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Predictors of attrition with buprenorphine/naloxone treatment in opioid dependent youth ☆

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ABSTRACT

Background: In opioid dependent youth there is substantial attrition from medication-assisted treatment. If youth at risk for attrition can be identified at treatment entry or early in treatment, they can be targeted for interventions to help retain them in treatment.
Methods: Opioid dependent adolescents and young adults (n = 152), aged 15–21, were randomized to 12 weeks (BUP, n = 74) or 2 weeks of detoxification (DETOX, n = 78) with buprenorphine/naloxone (Bup/Nal), both in combination with 12 weeks of psychosocial treatment. Baseline and early treatment related predictors of treatment attrition were identified in each group using bivariate and multivariate logistic regression.
Results: In the DETOX group 36% left between weeks 2 and 4, at the end of the dose taper, while in the BUP group only 8% left by week 4. In the BUP group, early adherence to Bup/Nal, early opioid negative urines, use of any medications in the month prior to treatment entry, and lifetime non-heroin opioid use were associated with retention while prior 30-day hallucinogen use was associated with attrition. In the DETOX group, only use of sleep medications was associated with retention although not an independent predictor. A broad range of other pre-treatment characteristics was unrelated to attrition.
Conclusions: Prompt attention to those with early non-adherence to medication or an early opioid positive urine, markers available in the first 2 weeks of treatment, may improve treatment retention. Extended Bup/Nal treatment appeared effective in improving treatment retention for youth with opioid dependence across a wide range of demographics, and pre-treatment clinical characteristics.

1. Introduction

Opioids are the second most frequently abused drugs among adolescents in the United States and the prevalence of opioid abuse and dependence in adolescents has been increasing (Johnston, O'Malley, Bachman, & Schulenberg, 2011). Between 1995 and 2010, while annual prevalence of heroin use with a needle increased from .3% to .7%, annual use of non-heroin opioids such as hydrocodone and oxycodone increased from 4.7% to 8.7% among 12th graders (Johnston et al., 2011). Emergency room visits for non-heroin opiates/opioids increased from 31,074 to 69,848 between 2004 and 2009 for youth under 21 (Drug Abuse Warning Network, 2011) and annual admissions to substance abuse treatment for opioids other than heroin increased from 388 to 2846 in the last decade (Substance Abuse and Mental Health Services Administration, 2011). Use of opioids among youth is associated with substantial social and legal dysfunction, more severe polysubstance dependence, and risk of hepatitis C and HIV infection (Clemmey, Payne, & Fishman, 2004; Hopfer, Mikulich, & Crowley, 2000; Subramaniam, Ives, Stitzer, & Dennis, 2010; Subramaniam & Stitzer, 2009).

In 2009, medication assisted opioid therapy was planned for 22% of younger adults 20–34 and 14% of those 12–19 according to the Treatment Episode Data Set (Substance Abuse and Mental Health Services Administration, 2011), although the exact nature of the treatment

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plan was not specified. Buprenorphine, a partial mu-opioid receptor agonist, has been generally accepted for treatment of opioid dependence in adults and is effective for both detoxification (Gowing, Ali, & White, 2009) and maintenance (Amato et al., 2005). It has minimal overdose risk, a good safety profile, and less intense withdrawal than full agonists (Amato, Davoli, Ferri, Gowing, & Perucci, 2004; Breen et al., 2003; Garfein, Vlahov, Galai, Doherty, & Nelson, 1996; Gowing et al., 2009; Hser, Hoffman, Grella, & Anglin, 2001; Levy, Vaughan, Angulo, & Knight, 2007; Walsh, Preston, Bigelow, & Stitzer, 1995). Recent evidence supports the efficacy of buprenorphine with adolescents and young adults (Marsch, Bickel, et al., 2005; Woody et al., 2008); however, the challenge of maximizing treatment outcome in opioid dependent youth is compounded by substantial attrition during medication assisted treatment (Bell & Mutch, 2006; Burns et al., 2009; Marsch, Bickel, et al., 2005; Woody et al., 2008).

In a randomized clinical trial (RCT) comparing clonidine and buprenorphine combined with behavioral treatment in opioid dependent adolescents, attrition was 28% after 4 weeks of buprenorphine treatment compared to 61% with clonidine (Marsch, Bickel, et al., 2005;). In a retrospective chart review of 25 adolescent heroin users receiving buprenorphine for long term maintenance, 50% left by day 30 (Bell & Mutch, 2006). In adults, attrition of 30–45% at 12-weeks has been reported in RCTs and observational studies where buprenorphine treatment extended beyond 12 weeks (Fischer et al., 1999; Johnson et al., 2000; Lee, Grossman, DiRocco, & Gourevitch, 2008; Soyka, Zingg, Koller, & Kuefner, 2008; Strain, Stitzer, Liebson, & Bigelow, 1994a; Strain, Stitzer, Liebson, & Bigelow, 1994b).

Retention during buprenorphine treatment has been associated with better outcomes in youth (Subramaniam et al., 2011). Retention in opioid substitution therapy has been associated with improved outcomes in adults (Armstrong, Kermode, Sharma, Langkham, & Crofts, 2010; Mintzer et al., 2007; Zhang, Friedman, & Gerstein, 2003), and discontinuation with relapse (Kakko, Svanborg, Kreek, & Heilig, 2003), overdose death (Davoli et al., 1993), and worse HIV treatment outcomes (Roux et al., 2009).

