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One-Year Follow-Up of Heroin-Dependent Adolescents Treated with Buprenorphine/Naloxone for the First Time in a Substance Treatment Unit



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ABSTRACT

The aims of the present study were to evaluate 1-year retention in program and buprenorphine/naloxone (BUP/NAL) treatment, and abstinence of heroin-dependent adolescents. The present study included the follow-up information of 112 heroin dependent adolescents who took BUP/NAL treatment for the first time in a specific inpatient unit. Retention and abstinence were assessed by self-report and urine drug screen at each visit. Mean age was 16.9 years, with 101 (90.2%) male. Program retention was 81.3% at day 30, and 24.1% at 1 year, while retention in BUP/NAL treatment was 69.6% at day 30 and 16.1% at 1 year. Rates of abstinence were 69.0% at day 30 and 10.3% at 1 year. There was a significant positive correlation between duration of inpatient treatment and program retention, treatment retention, abstinence ($p < 0.05$ for all), and between the dose and treatment retention, abstinence ($p < 0.05$ for both). Patients with comorbid psychiatric disease were more likely to be retained in treatment for 3 months, and in program for 6 months ($p < 0.05$, for all). Patients who completed inpatient treatment were more likely to be retained in treatment for 1 year, and in program for 9 months, and to be abstinent for 1 year ($p < 0.05$, for all). Findings suggested that starting BUP/NAL treatment in an inpatient unit might result in better outcomes compared to literature. Duration of inpatient treatment, the completion of inpatient treatment, BUP/NAL dose, and having a comorbid psychiatric disease seemed to be important factors for heroin-dependent adolescents in retention and abstinence within 1-year period.

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1. Introduction

Heroin has accounted for most of the drug treatment demands and social and health problems associated with illegal drug use in Europe for many years and this continues to be the case in more recent years (Barrio et al., 2013; UNODC, 2013). Heroin use and related admissions among adolescents appear to have increased over years (Hopfer et al., 2002; Wu & Howard, 2007; Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2012; Matson et al., 2014; Johnston et al., 2011). Alarming rates of opioid abuse among adolescents have increased the importance of medication assisted opioid therapy which was planned for 14% of those 12–19 in 2009 and 2011 (Substance Abuse and Mental Health Services Administration, 2011; Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2012).

Buprenorphine/naloxone (BUP/NAL) combination therapy (Suboxone) and buprenorphine monotherapy (Subutex) have become the first medications to be approved for opioid use disorder. As it has a good safety profile, they are effective for both detoxification (Gowing et al., 2009) and maintenance (Amato et al., 2005; Mattick et al., 2014). Its effect of partial opioid agonism at the m-opioid receptors usually decreases cravings for opioids, and prevents or alleviates withdrawal symptoms in opioid-dependent people. Several studies revealed the efficacy of the BUP/NAL combination treatment in adolescents and young adults (Marsch et al., 2005; Woody et al., 2008).

Attrition and dropout seem to be important factors hindering to maximize treatment outcome in opioid dependent youth (Warden et al., 2012; Bell & Mutch, 2006; Burns et al., 2009; Marsch et al., 2005; Woody et al., 2008; Smyth et al., 2012; Matson et al., 2014). However, retention and abstinence during buprenorphine treatment have been associated with better outcomes in youth (Subramaniam et al., 2011; Woody et al., 2008; Matson et al., 2014) and adults (Armstrong et al., 2010; Mintzer et al., 2007). In this context, retention in treatment of opioid dependence was investigated mostly in adults, with studies lasting 6 months (O'Connor et al., 1996; Fiellin et al., 2006; Armstrong et al., 2010) and those lasting 18 months or more (Fiellin et al., 2008; Parran et al., 2010). In youths, BUP/NAL treatment outcomes including retention were less examined in short-term

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(Marsch et al., 2005; Woody et al., 2008) and long-term (Smyth et al., 2012; Matson et al., 2014) studies conducted in outpatient settings. It is not known whether inpatient admissions impact the outcomes of BUP/NAL treatment. We believe that first initiation of BUP/NAL treatment in an inpatient unit with structured program may improve these outcomes better.

Therefore, the present study aimed to evaluate the long-term retention in treatment and program, and abstinence in heroin dependent adolescents. Also the associations of these outcomes with pre-treatment or early treatment characteristics of adolescents receiving BUP/NAL for the first time in a substance treatment inpatient unit were examined.

2. Methods

2.1 Study setting and participants

This retrospective study reflected an evaluation of 112 heroin-dependent adolescents aged 14–18 years hospitalized to the Health Ministry-licensed alcohol and substance treatment center at Bakirkoy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery in Istanbul, Turkey, between January 2011 and December 2013. Because of retrospective design of the study, there was no need for the approval of the Ethics Committee.

This center is a large urban drug abuse treatment center for children and adolescents located in Istanbul and offers counseling and treatment services to any alcohol and illicit use disorders of youths, as well as for their families. Treatment seeking can be voluntary (self-referral) or referral from doctors, other treatment centers, or other sources. This center includes an outpatient unit for daytime applications needing no appointments and inpatient unit for youth who want and accept to be treated and rehabilitated voluntarily with a structured 2-month (8 weeks) treatment program including weekly individual and group drug counseling and behavioral therapy. After discharge from the inpatient unit, patients are directed to participate to the outpatient treatment program necessitating of therapy, interview with both psychologist and child-adolescent psychiatrist and urine drug screen (UDS) once a week or twice a month, to have BUP/NAL prescribed.

