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Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial

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ABSTRACT

Aims To compare long-term outcomes among participants randomized to buprenorphine or methadone. **Design, Setting and Participants** Follow-up was conducted in 2011–14 of 1080 opioid-dependent participants entering seven opioid treatment programs in the United States between 2006 and 2009 and randomized (within each program) to receive open-label buprenorphine/naloxone or methadone for up to 24 weeks; 795 participants completed in-person interviews (~74% follow-up interview rate) covering on average 4.5 years. **Measurements** Outcomes were indicated by mortality and opioid use. Covariates included demographics, site, cocaine use and treatment experiences. **Findings** Mortality was not different between the two randomized conditions, with 23 (3.6%) of 630 participants randomized to buprenorphine having died versus 26 (5.8%) of 450 participants randomized to methadone. Opioid use at follow-up was higher among participants randomized to buprenorphine relative to methadone [42.8 versus 31.7% positive opioid urine specimens, $P < 0.01$, effect size (h) = 0.23 (0.09, 0.38); 5.8 days versus 4.4 days of past 30-day heroin use, $P < 0.05$, effect size (d) = 0.14 (0.00, 0.28)]. Opioid use during the follow-up period by randomization condition was also significant ($F_{(7.39\ 600)} = 3.16$; $P < 0.001$) due mainly to less treatment participation among participants randomized to buprenorphine than methadone. Less opioid use was associated with both buprenorphine and methadone treatment (relative to no treatment); no difference was found between the two treatments. Individuals who are white or used cocaine at baseline responded better to methadone than to buprenorphine. **Conclusions** There are few differences in long-term outcomes between buprenorphine and methadone treatment for opioid dependence, and treatment with each medication is associated with a strong reduction in opioid use.

Keywords Buprenorphine, methadone, opioid dependence, longitudinal, outcomes, opioid use, mortality.

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INTRODUCTION

Most long-term follow-up studies of individuals with opioid use disorder are based on participants recruited from methadone maintenance treatment, and results have generally shown positive outcomes in reduced opioid use and mortality [1]. For many individuals, opioid use disorder is a chronic condition that requires long-term care [2]. Both methadone (MET) and buprenorphine (BUP) are effective medications for opioid use disorder [3–7], and are often used as maintenance treatment to stabilize opioid use on a long-term basis. [8,9] In the United States, MET is a Schedule II full agonist that can be used in Federal- and State-approved programs; BUP is a partial agonist that was approved by the US Food and Drug Administration (FDA) in 2002 and can be used in general health-care settings by qualified practitioners. Currently, very limited information is available on the long-term outcomes of participants started on BUP treatment, particularly relative to those receiving MET treatment.

The present study takes advantage of a large multi-site prospective US study that randomized participants to BUP (as buprenorphine/naloxone) versus MET and compares their outcomes 2–8 years after randomization. The parent study, 'Starting Treatment with Agonist Replacement Therapy' (START), was a Phase IV, post-marketing study designed to examine the comparative effects of BUP and MET on indices of liver health in opioid-dependent participants [10]. The present paper reports on these participants' long-term outcomes in terms of mortality and opioid use. The aims are to: (1) compare mortality by the randomization conditions (BUP versus MET); (2) compare opioid use status at the follow-up interview and averaged days of opioid use during the 60-month follow-up period by the randomization conditions (BUP versus MET); (3) estimate treatment participation status at the follow-up interview and treatment retention during the 60-month period by the randomization conditions (BUP versus MET); and (4) estimate the effects of each type of opioid replacement treatment (i.e. BUP treatment or MET treatment) on the level of opioid use during the 60-month period.

METHODS

Study design

The START study [10] randomized 1269 individuals to BUP (n = 740) or MET (n = 529) at nine federally licensed opioid treatment programs during 2006–09. Because of higher dropout in the BUP arm, midway through the trial the randomization scheme was changed from 1 : 1 to 2 : 1 to achieve targeted evaluable BUP participants. This change accounts for the higher number randomized to BUP [11].

Long-term follow-up

A follow-up study of all randomized study participants was conducted during 2011–14, approximately 2–8 years (a mean of 4.5 years) post-randomization. Two sites (189 participants) were dropped due to logistical difficulties (i.e. one site recruited only two participants and the other had difficulty conducting follow-ups). The remaining sites were located in California, Connecticut, Oregon, Pennsylvania and Washington. Of the 1080 targeted participants, 89.4% were located with 797 interviewed (73.6% of patients randomized to MET; 73.7% of patients randomized to BUP), 49 were deceased, 54 refused to be interviewed, 29 were incarcerated and 36 were too mentally dysfunctional to be interviewed or otherwise not interviewed. Among the 797 interviewed, two did not provide time-line follow-back (TLFB) data and were excluded from further analysis. There were no differences in the demographic characteristics of participants included (n = 795) and omitted (n = 285) from analysis.

