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# A Naturalistic Comparison of the Effectiveness of Methadone and Two Sublingual Formulations of Buprenorphine on Maintenance Treatment Outcomes: Findings From a Retrospective Multisite Study

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***Objective:*** This study sought to compare the effectiveness of the 3 most commonly prescribed maintenance medications in the United States indicated for the treatment of opioid dependence in reducing illicit drug use and retaining patients in treatment. ***Method:*** Data were abstracted from electronic medical records for 3,233 patients admitted to 34 maintenance treatment facilities located throughout the United States during the period of July 1, 2012, through July 1, 2013. Patients were grouped into 1 of 3 medication categories based on their selection at intake (methadone [$n = 2{,}738$; $M^{\text{dosage}} = 64.64$ mg/d, $SD = 25.58$], Suboxone [$n = 102$; $M^{\text{dosage}} = 9.75$ mg/d, $SD = 4.04$], or Subutex [$n = 393$; $M^{\text{dosage}} = 12.21$ mg/d, $SD = 5.31$]) and were studied through retrospective chart review for 6 months or until treatment discharge. Two measures of patient retention in treatment and urinalysis drug screen (UDS) findings for both opioids and various nonopioid substances comprised the study outcomes. ***Results:*** The average length of stay (LOS) in terms of days in treatment for the methadone group ($M = 169.86$, $SE = 5.02$) was significantly longer than both the Subutex ($M = 69.34$, $SE = 23.43$) and Suboxone ($M = 119.35$, $SE = 20.82$) groups. The Suboxone group evinced a significantly longer average LOS relative to the Subutex group. After adjustment for relevant covariates, patients maintained on methadone were 3.73 times (95% confidence interval [CI]= 2.82–4.92) and 2.48 times (95% CI = 1.57–3.92) more likely to be retained in treatment at 6 months than patients prescribed Subutex and Suboxone, respectively. The 6-month prevalence rates of positive UDS findings for both opioids and nonopioid substances were similar across medication groups. ***Conclusions:*** Comparable rates of illicit drug use at 6 months may be expected irrespective of maintenance medication, while increased retention may be expected for patients maintained on methadone relative to those maintained on Suboxone or Subutex.

*Keywords:* methadone, buprenorphine, maintenance treatment, opioids, illicit drugs



Opioid use and opioid use disorders have been associated with a variety of untoward outcomes, including increased health care utilization and vulnerability to infection with human immunodeficiency virus (HIV) and other bloodborne infectious diseases (e.g., hepatitis B and C), economic burden, additional substance use and psychiatric comorbidity, cognitive impairment, and mortality (Brooner, King, Kidorf, Schmidt, & Bigelow, 1997; Centers for Disease Control and Prevention, 2012; Fals-Stewart, 1997; Hulse, English, Milner, & Holman, 1999; Kaushik, Kapila, & Praharaj, 2011; Mark, Woody, Juday, & Kleber, 2001; Pilowsky, Wu, Burchett, Blazer, & Ling, 2011; Strain, 2002; Substance Abuse and Mental Health Services Administration, 2008, 2009). Although the number of people treated in the past year for alcohol use and illicit drug (e.g., cannabis, cocaine) use problems has remained relatively stable between 2002 and 2010, the number treated for a problem related to the use of opioids (i.e., prescription pain relievers or heroin) more than doubled during this period (Substance Abuse and Mental Health Services Administration, 2011). In light of the range of impairment and adverse consequences associated with opioid use and opioid use disorders, effective treatment remains of paramount importance.

Methadone, a commonly used synthetic opioid, represents a viable treatment option with demonstrated effectiveness in the context of opioid agonist maintenance treatment (e.g., Amato et

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al., 2005). Considerable research has amassed to support the contention that maintenance treatment with methadone is associated with increased treatment retention, reduced opioid use and HIV seroconversion, decreased craving, and improved social functioning (for reviews, see Amato et al., 2005; Bart, 2012; Sorensen & Copeland, 2000). Thus, the preponderance of evidence in the form of several systematic reviews of the extant opioid use treatment literature and controlled clinical trials clearly point to the value of methadone treatment in maintenance programs.

Prior to enactment of the Drug Addiction Treatment Act of 2000 (Pub. L. No. 106–310), methadone and levo-alpha-acetylmethanol were the only unrestricted Schedule II opioid medications available for the treatment of opioid dependence in the United States. However, in 2002, the Food and Drug Administration (FDA) announced the approval of two sublingual formulations of the medication buprenorphine, a semisynthetic opioid partial-agonist, for the treatment of opioid dependence: (a) Subutex and (b) Suboxone (Food and Drug Administration, 2002).[1] The defining difference between these two formulations is that Subutex contains buprenorphine hydrochloride, while Suboxone contains an additional ingredient, naloxone hydrochloride HCL, in the ratio 4:1 of the bases (Food and Drug Administration, 2013; Reckitt Benckiser Pharmaceuticals Inc., 2012). Given the presence of naloxone, Suboxone appears to offer the additional benefit of having lower abuse liability when taken parenterally, which in turn, further reduces the potential for diversion and misuse of the medication (for review, see Mendelson & Jones, 2003; Simojoki, Vorma, & Alho, 2008).

