. Analyses were designed to examine the association between participant utilization of buprenorphine over the 24-month period after follow-up 1 and

participant indicators of buprenorphine accessibility and acceptability as measured at follow-up 1, while also considering participants' baseline randomization status, socio-demographic characteristics, and experiences of incarceration and methadone treatment. First, we computed utilization of buprenorphine treatment at each month over the 24-month follow-up period and plotted the resulting trajectory. Based on the plot, we then applied the generalized linear mixed effects model with a logit function to estimate the trajectory of buprenorphine treatment utilization over the 24-month period. Unstructured covariance was selected, as this model best fit the data with the lowest Akaike (AIC) and Bayesian (BIC) information criteria values (Schwarz, 1978). To examine the association between buprenorphine treatment accessibility and acceptability, participant characteristics, and subsequent buprenorphine treatment utilization over the two-year follow-up period, we built and tested models of greater complexity with stepwise inclusion of covariates. We present two models here. Covariates included randomization condition, and buprenorphine accessibility and acceptability scores. Demographics (e.g., age, gender, race, education), history of cocaine use, drug injection, treatment site, and cumulative methadone treatment utilization over 24 months were included as controlling covariates. Incarceration status was included as a time-varying covariate. Finally, we included a buprenorphine acceptability x buprenorphine accessibility interaction term.

The proportion of missing in each variable was less than 5%, except for incarceration status (27.3%). Missing data were imputed using a multiple imputation method. Ten datasets were generated, and the imputation was informed by the variables in the analysis. Estimates from the 10 datasets were pooled using PROC MI and MIANALYZE (Johnson and Young, 2011; von Hippel, 2009; Yuan, 2010).

Odds ratio (OR) obtained from the models represent change in the likelihood of receiving buprenorphine over time; OR > 1 means an increasing likelihood per month, whereas OR < 1 suggests a decreasing likelihood per month. All models were developed using PROC GLIMMIX in SAS 9.4 (SAS Institute Inc., 2013).

3. Results

3.1. Characteristics of participants

At baseline, mean (sd) age was 37.4 (11.2), 34.4% were female, and most were White (72.8%), followed by Hispanic (11.2%), Black (9.1%), and other race/ethnicity (7.0%) (See Table 1). Most participants had attained a high school degree (45.1%) or at least some college (36.0%), but few were currently employed full- or part-time (18.9%, 11.4%). On average, participants had used heroin for more than a decade (mean [sd] 12.4 [11.4] years) and other opioids for about half as many years (7.2 [8.0] years). Participants also reported a significant number of years using cocaine (7.7 [8.6] years), methamphetamine (7.9 [9.1]), cannabis (12.8 [10.5]), and alcohol (12.8 [10.6]). Participants had received treatment for substance use disorders previously, i.e., drug treatment (mean [sd] 7.1 [7.4] times) or drug detoxification (4.5 [4.8]), alcohol detoxification (3.8 [6.9]), and alcohol treatment (4.2 [6.3]).

3.2. Buprenorphine accessibility

Most participants at follow-up 1, 87.1%, reported knowing about buprenorphine treatment (Table 2; see Appendix A for characteristics of the 12.9% participants who reported not knowing about buprenorphine). Of participants who knew about buprenorphine, 51.0% reported problems being able to receive buprenorphine when needed, most commonly because of no health insurance to cover it (56.9%) and/or no pocket money (54.3%), inability to find free buprenorphine (50.9%), and not being able to find a nearby physician or clinic that prescribed it (41.1%). Few subjects reported clinic hours of operation as a reason for not being able to receive buprenorphine (4.6%) or other reasons. The mean (SD) buprenorphine accessibility score was −1.14 (1.32).

3.3. Buprenorphine acceptability

Only 17.3% reported taking buprenorphine at follow-up 1. Of those not taking it, almost half (48.2%) said they would take it if available (Table 3). Of the 51.8% who said they would not take buprenorphine even if it were available, reasons included not using opioids anymore (51.4%), preference for methadone (46.3%), dislike of buprenorphine (32.7%), inability to find free buprenorphine (17.4%), lack of knowledge about buprenorphine (10.5%), and having heard bad things about buprenorphine (7.5%).