In the present study, all the patients who met the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV-TR) (APA, 2000)* criteria for opioid dependence were eligible for BUP/NAL treatment and were admitted to the inpatient unit (as a standard procedure). Data represented the treatment with BUP/NAL for the first time including first inpatient admissions for 8-week treatment program with BUP/NAL treatment and subsequent follow-up period after discharge. As a standard procedure, at first visit after admission to inpatient unit, trained clinical staff (experienced psychologists) interviewed subjects using a semistructured questionnaire (the semi-structured socioeconomic form and the drug use questionnaire of The World Health Organization [WHO] for students) to obtain self-reported information (Adelekan & Odejide, 1989). Although this form was arranged by an experienced treatment team in this field, it has not yet been validated in Turkey.

The present study included some information from the study of our colleagues investigating the changes in liver enzyme levels associated with BUP/NAL treatment and co-medication with psychotropic agents in the same group who completed the 8-week BUP/NAL treatment at any inpatient admissions during the study period (Ciftci Demirci et al., 2015).

Dosing of BUP/NAL is adjusted in the inpatient unit in an individualized flexible titration, determined by the treating clinician based on treatment response and safety. Patients were abstained from opioids for at least 8 hours and present with opioid withdrawal before their first dose of BUP/NAL. Dosing was determined under direct observation every day within inpatient period. Participants were inducted on day 1 with a maximum dose of 6 mg (with starting dose of 2 mg). On following days, patients received the total dose of the previous day unless they

were overmedicated or undermedicated and, as clinically needed, received additional doses, as needed. Doses were generally stabilized in 1 to 2 weeks. Onset of the follow-up was defined as starting BUP/NAL treatment. Dates of clinic visits were documented. The patients who completed first 2 weeks of inpatient period took home privileges voluntarily for a weekend, and also for the following weekends. In the outpatient program, the patients were generally followed in dose at discharge for a long time. However, the dose of BUP/NAL could be changed minimally in outpatient follow-up based on clinical symptoms, clinical psychosocial functioning, and results of liver enzymes, renal function, blood count analyzed once per month.

The patients were followed by their same individual child-adolescent psychiatrist and psychologist during outpatient and inpatient period.

Follow-up visits occur daily during inpatient period, up to 7 days for the first visit after discharge, every 7 to 14 days for the first 6 months after discharge, and, with consistent compliance, every 4 weeks thereafter. Follow-up period after discharge includes scheduled appointments.

Definition of treatment retention encompassed patients remaining in BUP/NAL treatment along the period of study. As this, program retention was defined as remaining in follow-up visits. Retention duration was calculated as days from first treatment entry in inpatient unit and up to the date patients dropped out of treatment and/or program, or the end of the 1-year period. Participants who missed 3 or more consecutive days of BUP/NAL medication were considered as 'treatment dropout'. Treatment dropouts consisted of patients who were obligated to discontinue treatment due to medical complications/side effects or other medical conditions (involuntary treatment dropout) and who discontinued the BUP/NAL treatment by themselves (voluntary treatment dropout) during the 1-year follow-up period. Not attending to follow-up appointments for an interval of 4 weeks or more in the first 6 months after discharge and 8 weeks or more thereafter between two visits was considered as 'program dropout'.

Patients who started BUP/NAL treatment within the 1-year period after being considered as treatment dropouts were accepted as 'treatment re-entry'. Patients who returned for a visit within the 1-year period after being considered as program dropouts were accepted as 'program re-entry'. An admission to inpatient unit again within the 1-year period was considered as 'inpatient re-admission'.

Abstinence was defined as not using any substance (except tobacco), as documented by urine toxicology and/or self-reports during the treatment period. Duration of abstinence was calculated as days up to date of first substance use (except tobacco) within the 1-year period after beginning BUP/NAL treatment.

UDS was collected weekly at the inpatient unit and also after home privileges. After discharge, UDS was collected fortnightly and self-reported drug use data were collected at every follow-up visit at scheduled appointments. UDS collection was visually witnessed. UDS includes buprenorphine, opioids, heroin metabolite, cocaine, cannabis, amphetamine, ecstasy, benzodiazepines, barbiturates, hippuric acid and alcohol (as ethyl glucuronide). In order to identify possible adulteration, urine specimens were assessed for temperature, pH, bleach, nitrite, and creatinine. The UDS with possible adulterations were re-collected next day. Refusal to provide a urine sample for UDS or any/repeated failure for adulteration were presumed to be positive. The rate of possible adulteration was 0.7% (12/1684). After re-collection of these specimens, only one specimen (0.06%) was found to be adulterated.

2.2 Data collection and measures

Files and hospital database of 112 patients were reviewed for demographic variables (gender, age at admission, school status, family structure, family history of substance and alcohol use), clinical characteristics (age at first substance use, age at first heroin use, duration of heroin use, previous application for treatment of substance use, self-initiated

attempt to quit substance use), pre-treatment conditions (substance use [except opioids] in previous 30 days, injection use in previous 30 days, daily heroin use in previous 30 days, withdrawal and craving symptoms, opioids in UDS, other any substance in UDS, comorbid psychiatric disease), treatment conditions (withdrawal medication use, pain medication use, duration of inpatient treatment, duration of BUP/NAL treatment, maximum BUP/NAL dose, elevated liver enzymes [i.e., aspartate aminotransferase, alanine aminotransferase], duration of program participation, relapse to substance use, duration of abstinence, completion of inpatient treatment, program re-entry, inpatient re-admission, treatment re-entry). Substances were categorized as follows: heroin, cannabis (marijuana, hashish, hashish oil), inhalants/solvents (butane, kerosene, unspecified solvents), alcohol (beer, wine, spirits), ecstasy, synthetic cannabinoid, cocaine, benzodiazepines (used for non-medical purposes, such as diazepam, lorazepam, oxazepam, temazepam, triazolam, alprazolam, chlordiazepoxide), metamphetamine, hallucinogens (lysergic acid diethylamide [LSD]). Presence of withdrawal and craving symptoms was evaluated clinically by experienced clinicians, because there was no any valid and reliable scale assessing opioid withdrawal symptoms of adolescents within the study period in our country. In our inpatient unit, an opioid withdrawal symptoms form which has been formed and completed by clinicians is used in order to determine and follow whether these symptoms are present. Depression and anxiety were evaluated by HAM-D and HAM-A, respectively, at the beginning of the treatment. Comorbid psychiatric diseases were diagnosed clinically according to the DSM-IV-TR criteria.