Despite public health concern about opioid use, particularly among youth (Compton & Volkow, 2006), the few studies of agonist treatment outcome among opioid addicted youth provide little guidance about what factors might be associated with treatment dropout or what might be done to improve it. In the only available report on predictors of attrition in adolescents treated with buprenorphine, there was no difference in retention between those with heroin dependence compared to those with prescription opioid dependence (Motamed, Marsch, Solhkhah, Bickel, & Badger, 2008). In adults, pre-treatment characteristics associated with buprenorphine attrition in RCTs were lack of employment, younger age at onset of opioid use, more continuous opioid use, use of heroin rather than other opioids as the primary drug, higher levels of psychiatric symptoms, lower levels of general functioning, higher craving for cocaine, and absence of lifetime sedative dependence (Pani, Maremmani, Pirastu, Tagliamonte, & Gessa, 2000; Schottenfeld, Pakes, & Kosten, 1998; Soyka et al., 2008; Stein, Cioe, & Friedmann, 2005), although depression was associated with treatment retention in one study (Gerra et al., 2004). During treatment, predictors of attrition in adults included lower doses, greater severity of withdrawal, side effects, more positive urine tests for opioids and other drugs, opioid positive drug screens at week 1, and fewer addiction counseling sessions (Connock et al., 2007; Leonardi, Hanna, Laurenzi, Fagetti and I.D.A.C. Group, 2008; Soyka et al., 2008; Stein et al., 2005).

If youth at risk for attrition can be identified at treatment entry or during early weeks of treatment, they can be targeted for interventions to help retain them and maximize gains. In the first trial to compare a 12-week buprenorphine/naloxone (Bup/Nal) treatment (BUP) with a 14-day Bup/Nal detoxification (DETOX), both in combination with 12 weeks of psychosocial treatment in opioid dependent youth, there were fewer dropouts and opioid positive urines in the BUP group. At week 4, 61% of youth in DETOX and 26% in BUP had opioid positive urines. At week 8, 54% in DETOX and 23% in BUP had opioid positive urines. However, the urine test differences narrowed to the point (51% vs. 43%) where they were non-significant at 12-weeks, when both groups had completed a dose taper (Woody et al., 2008). Remaining on Bup/Nal for a shorter time was therefore an important determinant of opioid use and treatment attrition. This report evaluates for the first time whether specific pre-treatment or early treatment related characteristics were associated with attrition in either group, using secondary analysis of data from this trial to answer the following questions:

1) When during treatment did attrition occur in BUP and in DETOX?
2) Were there baseline socio-demographic or clinical characteristics that identified youth who dropped out?
3) Were there treatment related characteristics during the first 2 weeks of treatment that identified youth who dropped out?

2. Material and methods

Further information about the rationale, design and primary outcomes for the main study is available elsewhere (Woody et al., 2008). It was conducted in six community treatment programs from the National Institute of Drug Abuse Clinical Trials Network. Institutional review boards at the University of Pennsylvania and all participating sites reviewed and approved the study. All participants provided written assent or informed consent and written parental consent was provided for participants 15–17 years old.

2.1. Participants

Opioid dependent adolescents and young adults (n = 152) aged 15–21 seeking outpatient substance use treatment met DSM-IV criteria for opioid dependence with physiologic features and were randomized to BUP (n = 74) or DETOX (n = 78) between July 2003 and December 2005. Study candidates were excluded if they had medical or psychiatric disorders that could make participation unsafe or difficult; were suicidal, homicidal, or psychotic; were dependent on alcohol or sedatives; used benzodiazepines for more than 15 of the prior 28 days; had a sedative overdose in the prior 6 months or positive urine test results for benzodiazepine or methadone at baseline; were currently receiving addiction treatment; had an impending incarceration or move; were pregnant, breastfeeding or unwilling to use effective birth control; or were being prescribed psychotropic medication other than a selective serotonin reuptake inhibitor.

2.2. Study treatment

BUP participants received a dosing schedule of Bup/Nal that included a 1–2 week induction phase followed by a stable dosing phase with a target of 12–18 mg/day, and detoxification, a slow dose taper, beginning in week 9 and ending by week 12. The maximum dose for BUP participants was 24 mg/day. DETOX participants received short term detoxification with increasing doses, up to a maximum of 14 mg/day, with a target of 8–10 mg/day. This was followed by a dose taper that ended by day 14. Dosing was flexible, determined by the treating clinician based on treatment response and safety. Medication was discontinued for those who missed 3 days of medication and not restarted in the DETOX group. In the BUP group those that returned within 7 days could restart medication if they chose to do so and the treating physician agreed. Participants who discontinued medication were encouraged to continue with the 12 week psychosocial treatment that included manualized individual and group counseling, each once a week, based on cognitive, relapse prevention and twelve step programs.

2.3. Assessments

At screening and baseline participants provided demographic information and a brief history of lifetime and past 30-day drug use, and received a medical and psychiatric history and physical examination with routine laboratory tests including liver enzyme levels and serum Hepatitis B and C. Use of prescribed and over the counter medications and receipt of non-study treatment services, including therapy appointments, medical office visits, hospitalizations, and emergency room visits for medical, psychiatric or substance use treatment were collected for the month prior to treatment entry.

A medical evaluation, urine drug testing, and the opioid sections of the clinician administered Substance Dependence Severity Scale (SDSS) Lite (Miele et al., 2000), which evaluated substance use based on DSM-IV criteria, identified opioid dependence with physiological features. The Risk Behavior Survey (RBS) (Needle et al., 1995; NIDA, 1993), a clinician-administered scale, assessed prior 30-day HIV risk behavior such as injection drug use, sharing injection equipment, and sexual risk behaviors. The Young Adult Self-Report (YASR) and the Youth Self-Report (YSR) (Achenbach, 1991; Achenbach, 1997) measured internalizing symptoms such as anxiety or depression, and externalizing symptoms such as delinquent behavior, aggressive behavior, or attention problems, for the prior 90 days.