Of the 96 participants who said they did not like buprenorphine, reasons for not liking it included negative physical reactions (e.g. allergic reactions, headaches, nausea, stomach pain, and fatigue) (66.7%) or other side effects (e.g. depression, anxiety, anger, suicidal thoughts, sleep difficulties, irritability, paranoia) (40.6%), buprenorphine not being strong enough (35.4%), inability to feel effects of other opioids when taking buprenorphine (34.4%), and the study requirement to come to the clinic every day to receive buprenorphine (28.1%). The mean (SD) buprenorphine acceptability score was −0.62 (1.05).

3.4. Predictors of participant utilization of buprenorphine treatment over time

About 9.3 – 11.2% of participants used buprenorphine treatment and 39.8 – 42.0% of the participants used methadone treatment over 24 months after follow-up 1 (data not shown). Table 4 presents the results of the random-intercept model in which we examined the association between buprenorphine accessibility and acceptability and the trajectory of buprenorphine treatment utilization over 24 months, while also considering participants' socio-demographic characteristics and other covariates.

Initially (i.e., at the initiation of the 24-month follow-up period), higher buprenorphine acceptability score at follow-up 1 was associated with greater likelihood of receiving buprenorphine treatment (OR [CI] = 4.57 [2.55, 8.18], p<0.001) (Table 4, Model 1). Furthermore, Hispanic ethnicity (0.15 [0.04, 0.50], p<.01), West coast context (0.29 [0.14, 0.60], p<0.001), and experiences during follow-up of methadone treatment (0.81 [0.76, 0.85], p<0.001) and incarceration (0.29 [0.15, 0.54], p<0.001) were negatively associated with buprenorphine treatment utilization at the initiation of the 24-month follow-up period.

Overall, the likelihood of receiving buprenorphine treatment (i.e., slope) was decreasing across months (0.98 [0.97, 0.99], p<.01). However, the change in the likelihood of

buprenorphine treatment receipt over time was not affected by accessibility score, acceptability score, or other predictors.

The interaction term of buprenorphine accessibility x buprenorphine acceptability was significant (1.51 [1.05, 2.18], p<.05 on Table 4, Model 2). In other words, individuals who perceived buprenorphine to be both accessible and acceptable were more likely to use buprenorphine treatment at the initiation of the 24-month follow-up period. When the interaction effects were plotted (Figure 2), results indicated that individuals who perceived buprenorphine to be both accessible and also acceptable were most likely to use buprenorphine over time. In contrast, individuals who perceived buprenorphine to be unacceptable were least likely to use buprenorphine, no matter the perceived level of access to the medication.

4. Discussion

4.1. Summary of primary findings and implications

In the present paper, we analyze data from an extended long-term follow-up study of participants originally treated with methadone or buprenorphine as part of the START clinical trial. We examine utilization of buprenorphine treatment and its relationship with perceived access barriers and acceptability. Of the study participants, (1) about 9.3 – 11.2% used buprenorphine treatment over a 24-month follow-up period, (2) a significant proportion experienced buprenorphine to be inaccessible or unacceptable, and (3) independent of sociodemographics and other factors, participant likelihood of utilizing buprenorphine over time was associated with buprenorphine treatment accessibility and acceptability. Specifically, individuals who reported buprenorphine to be both accessible and also acceptable were most likely to use buprenorphine during follow-up. In contrast, individuals who reported buprenorphine to be unacceptable were least likely to use buprenorphine, no matter the reported level of access to the medication.