Participants

Clinical profiles at baseline for the total 1080 participants and the 795 interviewed participants are provided in Table 1. Demographic information on 795 participants is as follows: mean age at baseline was 37.4, 34.1% were female, 72.6% white, 11.2% Hispanic, 9.2% African American and 7.0% other race/ethnicity. The two medication groups were all similar in baseline measures, except that more participants in the MET group reported cocaine use (37.2%) than in the BUP group (30.2%).

Interview procedures

Research staff at the clinics where participants were recruited originally conducted face-to-face follow-up interviews. The assessment interview lasted approximately 1.5–2 hours. Staff also collected a urine sample for drug testing and a saliva swab for rapid HIV testing. Participants were compensated for their time in accord with local policies. Payment generally consisted of a $50 gift card for the assessment, $10 for a urine sample and $10 for a saliva sample. All study procedures were approved by the institutional review board (IRB) at UCLA and by the local IRB overseeing each study site. A federal Certificate of Confidentiality was obtained to protect against disclosure of sensitive participant information.

Main measures

Death

Occurrence and date of death before November 2014 (i.e. the most recent date for which data were available) were searched and determined for all 1080 participants using the National Death Index.

Opioid use

Current use is indicated by (1) self-reported days of opioid use in the past 30 days at the follow-up interview or (2) positive opioid urine test. Opioid use during the follow-up period was measured by self-reported days of opioid use per month from enrollment to the follow-up interview using TLFB methodology [12] aided by a calendar and other memory prompts [13,14]. Opioid use included heroin and prescription opioids (i.e. hydrocodone, oxycodone, other opiates or analgesics).

Treatment participation

TLFB was also used to collect treatment status over time from START enrollment to the follow-up, thus including

Table 1 Clinical profiles at baseline.

	Total sample			*Interviewed sample*		
	Randomized to buprenorphine (n = 630)	*Randomized to methadone (n = 450)*	*Total (n = 1080)*	*Randomized to buprenorphine (n = 464)*	*Randomized to methadone (n = 331)*	*Total (n = 795)*
Age at baseline (years, %)						
18–24	15.1	14.4	14.8	15.1	15.4	15.2
25–34	31.3	33.6	32.2	31.7	33.5	32.5
35–44	22.4	22.9	22.6	22.6	20.2	21.6
45–54	24.1	23.1	23.7	24.1	24.8	24.4
55+	7.1	6.0	6.7	6.5	6.0	6.3
Mean (SD)	37.7 (11.3)	37.5 (11.1)	37.6 (11.2)	37.4 (11.1)	37.4 (11.3)	37.4 (11.2)
Gender (%)						
Male	67.8	66.9	67.4	67.2	64.1	65.9
Female	32.2	33.1	32.6	32.8	35.9	34.1
Race/ethnicity (%)						
White	69.4	72.7	70.7	72.0	73.4	72.6
African American	8.6	9.3	8.9	8.8	9.7	9.2
Hispanic	13.5	10.7	12.3	13.2	8.5	11.2
Other	8.6	7.3	8.1	6.0	8.4	7.0
No. of cigarettes smoked per day (%)						
0	12.4	10.0	11.4	11.6	10.0	10.9
<10	27.5	26.9	27.2	26.7	28.4	27.4
11–20	45.7	45.6	45.7	47.2	44.4	46.0
21–30	12.1	11.8	11.9	12.1	10.9	11.6
31+	2.4	5.8	3.8	2.4	6.3	4.0
In past 30 days, self-reported use of... (%)						
Alcohol	28.1	31.0	29.3	28.3	34.2	30.8
Cocaine	30.8	38.7	34.1**	30.2	37.2	33.1*
Amphetamine	7.8	8.0	7.9	7.3	7.3	7.3
Cannabis	23.0	19.6	21.6	21.6	20.8	21.3
Drugs by injection	67.6	66.4	67.1	67.2	63.9	65.8
SF-36 Physical Component Summary, mean (SD)	49.2 (9.1)	49.0 (9.4)	49.1 (9.2)	49.6 (9.0)	48.9 (9.4)	49.3 (9.2)
SF-36 Mental Component Summary, mean (SD)	39.8 (12.3)	39.2 (13.1)	39.5 (12.6)	39.2 (12.5)	39.4 (13.2)	39.3 (12.8)

χ^2 tests for categorical variables and *t*-tests for continuous variables between buprenorphine and methadone. *$P < 0.05$. **$P < 0.01$. [a]SD= standard deviation; [b]SF-36 = Short Form 36.

periods during the original START trial. Types of treatment include (1) BUP, (2) MET, (3) other opioid medication and (4) treatment with no opioid medication.