The efficacy of buprenorphine has been rigorously evaluated in terms of its clinical utility in both relieving withdrawal symptoms during short-term medically supervised withdrawal treatment (Gowing, Ali, & White, 2009), as well as reducing opioid use and increasing patient retention in the context of maintenance treatment (Ling & Wesson, 2003). Regarding maintenance, indications of the comparative efficacy of buprenorphine and methadone in the treatment of opioid dependence suggest that both medications are highly and equally effective in preventing relapse to regular opioid use in that patient performance during maintenance is often similar across groups (Kamien, Branstetter, & Amass, 2008; McKeganey, Russell, & Cockayne, 2013; Petitjean et al., 2001). Other comparison studies, however, have tended to favor methadone, particularly with respect to patient retention (Hser et al., 2014; Petitjean et al., 2001; Saxon et al., 2013). Meta-analytic findings from a review of 24 comparison studies also suggest that buprenorphine may be less effective than methadone delivered at adequate dosage ranges (Mattick, Kimber, Breen, & Davoli, 2008).

Despite the disparate findings regarding the superiority of buprenorphine relative to methadone in terms of a number of clinical outcomes, buprenorphine appears to possess several advantages over methadone. For instance, Subutex and Suboxone represent the first opioid medications eligible for use under the Drug Abuse Treatment Act of 2000 in the treatment of opioid dependence that may be dispensed or prescribed in less restrictive settings, which affords significantly more patients with the opportunity to access treatment. Similarly, because buprenorphine is less subject to diversion, at least with respect to enteral methods of administration, buprenorphine is available in 30-day packaging—thereby easing the potential burden of daily appointments on patients. Although the maximal opioid agonist effects (e.g., euphoria) produced by buprenorphine are generally milder than those of full agonists like methadone (Reckitt Benckiser Pharmaceuticals, Inc., 2002), alleviation of uncomfortable withdrawal symptoms may still be achieved with less risk for diversion of the medication. Additional strengths of buprenorphine include high patient satisfaction (Barry et al., 2007), significant bioavailability and a long duration of action allowing for alternate-day dosing (Amass, Kamien, & Mikulich, 2000; Johnson et al., 1995), and relatively mild withdrawal symptoms following abrupt cessation of the medication compared with those of methadone (Bickel et al., 1988; Jasinski, Pevnick, & Griffith, 1978). Finally, the occurrence of less intense undesirable side effects, improved cognitive performance and decision-making, more rapid stabilization, improved respiratory functioning, and fewer drug interactions have all been observed among patients maintained on buprenorphine relative to methadone (Doran, Holmes, Ladewig, & Ling, 2005; Law, Myles, Daglish, & Nutt, 2004; McCance-Katz, Sullivan, & Nallani, 2010; O'Connor & Fiellin, 2000; Pirastu et al., 2005; Rapelli et al., 2007).

Although the clinical efficacy of both buprenorphine formulations relative to methadone has been evaluated extensively (e.g., Hser et al., 2014; Mattick et al., 2008), there remains considerably less evidence directly comparing the effectiveness of buprenorphine alone (Subutex) with the combination product (Suboxone). Of the limited available research, findings from a multicenter, randomized, placebo-controlled trial involving opioid-dependent patients presenting for office-based treatment revealed that both formulations were safe, well tolerated, and reduced the use of opioids and craving for opioids relative to placebo (Fudala et al., 2003). Further evidence, primarily in the form of results from small-scale experimental designs, suggest that following acute sublingual administration at equivalent dosage levels of buprenorphine, both formulations produce similar physiological and subjective effects, and the combination product has not been shown to possess any significant additional antagonistic properties beyond those associated with buprenorphine alone (Strain, Walsh, & Bigelow, 2002; Weinhold, Preston, Farre, Liebson, & Bigelow, 1992). Thus, additional comparison research investigating the long-term clinical outcomes associated with Subutex and Suboxone is clearly warranted in an effort to better inform clinical practice in settings in which both formulations are available to patients.

In sum, opioid dependence is associated with a variety of negative consequences and represents a serious public health concern. The efficacy of maintenance treatment utilizing methadone and both formulations of buprenorphine in reducing opioid use and increasing treatment retention relative to placebo among patients with opioid-dependence is well documented. Buprenorphine pos-

[1] It is important to note that the general term "buprenorphine," at least as it will be discussed in the context of the present report, will be used to encompass both formulations of the medication (i.e., Subutex and Suboxone), unless otherwise specified. Although naltrexone, a nonopioid antagonist marketed under the brand name Vivitrol, has also been approved by the FDA for the treatment of opioid dependence to prevent relapse, the present investigation will focus on methadone and buprenorphine formulations exclusively.

sesses several advantages over methadone, including most notably, a lower potential for misuse and diversion via nonparenteral routes, greater accessibility in office-based settings, as well as the prospect for alternate-day dosing. Clinical comparison studies, however, have produced somewhat divergent findings regarding the perceived superiority of buprenorphine versus methadone. Studies asserting clinical equivalence between the two medications, although promising, require replication in a well-powered investigation to determine whether or not one should be preferred over another. Furthermore, many studies have included relatively small samples and/or brief follow-up periods, and some have relied on self-reported indices of illicit drug use.