Participant-reported reasons for finding buprenorphine to be unacceptable were consistent with findings from other studies (e.g., Teruya et al., 2014). About half of those who were unwilling to use buprenorphine reported no longer using opioids. Other reasons included negative physical reactions or other adverse side effects, perceived weakness of buprenorphine (“it’s not holding me”), and not being able to feel the effects of other opioids when taking buprenorphine. Results suggest that to increase continued use of buprenorphine over time, we need to address individuals’ experiences that buprenorphine is unacceptable and these engagement strategies should be tailored to the specific reason why there is dislike for the medication. For example, individuals who experience buprenorphine-related negative physical reactions and unwanted side effects, or report that the medication is not strong enough, could benefit from optimization of the medication dosage. In contrast, individuals who report a dislike of their inability to feel the effects of other opioids when taking buprenorphine may be best treated with motivational methods for supporting behavioral changes and strategies to address the underlying causes of opioid misuse. Consideration could also be given to prescribing adjunctive clonidine which has been demonstrated to decrease opioid craving when added to a buprenorphine regimen (Kowalczyk et al., 2015).

We also found that relatively few participants reported utilizing buprenorphine, but about half who were not taking it said they would take it if it were available. Extended duration buprenorphine formulations were developed to improve treatment adherence (Blanco & Volkow, 2019) and may help to improve overall buprenorphine utilization rates, presenting an area for research. We also found that participants' ability to access buprenorphine when needed was most commonly hindered by the price of buprenorphine, difficulty finding buprenorphine prescribers, and lack of insurance coverage for buprenorphine. In other analyses (data not shown), about two-thirds of participants had health insurance - mostly Medicaid, although significant proportions had private insurance or other forms of insurance – but many did not know if their health insurance covered buprenorphine. Nationwide there have been considerable efforts to expand buprenorphine treatment capacity. This work has focused on needed increases in buprenorphine accessibility, for example by reducing its price, ensuring Medicaid, Medicare, and other types of health insurance cover it, removing barriers such as prior authorization, and training more providers to prescribe it. However, our findings suggest that simply making buprenorphine treatment more available is not enough. To increase buprenorphine utilization, we must also increase knowledge of its benefits and applicable health insurance coverage and develop interventions to improve both accessibility and also acceptability.

About 13% of participants reported not being familiar with buprenorphine. This finding likely reflects, in part, the inability of participants to remember the buprenorphine information that had been provided at baseline. Our findings revealed that compared with participants who did know about buprenorphine, more of those who lacked buprenorphine knowledge were older, living in California, and had less education, more years of alcohol and cocaine use, and less exposure to prior treatment. It is well-known that prior to adopting an innovation it is important to ensure that intended adopters are aware of the innovation, have sufficient information about what it does and how to use it, and are clear about how its use would affect them personally (Hser et al., 2007). When applied to the findings from the present study, it is clear there is a need to implement location-specific strategies for raising individual awareness of buprenorphine as an option for evidence-based OUD treatment. Reducing gaps in knowledge about buprenorphine may also benefit from information dissemination efforts that utilize repeated messaging that is designed to be simple and clear or utilize other techniques that advance understanding. Such an information campaign has already been launched in New York City where advisements about buprenorphine treatment are posted in subway cars and other public venues.

Finally, certain participant sociodemographic characteristics were associated with a greater likelihood of participant utilization of buprenorphine during follow-up. Specifically, greater addiction severity (as indicated by injection drug use and cocaine positive urines) was negatively associated with buprenorphine treatment utilization, as was Hispanic ethnicity and living on the West coast relative to the East coast. Results underscore the need to target vulnerable groups who could benefit from buprenorphine and work to curb OUD progression before it worsens.