Statistical analysis

χ^2 effect sizes for comparing proportions (h) and for comparing means (d) with 95% confidence interval of the effect sizes were also computed [15]. Proportional hazard (Cox) regression investigated predictors of time to death since randomization.

A growth modeling approach was used to examine opioid use during the 60-month period after randomization. This approach allows for variation in the length of the observation. Patterns of opioid use over time were compared according to the two conditions (BUP and MET) and also in relation to other covariates, including demographics, other types of drug use at baseline and time-varying treatment status during the 60-month period. The 60-month period was chosen to maximize the length of observation, with 39% of BUP participants and 51% of MET participants contributing complete data. Because these longitudinal data exhibit distinct non-linear time trends, we modeled time trends with piecewise linear splines [16], which allow the time trend to change its slope at pre-determined time-points called knots. We plotted means and box-plots of opioid use against time separately for different levels of covariates, particularly MET and BUP, to determine the number of knots. Five knots were evident at months 1, 5, 9, 26 and 40 following randomization. We selected Antedependence covariance structure available in SAS PROC MIXED, as this model fitted the data most closely with the lowest BIC and AIC values [12].

We built and tested models for opioid use with greater complexity by adding covariates. First, we included only the randomization condition (BUP versus MET) and the randomization × time interaction with time parameterized according to the bent line spline, as described above (model 1). Next, because participants ending participation in the original trial could enter different types of treatment over time or discontinue it at any time, we tested model 2, which elaborates on model 1 by adding treatment status (BUP, MET and no BUP or MET) at each point as a time-varying covariate. Hereafter, we use the terms BUP or MET groups or conditions to denote the specific randomized medication group or condition, and we use the terms BUP or MET treatment to denote the status or type of treatment that the participant actually received after the baseline assessment. Because the accessibility and availability of BUP and MET treatment varied by study site, in model 2 we controlled for clinic site at baseline enrollment. The number of sites is small. Therefore, study site was incorporated as a fixed effect. Nevertheless, we also tested study site as a random effect and found it was not significant (in model 2, as well as in the subsequent models). Further, all fixed site effects modeling results were similar to those produced by the random site effect models. We thus report findings based on the fixed site effect. For model 3 we added demographics (age, gender, ethnicity) and baseline cocaine use to model 2. Model 4 also included interactions of ethnicity and baseline cocaine use with BUP or MET treatment. All data analyses were performed in SAS version 9.3 (Cary, NC, USA); longitudinal models were fitted using SAS PROC MIXED [17].

RESULTS

Results on mortality based on the total target sample ($n = 1080$) are reported first, followed by descriptive summary statistics on opioid use and treatment participation using data collected from the interviewed sample ($n = 795$). The section concludes with the modeling results on opioid use during the follow-up period.

Mortality

There were 23 deaths in the BUP group ($n = 630$, 3.6%) and 26 deaths in the MET group ($n = 450$, 5.8%); the difference was not statistically different ($\chi^2_{(1)} = 2.74$; $P = 0.10$). The hazard ratio in the Cox regression that included covariates (age, gender, race/ethnicity, cocaine use at the baseline) showed no difference in time to death between the two randomized conditions ($\chi^2_{(1)} = 2.71$; $P = 0.10$).

Opioid use: summary statistics

Current opioid use at the follow-up interview

Opioid use was higher among participants randomized to BUP relative to MET at the follow-up interview [42.8 versus 31.7% positive opioid urine specimens, $P < 0.01$, effect size (h) = 0.23 (0.09, 0.38); 5.8 days versus 4.4 days of past 30-day heroin use, $P < 0.05$, effect size (d) = 0.14 (0.00, 0.28)]. Overall, 46.8% participants were currently using opioids, as indicated by a positive urine test or self-reported past 30-day opioid use with significantly more opioid use among BUP than MET participants [50.9 versus 41.1%, effect size (h) = 0.20 (0.06, 0.34); Table 2].

Opioid use during the follow-up period

Figure 1 displays the average number of days of opioid use by the two randomized conditions during the follow-up period. Visual inspection of the figure indicates that, for both conditions, opioid use drops immediately after entering START, increases somewhat thereafter (approximately 6 months after randomization for both groups), reaches a high point approximately 10–12 months post-randomization, and then gradually tapers off; relative to those in BUP, opioid use by individuals in the MET condition dropped more and had lower relapse rates immediately after the trial, although the groups converged approximately 2 years post-randomization.