The present retrospective longitudinal study sought to compare the effectiveness of the three most commonly prescribed medications in the United States indicated for the treatment of opioid dependence (i.e., methadone, Subutex, and Suboxone) in reducing illicit drug use and retaining patients in treatment. In accord with prior work (e.g., McKeganey et al., 2013), it is hypothesized that both buprenorphine formulations will be as effective in reducing illicit drug use at the 6-month follow-up among patients presenting for maintenance treatment as methadone. With respect to patient retention, however, it is hypothesized that patients prescribed methadone will evince a significantly longer average length of stay (LOS) relative to patients prescribed Subutex or Suboxone. Finally, the null hypothesis that Subutex and Suboxone are not differentially effective in retaining patients in treatment at 6 months will also be tested.

## Method

Demographic and clinical data for the present study were derived from patient records utilizing the management information system of a large U.S. health care provider (CRC Health Group Inc.). A total of 8,442 active and discharged patients admitted to a CRC Health Group-operated substance use treatment facility during the period of July 1, 2012, through July 1, 2013 were initially identified from the management information system. All active patients had a minimum LOS of at least 6 months. All patients presented for medication-assisted treatment for opioid dependence in the context of a maintenance treatment clinic setting and were subsequently treated with methadone or one of two buprenorphine formulations (i.e., Subutex or Suboxone). However, only those patients who attended a program that offered both methadone and buprenorphine as available medication options were included (i.e., patients who attended a treatment program that offered only methadone were excluded from the final data set). Furthermore, only those patients for whom complete demographic data were available (i.e., gender, ethnicity, employment status, age, and marital status) comprised the final sample. The primary reason for study exclusion was missing or incomplete demographic data.

The final sample consisted of all patients admitted to 34 treatment facilities located throughout the United States. (e.g., California, Oregon, Virginia, Louisiana, West Virginia, North Carolina, Kansas) during the aforementioned observational period. Given that the 34 treatment facilities utilized in the present study were operated by the same national health care provider, all facilities followed similar maintenance treatment practices as outlined in a common Policy and Procedure manual. Although dosing decisions are ultimately made by the prescribing physician, all physicians followed the same set of induction guidelines per the Policy and Procedure manual, which encourages them to induce patients as quickly and safely as possible. All patients, irrespective of medication group, were dispensed their medication daily and earned take home dosages according to the same treatment guidelines across participating sites. In general, patients earned 1-day take home doses relatively early in the treatment process, with the opportunity to earn extended take home doses on the basis of their time in treatment and response to treatment. Patients were studied through retrospective electronic chart review for 6 months or until treatment discharge; whichever came first. Release of the de-identified data set was approved by the CRC Health Group, Inc. Institutional Review Board for use in secondary analyses.

### Participants

Demographic characteristics for the total sample, stratified by medication type, are detailed in Table 1. The total sample was comprised of 3,233 patients (55.9% men) with an average age of 32.9 years ($SD = 9.37$) and a range of 18 to 71 years. Ethnic composition was predominately White (91.5%), and Hispanics constituted the largest racial-minority group (3.7%). Slightly more than half (51.9%) of the patients were single, and 45.7% indicated that they were currently employed at the time of intake. Regarding payment method for maintenance treatment services, over four fifths (82.3%) of the sample were classified as self-pay. Patients were grouped into one of three medication categories based on their selection at intake. Patients were prescribed methadone ($M^{\text{dosage}} = 64.64$ mg/d, $SD = 25.58$), Suboxone in the form of 2 mg/500 μg or 8 mg/2 mg sublingual tablets ($M^{\text{dosage}} = 9.75$ mg/d, $SD = 4.04$), or Subutex in the form of 2 mg or 8 mg sublingual tablets ($M^{\text{dosage}} = 12.21$ mg/d, $SD = 5.31$).

### Measures

UDS testing was conducted at the discretion of the various treatment facilities for individual treatment planning purposes or, in some cases, as a mandate in partial fulfillment of the terms of a patient's parole. Although testing was performed at various intervals, defined by both the State and type of patient, standard procedures at all facilities required that a minimum of eight UDS tests be conducted per year for each patient. In fact, despite the variability in the timing and frequency of UDS testing procedures across sites, all active patients received a UDS for opioids and the various nonopioid substances at the 6-month follow-up. The medication dispensing software utilized by all of the treatment facilities identified patients due for a UDS on a specific day on a random interval schedule, and the dispensing of an individual patient's prescribed methadone or buprenorphine dosage was contingent on UDS submission. Collection of specimens was observed via nonrecording camera observation in accordance with each respective facility's State requirements to ensure authenticity. The type of testing performed and the panel chosen was dictated by the State's requirements, the certification of the program, and the compliance requirements of the individual facility. Thus, upon request, specimens were subjected to an initial immunoassay