2.3 Statistical analysis

Data analysis was performed using PASW version 18.0 statistical software (SPSS Inc., Chicago, IL). Prior to analyses, Kolmogorov–Smirnov test was performed to assess the normal distribution of data. Mann–Whitney *U* test was used to compare non-normal distributed continuous variables. The chi-square test or Fisher's exact test was used to compare categorical variables. Pearson correlations were used to determine the correlation between age at admission, age at first substance use, age at first heroin use, duration of heroin use, and maximum BUP/NAL dose, and duration of treatment retention, program retention and abstinence. Pre-treatment conditions (substance use [except opioids] in previous 30 days, injection use in previous 30 days, other any substance in UDS, and comorbid psychiatric disease) and treatment conditions (withdrawal medication use, pain medication use, completion of inpatient treatment, and elevated liver enzymes) were used in analysis of these variables with treatment retention, program retention and abstinence. Completion of inpatient treatment was analyzed for retention and abstinence at days 90, 180, 270 and 365. Associations between completion of inpatient treatment and duration of treatment and program retention and abstinence were analyzed only for these days. Analysis of sex difference was not performed due to small sample of females ($n = 11$, 9.8%). Also, because of the low number of involuntary treatment dropout ($n = 8$, 7.1%) and patients ($n = 3$, 2.7%; only 1 of them completed inpatient treatment) sent from forensic authorities for inpatient treatment, these patients were not excluded from analyses. Our analysis for outcomes including program retention and treatment retention did not include the data after the patient were considered as dropout. Abstinence was analyzed in 87 patients because there was no any related follow-up information of 25 patients who lost to follow. One-year period was accepted as '365 days' in analyses. Significance was defined as a p value <0.05 .

3. Results

Between 2011 and 2013, 112 adolescents (average age = 16.91 ± 0.96, with a range of 14–18 years) were admitted for BUP/NAL treatment of heroin dependence. Within 1-year period for each patient, 36 (32.1%) had one or more inpatient re-admission. Of the adolescents,

101 (90.2%) were male. The mean duration of education was 7.5 ± 1.5 years. Family history of substance use was reported by 49 (43.8%) patients. Mean age at first heroin use was 14.8 years and mean duration of heroin use was 24.2 months. Of the patients, 107 (95.5%) used heroin daily in previous 30 days, 88 (78.6%) had withdrawal symptoms and UDS was positive for opioids in 106 (94.6%) at admission. Comorbid psychiatric diseases, diagnosed in 53 patients (47.3%), were depression ($n = 32$, 28.6%), conduct disorder ($n = 10$, 8.9%), anxiety disorder ($n = 7$, 6.2%), ADHD ($n = 7$, 6.2%), enuresis nocturna ($n = 4$, 3.6%). Seven patients could have more than one comorbid psychiatric disease. Mean duration was 118.3 days for BUP/NAL treatment, 160.6 days for program participation, and 65.3 days for abstinence. Among relapses, 71 (91%) relapsed to opioid. Eight patients (7.1%) were obligated to discontinue BUP/NAL treatment due to elevated liver enzymes (involuntary treatment dropout). Twenty five patients (22.3%) lost to follow. Demographic, clinical and treatment characteristics were shown in Table 1.

At 30 days, 70% of patients continued the BUP/NAL treatment, and by 1 year 16% were still retained in the treatment. At 30 days, 81% of patients were retained, and by 1 year 24% were still retained in the program. By 1 year, 10% of patients were abstinent. Rates of retention and abstinence in 1-year follow-up are shown in Table 2 and Fig. 1.

Duration of inpatient treatment was significantly positively correlated with treatment retention, program retention and abstinence ($p < 0.05$ for all). Duration of treatment retention was significantly positively correlated with BUP/NAL dose, and duration of program retention and abstinence ($p < 0.05$ for all). Also, duration of abstinence was significantly positively correlated with BUP/NAL dose and duration of program retention ($p < 0.05$ for all). Age at admission, age at first substance use, age at first heroin use and duration of heroin use were not correlated with duration of treatment retention, program retention and abstinence ($p > 0.05$ for all) (Table 3). Consistently, there were no

Table 1
Demographic and clinical characteristics, pre-treatment and treatment conditions.