4.2. Limitations

Study findings must be considered within the context of several limitations. The composite measures of buprenorphine accessibility and buprenorphine acceptability were created specifically for the present study. Key stakeholders from the research team (i.e. physicians and clinical directors with expertise in buprenorphine treatment) assessed the face validity of these independent variables and determined they adequately covered the concepts being measured. Also, participants' experiences of buprenorphine treatment accessibility and acceptability may have changed over time, particularly in terms of access. However, we lacked repeated measurement of these constructs. Therefore, findings reflect the influence of participants' experiences as measured at a single time-point. While treatment utilization was tracked during the 2-year period, the access and acceptability scores were measured once at the beginning of the 2-year period. Therefore, those with a high acceptability score who started using buprenorphine at the beginning of the 2-year period and had a negative experience, would have yielded a decreased acceptability score. Similarly, participants who did not seek buprenorphine and had a high accessibility score at the beginning of the 2-year follow-up period, but became aware of barriers once they did seek buprenorphine treatment would have yielded a decreased accessibility score. Investigating the dynamic nature of the relationships between buprenorphine treatment access, acceptability, and utilization is an area for future research. Also, the range of 2-7 years post-randomization is quite wide, which could have implications that we did not account for in relation to recall, persistence of effects of original study arm on acceptability, as well as time trends in the broader diffusion of buprenorphine in the communities. We did not examine predictors of buprenorphine access and acceptability, which are areas for future work. The trial lasted for only 6 months, and across study sites there was variability in post-trial buprenorphine treatment availability and local buprenorphine policies. For these reasons, we have included site as a covariate. Also, to remain in treatment after the trial ended, participants had to make additional arrangements. Therefore, rates of continuing buprenorphine treatment may not reflect what would occur in routine clinical care. Finally, findings are generated from a sample of treated individuals who participated in a clinical trial implemented by a limited number of sites that was designed to evaluate effects of buprenorphine versus methadone on liver function (Saxon et al., 2013). We believe our cohort is reasonably representative of U.S. adults with OUD. Nevertheless, findings may not be representative of the general population of individuals with OUD.

5. Conclusions

To engage more individuals with opioid use disorders in long-term treatment with buprenorphine, interventions should target their experiences regarding buprenorphine treatment acceptability, in addition to increasing buprenorphine access, and tailor efforts to meet the needs of vulnerable populations.

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Appendix

Appendix A.

Characteristics and experiences of participants by knowledge of buprenorphine treatment

	Do you know about buprenorphine?		
	No (n=102; 13%)	**Yes (n=687; 87%)**	**Total (n=789)**
Randomization status, % ***			
Buprenorphine	3.0	66.5	58.3
Methadone	97.1	33.5	41.7
Female, %	37.3	34.0	34.4
Age, % ***			
22-24	0.0	2.0	1.8
25-34	16.7	37.9	35.1
35-44	17.7	22.1	21.6
45-54	42.2	23.7	26.1
55-64	22.6	13.7	15.0
65+	1.0	0.6	0.6
Age, mean (sd) **	46.6 (10.3)	40.9 (11.1)	41.6 (11.2)
Race/ethnicity, %			
White	63.7	74.1	72.8
Black	11.8	8.7	9.1
Hispanic	17.7	10.2	11.2
Other	6.9	7.0	7.0
Years of education, % *			
Less than high school	27.5	17.6	18.9
High school	46.1	45.0	45.1

	Do you know about buprenorphine?		
	No (n=102; 13%)	**Yes (n=687; 87%)**	**Total (n=789)**
College or more	26.5	37.4	36.0
Years of education, mean (sd) **	11.9 (1.9)	12.5 (1.9)	12.4 (1.9)
Employment status, % ***			
Employed full time	12.8	19.8	18.9
Employed part time	5.9	12.2	11.4
Unemployed, looking for work	22.6	30.3	29.3
Not in the labor force	58.8	37.7	40.4
Months incarcerated in lifetime, mean (sd)	29.5 (37.4)	23.9 (33.5)	24.5 (34.0)
ASI severity scores, mean (sd)			
Alcohol	0.07 (0.16)	0.07 (0.15)	0.07 (0.15)
Drug	0.18 (0.13)	0.18 (0.14)	0.18 (0.14)
Medical	0.31 (0.35)	0.31 (0.36)	0.31 (0.36)
Employment	0.69 (0.30)	0.64 (0.32)	0.64 (0.32)
Legal	0.08 (0.15)	0.14 (0.19)	0.09 (0.17)
Family	0.12 (0.16)	0.14 (0.19)	0.14 (0.18)
Psychiatric	0.24 (0.22)	0.23 (0.23)	0.23 (0.23)
Age at first use of primary drug, mean (sd)	21.4 (7.9)	22.3 (7.8)	22.2 (7.8)
Years of alcohol and drug use in lifetime, mean (sd)			
Alcohol *	13.3 (12.2)	10.2 (10.5)	10.6 (10.8)
Heroin	12.7 (11.4)	10.8 (9.9)	11.0 (11.4)
Opiates	5.0 (8.1)	4.4 (7.1)	4.5 (7.2)
Cocaine *	7.2 (10.1)	5.0 (9.5)	5.3 (8.0)
Amphetamine *	0.5 (1.1)	0.8 (3.0)	0.7 (2.8)
Methamphetamine	3.4 (7.2)	2.4 (6.2)	2.5 (6.3)
Cannabis	10.6 (11.1)	10.2 (10.6)	10.2 (10.7)
AUDIT-C score, mean (sd)	2.0 (3.0)	1.9 (2.6)	1.9 (2.6)
Exposure to treatment in lifetime, mean (sd)			
Number of drug treatments **	4.9 (3.4)	7.5 (7.8)	7.1 (7.5)
Number of drug detoxifications **	1.7 (2.3)	3.2 (2.9)	3.0 (4.5)
Number of alcohol treatments	0.5 (0.3)	0.6 (0.4)	0.6 (2.8)
Number of alcohol detoxifications *	0.7 (0.9)	2.1 (5.7)	1.8 (5.1)
Total number of drug and alcohol treatments in lifetime, mean (sd) **	6.5 (5.3)	10.7 (12.0)	10.1 (11.5)
Total number of drug and alcohol detoxifications in lifetime, mean (sd)	0.7 (1.6)	0.9 (5.0)	0.9 (4.7)
State, % **			
California	43.1	26.8	28.9
Connecticut	13.7	30.1	28.0
Oregon	11.8	23.0	21.6