Table 1
*Patient Demographic and Clinical Characteristics at Study Intake, Stratified by Medication Type*

| Variable | Medication, % (*n*) | | |
|---|---|---|---|
| | Methadone (*N* = 2,738) | Subutex (*N* = 393) | Suboxone (*N* = 102) |
| Age, *M* (*SD*) (years)* | 33.1 (9.48) | 31.6 (9.33) | 31.8 (8.47) |
| 18–24 | 19.8 (543) | 19.6 (77) | 26.5 (27) |
| 25–34 | 46.7 (1,279) | 52.9 (208) | 44.1 (45) |
| 35–44 | 21.0 (576) | 18.1 (71) | 18.6 (19) |
| 45+ | 12.4 (340) | 9.4 (37) | 10.8 (11) |
| Gender | | | |
| Male | 55.9 (1,530) | 57.8 (227) | 50.0 (51) |
| Female | 44.1 (1,208) | 42.2 (166) | 50.0 (51) |
| Ethnicity | | | |
| White | 91.4 (2,503) | 91.1 (358) | 95.1 (97) |
| Hispanic | 4.1 (112) | 1.8 (7) | 1.0 (1) |
| African American | 2.3 (62) | 4.1 (16) | 1.0 (1) |
| American Indian | 0.8 (21) | 0.8 (3) | 0.0 |
| Asian American | 0.2 (6) | 0.5 (2) | 0.0 |
| Other | 1.2 (34) | 1.8 (7) | 2.9 (3) |
| Marital status | | | |
| Single | 51.8 (1,418) | 54.2 (213) | 47.1 (48) |
| Married/significant other | 29.6 (810) | 28.5 (112) | 39.2 (40) |
| Separated | 8.1 (222) | 6.9 (27) | 4.9 (5) |
| Divorced | 9.2 (252) | 9.7 (38) | 8.8 (9) |
| Widowed | 1.3 (36) | 0.8 (3) | 0.0 |
| Employment status | | | |
| Unemployed | 44.7 (1,224) | 47.1 (185) | 34.4 (35) |
| Employed | 45.2 (1,237) | 46.1 (181) | 57.8 (59) |
| Disabled | 5.8 (158) | 3.6 (14) | 3.9 (4) |
| Student | 2.9 (79) | 1.3 (5) | 2.9 (3) |
| Other | 1.4 (40) | 2.0 (8) | 1.0 (1) |
| Payment plan | | | |
| Self-pay*** | 82.6 (2,261) | 84.0 (330) | 69.6 (71) |
| Government | 6.2 (171) | 8.4 (33) | 22.6 (23) |
| Private insurance | 3.7 (100) | 0.0 | 2.9 (3) |
| Other | 7.5 (206) | 7.6 (30) | 4.9 (5) |
| Intake UDS+ | | | |
| Alcohol | 0.5 (15) | 0.5 (2) | 0.0 |
| Amphetamines | 11.8 (323) | 9.7 (38) | 6.9 (7) |
| Barbiturates | 1.8 (48) | 2.3 (9) | 0.0 |
| Benzodiazepines* | 33.2 (909) | 27.5 (108) | 23.6 (24) |
| Cannabinoids** | 31.0 (850) | 38.2 (150) | 26.6 (27) |
| Cocaine | 10.7 (293) | 12.0 (47) | 3.9 (4) |

*Note.* UDS+ = positive urinalysis drug screen finding. Differences between patient groups were tested using $\chi^2$ tests for categorical variables and analysis of variance for continuous variables.
* $p < .05$. ** $p < .01$. *** $p < .001$.

screen to assess for recent use of methadone, buprenorphine, alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, heroin, and oxycodone.

## Data Analyses

Primary outcome variables are consistent with those reported in the maintenance treatment literature (Mattick et al., 2008): (a) recent use of opioids as indicated by positive UDS results (UDS+) for heroin or oxycodone; (b) recent use of other illicit drugs as indicated by UDS+ results for alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, and cocaine; and (c) retention in treatment as indicated by average LOS in treatment measured in days and the number of patients still in treatment at the 6-month follow-up (i.e., 6 months posttreatment admission).

All UDS findings were dichotomized to indicate the detection of the presence or absence of the various substances for which a UDS was administered. Two outcome variables were constructed based on UDS+ findings for (1) all opioids, and (2) all nonopioid substances at the 6-month follow-up. First, an algorithm was utilized to place patients into a composite "opioids" category based on UDS findings for both heroin and oxycodone at the 6-month interval. Thus, if a patient produced a UDS+ finding for heroin, oxycodone, or both at 6 months, they received a positive designation when grouped in the composite opioids category. The algorithm utilized to classify patients at intake based on opioid use, however, included UDS+ findings for methadone and buprenorphine in addition to heroin or oxycodone given that these substances may have been used recreationally prior to treatment admission. Furthermore, given all patients were positive for either methadone or buprenorphine at 6 months, these substances were excluded from the algorithm used to classify patients based on opioid use at this assessment point.