<i>Demographic characteristics</i>	
Male, n (%)	101 (90.2)
Age, mean ± SD years	16.91 ± 0.96
Drop out of school, n (%)	82 (73.2)
Intact family, n (%)	86 (76.8)
Family history of	
Substance use, n (%)	49 (43.8)
Alcohol use, n (%)	39 (34.8)
<i>Clinical characteristics</i>	
Age at first substance use, mean ± SD years	13.05 ± 1.55
Age at first heroin use, mean ± SD years	14.83 ± 1.28
Duration of heroin use, mean ± SD months	24.20 ± 12.73
Previous application for treatment of substance use, n (%)	63 (56.3)
Self-initiated attempt to quit substance use, n (%)	69 (61.6)
<i>Pre-treatment conditions</i>	
Substance use (except opioids) in previous 30 days, n (%)	46 (41.1)
Injection use in previous 30 days, n (%)	11 (9.8)
Daily heroin use in previous 30 days, n (%)	107 (95.5)
Withdrawal symptom, n (%)	88 (78.6)
Craving, n (%)	104 (92.9)
Opioids in UDS, n (%)	106 (94.6)
Other any substance in UDS, n (%)	28 (25.0)
Comorbid psychiatric disease, n (%)	53 (47.3)
<i>Treatment conditions</i>	
Withdrawal medication use, n (%)	74 (66.1)
Pain medication use, n (%)	71 (63.4)
Duration of inpatient treatment, mean ± SD (range) days	35.48 ± 21.20 (1–75)
Duration of BUP/NAL treatment, mean ± SD days	118.31 ± 126.97
Maximum BUP/NAL dose, mean ± SD (range) mg/day	4.14 ± 1.85 (2–8)
Elevated liver enzymes, n (%)	25 (22.3)
Duration of program participation, mean ± SD days	160.62 ± 135.54
Relapse to substance use, n (%)	78 (89.6)
Duration of abstinence, mean ± SD days	65.28 ± 61.83
Completion of inpatient treatment, n (%)	35 (31.3)
Program re-entry, n (%)	24 (21.4)
Inpatient re-admission, n (%)	36 (32.1)
Treatment re-entry, n (%)	6 (5.4)

SD: standard deviation; UDS: urine drug screen; BUP/NAL: buprenorphine/naloxone.

Table 2
Rates of treatment retention, program retention and abstinence in 1-year follow-up.

	Day 30	Day 60	Day 90	Day 180	Day 270	Day 365
Program retention, n (%)	91 (81.3)	72 (64.3)	65 (58.0)	44 (39.3)	31 (27.7)	27 (24.1)
Treatment retention, n (%)	78 (69.6)	55 (49.1)	45 (40.2)	29 (25.9)	20 (17.9)	18 (16.1)
Abstinence, n (%) ^a	60 (69.0)	37 (42.5)	28 (32.2)	17 (19.5)	10 (11.5)	9 (10.3)

^a Calculated from 87 patients.

significant differences for age at admission, age at first substance use, age at first heroin use and duration of heroin use at all days between patients who were retained and not, and between those who were abstinent and not ($p > 0.05$ for all) (not shown in Tables).

Patients who had comorbid psychiatric disease were more likely to be retained in BUP/NAL treatment at 30, 60 and 90 days, and in program at 30, 60, 90 and 180 days ($p < 0.05$, for all). Patients who completed inpatient treatment were more likely to be retained in BUP/NAL treatment at 90, 180, 270 and 365 days, and in program at 90, 180 and 270 days, and to be abstinent at 90, 180, 270 and 365 days ($p < 0.05$, for all). Patients who had elevated liver enzymes were less likely to be retained in BUP/NAL treatment at 90 days and more likely to be retained in program at 30 days ($p < 0.05$, for both). Comparisons of variables with treatment and program retention, and abstinence are shown in Tables 4 and 5.

4. Discussion

The present study described the 1-year follow up of a sample of heroin-dependent adolescents treated with BUP/NAL for the first time. Approximately two-thirds of patients left the treatment program in 6 months, and half discontinued the BUP/NAL treatment and relapsed in 2 months. Duration of inpatient treatment was associated with all three outcomes, while maximum BUP/NAL dose was associated with treatment retention and abstinence. Adolescents who completed the inpatient treatment were more likely to remain in BUP/NAL treatment for 1 year and in program for 9 months, and to be abstinent within the 1-year period. Also, we found that adolescents with a comorbid psychiatric disease were more likely to remain in BUP/NAL treatment for 3 months and in program for 6 months.

4.1 Program retention

An important factor in treatment success of people with opioid dependence is program retention. It is associated with better outcomes in youth (Subramaniam et al., 2011; Woody et al., 2008) and adults (Armstrong et al. 2010; Mintzer et al., 2007). Adult studies examining

long term treatment with BUP/NAL revealed a 39 to 63% program retention rate at 6 months, and 53% at 1 year (Fiellin et al., 2006; Armstrong et al., 2010; Fiellin et al., 2008). A study conducted on youth with opioid dependence reported these rates of 45% at 60 days and 9% by 1 year (Matson et al., 2014). In the present study, rates of program retention were 81% at day 30, 64% at day 60, 39% at day 180 and by 1 year 24%. Our findings demonstrated higher program retention rates compared to another adolescent study and almost similar rates to adult studies. This may be attributed to the fact that treatment in our program is often sought by the patient, and also to intense rehabilitation program in this special inpatient unit. Also, having an opportunity for patients to continue the program despite the positive results for opioids or negative for BUP/NAL, and urine drug screening at prior visit might have increased the rate of program retention (Matson et al., 2014).