	Do you know about buprenorphine?		
	No (n=102; 13%)	Yes (n=687; 87%)	Total (n=789)
Pennsylvania	11.8	9.3	9.6
Washington	19.6	10.8	11.9

*
p<.05
**
p<.01
***
p<.001

About 13% of participants reported not knowing about buprenorphine at follow-up 1. Assignment to buprenorphine or methadone in the trial was strongly associated with familiarity with buprenorphine at follow-up 1 (97.1% vs. 33.5%). The group who did not know about buprenorphine was older on average than the group who knew about it (mean age 46.6 vs. 40.9), and more subjects in this group had not attained a high school degree (27.5% vs. 17.6%), and more were not in the labor force (58.8% vs. 37.7%). Participants who did and did not know about buprenorphine began using their primary drug at about the same age on average (at about age 22), and patients in both groups had used heroin and opiates for a similar number of years (11-12 years, 5 on average, respectively), but patients who did not know about buprenorphine had used alcohol (13.3 vs. 10.2 years) and cocaine (7.2 vs. 5.1 years) for more years than participants who did know about buprenorphine. Finally, participants who did not know about buprenorphine had less prior exposure to treatment as indicated by a fewer number of drug treatments (mean [sd] treatments 4.9 [3.4] vs. 7.5 [7.8]) and drug detoxifications (mean [sd] detoxifications 1.7 [2.3] vs. 3.2 [2.9]). Compared with participants who knew about buprenorphine, more of those who did not know about it were living in California (43.1%) than in the other locales [Washington (19.6%), Oregon (11.8%), Pennsylvania (11.8%), or Connecticut (13.7%)].

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Highlights

- Patients who perceive buprenorphine to be unacceptable are least likely to use it.
- Vulnerable populations are least likely to use buprenorphine.
- To increase buprenorphine utilization, increase acceptability and target vulnerable populations.

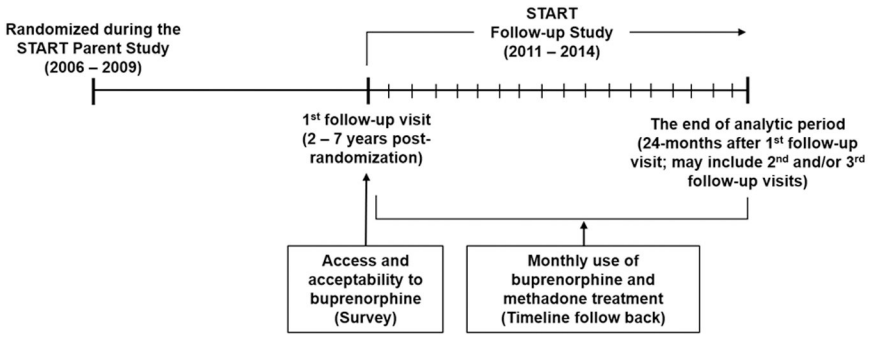

Figure 1.