Second, a similar procedure was utilized to create a composite variable based on all nonopioid substances (i.e., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, and cocaine) for which a UDS was administered at 6 months. Thus, a UDS+ finding for any one of the six nonopioid substances included on the panel resulted in the patient receiving a positive designation when grouped in the composite nonopioids category. Both composite outcome variables included findings for which a UDS was administered within 15 days of the 6-month mark for the various substances. For example, for the 6-month nonopioid composite UDS variable, all patients administered a UDS for a substance other than opioids between 165 and 195 days following treatment admission were included. A Pearson's chi-square test of independence was conducted to explore the relationships involving the three medication groups (i.e., methadone, Subutex, and Suboxone) with the two composite outcome variables indicative of treatment response at 6 months (i.e., UDS+ findings for opioids and UDS+ findings for nonopioid substances) to ascertain whether particular medication groups were more strongly associated with UDS+ findings at the 6-month follow-up.

Patient retention in treatment was the third outcome variable of interest, evaluated by medication group using two models. First, as per the recommendation of Dimitrov and Rumrill (2003), comparative effectiveness was examined via analysis of covariance (ANCOVA) with patients' LOS in treatment used as the dependent variable. Thus, a two-way mixed effects ANCOVA was performed to test the hypothesis that the methadone group would be more effective than the two buprenorphine groups in retaining patients in treatment after controlling for relevant covariates. Given that the present study was designed with an emphasis on generalizability of outcomes to clinical practice, the data were modeled with medication group as a fixed effect with three levels (i.e., methadone, Subutex, and Suboxone) and treatment site as a random effect. This procedure allowed for differences in LOS at the various sites, as well as expected variations in the standard treatment practices across the different sites by including the within groups variance at the site level in the model. The covariates included baseline UDS+ findings for nonopioid substances and relevant demographic characteristics shown to impact maintenance treatment retention (Mad-

dux, Prihoda, & Desmond, 1994; Magura, Nwakeze, & Demsky, 1998; Mancino et al., 2010; Saxon, Wells, Fleming, Jackson, & Calsyn, 1996; Schottenfeld, Pakes, & Kosten, 1998).

Second, patients were dichotomized as either treatment successes or treatment dropouts at the 6-month follow-up interval on the basis of their LOS in treatment (measured in days). Thus, patients with an LOS >179 days were classified as treatment successes. In an effort to avoid artificially inflating the attrition rate, patients who successfully completed treatment or were transferred to another treatment facility (presumably to a higher level of care) prior to the 6-month follow-up interval were excluded and subsequently not classified as treatment dropouts. Patients discharged after 179 days because of successful treatment completion or transfer to another treatment facility, however, were still classified as treatment successes at 6 months. Separate hierarchical binary logistic regression models were fitted to the data to test the hypothesis regarding whether patient retention in maintenance treatment could be predicted at 6 months by medication group after adjustment for relevant covariates. Thus, three logistic regressions were conducted to compare patient retention across the various medication group comparisons (i.e., methadone vs. Subutex, methadone vs. Suboxone, and Subutex vs. Suboxone) after controlling for age, gender, ethnicity, marital status, employment status, payment method, and UDS+ findings for nonopioid substances at baseline. The dependent variable for the logistic regressions was a binary variable coded as 1 if the patient was still enrolled in treatment at the a priori follow-up interval, and 0 if prematurely discharged because of various reasons (i.e., administrative, financial, or medical) or against medical advice prior to 6 months; this provided for a dichotomous measure of treatment retention. Goodness-of-fit statistics were examined to assess the fit of each respective logistic model against actual outcome (i.e., whether patients were classified as treatment successes at 6 months). Two descriptive measures of goodness-of-fit (i.e., $R^2$ indices defined by Cox & Snell and Nagelkerke) were utilized to determine whether the various models fit to the data well.

## Results

### Equivalence of Medication Groups at Intake

Several analyses were conducted to determine whether there were preliminary descriptive differences on a number of variables known to be independently associated with treatment outcomes. Comparisons on continuous variables were examined using one-way between-groups analysis of variance (ANOVA), while separate chi-square analyses of independence were conducted for all dichotomous variables. The data in Table 1 show that there were no baseline demographic or clinical differences between medication groups on gender, ethnicity, marital status, employment status, and intake UDS+ findings for alcohol, amphetamines, barbiturates, and cocaine. However, the Suboxone group included significantly fewer self-pay patients, $\chi^2$ (6, $N$ = 3,233) = 55.922, $p <$ .001, V = .093, and the average age reported for the methadone group was slightly higher than that of the Suboxone and Subutex groups, $F$(2, 3,230) = 4.152, $p <$ .05. The methadone group was also comprised of significantly more patients with a UDS+ finding for benzodiazepines at intake, $\chi^2$ (2, $N$ = 3,233) = 8.774, $p <$ .05, V = .052, relative to the Subutex and Suboxone groups. Finally, the Subutex group included a slightly larger proportion of patients found positive for cannabinoids based on UDS findings obtained at intake compared with the methadone and Suboxone groups, $\chi^2$ (2, $N$ = 3,233) = 9.408, $p <$ .01, V = .054.

### UDS Findings

Rates of UDS+ findings for opioids and nonopioids at 6 months for the three medication groups are included in Table 2. Overall, associations involving UDS+ results at 6 months for both opioids and nonopioid substances with medication group revealed convergent findings in that there were no significant differences found between medication groups on the prevalence of UDS+ findings for both opioids and nonopioids. Further investigation of the impact of medication group on the likelihood of producing a UDS+ finding for opioids at 6 months, analyzed in logistic regressions, revealed that medication group was not an independent significant predictor of outcome after adjustment for demographic characteristics and baseline UDS+ findings for nonopioid substances, including comparisons involving methadone relative to Subutex and Suboxone, as well as Subutex versus Suboxone. Similar findings were also noted across comparisons with respect to nonopioid UDS+ findings at 6 months in that medication group was not found to be an independent significant predictor of outcome after controlling for the effects of relevant covariates.