4.2 Treatment retention

Retention in BUP/NAL treatment is another most important condition in treatment of opioid dependence in adolescents as well as in adults, improving the outcomes. Rates of treatment retention in adolescents were reported 72% at 4-weeks in a randomized clinical trial (Marsch et al., 2005), and 50% at day 30 and 25% at day 132 in a retrospective chart review (Bell & Mutch, 2006). Opiate users aged 15–21 in BUP/NAL treatment had a 3-month retention rate of 70% in a multi-site trial (Woody et al., 2008) and of 44% in a randomized trial (Subramaniam et al., 2011). Warden et al. (2012) reported a treatment retention rate of 92% at 4-weeks, 78% at 8-weeks and 72% at 12-weeks in youth aged 15–21. Young adults aged 18–25 remained in treatment at a rate of 56% at 3 months and 17% at 12 months (Schuman-Olivier et al., 2014). Armstrong et al. (2010) found the retention rates of 73, 63 and 51% at 3, 6, 12 months, respectively, in people on opioid substitution treatment. In adults, treatment retention rates have ranged from 43 to 71% in studies lasting 6 months (O'Connor et al., 1996; Fiellin et al., 2006; Soyka et al., 2008; Armstrong et al. 2010), from 40 to 50% in studies lasting 12 months (Alford et al., 2011; Fiellin et al., 2008), and from 38 to 77% in studies lasting 18 months or more (Fiellin et al., 2008; Parran et al., 2010). In the present study, rate of retention in BUP/NAL treatment was higher than those in adolescents, and lower than those in youth and adults. Also, adolescents with heroin dependence in the present study were retained average of 118 days in BUP/NAL treatment, longer than those reported in adolescents (58 days) (Bell & Mutch, 2006) and in adults (104 days) (Hser et al., 2014). The difference for adolescents despite the lower doses and higher male/female ratio in the present study may be associated with starting the medication and following for the first 8 weeks in an inpatient unit where they have motivation to be treated. However, the lower treatment retention rate in youth compared to adult studies may be attributed to shorter and less complex history of drug use in youth.

4.3 Abstinence

The ultimate goal of substance abuse treatment is to provide maximum abstinence period. Abstinence was the main outcome assessed generally with negative UDS in several studies (Fiellin et al., 2008; Woody et al., 2008; Subramaniam et al., 2011; Marsch et al., 2005). Fiellin et al. reported that 32% of adults patients achieved at least 9 weeks of abstinence at any point during the trial. In youth aged 15–21,

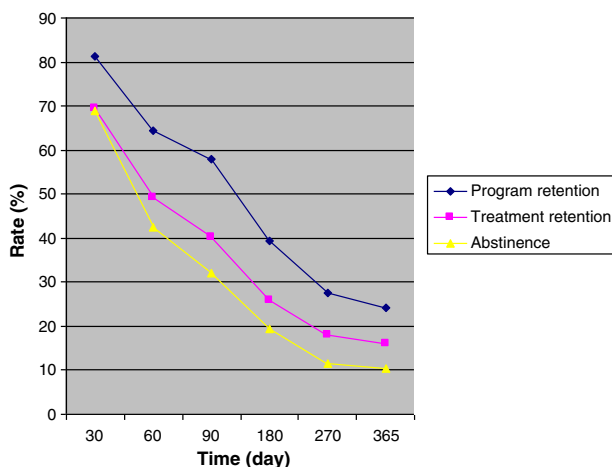


Fig. 1. Rates of program retention, treatment retention and abstinence in 1-year follow-up.

Table 3
Correlations among age at admission, clinical characteristics and outcomes.

	Treatment retention	Program retention	Abstinence
Age at admission	0.068	−0.055	0.174
Age at first substance use	0.139	0.072	−0.011
Age at first heroin use	0.039	−0.038	0.172
Duration of heroin use	0.017	−0.011	−0.126
Duration of inpatient treatment	0.519***	0.528***	0.505***
Maximum BUP/NAL dose	0.249**	0.154	0.221*
Treatment retention		0.812***	0.510***
Program retention			0.421***

BUP/NAL: buprenorphine/naloxone.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

negative UDS for opioids was detected in 74% at 4 weeks (Woody et al., 2008), 77% at 8 weeks (Woody et al., 2008) and 30% at 12 weeks (Subramaniam et al., 2011). Marsch et al. reported opioid negative UDS in 64% of adolescents using BUP in a double-blind randomized controlled trial of a 28-day outpatient medication assisted withdrawal treatment. Similarly, in the present study, rates of abstinence were 69% at 30 days and 32% at 90 days. Moreover, more than half were relapsed at 60 days, suggesting a need of more attention and special efforts for preventing relapse in first 2 months after starting BUP/NAL treatment. An interesting finding was that abstinence/treatment rate ratio decreased over months, suggesting possible decrease in success of BUP/NAL on abstinence with time. This may also reflect the chronic and relapsing nature of substance use disorders.

4.4 Associations of BUP/NAL dose and completed inpatient treatment with retention and abstinence

Although many demographic and clinical variables were examined in the present study, some were found to be associated with treatment

and program retention and abstinence. BUP/NAL compliance is an important factor in long-term success. In the present study, retention in BUP/NAL treatment was found to be associated with program retention and abstinence. Similarly, studies identifying the role of retention or compliance in BUP/NAL treatment in the long-term success of opioid dependence treatment reported positive correlation between adherence to treatment and abstinence (Fiellin et al., 2006), the increased risk of relapse with frequent missed BUP/NAL doses (Armstrong et al., 2010), over 10 times as likely to relapse in BUP/NAL noncompliant patients as compared with their BUP/NAL compliant counterparts (Tkacz et al., 2012), and the predictive impact of BUP/NAL compliance and opioid-negative UDS on program retention (Matson et al., 2014). Short-term studies in youths and adults reported that lower adherence to counseling visits was associated with attrition at 12 weeks (Warden et al., 2012; Stein et al., 2005), while Fiellin et al. (2006) reported no association between treatment retention and level of counseling in programs. As well as treatment retention, duration of program retention was associated with duration of abstinence, indicating that continuation to program might contribute to prevent a relapse as expected. Also, in the present study, BUP/NAL dose was found to be associated with treatment retention and abstinence, as reported by other studies (Hser et al., 2014; Mattick et al., 2014). In the review study of Mattick et al., it was concluded that BUP retained people in treatment at any dose above 2 mg, and suppressed illicit opioid use (at doses 16 mg or greater) based on placebo-controlled trials in the maintenance treatment of heroin dependence. On the other hand, Warden et al. reported that medication dose and withdrawal symptoms in the first 2 weeks were also not related to attrition while early adherence to BUP/NAL and early opioid negative urines were associated with treatment retention. It is suggested that retention in BUP/NAL treatment or in program, BUP/NAL dose, and abstinence may impact each other and these associations may be reciprocal. The findings confirmed the importance of BUP/NAL compliance and dose as well as continuity of program participation in long-term success of heroin dependent adolescents.