Measurement points, sources of data, and time horizon of the analysis

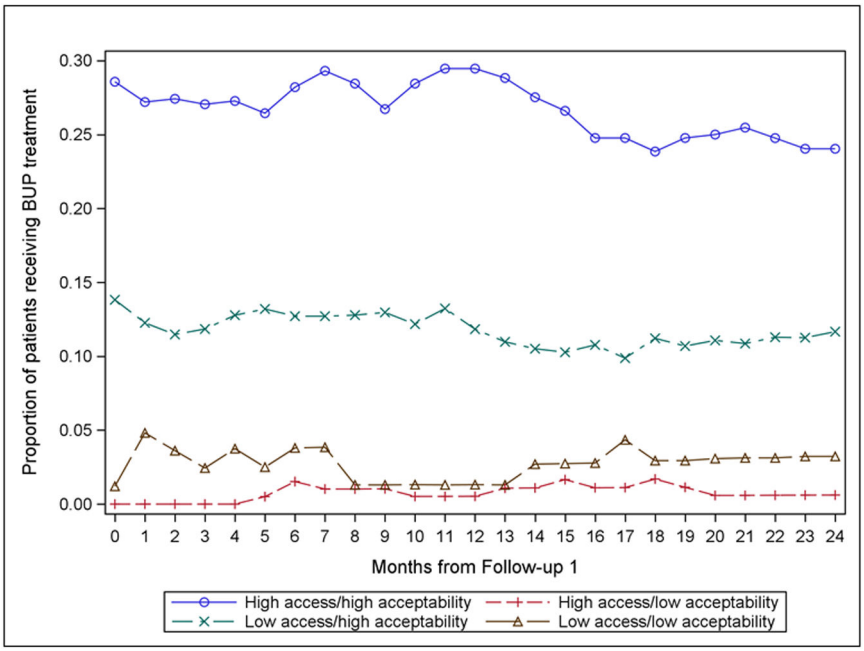

Figure 2. Buprenorphine (BUP) treatment utilization for opioid use disorder over 24 months after follow-up 1, by BUP accessibility score and BUP acceptability score (n=789)

Note: The median score was used as a cut-off to form low and high groups for access and acceptability scores.

Table 1.

Participant characteristics and experiences at baseline, by assigned condition in the parent study

	BUP (N=460)	MET (N=329)	Total (N=789)
Female (%)	33.0	36.2	34.4
Age (%)			
18-24	13.0	14.3	13.6
25-34	32.8	34.0	33.3
35-44	23.3	19.2	21.6
45-54	23.9	25.8	24.7
55-64	6.7	6.1	6.5
65+	0.2	0.6	0.38
Age (years), Mean (SD)	37.4 (11.1)	37.4 (11.3)	37.4 (11.2)
Race/ethnicity (%)			
White	72.4	73.3	72.8
Black	8.7	9.7	9.1
Hispanic	13.0	8.5	11.2
Other	5.9	8.5	7.0
Education completed (%)			
Less than high school	17.2	21.3	18.9
High school graduate or equivalent (GED)	45.0	45.3	45.1
More than high school	37.8	33.4	36.0
Education completed (years), Mean (SD)	12.5 (1.9)	12.3 (1.9)	12.4 (1.9)
Employment status (%)			
Employed full time	18.7	19.2	18.9
Employed part time	12.0	10.6	11.4
Unemployed, looking for work	29.6	28.9	29.3
Not in the labor force	39.8	41.3	40.4
Drug and alcohol use in lifetime			
Heroin (%)	88.9	88.8	88.9
Number of years, Mean (SD)	12.2 (10.9)	12.7 (12.0)	12.4 (11.4)
Other opioids (%)	63.3	60.2	62.0
Number of years, Mean (SD)	6.9 (7.5)	7.5 (8.7)	7.2 (8.0)
Cocaine (%)	66.5	71.1	68.4
Number of years, Mean (SD)	7.3 (8.0)	8.1 (9.3)	7.7 (8.6)
Methamphetamine (%)	31.3	31.9	31.6
Number of years, Mean (SD)	7.9 (8.7)	7.8 (9.7)	7.9 (9.1)
Amphetamine (%)	18.3	18.2	18.3
Number of years, Mean (SD)	4.0 (4.7)	4.1 (6.5)	4.0 (5.5)
Cannabis (%)	80.0	79.6	79.9