After treatment initiation, the Short Opiate Withdrawal Scale (SOWS) (Gossop, 1990), a 10 item self-report, measured signs and symptoms of opioid withdrawal weekly during weeks of Bup/Nal administration. The Medication Experience-Participant Form, a three-item self-report, assessed participants' experience/satisfaction with Bup/Nal weekly, including their perception of its helpfulness and side effects. Adherence to medication was defined a priori as taking at least 5 of 7 doses per week, as previously reported (Subramaniam et al., 2011), and was recorded weekly on daily logs. Adherence to (i.e., attendance at) study counseling visits was recorded weekly. Receipt of prescribed and over the counter medications was collected weekly and non-study services documented monthly. Urine drug tests, the primary outcome measure, were collected at screening and weekly. To identify characteristics associated with attrition in sufficient time to allow for a rapid intervention, this report focuses on data from the first 2 weeks of the study except for data on receipt of non-study treatment, collected at week 4.

2.4. Definition of attrition

Treatment dropout was defined, as in the primary study, as not attending any study counseling session lasting 30 min or longer for two or more consecutive weeks, missing medication for three consecutive days in the DETOX group or 7 days in the BUP group, enrolling in another treatment program, asking to be withdrawn, leaving the area, administrative withdrawal for inappropriate conduct, or going to jail. Dropouts did not attend a treatment visit at day 77, the beginning of the week 12 visit window, or later. One participant who discontinued due to pregnancy was not considered a dropout in this analysis.

2.5. Analytical methods

Logistic regression models were used to identify predictors of attrition. Since attrition rates were very different in the DETOX and BUP groups, predictors were examined separately in each group. Since the number of potential predictors was large relative to the sample size, each variable was examined in a separate bivariate logistic regression model. There was no correction for multiple comparisons due to the hypothesis generating nature of the study.

We also evaluated independent predictors of attrition in both the DETOX and BUP groups by examining the contribution of selected variables to attrition after adjustment for other variables in the model. Predictors were entered into these multivariate models based on their p-values (<0.10) in the bivariate models. The number of potential predictors that could be included in each model in BUP and DETOX was contingent upon the number of participants in the smaller of the two groups (dropouts and non-dropouts) being compared (Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996). When more predictors with p-values<0.10 were available than could be entered predictors were selected in the order of increasing p-value. We selected this approach rather than identifying variables for the model a priori given the limited data in the literature regarding predictors of attrition in youth treated with buprenorphine.

3. Results

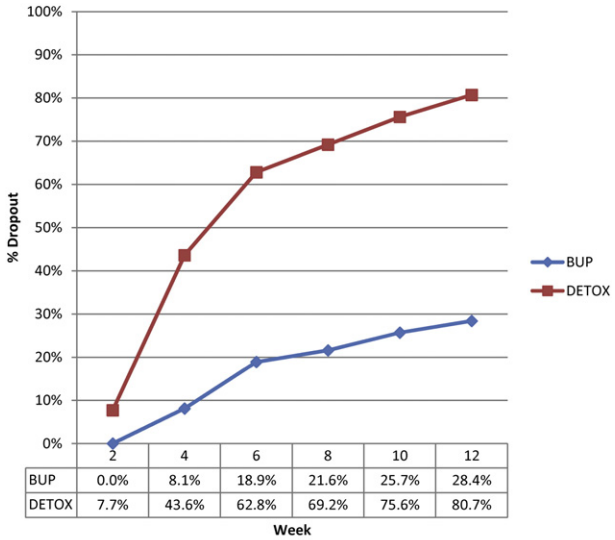
3.1. Sample characteristics

The two groups were generally similar in baseline characteristics. Mean ages were 19.1 years (standard deviation (SD) 1.4) in BUP, and 19.2 years (SD 1.6) in DETOX, with few participants less than 18 (16% in BUP and 18% in DETOX). The sample was primarily white (76% in BUP and 72% in DETOX). There were few African Americans, 1% and 3% in BUP and DETOX respectively. In BUP 24% were Hispanic with 26% Hispanic in DETOX. There were fewer females than males (43% in BUP and 38% in DETOX).

In the 30 days prior to treatment 41% in BUP and 39% in DETOX used only heroin, 26% in BUP and 22% in DETOX used only other opioids, and 34% in BUP and 39% in DETOX used both. In addition, 47% in BUP, and 40% in DETOX used alcohol, while 85% in both BUP and DETOX used at least one additional non-opioid drug in the prior 30 days. Many had a concurrent active psychiatric symptom (28% in BUP and 23% in DETOX). The mean maximum dose of Bup/Nal received in the first 2 weeks was 14.6 mg (SD 4.8) in BUP and 11.5 mg (SD 2.9) in DETOX.

3.2. Timing of attrition (Fig. 1)

In the BUP group, 28% (21/74) dropped out before week 12. There were no dropouts before week 2, 8.1% (6) before week 4, 10.8% (8) before week 6, 2.7% (2) before week 8, 4.1% (3) before week 10, and 2.7% (2) before week 12. In the DETOX group, 81% (63/78) dropped out before week 12, 7.7% (6) before week 2, 35.9% (28) before week 4, 19.2% (15) before week 6, 6.4% (5) before week 8, 6.4% (5) before week 10, and 5.1% (4) before week 12.



	2	4	6	8	10	12
BUP	0.0%	8.1%	18.9%	21.6%	25.7%	28.4%
DETOX	7.7%	43.6%	62.8%	69.2%	75.6%	80.7%

BUP-Buprenorphine/Naloxone group; DETOX-Detoxification group

Fig. 1. Timing of attrition.

3.2.1. Baseline predictors of attrition (Table 1)

In the BUP group those with hallucinogen use in the prior 30 days were more likely to drop out (odds ratio (OR) = 7.97; 95% confidence interval (CI) = 1.41, 45.09; p = 0.019). For each additional substance abused the likelihood of dropout increased (OR = 1.67; 95% CI = 1.01, 2.76; p = 0.046). Those with lifetime non-heroin opioid abuse (with or without lifetime heroin use), compared with lifetime use of heroin and/or any other drug were less likely to drop out (OR = 0.34; 95% CI = 0.12, 0.98; p = 0.045), as were those who used any medications, such as for sleep, withdrawal, pain, psychiatric symptoms or other reasons, in the prior month (OR = 0.12; 95% CI = 0.03, 0.45; p = 0.002).