Several studies reported that treatment completion, therefore longer periods of treatment participation, was associated with better outcomes

Table 4
Association of pre-treatment and treatment conditions with retention and abstinence at day 30, 60, and 90.

	Day 30		<i>p</i>	Day 60		<i>p</i>	Day 90	
	Yes/no			Yes/no			Yes/no	<i>p</i>
<i>Treatment retention</i>								
Substance use (except opioids) in previous 30 days, <i>n</i> (%)	32 (41.0)/14 (41.2)		0.988	21 (38.2)/25 (43.9)		0.541	18 (40.0)/28 (41.8)	0.850
Injection use in previous 30 days, <i>n</i> (%)	9 (11.5)/2 (5.9)		0.499 ^a	5 (9.1)/6 (10.5)		0.799	4 (8.9)/7 (10.4)	1.000 ^a
Other any substance in UDS, <i>n</i> (%)	19 (24.4)/9 (26.5)		0.812	13 (23.6)/15 (26.3)		0.743	11 (24.4)/17 (25.4)	0.911
Comorbid psychiatric disease, <i>n</i> (%)	45 (57.7)/8 (23.5)		0.001	35 (63.6)/18 (31.6)		0.001	29 (64.4)/24 (35.8)	0.003
Withdrawal medication use, <i>n</i> (%)	54 (69.2)/20 (58.8)		0.285	38 (69.1)/36 (63.2)		0.507	30 (66.7)/44 (65.7)	0.913
Pain medication use, <i>n</i> (%)	49 (62.8)/22 (64.7)		0.849	37 (67.3)/34 (59.6)		0.402	31 (68.9)/40 (59.7)	0.322
Completion of inpatient treatment, <i>n</i> (%)	–		–	–		–	25 (55.6)/10 (14.9)	0.000
Elevated liver enzymes, <i>n</i> (%)	17 (21.8)/8 (23.5)		0.839	9 (16.4)/16 (28.1)		0.137	5 (11.1)/20 (29.9)	0.020
<i>Program retention</i>								
Substance use (except opioids) in previous 30 days, <i>n</i> (%)	36 (39.6)/10 (47.6)		0.499	28 (38.9)/18 (45.0)		0.529	24 (36.9)/22 (46.8)	0.294
Injection use in previous 30 days, <i>n</i> (%)	9 (9.9)/2 (9.5)		1.000 ^a	6 (8.3)/5 (12.5)		0.518	4 (6.2)/7 (14.9)	0.197 ^a
Other any substance in UDS, <i>n</i> (%)	22 (24.2)/6 (28.6)		0.675	18 (25.0)/10 (25.0)		1.000	15 (23.1)/13 (27.7)	0.580
Comorbid psychiatric disease, <i>n</i> (%)	48 (52.7)/5 (23.8)		0.017	40 (55.6)/13 (32.5)		0.019	37 (56.9)/16 (34.0)	0.017
Withdrawal medication use, <i>n</i> (%)	60 (65.9)/14 (66.7)		0.949	47 (65.3)/27 (67.5)		0.812	41 (63.1)/33 (70.2)	0.431
Pain medication use, <i>n</i> (%)	57 (62.6)/14 (66.7)		0.730	48 (66.7)/23 (57.5)		0.335	44 (67.7)/27 (57.4)	0.267
Completion of inpatient treatment, <i>n</i> (%)	–		–	–		–	29 (44.6)/6 (12.8)	0.000
Elevated liver enzymes, <i>n</i> (%)	25 (27.5)/– (–)		0.003	17 (23.6)/8 (20.0)		0.660	14 (21.5)/11 (23.4)	0.815
<i>Abstinence</i>								
Substance use (except opioids) in previous 30 days, <i>n</i> (%)	20 (33.3)/13 (48.1)		0.188	12 (32.4)/21 (42.0)		0.363	7 (25.0)/26 (44.1)	0.087
Injection use in previous 30 days, <i>n</i> (%)	6 (10.0)/2 (7.4)		1.000 ^a	4 (10.8)/4 (8.0)		0.718 ^a	3 (10.7)/5 (8.5)	0.709
Other any substance in UDS, <i>n</i> (%)	14 (23.3)/8 (29.6)		0.532	8 (21.6)/14 (28.0)		0.499	4 (14.3)/18 (30.5)	0.104
Comorbid psychiatric disease, <i>n</i> (%)	34 (56.7)/10 (37.0)		0.090	24 (64.9)/20 (40.0)		0.022	18 (64.3)/26 (44.1)	0.078
Withdrawal medication use, <i>n</i> (%)	41 (68.3)/16 (59.3)		0.410	24 (64.9)/33 (66.0)		0.912	17 (60.7)/40 (67.8)	0.516
Pain medication use, <i>n</i> (%)	40 (66.7)/15 (55.6)		0.320	24 (64.9)/31 (62.0)		0.784	18 (64.3)/37 (62.7)	0.887
Completion of inpatient treatment, <i>n</i> (%)	–		–	–		–	20 (71.4)/9 (15.3)	0.000
Elevated liver enzymes, <i>n</i> (%)	16 (26.7)/6 (22.2)		0.659	10 (27.0)/12 (24.0)		0.748	5 (17.9)/17 (28.8)	0.272

UDS: Urine Drug Screen.