### Retention in Treatment

Results from the mixed effects ANCOVA revealed that after adjustment for baseline UDS+ findings for nonopioid substances and relevant demographic characteristics (i.e., patient age, ethnicity, employment status, gender, payment method, and marital status), there was a significant main effect of medication group on LOS in maintenance treatment, $F$(2, 3,230) = 8.004, $p <$ .001. Pairwise comparisons indicated that the estimated marginal mean representing LOS in treatment for the methadone group ($M$ = 169.86, $SE$ = 5.02) was significantly higher than both the Subutex ($M$ = 69.34, $SE$ = 23.43) and Suboxone ($M$ = 119.35, $SE$ = 20.82) groups. Further, the two buprenorphine formulations also differed significantly in that patients prescribed Suboxone evinced a significantly longer average LOS relative to those prescribed Subutex. The effect size, calculated using partial $n^2$, was .047, which suggests that as well as being statistically significant, the effect of medication on treatment retention is a substantive finding.

Table 2
*Rates of Positive Urinalysis Drug Screen (UDS+) Findings and Patient Retention at 6 Months*

| Medication group | UDS+ opioids (%) | UDS+ nonopioids (%) | Retention (%) |
|---|---|---|---|
| Methadone | 17.4 | 34.8 | 48.3 |
| Subutex | 21.4 | 44.6 | 20.2* |
| Suboxone | 11.1 | 22.2 | 30.4 |

*Note.* The "UDS+ opioids" category included UDS findings positive for heroin or oxycodone. The "UDS+ nonopioids" category included UDS findings positive for alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, and cocaine.
* $p <$ .001.

There was no significant main effect of treatment site on LOS, nor was there a significant interaction effect between medication group and treatment site on LOS.

With respect to the observed retention rates among the three medication groups after accounting for patients discharged due to successful treatment completion or transfer to another facility prior to the 6-month follow-up (Figure 1), nearly half (48.3%) of patients prescribed methadone were still enrolled in treatment at 6 months, compared with only 30.4% and 20.2% of patients prescribed Suboxone and Subutex, respectively; which represented a significant difference. The retention rate for the Suboxone group was also significantly higher than that of the Subutex group. As discussed earlier, it is important to note that patients who successfully completed treatment or were transferred to another facility during the observational period ($n$ = 271; 8.4% of the total sample) were excluded in an effort to avoid inflation of the attrition rate.

The dichotomous measure of treatment retention (i.e., whether the patient was still enrolled in maintenance treatment 6 months following admission) was modeled utilizing separate hierarchical binary logistic regressions accounting for baseline UDS+ findings and relevant demographic characteristics (Table 3). Results revealed that patients prescribed methadone were 3.73 times more likely to be retained in treatment at 6 months than patients prescribed Subutex, $R^2$ = .06 (Cox & Snell), $R^2$ = .08 (Nagelkerke). Medication group also remained a significant independent predictor of outcome when methadone was compared to Suboxone in that patients prescribed methadone were 2.48 times more likely to be retained in treatment at 6 months than patients prescribed Suboxone, $R^2$ = .03 (Cox & Snell), $R^2$ = .04 (Nagelkerke). The final model that was fitted to the data, which involved a comparison of patients prescribed Suboxone relative to Subutex, found that medication group was not a significant independent predictor of patient retention in treatment at 6 months, $R^2$ = .05 (Cox & Snell), $R^2$ = .07 (Nagelkerke).

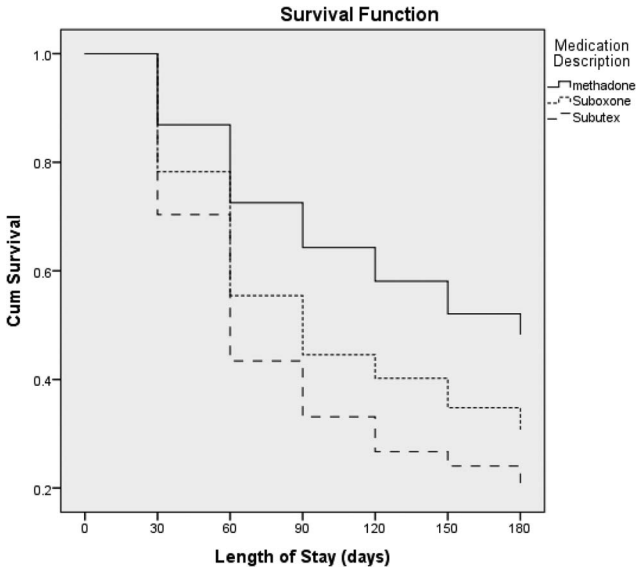


*Figure 1.* Treatment retention by medication category.