In the DETOX group, no baseline characteristics were associated with attrition.

3.2.2. Early treatment predictors of attrition (Table 2)

In the BUP group the odds of attrition were higher if the last urine drug screen collected during weeks 1 and 2 was positive for opioids (OR = 5.86; 95% CI = 1.72, 19.90; p = 0.005). Those who had at least one individual or group counseling session in both weeks 1 and 2 were less likely to drop out compared with those with one or no visits (OR = 0.24; 95% CI = 0.08, 0.74; p = 0.013). Those who reported medication adherence five or more days a week in the first 2 weeks were also less likely to drop out (OR = 0.11; 95% CI = 0.03, 0.41; p = 0.001).

In the DETOX group the use of concomitant medications for sleep in the first 2 weeks was associated with less dropout (OR = 0.14; 95% CI = 0.02, 0.85; p = 0.033).

3.2.3. Independent baseline and early treatment predictors of attrition (Table 3)

In the BUP group those using more prescribed or over the counter medications of any kind in the month prior to treatment were less likely to drop out (OR = 0.03; 95% CI = 0.00, 0.29; p = 0.002). Those using hallucinogens in the 30 days prior to treatment entry were more likely to drop out (OR = 28.87; 95% CI = 1.59, 525.2; p = 0.023) and those with lifetime non-heroin opioid abuse were less likely to drop out (OR = 0.18; 95% CI: 0.05, 0.70; p = 0.013).

The early treatment characteristic independently associated with dropout in the BUP group was an opioid positive urine on the last urine drug screen obtained during weeks 1 and 2 (OR = 4.83; 95% CI = 1.29, 8.06; p = 0.019) while those adherent to medication 5 or more days per week in the first 2 weeks were less likely to discontinue (OR = 0.07; 95% CI = 0.01, 0.89; p = 0.040).

In the DETOX group there were no significant independent predictors of attrition at baseline or during early treatment.

4. Discussion

This is the first report of pre-treatment and early treatment characteristics associated with treatment attrition in youth treated with Bup/Nal. In youth receiving 12 weeks of Bup/Nal, early adherence to prescribed Bup/Nal was associated with retention and an early non-abstinence indicator, an opioid positive urine, was associated with attrition. A few pre-treatment characteristics, use of prescribed and over the counter medications of any kind in the month prior to treatment, and lifetime non-heroin opioid abuse were associated with retention while prior 30 day hallucinogen use was associated with attrition. In youth receiving 2 weeks of Bup/Nal, only medications for sleep were associated with retention, although this was not an independent predictor. What is striking, however, is that characteristics such as gender, injection drug use, the presence of hepatitis C, current use of heroin compared with non-heroin opioids, concurrent use of other drugs and alcohol, and comorbid psychiatric symptoms were not associated with attrition in either group. Extended use of Bup/Nal appears to help improve retention in youth with a wide range of characteristics, at least in this sample. Medication dose and withdrawal symptoms in the first 2 weeks were also not related to attrition.

The timing of increased dropout in the DETOX group corresponded with the end of the Bup/Nal taper at day 14, with 8% leaving before week 2 and 36% leaving between weeks 2 and 4. In the BUP group dropout was only 8% in the first 4 weeks. These newly reported data about the timing of attrition in the first few weeks in DETOX provides additional evidence that continuing Bup/Nal for a longer time is a key determinant of treatment retention (Woody et al., 2008), as in adults (Sees et al., 2000, Katz et al., 2009).

The 8% 4-week dropout rate in the BUP group was similar to the lowest 4-week attrition rates reported in adult studies where a dose taper was not expected to occur until after week 4 (Fischer et al., 1999; Johnson et al., 2000; Lee et al., 2008; Soyka et al., 2008; Strain et al., 1994a, 1994b). Given that youth have a shorter and less complex history of drug use than adults this outcome is not surprising.

An early opioid positive urine test was associated with attrition in opioid addicted adults (Stein et al., 2005), and an early cocaine positive urine with attrition in cocaine addicted adults (Kampman et al., 2001), consistent with findings in this sample. This marker may reflect low motivation for treatment or inadequate dosing (Stein et al., 2005), although mean maximum dosing in BUP was within the usual dosing range and consistent with study guidelines at 14.6 mg/day in the first 2 weeks. An early opioid positive urine was also associated with worse treatment outcomes (i.e., opioid positive urines at 12 weeks) in this sample (Subramaniam et al., 2011), further highlighting the importance of this marker in identifying youth at risk for both attrition and poorer drug use outcomes.

Lower adherence to counseling visits was a significant, although not independent predictor of attrition in our sample, similar to findings in adults (Stein et al., 2005). Adherence to counseling or medication use may directly impact retention or adherence to either may be an indicator of future adherence as well.

Receipt of at least one prescribed or over the counter medication prior to treatment entry was associated with retention in the BUP group, although no specific category of medications, such as those for sleep or pain, was identified as related. Possible explanations are that entry into treatment with generally reduced or resolved symptoms may impact retention by limiting symptom discomfort, or that prior medication use reflects a history of adherence and suggests continued adherence.

Youth in the BUP group who reported lifetime abuse of non-heroin opioids (with or without lifetime heroin use) were less likely to drop out compared with those with lifetime use of heroin and/or any other drug. This is an intriguing finding given the alarming increase in the non-medical use of non-heroin opioids and related emergency care in youth (Drug Abuse Warning Network, 2011; Johnston et al., 2011). Lifetime non-heroin opioid abusers may represent a different population that samples these drugs but adheres to treatment. However, there were no differences in dropout between (1) past 30-day abusers of non-heroin opioids (with or without past 30-day heroin use) compared to past 30-day abusers of heroin, or (2) past 30 day or lifetime abusers of only non-heroin opioids (as their choice of opioids) compared with heroin only abusers, consistent with a previous report that found no difference in attrition between adolescents using non-heroin or heroin opioids (Motamed et al., 2008). Further assessment of the characteristics and outcomes of young users of non-heroin opioids will be important.