Treatment participation: summary statistics

Compared to participants randomized to MET, participants randomized to BUP had significantly fewer days in their original treatment (111 versus 149), spent fewer months in any treatment during the 60 months after randomization [51.7 versus 62.6% of follow-up months, effect size (h) = −0.22 (−0.36, −0.08)] and fewer were in any treatment at follow-up [53.7% versus 63.1%, effect size (h) = −0.19 (−0.33, −0.05)] (Table 3). However, being in BUP treatment during the 60-month follow-up period was significantly more common in those randomized to BUP than those randomized to MET [19.8% versus 6.3% of follow-up months, effect size (h) = 0.41 (0.27, 0.56)].

Shown in Figure 2, the percentage of participants in both MET and BUP treatment decreased from months 1–10, with fewer BUP participants in treatment compared to those randomized to MET (χ^2 test value at each timepoint from months 1 to 10 ranged from 16.9 to 33.3; $P < 0.01$ for all tests). The proportion in treatment remained relatively stable after month 10 for both groups.

Table 2 Current heroin and opiate use at the follow-up interview.

	Randomized to buprenorphine (n = 464)	*Randomized to methadone (n = 331)*	*Total (n = 795)*
Heroin use in the past 30 days (%)			
0	63.2	69.5	65.8
1–5	12.6	11.8	12.2
6–20	8.9	8.1	8.6
21–30	15.4	10.6	13.4
Mean (SD)*	5.8 (10.5)	4.4 (9.3)	5.2 (10.1)
Use of other opiates/analgesics[a] in the past 30 days (%)**			
0	77.9	85.2	81.0
1–5	10.6	8.5	9.7
6–20	5.2	2.4	4.0
21–30	6.3	3.9	5.3
Mean (SD)*	2.7 (7.4)	1.6 (5.9)	2.2 (6.9)
Positive urine test on heroin or opiate use (%)**	42.8	31.7	38.1
Used heroin or opiates as indicated by urine test or self-report (%)**	50.9	41.1	46.8

χ^2 tests for categorical variables and *t*-tests for continuous variables. *$P < 0.05$. **$P < 0.01$. SD = standard deviation. [a] This category was defined to be comparable with the definition of a positive urine test (i.e. opiates 300 ng).

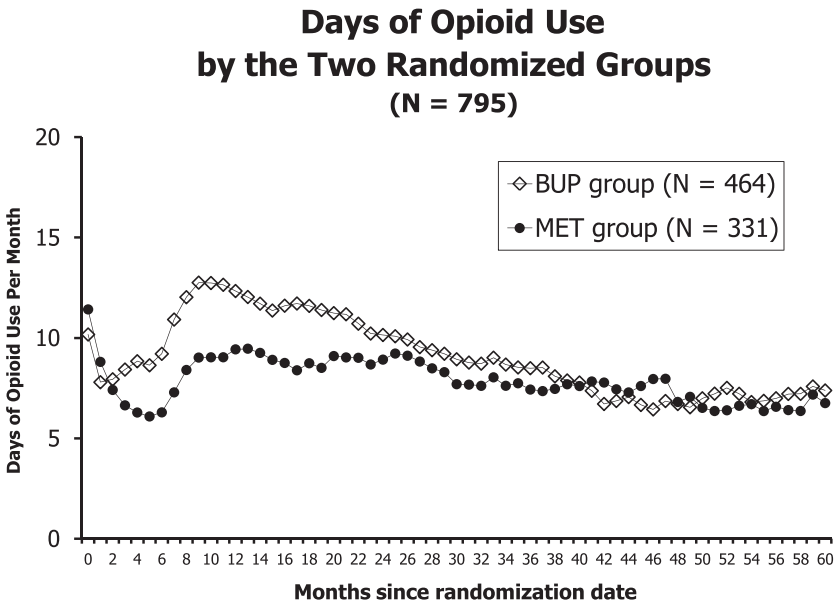

Figure 1 Days of opioid use by the two randomized groups (*n* = 795)

Modeling opioid use during the follow-up period

The results of four longitudinal models of opioid use during the follow-up period are presented in Table 4. The pattern of results is consistent across models (with various covariates). For parsimony, we describe the results of model 4 only.