	BUP (N=460)	MET (N=329)	Total (N=789)
Number of years, Mean (SD)	13.2 (10.5)	12.2 (10.4)	12.8 (10.5)
Alcohol (%)	81.1	84.2	82.4
Number of years, Mean (SD)	12.9 (10.9)	12.8 (10.2)	12.8 (10.6)
Treatment for substance use disorders in lifetime			
Drug treatment (%)	100.0	100.0	100.0
Number of times, Mean (SD)	7.3 (7.1)	6.9 (7.9)	7.1 (7.4)
Drug detoxification (%)	68.5	65.1	67.1
Number of times, Mean (SD)	4.5 (4.9)	4.4 (4.8)	4.5 (4.8)
Alcohol treatment (%)	13.7	15.8	14.6
Number of times, Mean (SD)	4.4 (5.5)	4.0 (7.1)	4.2 (6.3)
Alcohol detoxification (%)	7.0	7.0	7.0
Number of times, Mean (SD)	3.7 (4.7)	3.9 (9.2)	3.8 (6.9)
State of residence (%)			
California	29.4	28.3	28.9
Oregon	22.0	21.0	21.6
Washington	11.7	12.2	11.9
Pennsylvania	8.7	10.9	9.6
Connecticut	28.3	27.7	28.0

There was no statistically significant difference between groups on any variable.

Table 2.

Accessibility of buprenorphine treatment as reported by participants, by assigned condition in the parent study

	BUP N=460	MET N=329	Total N=789
Knowledge of buprenorphine treatment* **	N (%)	N (%)	N (%)
Yes	457 (99.4)	230 (69.9)	687 (87.1)
Problem getting buprenorphine treatment when needed			
Among participants with knowledge of buprenorphine treatment	n=457	n=230	n=687
Yes	237 (51.9)	113 (49.1)	350 (51.0)
Reason for not getting buprenorphine treatment when needed			
Among participants with problem getting buprenorphine treatment when needed	n=237	n=113	n=350
Unaffordable, no health insurance^	137 (57.8)	62 (54.9)	199 (56.9)
Unaffordable, no pocket money^	134 (56.5)	56 (49.6)	190 (54.3)
Can't find free buprenorphine^	117 (49.4)	61 (54.0)	178 (50.9)
Can't find nearby physician/clinic prescriber^*	106 (44.7)	38 (33.6)	144 (41.1)
Can't attend clinic hours of operation^	13 (5.5)	3 (2.7)	16 (4.6)
Other reasons*	40 (16.9)	30 (26.6)	70 (20.0)
Accessibility of buprenorphine treatment composite score (range: −5 to 0), Mean (SD)	−1.20 (1.44)	−1.06 (1.14)	−1.14 (1.32)

* p<0.05,

** p<0.01,

*** p<0.001; X^2 tests for categorical variables and t-tests for continuous variables.

^ item was used to create the accessibility composite score.

Table 3.