The finding that hallucinogen use in the 30 days prior to treatment entry was associated with dropout in the BUP group may be an artifact of the small number of hallucinogen users (n = 7).

Based on the bivariate analyses, only medications for sleep assisted with retention during treatment in DETOX, suggesting that offering relief from sleep disturbance, possibly as a lingering symptom of withdrawal, helps youth remain in psychosocial treatment when only very short term Bup/Nal is available.

We found that co-occurring psychiatric symptoms, as measured by the YSR and YASR, were unrelated to attrition, although higher rates of

Table 1
Baseline characteristics associated with attrition.

Characteristic	Buprenorphine/naloxone group n = 74				Detoxification group n = 78			
	Attrition n (%) (mean (SD))	Nonattrition n (%) (mean (SD))	Odds ratio (95% CI)	p-Value	Attrition n (%) (mean (SD))	Nonattrition n (%) (mean (SD))	Odds ratio (95% CI)	p-Value
Sociodemographic								
Age ≥ 18	18 (85.7)	44 (83.0)	1.23 (0.30, 5.06)	0.777	52 (82.5)	12 (80.0)	1.18 (0.28, 4.90)	0.818
Female	8 (38.1)	24 (45.3)	0.74 (0.26, 2.09)	0.574	24 (38.1)	6 (40.0)	0.92 (0.29, 2.92)	0.892
White[a]	16 (76.2)	40 (75.5)	1.04 (0.32, 3.39)	0.948	47 (74.6)	9 (60.0)	1.96 (0.60, 6.36)	0.264
Employed (30 days)	12 (57.1)	30 (56.6)	1.02 (0.37, 2.84)	0.966	29 (46.0)	10 (66.7)	0.43 (0.13, 1.39)	0.158
Never married/not cohabiting[b]	19 (90.5)	47 (88.7)	1.21 (0.22, 6.55)	0.823	51 (81.0)	13 (86.7)	0.65 (0.13, 3.29)	0.606
Years of education	(10.9 (1.5))	(11.1 (1.7))	0.91 (0.67, 1.23)	0.546	(11.3 (1.4))	(11.0 (1.7))	1.16 (0.79, 1.73)	0.446
Substance use								
Alcohol use (30 days)	7 (33.3)	28 (52.8)	0.45 (0.16, 1.28)	0.134	24 (38.1)	7 (46.7)	0.70 (0.23, 2.19)	0.543
Alcohol use (lifetime)[c]	9 (42.9)	25 (47.2)	0.84 (0.30, 2.33)	0.737	25 (39.7)	8 (53.3)	0.58 (0.19, 1.79)	0.339
Heroin use (30 days)	18 (85.7)	37 (69.8)	2.59 (0.67, 10.07)	0.168	50 (79.4)	10 (66.7)	1.92 (0.56, 6.61)	0.299
Heroin use (lifetime)[c]	16 (76.2)	33 (62.3)	1.94 (0.62, 6.11)	0.258	48 (76.2)	10 (66.7)	1.60 (0.47, 5.42)	0.450
Barbiturate use (30 days)	6 (28.6)	17 (32.1)	0.85 (0.28, 2.57)	0.769	20 (31.7)	2 (13.3)	3.02 (0.62, 14.68)	0.170
Barbiturate use (lifetime)[c]	5 (23.8)	8 (15.1)	1.76 (0.50, 6.16)	0.378	10 (15.9)	1 (6.7)	2.64 (0.31, 22.41)	0.373
Cocaine use (30 days)	12 (57.1)	18 (34.0)	2.59 (0.92, 7.29)	0.071	32 (50.8)	5 (33.3)	2.06 (0.63, 6.73)	0.229
Cocaine use (lifetime)[c]	7 (33.3)	13 (24.5)	1.54 (0.51, 4.63)	0.444	20 (31.7)	6 (40.0)	0.70 (0.22, 2.23)	0.543
Stimulant use (30 days)	12 (57.1)	20 (37.7)	2.20 (0.79, 6.15)	0.133	34 (54.0)	5 (33.3)	2.34 (0.72, 7.65)	0.158
Stimulant use (lifetime)[c]	7 (33.3)	16 (30.2)	1.16 (0.39, 3.41)	0.792	21 (33.3)	6 (40.0)	0.75 (0.24, 2.39)	0.626
Marijuana use (30 days)	15 (71.4)	32 (60.4)	1.64 (0.55, 4.90)	0.376	44 (69.8)	10 (66.7)	1.16 (0.35, 3.85)	0.811
Marijuana use (lifetime)[c]	18 (85.7)	41 (77.4)	1.76 (0.44, 6.99)	0.424	55 (87.3)	13 (86.7)	1.06 (0.20, 5.58)	0.947
Hallucinogen use (30 days)	5 (23.8)	2 (3.8)	**7.97 (1.41, 45.09)**	**0.019**	5 (7.9)	1 (6.7)	1.21 (0.13, 11.17)	0.868