## Discussion

The findings replicate and extend prior work regarding the effectiveness of the three most commonly utilized medications in the United States for the treatment of opioid dependence in reducing illicit drug use and retaining patients in maintenance treatment. Unlike most published maintenance treatment outcomes research, however, the present study utilized a substantially larger treatment sample, examined a longer timeframe, and controlled for relevant demographic and clinical characteristics shown to impact outcomes. This strategy yielded several important clinical implications. For instance, both the mixed effects ANCOVA and hierarchical logistic regression models indicated a significant effect of medication group on retention in treatment. Specifically, the average LOS observed for the methadone group was longer than that of both the Subutex and Suboxone groups. It is interesting that patients in the Suboxone group were also found, on average, to remain in treatment longer than the Subutex group. Considered from another perspective using the dichotomous measure, patients prescribed methadone were nearly 4 times more likely to be enrolled in treatment at 6 months following admission than those prescribed Subutex, and 2.5 times more likely than patients treated with Suboxone. Thus, the results from logistic regressions confirmed that methadone was superior to both buprenorphine formulations in retaining patients. However, it is noteworthy that the direct comparison involving Subutex versus Suboxone, analyzed in logistic regression, did not lead to any definitive conclusion regarding the perceived superiority of either medication.

Potential reasons for the disparate findings between the two models concerning patient retention in treatment include that the logistic regressions accounted for relevant demographic characteristics and baseline UDS+ findings known to significantly impact retention in treatment. Similarly, as noted previously, the dichotomous measure of treatment retention excluded patients for various a priori reasons for discharge to avoid artificially inflating the attrition rates. This procedure revealed that 8.4% ($n$ = 271) of the total sample successfully completed maintenance treatment or were transferred to another facility prior to 6 months, and that the Subutex group included a slightly greater proportion of patients satisfying this condition (13.2%) compared with the Suboxone (9.8%) and methadone (7.6%) groups. Thus, retention estimates were significantly lower even after adjustment for the fact that slightly more Subutex patients successfully completed treatment or were transferred to another facility prior 6 months.

Although as hypothesized, both buprenorphine formulations did not perform as well as methadone with respect to patient retention in treatment, it is of great clinical interest that illicit drug use rates were similar across all three medication groups at 6 months. That is, consistent with previous work (McKeganey et al., 2013; Petitjean et al., 2001), patients prescribed either one of the two buprenorphine formulations evidenced comparable outcomes in terms of UDS+ findings for both opioids and nonopioid substances relative to those prescribed methadone. This finding, coupled with earlier work which has shown buprenorphine (i.e., both Subutex and Suboxone) to possess several advantages relative to methadone (e.g., Maremmani & Gerra, 2010), suggests that a

Table 3
*Clinical Predictors of Treatment Retention at 6 Months*

| Medication comparison[a] | β (*SE*) | Wald's $\chi^2$ | *p* | Odds ratio | 95% Confidence interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Methadone vs. Subutex | 1.32 (0.14) | 85.745 | .001 | 3.73 | 2.82 | 4.92 |
| Constant | −1.13 (0.22) | | | | | |
| Methadone vs. Suboxone | 0.91 (0.23) | 15.183 | .001 | 2.48 | 1.57 | 3.92 |
| Constant | −0.69 (0.28) | | | | | |
| Suboxone vs. Subutex | 0.50 (0.28) | 3.098 | .078 | 1.64 | 0.95 | 2.85 |
| Constant | −1.13 (0.60) | | | | | |

*Note*. For all models, relevant demographic variables and baseline urinalysis drug screen findings for nonopioid substances were entered as covariates at block 1, with the respective medication comparison entered as a predictor variable at block 2.



buprenorphine-based regimen, irrespective of whether it includes naloxone, appears to represent a viable alternative at least in regard to achieving abstinence from illicit drugs during the first 6 months of treatment.

An additional strength of the present investigation is that the study design allowed for a direct comparison of outcomes between patients maintained on Suboxone versus Subutex. Prior comparative studies have demonstrated that both formulations were safe, well tolerated, produced similar physiological and subjective effects, and reduced the use of opioids and craving for opioids relative to placebo (Fudala et al., 2003; Strain et al., 2002; Weinhold et al., 1992), but have failed to provide an indication of the perceived clinical superiority (or equivalence for that matter) associated with any one of the medications over the other. In the context of the present study, patients maintained on Suboxone and Subutex evinced comparable illicit drug use rates at 6 months and the two groups were not found to differ in terms of the proportion of patients enrolled in treatment at the 6-month follow-up. However, the mean LOS for Suboxone patients was 4 months, while patients maintained on Subutex were found to remain in treatment, on average, for only 2 months; which represented a statistical difference between groups. The present findings, although preliminary in nature, suggest that there may be a minor advantage associated with maintaining patients on Suboxone relative to Subutex, at least with respect to treatment retention. The findings have important clinical implications for settings in which methadone may not be an available medication option for maintenance treatment (e.g., office-based services).