Acceptability of buprenorphine treatment as reported by participants at follow-up 1, by assigned condition in the parent study

	BUP N=460	MET N=329	Total N=789
Currently taking buprenorphine	N (%)	N (%)	N (%)
Among participants with knowledge of buprenorphine	n=457	n=230	n=687
Yes	80 (17.5)	39 (17.0)	119 (17.3)
Willingness to take buprenorphine if available *			
Among patients not taking buprenorphine	n=377	n=191	n=568
No	183 (48.5)	111 (58.1)	294 (51.8)
Reasons not willing to take buprenorphine			
Among patients not taking buprenorphine and unwilling to take buprenorphine	n=183	n=111	n=294
Not using opioids now	99 (54.1)	52 (46.9)	151 (51.4)
Prefer methadone	81 (44.3)	55 (49.6)	136 (46.3)
Do not like buprenorphine^**	70 (38.3)	26 (23.4)	96 (32.7)
Cannot find free buprenorphine *	39 (21.3)	12 (10.8)	51 (17.4)
Don't know much about buprenorphine	15 (8.2)	16 (14.4)	31 (10.5)
Heard bad things about buprenorphine^	15 (8.2)	7 (6.3)	22 (7.5)
Other reasons	26 (14.2)	23 (20.7)	49 (16.7)
Reasons for not liking buprenorphine			
Among patients not taking buprenorphine who do not like buprenorphine	n=70	n=26	n=96
Had negative physical reactions^*	51 (72.9)	13 (50.0)	64 (66.7)
Did not like the side effects^*	33 (47.1)	6 (23.1)	39 (40.6)
Medication was not strong enough^	21 (30.0)	13 (50.0)	34 (35.4)
Can’t feel opioids when taking buprenorphine^*	29 (41.4)	4 (15.4)	33 (34.4)
Had to come to clinic everyday ***	27 (38.6)	0 (0.0)	27 (28.1)
Other reasons	10 (14.3)	7 (26.9)	17 (17.7)
Acceptability of buprenorphine treatment composite score (range: −6 to 0), Mean (SD)	−0.72 (1.19)	−0.46 (0.81)	−0.62 (1.05)

* p<0.05,

** p<0.01,

*** p<0.001;

X^2 tests for categorical variables and t-tests for continuous variables.

^ item was used to create the acceptability composite score.

Table 4.

Random-intercept model predicting utilization of buprenorphine treatment over 24 months after 1st follow-up (n=789)

Covariates	OR (95% CI)	
	Model 1	**Model 2**
Intercept	1.18 (0.25, 5.67)	1.35 (0.28, 6.48)
Slope (months)	0.98 (0.97, 0.99) **	0.98 (0.97, 0.99) **
Interaction with intercept		
Participant characteristics		
Randomized to BUP (ref: MET)	1.55 (0.77, 3.15)	1.65 (0.81, 3.36)
Age (years)	0.97 (0.94, 1.01)	0.97 (0.94, 1.01)
Male (ref: female)	0.75 (0.36, 1.56)	0.78 (0.37, 1.65)
Race/ethnicity (ref: White)		
Black	0.35 (0.08, 1.50)	0.33 (0.08, 1.40)
Hispanic	0.15 (0.04, 0.50) **	0.14 (0.04, 0.49) **
Other race	0.82 (0.17, 4.07)	0.78 (0.16, 3.85)
Less than high school education (ref: HS or more)	0.92 (0.37, 2.30)	0.96 (0.38, 2.43)
Cocaine positive at baseline (ref: negative)	0.70 (0.33, 1.50)	0.74 (0.35, 1.58)
Injection drug use (ref: no injection)	0.67 (0.33, 1.36)	0.57 (0.27, 1.19)
West coast site (ref: East coast)	0.29 (0.14, 0.60) ***	0.29 (0.14, 0.61) ***
Total no. of MET treatment received since 1st follow-up	0.81 (0.76, 0.85) ***	0.81 (0.76, 0.85) ***
Time-varying covariate		
Incarceration since 1st follow-up	0.29 (0.15, 0.54) ***	0.28 (0.15, 0.52) ***
Participant experiences of buprenorphine treatment		
BUP Accessibility	0.94 (0.73, 1.22)	1.06 (0.80, 1.40)
BUP Acceptability	4.57 (2.55, 8.18) ***	7.11 (3.35, 15.10) ***
Interaction term BUP Accessibility × BUP Acceptability	--	1.51 (1.05, 2.18) *

BUP=buprenorphine; MET=methadone

* p<0.05,

** p<0.01,

*** p<0.001