Association of baseline randomization condition with opioid use

There was no difference by randomization condition in opioid use at baseline; however, subsequent opioid use patterns were significantly different by randomization condition ($F_{(7,\ 39\ 600)} = 3.16$; $P < 0.01$). Adjusting for covariates, the estimated days of opioid use by participants randomized to the MET condition compared to BUP exhibited a greater decrease from months 1 to 6 (as indicated by a steeper drop in slope) and a lower level of use from month 6 onwards, and then the level of use by the two groups gradually merged after approximately 22 months and for the rest of the observation period (see Fig. 3).

Table 3 Treatment retention and status.

	Randomized to buprenorphine (n = 464)	*Randomized to methadone (n = 331)*	*Total (n = 795)*
During the trial and during the follow-up period			
Days in START during 24 weeks of the trial, mean (SD)**	111.4 (65.0)	149.4 (42.0)	127.3 (59.5)
% of months in any treatment during 60 months of follow-up**	51.7	62.6	56.2
% of months in methadone treatment**	28.0	53.3	38.5
% of months in buprenorphine treatment**	19.8	6.3	14.2
% of months in other opioid medication treatment[a]	0.3	0.0	0.2
% of months in other treatment without opioid medications[b]	3.6	2.9	3.3
% of months without any treatment during 60 months of follow-up**	48.1	37.1	43.6
Treatment status at follow-up			
Not in any treatment (%)**	46.3	37.0	42.4
In methadone treatment (%)**	37.3	48.2	41.8
In buprenorphine treatment (%)	12.3	10.0	11.3
In other opioid medication treatment (%)	0.4	0	0.3
In other treatment without opioid medications (%)	3.7	4.9	4.2

χ^2 tests for categorical variables and *t*-tests for continuous variables. *$P < 0.05$. **$P < 0.01$. SD = standard deviation. [a] 'Other opioid medication treatment' includes opioid medications other than buprenorphine (BUP) or methadone (MET) (e.g. levo-α-acetylmethadol or LAAM). [b] 'Other treatment without opioid medications' includes out-patient, residential, detoxification or other treatments with no receipt of opioid medications.

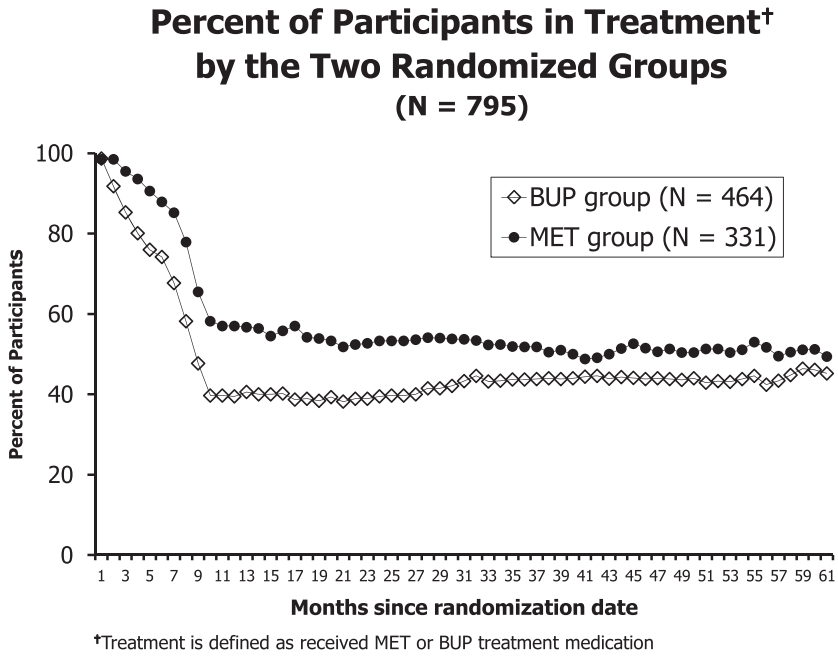

Figure 2 Percentage of participants in treatment† by the two randomized groups (*n* = 795). BUP: buprenorphine; MET: methadone.

Association of baseline participant characteristics with opioid use

Being white (compared to non-white), younger age and cocaine use at baseline were each associated with significantly higher opioid use at baseline. Opioid use during the follow-up period was not related to gender or age, but was related to ethnicity ($F_{(7,\ 39\ 600)} = 3.11$; $P < 0.01$) and cocaine use ($F_{(7,\ 39\ 600)} = 2.77$; $P < 0.01$).

Association of treatment status with opioid use

Participation in MET or BUP treatment, relative to no MET or BUP treatment, was associated with reduced opioid use. The estimated reduction on days of opioid use was 8.5 days for MET and 7.8 days for BUP treatment, respectively, with no statistically significant difference between the two treatment types ($F_{(1,\ 39\ 606)} = 3.65$; $P = 0.06$). Figure 4 presents the estimated days of opioid use during the 60-month

Table 4 Modeling results predicting days of opioid use during the 60-month follow-up period (n = 795).