Hallucinogen use (lifetime)[c]	4 (19.0)	5 (9.4)	2.26 (0.54, 9.41)	0.263	16 (25.4)	1 (6.7)	4.77 (0.58, 39.18)	0.146
Nicotine use (30 days)	20 (95.2)	51 (96.2)	0.78 (0.07, 9.14)	0.846	56 (88.9)	13 (86.7)	1.23 (0.23, 6.63)	0.809
Nicotine use (lifetime)[c]	19 (90.5)	49 (92.5)	0.78(0.13, 4.59)	0.779	53 (84.1)	11 (73.3)	1.93 (0.51, 7.28)	0.333
Non-heroin opioid use (30 days)	11 (52.4)	33 (62.3)	0.67 (0.24, 1.85)	0.436	39 (61.9)	8 (53.3)	1.42 (0.46, 4.42)	0.543
Non-heroin opioid use (lifetime)[c]	8 (38.1)	34 (64.2)	**0.34 (0.12, 0.98)**	**0.045**	39 (61.9)	6 (40.0)	2.44 (0.77, 7.71)	0.129
Heroin only vs. non-heroin opioids only (30 days)	10 (76.9)	20 (55.6)	2.67 (0.63, 11.35)	0.184	24 (64.9)	6 (60.0)	1.23 (0.29, 5.16)	0.777
Heroin only vs. non-heroin opioids only (lifetime)[c]	12 (75.0)	17 (48.6)	3.18 (0.86, 11.79)	0.084	23 (62.2)	8 (66.7)	0.82 (0.21, 3.24)	0.779
Number of types of substances used (30 days)	(2.9 (1.4))	(2.3 (0.9))	**1.67 (1.01, 2.76)**	**0.046**	(2.7 (1.2))	(2.1 (1.1))	1.57 (0.92, 2.66)	0.097
Number of types of substances used (lifetime)[c]	(2.7 (1.5))	(2.3 (1.0))	1.29 (0.85, 1.96)	0.231	(2.6 (1.2))	(2.4 (1.2))	1.19 (0.72, 1.97)	0.491
Clinical/comorbid conditions								
Hepatitis C positive	4 (19.0)	8 (15.1)	1.32 (0.35, 4.97)	0.678	14 (22.6)	2 (13.3)	1.90 (0.38, 9.42)	0.434
No medical/psychiatric symptoms	7 (33.3)	12 (22.6)	1.71 (0.56, 5.20)	0.345	16 (25.4)	4 (26.7)	0.94 (0.26, 3.36)	0.919
Any active medical/psychiatric symptom	10 (47.6)	31 (58.5)	0.65 (0.23, 1.78)	0.398	36 (57.1)	6 (40.0)	2.00 (0.64, 6.30)	0.236
No psychiatric symptoms	15 (71.4)	31 (58.5)	1.77 (0.59, 5.29)	0.304	33 (52.4)	10 (66.7)	0.55 (0.17, 1.79)	0.322
Any active psychiatric symptom	3 (14.3)	18 (34.0)	0.32 (0.08, 1.25)	0.101	15 (23.8)	3 (20.0)	1.25 (0.31, 5.03)	0.753
Any medication use[d]	3 (14.3)	31 (58.5)	**0.12 (0.03, 0.45)**	**0.002**	20 (32.3)	6 (46.2)	0.56 (0.17, 1.87)	0.342
Withdrawal medication use[d]	0 (0.0)	10 (18.9)	[e]		8 (12.9)	1 (7.7)	1.78 (0.20, 15.58)	0.603
Sleep medication use[d]	1 (4.8)	11 (20.8)	0.19 (0.02, 1.58)	0.125	2 (3.2)	2 (15.4)	0.18 (0.02, 1.44)	0.107
Pain medication use[d]	1 (4.8)	6 (11.3)	0.39 (0.04, 3.47)	0.400	6 (9.7)	1 (7.7)	1.29 (0.14, 11.68)	0.823
Psychiatric medication use[d]	1 (4.8)	8 (15.1)	0.28 (0.03, 2.40)	0.246	3 (4.8)	2 (15.4)	0.28 (0.04, 1.87)	0.189
Other medication use[d]	1 (4.8)	10 (18.9)	0.22 (0.03, 1.80)	0.156	8 (12.9)	2 (15.4)	0.81 (0.15, 4.37)	0.811
Non-study treatment[f]	2 (9.5)	8 (15.4)	0.58 (0.11, 2.99)	0.514	13 (21.0)	1 (8.3)	2.92 (0.34, 24.71)	0.326
Injection drug use[g]	11 (52.4)	24 (45.3)	1.33 (0.48, 3.66)	0.582	32 (51.6)	4 (30.8)	2.40 (0.67, 8.62)	0.180
Number of injection drugs used (30 days)	(14.3 (14.2))	(11.0 (13.3))	1.02 (0.98, 1.06)	0.344	(13.3(13.6))	(6.3(11.0))	1.05 (0.99, 1.10)	0.098
Elevated liver enzymes	5 (23.8)	14 (26.4)	0.87 (0.27, 2.82)	0.817	17 (27.0)	2 (13.3)	2.40 (0.49, 11.77)	0.280
Internalizing symptoms T-score[h]	(64.6 (11.5))	(64.3 (11.2))	1.00 (0.96, 1.05)	0.900	(60.1 (12.2))	(64.8 (12.7))	0.97 (0.92, 1.02)	0.215
Externalizing symptoms T-score[h]	(60.6 (10.7))	(57.5 (7.9))	1.04 (0.98, 1.11)	0.190	(57.7 (9.8))	(60.1 (11.2))	0.98 (0.92, 1.04)	0.430