^a Fisher exact test.

Table 5
Association of pre-treatment and treatment conditions with retention and abstinence at day 180, 270 and 365.

	Day 180		p	Day 270		p	Day 365	
	Yes/no			Yes/no			Yes/no	p
<i>Treatment retention</i>								
Substance use (except opioids) in previous 30 days, n (%)	11 (37.9)/35 (42.2)		0.690	9 (45.0)/37 (40.2)		0.694	8 (44.4)/38 (40.4)	0.751
Injection use in previous 30 days, n (%)	3 (10.3)/8 (9.6)		1.000	2 (10.8)/9 (9.8)		1.000 ^a	2 (11.1)/9 (9.6)	1.000 ^a
Other any substance in UDS, n (%)	5 (17.2)/23 (27.7)		0.262	5 (25.0)/23 (25.0)		1.000	4 (22.2)/24 (25.5)	1.000 ^a
Comorbid psychiatric disease, n (%)	17 (58.6)/36 (43.4)		0.230	12 (60.0)/41 (44.6)		0.210	11 (61.1)/42 (44.7)	0.307
Withdrawal medication use, n (%)	19 (65.5)/55 (66.3)		0.942	13 (65.0)/61 (66.3)		0.911	11 (61.1)/63 (67.0)	0.628
Pain medication use, n (%)	20 (69.0)/51 (61.4)		0.469	12 (60.0)/59 (64.1)		0.728	10 (55.6)/61 (64.9)	0.451
Completion of inpatient treatment, n (%)	18 (62.1)/17 (20.5)		0.000	11 (55.0)/24 (26.1)		0.011	10 (55.6)/25 (26.6)	0.015
Elevated liver enzymes, n (%)	5 (17.2)/20 (24.1)		0.445	5 (25.0)/20 (21.7)		0.770 ^a	5 (27.8)/20 (21.3)	0.545
<i>Program retention</i>								
Substance use (except opioids) in previous 30 days, n (%)	16 (36.4)/30 (44.1)		0.415	11 (35.5)/35 (43.2)		0.457	9 (33.3)/37 (43.5)	0.348
Injection use in previous 30 days, n (%)	3 (6.8)/8 (11.8)		0.523 ^a	3 (9.7)/8 (9.9)		1.000	3 (11.1)/8 (9.4)	0.725
Other any substance in UDS, n (%)	9 (20.5)/19 (27.9)		0.372	7 (22.6)/21 (25.9)		0.715	6 (22.2)/22 (25.9)	0.702
Comorbid psychiatric disease, n (%)	26 (59.1)/27 (39.7)		0.045	18 (58.1)/35 (43.2)		0.159	15 (55.6)/38 (44.7)	0.325
Withdrawal medication use, n (%)	28 (63.6)/46 (67.6)		0.662	19 (61.3)/55 (67.9)		0.509	16 (59.3)/58 (68.2)	0.391
Pain medication use, n (%)	31 (70.5)/40 (58.8)		0.212	21 (67.7)/50 (61.7)		0.554	17 (63.0)/54 (63.5)	0.958
Completion of inpatient treatment, n (%)	21 (47.7)/14 (20.6)		0.002	16 (51.6)/19 (23.5)		0.004	12 (44.4)/23 (27.1)	0.090
Elevated liver enzymes, n (%)	7 (15.9)/18 (26.5)		0.190	6 (19.4)/19 (23.5)		0.641	6 (22.2)/19 (22.4)	0.989
<i>Abstinence</i>								
Substance use (except opioids) in previous 30 days, n (%)	4 (23.5)/29 (41.4)		0.172	4 (40.0)/29 (37.7)		1.000 ^a	3 (33.3)/30 (38.5)	1.000
Injection use in previous 30 days, n (%)	2 (11.8)/6 (8.6)		0.651 ^a	1 (10.0)/7 (9.1)		1.000 ^a	1 (11.1)/7 (9.0)	1.000 ^a
Other any substance in UDS, n (%)	3 (17.6)/19 (27.1)		0.543 ^a	3 (30.0)/19 (24.7)		0.709 ^a	2 (22.2)/20 (25.6)	1.000 ^a
Comorbid psychiatric disease, n (%)	10 (58.8)/34 (48.6)		0.448	5 (50.0)/39 (50.6)		1.000 ^a	5 (55.6)/39 (50.0)	1.000
Withdrawal medication use, n (%)	10 (58.8)/47 (67.1)		0.517	6 (60.0)/51 (66.2)		0.732 ^a	5 (55.6)/52 (66.7)	0.489 ^a
Pain medication use, n (%)	11 (64.7)/44 (62.9)		0.887	5 (50.0)/50 (64.9)		0.488 ^a	5 (55.6)/50 (64.1)	0.720 ^a
Completion of inpatient treatment, n (%)	13 (76.5)/16 (22.9)		0.000	7 (70.0)/22 (28.6)		0.014 ^a	7 (77.8)/22 (28.2)	0.003
Elevated liver enzymes, n (%)	3 (17.6)/19 (27.1)		0.543 ^a	3 (30.0)/19 (24.7)		0.709 ^a	3 (33.3)/19 (24.4)	0.686 ^a

UDS: urine drug screen.

^a Fisher exact test.