	Coefficients			
Covariates[a]	*Model 1*	*Model 2*	*Model 3*	*Model 4*
Intercept	11.28**	21.01**	21.41**	20.73**
Randomized condition				
Buprenorphine (versus methadone)	−1.09	−1.10	−0.89	−0.81
Male (versus female)			−0.72	−0.84
White (versus non-white)			2.69**	3.57**
Age at randomization			−0.08*	−0.08*
Cocaine use positive at randomization (versus negative)			2.44**	3.00**
Clinical sites (ref = site 7)				
Site 1		−0.84	−0.83	−1.16
Site 2		−2.36**	−2.40**	−2.41**
Site 3		−1.23	−0.99	−1.56
Site 4		−3.57**	−3.55**	−3.64**
Site 5		−0.24	0.01	−0.14
Site 6		−1.28	−1.08	−1.15
Time-varying covariates				
Methadone treatment (versus no treatment[b])		−8.64**	−8.61**	−6.16**
Buprenorphine treatment (versus no treatment[b])		−6.82**	−6.79**	−7.15**
Interaction of randomized condition and treatment status				
Buprenorphine group × methadone treatment		−0.51	−0.53	−0.52
Buprenorphine group × buprenorphine treatment		−1.78**	−1.78**	−1.76**
Cocaine use × methadone treatment				−1.44**
Cocaine use × buprenorphine treatment				0.004
White × methadone treatment				−2.69**
White × buprenorphine treatment				0.40
Global F-test[c] for intercept and slopes[d] of spline				
Intercept and slopes × randomization interactions	F = 4.32**	F = 2.94**	F = 3.09**	F = 3.16**
Intercept and slopes × gender interactions			F = 0.78	F = 0.83
Intercept and slopes × ethnicity interactions			F = 3.67**	F = 3.11**
Intercept and slopes × age interactions			F = 1.95	F = 1.88
Intercept and slopes × cocaine use interactions			F = 2.08*	F = 2.77**

*$P < 0.05$. **$P < 0.01$. [a] In addition to the covariates summarized in Table 4, other covariates in the models included six spline-time indicators (i.e. a slope indicator at months 0–1 and five slope change indicators at months 1, 5, 9, 26 and 40), six slopes × randomization interactions (i.e. a slope × randomization interaction at months 0–1 and five change in slope × randomization interactions at months 1, 5, 9, 26 and 40), six slopes × gender interactions (i.e. a slope × gender interaction at months 0–1 and five change in slope × gender interactions at months 1, 5, 9, 26 and 40), six slopes × ethnicity (i.e. whites versus non-whites) interactions (i.e. a slope × whites interaction at months 0–1 and five change in slope × whites interactions at months 1, 5, 9, 26 and 40), six slopes ×age interactions (i.e. a slope × age interaction at months 0–1 and five change in slope × age interactions at months 1, 5, 9, 26 and 40) and six slopes × cocaine-use status (i.e. positive versus negative) interactions (i.e. a slope × cocaine-use interaction at month 0–1 and five change in slope × cocaine-use interactions at months 1, 5, 9, 26 and 40). [b] 'No treatment' is defined as no buprenorphine (BUP) or methamphetamine (MET) treatment, but could include other opioid medication treatment, treatment with no opioid medications or no treatment. [c] The degree of freedom for global F-test is $F_{(7,\ 39\ 600)}$. The 7 indicates the seven parameters (i.e. one intercept and six slope and change in slope indicators) simultaneously, and the 39 600 indicates the rest of the degrees of freedom, which was computed as the total number of observations-7 (i.e. 39 607–7). [d] Estimated coefficients of slopes and changes in slopes across spline-time indicators were tested simultaneously by global F-tests.

period given each type of treatment (i.e. MET treatment, BUP treatment or neither MET nor BUP treatment).

Moderation of treatment effects

The effects of MET and BUP treatment on opioid use differed by ethnicity. Compared to being in no treatment, MET treatment was associated with a reduction of opioid use by 9.8 days per month for white participants and by 7.1 days for non-white participants. BUP treatment, compared to being in no treatment, was associated with a reduction of opioid use by 7.6 days for white participants and by 8.0 days for non-white participants. Differences in reduction of days of opioid use between treatments for whites were significant ($F_{(1,\ 39\ 606)}$ = 49.8, $P < 0.01$), but not significant among non-whites ($F_{(1,\ 39\ 606)}$ = 2.75, P = 0.10).