Bold: Statistically significant at p ≤ .05.

Note: All measures are categorical (present/absent) except where noted (e.g. years of education, number of injection drugs used, internalizing T-score). For the categorical measures the number of participants in the attrition or non-attrition group who had that characteristic and dropped out (attrition group) or had that characteristic and did not drop out (non-attrition group), and the percent of dropouts or non-dropouts this n represents (%) are listed. For continuous measures, the mean and standard deviation for that measure in each group are listed instead in the format (mean (SD)).

[a] White compared with any other race/ethnicity. Demographic data collected offered the choices White, Black/African American, American Indian/Alaskan Native, Spanish/Hispanic/Latino, Asian, Native Hawaiian/Pacific Islander or other, and permitted choice of multiple options.

[b] Never married/not cohabiting compared with married, cohabiting, separated, divorced.

[c] Lifetime use defined as 3 days or more a week for more than 6 months, binges, or patterned problematic use.

[d] Medication use in the month prior to screening.

[e] A valid model could not be fit due to inadequate frequency of the event.

[f] Non-study treatment in the month prior to treatment includes therapy appointments, medical office visits, hospitalizations, and emergency room visits.

[g] Injection drug use includes opioids, cocaine or amphetamines.

[h] T-scores from the Youth Self-Report and Young Adult Self-Report.

depression were associated with retention (Gerra et al., 2004) and more severe depression and psychopathology were associated with attrition (Pani et al., 2000) in adults with opioid dependence. However, the YSR and YASR provide only general measures of internalizing or externalizing symptoms, and do not indicate the presence of a specific psychiatric disorder, which was not assessed in this study. Early withdrawal symptoms were also not associated with attrition in this analysis, consistent with some (Scherbaum, Heppkausen, & Rist, 2004), but not all studies in adults (Soyka et al., 2008). Maximum dose of Bup/Nal in the first 2 weeks or number of days at this dose were not

Table 2
Early treatment characteristics associated with attrition (weeks 1–2).

Characteristic	Buprenorphine/naloxone group n = 74				Detoxification group n = 78			
	Attrition n (%) (mean (SD))	Nonattrition n (%) (mean (SD))	Odds ratio (95% CI)	p-Value	Attrition n (%) (mean (SD))	Nonattrition n (%) (mean (SD))	Odds ratio (95% CI)	p-Value
Study treatment								
Counseling visits ≥ 1 each week[a]	10 (50.0)	41 (80.4)	**0.24 (0.08, 0.74)**	**0.013**	32 (53.3)	6 (40.0)	1.71 (0.54, 5.42)	0.359
Medication adherence 5 + days/week	12 (57.1)	49 (92.5)	**0.11 (0.03, 0.41)**	**0.001**	38 (63.3)	9 (64.3)	0.96 (0.29, 3.23)	0.947
Maximum dose of Bup/Nal	(13.7 (5.2))	(15.0 (4.6))	0.94 (0.84, 1.05)	0.299	(11.6 (2.9))	(11.0 (3.1))	1.07 (0.88, 1.30)	0.517
Days at maximum dose	(7.4 (4.4))	(8.7 (3.9))	0.93 (0.82, 1.05)	0.224	(4.0 (1.6))	(4.0 (2.8))	0.99 (0.73, 1.35)	0.954
Mean SOWS score	(6.6 (8.1))	(5.3 (4.1))	1.05 (0.95, 1.15)	0.378	(7.5 (5.6))	(5.9 (4.0))	1.06 (0.91, 1.24)	0.464
Last urine drug screen positive	9 (56.3)	9 (18.0)	**5.86 (1.72, 19.90)**	**0.005**	19 (39.6)	4 (44.4)	0.82 (0.19, 3.44)	0.785
Number of drug related AEs	(0.8 (1.1))	(1.6 (2.6))	0.78 (0.55, 1.11)	0.170	(0.92 (1.6))	(80.0 (1.9))	1.05 (0.73, 1.51)	0.797
Minimum MEP score[b]	(13.3 (4.3))	(15.6 (1.8))	0.74 (0.52, 1.04)	0.082	(15.3 (2.4))	(15.9 (1.5))	0.87 (0.58, 1.30)	0.489
Treatment outside the study								
Any medication use	5 (31.3)	29 (56.9)	0.34 (0.10, 1.14)	0.081	19 (36.5)	4 (40.0)	0.86 (0.22, 3.45)	0.836
Withdrawal medication use	0 (0.0)	3 (5.9)	[c]		5 (9.6)	0 (0.0)	[c]	
Sleep medication use	4 (25.0)	9 (17.6)	1.56 (0.41, 5.95)	0.518	3 (5.8)	3 (30.0)	**0.14 (0.02, 0.85)**	**0.033**
Pain medication use	2 (12.5)	12 (23.5)	0.46 (0.09, 2.34)	0.352	10 (19.2)	2 (20.0)	0.95 (0.17, 5.19)	0.955
Psychiatric medication use	0 (0.0)	6 (11.8)	[c]		2 (3.8)	2 (20.0)	0.16 (0.02, 1.30)	0.087
Other medication use	0 (0.0)	12 (23.5)	[c]		5 (9.6)	0 (0.0)	[c]	
Non-study treatment[d]	3 (33.3)	6 (12.2)	3.58 (0.70, 18.25)	0.124	8 (22.9)	2 (18.2)	1.33 (0.24, 7.47)	0.744

Bold: Statistically significant at p ≤ .05.
Note: Early treatment data were available for all participants. All measures are categorical (present/absent) except where noted (e.g. maximum dose, mean SOWS score). For the categorical measures the number of participants in the attrition or non-attrition group who had that characteristic and dropped out (attrition group) or had that characteristic and did not drop out (non-attrition group), and the percent of dropouts or non-dropouts this n represents (%) are listed. For continuous measures, the mean and standard deviation for that measure in each group are listed instead in the format (mean (SD)). Bup/Nal—buprenorphine/naloxone. SOWS—Short Opiate Withdrawal Scale. AEs—adverse events. MEP—Medication Experience-Participant version.
[a] At least one visit in week 1 and in week 2 compared to a total of one visit or no visit.
[b] A higher score on MEP reflects more positive attitude about medication experience.
[c] A valid model could not be fit due to inadequate frequency of the event.
[d] Non-study treatment includes therapy appointments, medical office visits, hospitalizations, and emergency room visits and was collected at week 4. It therefore is associated with attrition after week 4.

associated with attrition in either group, similar to findings in adults treated with comparable mean daily doses of 9–12 mg (Soyka et al., 2008; Gerra et al., 2004; Vigezzi et al., 2006). In one observational study with adults, initial induction doses of 16 mg were associated with better retention (Leonardi et al., 2008). However, this study may not have had enough power to identify such an effect in youth. It may also be that dosing was adequate enough to reduce the discomfort of withdrawal and therefore not impact attrition.