(Subramaniam et al., 2011; Kakko et al., 2003; Katz et al., 2009). Also, it was found that adolescents who completed inpatient treatment were more likely to be retained in treatment and program (for 9 months), and also to be abstinent for a year, suggesting the importance of intensive 8-week medication assisted inpatient treatment in one-year success of heroin-dependent adolescents. Completion of inpatient treatment might lead the patients to achieve opioid abstinence and, in this way, to be driven by a motivation to get well, resulting in adherence to BUP/NAL medication and program.

4.5 Association of comorbid psychiatric disease with retention and abstinence

Some studies have demonstrated contradictory relationships between comorbid psychiatric diseases and success in patients receiving BUP (Gerra et al., 2004; Marsch et al., 2005; Tkacz et al., 2012; Subramaniam et al., 2011; Matson et al., 2014). In adults with opioid dependence, associations were found between depression and retention in BUP treatment (Gerra et al., 2004; Dreifuss et al., 2013), and between more severe depression and psychopathology and attrition (Pani et al., 2000), while Warden et al. (2012) reported no association between co-occurring psychiatric symptoms and attrition in youths. Also, Matson et al. (2014) found no relationship between mental health problems and program retention in adolescents with opioid dependence. On the other hand, it was reported that youth with more active medical/psychiatric problems were less likely to have an opioid positive urine test at 12 weeks (Subramaniam et al., 2011). Conversely, Tkacz et al. found that increased problem severity at baseline was associated with patient relapse but was not predictive of relapse. In the present study, it was found that patients with baseline comorbid psychiatric disease were more likely to be retained in BUP/NAL treatment for 3 months and in program for 6 months, while no association was found between baseline comorbid psychiatric disease and abstinence, suggesting the possible impact of baseline comorbid psychiatric disease on retention either in treatment and program at least in a group of adolescents with opioid dependence. Also, this may be explained by possibly

increased motivation due to their awareness of being in a downward life. Moreover, it should be considered that the different findings among studies might be related to unstandardized mental health evaluation.

4.6 Associations of other factors with retention and abstinence

Several clinical factors including substance use except opioids in previous 30 days, injection use in previous 30 days, positive UDS for substances except opioids, withdrawal and/or pain medication use with BUP/NAL were not associated with treatment and program retention, and abstinence, generally similar to the findings from other studies (Matson et al., 2014; Warden et al., 2012). Matson et al. found that prior visit UDS positive for opioids increased the likelihood of not returning for further program treatment. Warden et al. reported that receipt of at least one prescribed or over the counter medication (with no specific category of medications) prior to treatment entry was associated with retention in the BUP treatment. Also, they found that gender, injection drug use, 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 line with this, our findings suggested that concurrent use of other substances, positive UDS for other substances, injection use prior to BUP/NAL treatment and withdrawal and/or pain medication use with BUP/NAL might not impact the treatment and program retention, and abstinence in heroin-dependent adolescents.

In the present study, number of patients with IV use was lower than those of other studies on adolescents (Marsch et al., 2005) and youths (Woody et al., 2008; Warden et al., 2012; Subramaniam et al., 2011). In youth studies, there were controversial results in respect of impact on treatment retention (Woody et al., 2008; Warden et al., 2012; Subramaniam et al., 2011), while an adolescent study (Marsch et al., 2005) reported lower treatment retention rates compared to our results. On the other hand, Marsch et al. and Subramaniam et al. found similar rates of abstinence compared to our study, while Woody et al. revealed higher rates. These findings suggested that IV opioid

use might impact on treatment retention and abstinence, needing further investigation.

4.7 Limitations

Despite the all findings given above, there are several limitations in this study. First, the study was retrospective and made in one center, indicating difficulties to draw definite conclusions about causal relationships. Second, the participants in this study may not be representative of dependent heroin users who have sought treatment without their own request. The outcomes might be biased by the fact that only highly and often externally motivated patients would complete 2 months of residential treatment. Also, due to the lack of knowledge about the patients who lost to follow up, rates of abstinence in the study might reflect optimistic results. On the other hand, analyses of abstinence for only opioids were not performed, speculating that the rates of abstinence might be slightly higher if only opioids were considered. Third, any presumptive positives on the UDS were not sent for mass spectrometry/gas chromatography confirmatory testing. Fourth, this study did not use standard instruments for evaluating the severity of heroin dependence and comorbid psychiatric diseases. In the follow up period, we did not evaluate the duration of additional psychotropic drugs use and whether the severity of comorbid disease changed. Also, we did not investigate the association of dose tapering with the outcomes, particularly abstinence. Finally, we could not have a facility to measure synthetic cannabinoids within the study period.

4.8 Conclusion

The present study described 1-year follow up of a sample of heroin-dependent adolescents being started on BUP/NAL treatment in a specific inpatient unit and contributed new and important clinical information on pre-treatment and during-treatment factors linked to retention in treatment and program, and abstinence. Approximately half of the patients discontinued the BUP/NAL treatment and relapsed in 2 months, suggesting a critical 2-month period calling for special efforts in retaining in medication and preventing relapse. Rates of retention in treatment and program, and abstinence were higher than previous outpatient studies of adolescents with opioid dependence, suggesting that starting BUP/NAL treatment in inpatient unit may result in better outcomes. In line with that, adolescents who completed the inpatient treatment were more likely to remain in BUP/NAL treatment for 1 year and in program for 9 months, and to be abstinent within the 1-year period. Also, adolescents who had a comorbid psychiatric disease were more likely to remain in BUP/NAL treatment for 3 months and in program for 6 months, indicating that clinicians should consider the comorbidity in planning the treatment of adolescents with opioid use disorder.

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