The effects of MET and BUP treatment on opioid use also differed according to whether participants used cocaine. MET treatment was associated with a reduction of opioid use by 9.2 days among cocaine-using participants and by 7.8 days among non-cocaine-using participants. BUP treatment was associated with a reduction of opioid use by 7.8 days among both cocaine-using participants

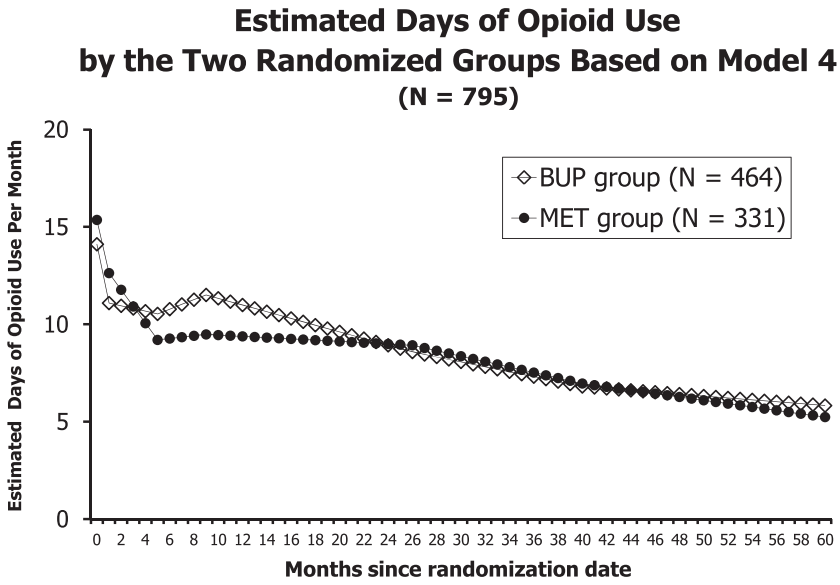

Figure 3 Estimated days of opioid use by the two randomized groups based on model 4 (n = 795). BUP: buprenorphine; MET: methadone.

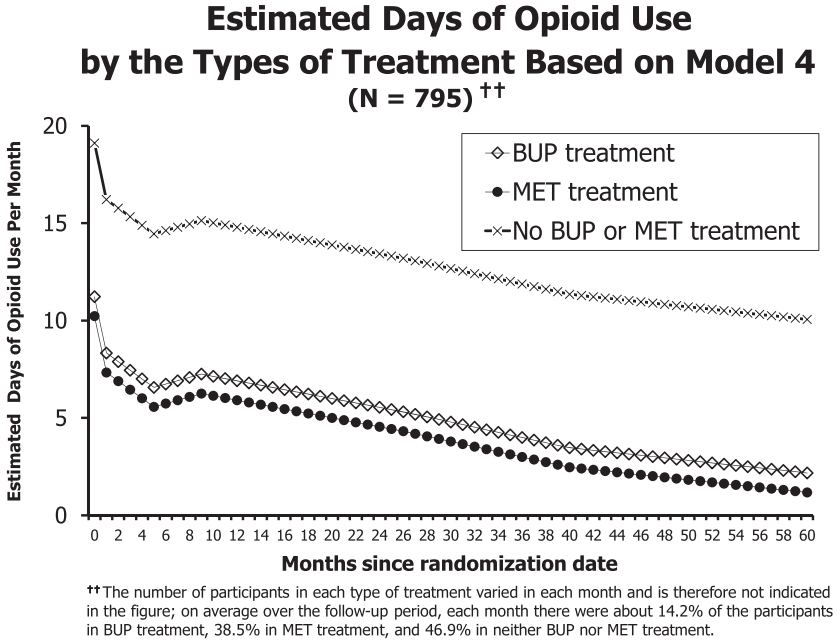

Figure 4 Estimated days of opioid use by the types of treatment based on model 4 (n = 795)††. BUP:buprenorphine; MET:methadone.

and non-cocaine-using participants. The reduction of opioid use was greater for MET treatment than BUP treatment among cocaine-using participants (reduction of 9.2 versus 7.8 days; $F_{(1,\ 39\ 606)} = 8.50$, $P < 0.01$), while among non-cocaine-using participants the two types of treatment yielded a similar reduction in opioid use (reduction of 7.8 days; $F_{(1,\ 39\ 606)} = 0.04$, $P = 0.84$).