Attrition is a very serious problem in the treatment of opioid dependent adolescents. The limited number of pre-treatment characteristics identified as associated with attrition highlights the importance of comprehensively measuring other factors that could have a meaningful impact on retention such as those related to family support, housing or transportation, in the search for areas in which clinicians and researchers can intervene to improve retention.

The main study (Woody et al., 2008) had sufficient power to detect differences in the primary outcome of opioid positive urines at 4, 8, and 12 weeks. If the sample sizes had been larger we would have had more power to detect factors associated with attrition in both groups. Given the number of dropouts and non-dropouts in each group, we were limited in the number of variables that could be included in analyses of independent predictors of attrition and could have missed other potentially significant predictors. While findings in the multivariate models are consistent with bivariate analyses,

Table 3
Baseline and early treatment characteristics independently associated with attrition.

Characteristic	Buprenorphine/naloxone group n = 74		Detoxification group n = 78	
	Odds ratio (95% CI)	p-Value	Odds ratio (95% CI)	p-Value
Baseline				
Number of injection drugs used (30 day)			1.04 (0.99, 1.10)	0.123
Number of types of substances used (30 day)	1.48 (0.71, 3.09)	0.292	1.39 (0.82, 2.37)	0.222
Any medication use[a]	**0.03 (0.00, 0.29)**	**0.002**		
Hallucinogen use (30 day)	**28.87 (1.59, 525.2)**	**0.023**		
Non-heroin opioid use (lifetime)	**0.18 (0.05, 0.70)**	**0.013**		
Early treatment (weeks 1–2)				
Psychiatric medication use			0.35 (0.05, 2.56)	0.300
Sleep medication use			0.22 (0.03, 1.83)	0.161
Last urine drug screen positive	**4.83 (1.29, 18.06)**	**0.019**		
Medication adherence 5 + days/week	**0.07 (0.01, 0.89)**	**0.040**		
Therapy visits ≥ 1 each week[b]	0.45 (0.11, 1.90)	0.277		

Bold: Statistically significant at p ≤ .05.
Note: All variables entered into the two models (one for baseline characteristics and one for early treatment characteristics) completed for each group are listed above. All measures are categorical (present/absent) except where noted (e.g. number of injection drugs used).
[a] Medication use in the month prior to screening.
[b] At least one visit in week 1 and in week 2 compared to a total of one visit or no visits.

actual odds ratios may have been sensitive to small sample sizes. Other factors, such as motivation to receive treatment or intent to remain in treatment may be associated with attrition; however, data about these factors were not collected. Finally, all findings must be confirmed in other youth samples.

4.1. Conclusions

In summary, early evidence of medication adherence and opioid abstinence was strongly predictive of treatment retention, reinforcing the need to aggressively target those with early non-adherence to medication or an early opioid positive urine drug screen to further improve treatment retention and outcome. It is salient that there were few notable findings among a large group of possible pre-treatment characteristics that could be related to attrition, other than assignment to brief or extended administration of Bup/Nal. In this sample extended Bup/Nal treatment was effective in improving treatment retention for youth with opioid dependence across a wide range of demographic characteristics, pre-treatment clinical severity, current use of heroin or non-heroin opioids, concurrent abuse of a variety of other drugs and alcohol, the presence or absence of comorbid psychiatric symptoms or hepatitis C infection, or concurrent medication use. If replicated this finding could be of considerable importance to clinicians. However, other factors that may be barriers to retention, such as housing, transportation, and family support of treatment should be measured and further investigated as well.

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Contributors

Drs. Warden, Subramaniam, Carmody, Minhajuddin and Trivedi developed the plan for the secondary analysis conducted. Drs. Carmody and Minhajuddin conducted the statistical analyses. All authors have participated in the research trial and/or manuscript preparation and have approved the final manuscript. Dr. Woody designed the larger multisite trial and was the Lead Investigator for that trial.

Conflict of interest

Dr. Warden previously held stock in Pfizer and Bristol-Myers Squibb. She has received funding from the National Alliance for Research on Schizophrenia and Depression. Dr. Woody has served on the advisory board of the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System. Dr. Fishman is the medical director of Mountain Manor Treatment Center (MMTC), one of multiple research sites in this study. He is a beneficiary of the trust that owns MMTC and serves on the governing board of the trust and the board of directors of MMTC. The terms of Dr. Fishman's potential conflict of interest in research are managed by Johns Hopkins University in accordance with its conflicts of interest policies. Dr. Patkar has received research support from NIH (NIDA/NIAAA), Duke Endowment, AstraZeneca, Forest Pharmaceuticals, Cephalon, Janssen, Jazz, McNeil, Organon, Orphan, Merck, Lundbeck, Pfizer, Titan, Shire, Sunovion; has been a consultant/Advisory Board member of Forest Pharmaceuticals, Gilead, Dey Pharmaceuticals, Titan, Reckitt Benckiser, and on Speakers Bureau of Alkermes, Bristol-Myers Squibb, Dey Pharmaceuticals, and Sunovion. Dr. Trivedi is a consultant to or on speaker bureaus for Alkermes, AstraZeneca, Axon Advisors, Bristol-Myers Squibb Company, Cephalon, Inc., Eli Lilly & Company, Evotec, Forest Pharmaceuticals, GlaxoSmithKline, Johnson & Johnson PRD, Lundbeck, MedAvante, Neuronetics, Otsuka Pharmaceuticals, Pamlab, Pfizer Inc., PGxHealth, Rexahn Pharmaceuticals, SHIRE Development, Takeda, Tal Medical/Purtech Venture, Targacept, and Transcept. He receives research support from the Agency for Healthcare Research and Quality (AHRQ), National Institute of Mental Health, National Institute on Drug Abuse, Naurex, Targacept, and Valient. Drs. Subramaniam, Carmody, Minhajuddin, and Potter, and Ms. Poole report no biomedical financial interests or potential conflicts of interest.

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