The observed differences in terms of patient retention in treatment may be attributable to the pharmacological properties of the various medications and or important baseline differences noted between the groups. Although the three medication groups were equivalent on a number of pretreatment demographic characteristics and baseline clinical variables, some differences were detected. In particular, the Suboxone group included significantly fewer self-pay patients, and the Subutex group included a slightly larger proportion of patients with a UDS+ finding for cannabinoids relative to the other groups. Thus, payment method and UDS+ findings for cannabinoids may account for the observed differences between the two buprenorphine groups in terms of patient retention in treatment. In fact, patient fees have long been considered one of the major barriers to maintenance treatment and have been associated with lower rates of patient retention compared to patients who paid nothing for treatment services (Maddux et al., 1994). Given that the Subutex group included significantly more self-pay patients than the Suboxone group, it is possible that the cumulative out-of-pocket expense that these patients would have acquired had they remained in treatment through the 6-month mark may have presented a problem in affording services and subsequently impacted outcome. However, the potential role of self-pay status on treatment retention did not appear to be present for patients in the methadone group in that patients maintained on methadone were found to demonstrate the best outcome. It is also noteworthy that payment method did not appear to exert a similar influence on UDS+ findings for opioids and nonopioids at 6 months. Likewise, the dichotomous measure of treatment retention, analyzed in separate logistic regressions, controlled for the potential confounding effects of all relevant baseline demographic and clinical characteristics. Thus, it appears that the observed differences in terms of clinical outcomes may be better attributed to other potential variables rather than any baseline differences noted between groups.

Although there may be some pharmacological basis for the observed differential findings, the outcomes are likely to be multiply determined, and as such, require additional discussion regarding alternative interpretations. That is, there may be clinical expectancies and biases operating that are not apparent in the data but that played a role in determining both medication selection and patient retention in treatment. For instance, research has shown that heroin use, either alone or in combination with prescription pain relievers, as well as use of opioids via the injection route, were both associated with treatment attrition and illicit drug use at 6 months among patients receiving maintenance treatment with buprenorphine or methadone (Potter et al., 2013). Although an admission requirement for all patients across treatment sites in the present study was the presence of a current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM–IV*) primary diagnosis of opioid dependence, additional clinical data regarding patients' primary opioid of choice and preferred route of administration at treatment entry were not available and therefore, represents a limitation of the present study.

In addition, given that patients tapered off methadone maintenance treatment are likely to experience a more severe withdrawal syndrome than that of buprenorphine, it is possible that some patients may have been aware of buprenorphine's reputation regarding the relative ease of cessation (Bickel et al., 1988; Jasinski

et al., 1978), and self-selected to receive buprenorphine at treatment entry. Patients who received methadone may have also perceived the medication as more reinforcing because of a greater euphoric effect, at least at higher dosages, relative to patients who received one of the buprenorphine formulations, which in turn, may have impacted retention in treatment. Although the decision regarding maintenance treatment with Subutex versus Suboxone was a matter of patient preference as opposed to one based on stability, given that the cost of Subutex is lower than that of Suboxone and closer to that of methadone, patients may have self-selected to receive Subutex because of financial reasons. From the perspective of the physician, treatment with Suboxone may have been encouraged over Subutex because of its lower risk for diversion and abuse by parenteral routes because of the presence of naloxone. Thus, both patient and physician biases—although not apparent from patient data derived from electronic medical records—may be important sources of variance in terms of outcomes, which warrant the need for further investigation.

The findings from the present study should be considered in light of several limitations. First, the present study utilized a convenience sample comprised exclusively of patients presenting for long-term maintenance treatment in the United States, which warrants caution in generalizing the findings to other programs given the disparate practices and treatment philosophies that may accompany them (D'Aunno & Pollack, 2002). The finding that nearly four fifths of the total sample funded their own treatment represents another potential limitation pertaining to the generalizability of the findings. Second, the observed findings, although promising, are predictive associations and as such, causal interpretations cannot be assumed. Third, the present study design did not allow for the random assignment of patients into one of the three available medication categories and instead, group composition was determined by the patients' self-selection based on their personal preference and the knowledge of the prescribing physician. As such, this procedure may have introduced several biases including the possibility of confounding by indication. It is also important to note that observational studies of naturalistic treatment settings, in which substance users exercise a considerable degree of control over their treatment, have the potential to offer important evidence about treatment effectiveness not readily available from randomized clinical trials. Although a relative strength, the present study's 6-month observational period may also be considered a limitation in some respects. That is, it remains unclear if the observed findings would have sustained themselves over a longer follow-up period, or conversely in the case of nonsignificant findings, if they would have been associated with the studied outcomes at a later point in time. Finally, an additional limitation involved the issue of missing or incomplete demographic data for a sizable number of patients initially identified for study participation.

Despite the relative strengths of the present study's design, some caution is warranted in making a priori judgments regarding long-term patient performance based solely on one of the two buprenorphine formulations given the relatively small number of patients that comprised the Suboxone group. Therefore, the conclusions derived from the clinical comparisons involving buprenorphine alone with the combination product can only be made tentatively at this time and as such, require further replication work. In light of the aforementioned study limitations, these positive but preliminary indications of the comparative effectiveness of methadone and both formulations of buprenorphine for the treatment of opioid dependence do suffice to demonstrate that all three medication groups evinced comparable illicit drug use rates, and that methadone was clearly associated with the highest rate of patient retention in treatment at 6 months.

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