DISCUSSION

The ongoing patterns of opioid use in the present study are consistent with many other long-term observations of opioid-dependent individuals. Also not surprising is that participation in both MET treatment and BUP treatment was effective at reducing opioid use. There was no difference in the mortality rate according to medication type. Nevertheless, opioid use was higher and treatment participation was consistently lower among BUP participants during the observation period and at the follow-up assessment. These findings are consistent with those reported by prior studies [3,5]. We speculate that to improve treatment retention in these two medication conditions, efforts should target factors (at both the patient and contextual level) that contribute to medication discontinuation, such as patients'

lack of medication knowledge [18], concurrent use of cocaine or other substances [11,19], inadequate medication dosage [11], co-occurring psychological conditions or stress [19,20] and involuntary medication discontinuation due to strict clinical requirements [21] or incarceration [22].

Because participants did not always stay in the randomized treatment condition, we included both randomization condition and treatment in the model as separate factors and found similar positive treatment effects of BUP and MET (relative to no treatment) in reduced opioid use. Even after adjusting for covariates (particularly the time-varying treatment status), the difference in opioid use over time between BUP and MET remained significant. The reasons for this finding are not immediately clear. It is important to recognize the overall public health benefits of BUP, given that it is available more widely, as it can be offered by qualified practitioners in primary care settings as well as in specialty methadone clinics.

In this study, we observed consistently lower treatment participation among participants randomized to BUP than MET. The differential dropout rate between MET and BUP was noted in the original study. That this pattern carried over into the follow-up period is consistent with the differential pharmacology of these two medications. Methadone is a full agonist at the mu opioid receptor and is thus more reinforcing, and produces a stronger level of physiological dependence than buprenorphine, which is a partial mu opioid agonist. As treatment was provided by the study for a limited period, and to remain in treatment participants had to make additional arrangements, the rates of follow-up treatment engagement may not reflect what would occur in routine clinical care. Randomization to MET, as opposed to BUP, conferred an advantage of having more time in treatment and less drug use during the ensuing 5 years in this study. Nevertheless, participants randomized to BUP were more likely to engage in BUP treatment after completing the study. Given that access routes to BUP treatment, which often occurs in office-based primary care settings, are somewhat different to those for opioid treatment programs, this finding may suggest that a subset of participants randomized to BUP had a sufficiently positive response to the medication, such that they sought it out after the study. Nevertheless, opioid users who are unsuccessful with BUP should receive encouragement to enter MET or another effective treatment immediately.

Researchers and practitioners need to understand more clearly which medications work best for which type of drug users. The present study has shown that opioid-dependent users who are white or using cocaine appeared to respond better to MET than BUP in terms of reductions in opioid use. It is also worth noting that cocaine use was associated with negative outcomes among these study participants. Polydrug use, or the concurrent use of multiple substances, has been associated with greater psychopathology [23,24]; higher levels of risky health behaviors [25]; poorer treatment engagement [26]; and worse treatment outcomes [27,28]. Thus, treatment for opioid addiction needs to pay special attention to polydrug use, particularly use of cocaine.

The current findings need to be considered within the context of several limitations. The study was based on a randomized medication trial; however, many participants dropped from the study and did not remain in their initial randomization condition. Also, the trial lasted for only 6 months, and across study sites there was tremendous variability in post-trial treatment availability and local BUP policies. For these reasons, we have included site as a covariate. Finally, the original trial was conducted among community methadone maintenance programs, and most participants came to these programs for methadone treatment. Surveillance studies of heroin users indicate that approximately two-thirds have been treated [29]. Thus, we believe that our cohort is reasonably representative of opioid-dependent users in the United States. Nevertheless, because the trial recruited from specialty methadone clinics, a setting that is different from general office-based practices, study findings may not be generalizable to those participants treated typically in office-based BUP treatment.

This study, the first to follow opioid-dependent individuals randomized to two opioid maintenance treatments prospectively during 5 or more years, is instructive about longer-term outcomes and poses a challenge to the field to enhance retention in opioid maintenance treatment. This study shows that many individuals with opioid use disorder cycle in and out of maintenance treatment and confirms that they show better outcomes when retained in maintenance treatment. Efforts are needed, especially in the context of the current opioid epidemic, to improve both BUP and MET treatment retention.

Clinical trial registration

The START Follow-up Study on ClinicalTrials.gov (NCT01592461).

Declaration of interests

Authors disclosing relevant financial interests, activities, relationships, and affiliations are as follows: W.L. is a consultant to Reckitt Benckiser Pharmaceuticals; A.S. is a consultant to Reckitt Benckiser Pharmaceuticals, advisory board member for Alkermes, Inc. and receives royalties as an editor for UpToDate; G.W. is a consultant to Reckitt Benckiser Pharmaceuticals. All other authors report no financial or other possible conflicts of interest.

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