Original Paper

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Predictors of Outcome During a 6-Month Follow-Up Among Heroin Dependent Patients Receiving Buprenorphine/ Naloxone Maintenance Treatment

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ÖZET:

Buprenorfin/nalokson idame tedavisindeki eroin bağımlısı hastalarda 6 aylık izlem süresinde seyrin belirleyicileri

Amaç: Bu çalışmanın amacı buprenorfin/nalokson (BN) idame tedavisi altındaki hastalarda 6 aylık izlem süresinde seyrin belirleyicilerini araştırmaktı.
Yöntem: Çalışmaya kliniğimize yatışı yapılan (n=106, %27.04) ya da ayaktan BN idame tedavisi programına alınan (n=286, %72.96) ardışık 392 eroin bağımlısı hasta alındı. Hastalara Bakırköy Opioid Yoksunluk Ölçeği (BOYÖ), Madde Aşerme Ölçeği (MAÖ), Madde Kullanım Bozuklukları Tanıma Testi (MKBTT-DUDIT), Madde Kötüye Kullanımı Tarama Testi (MKKTT-DAST-10) ve Değişime Hazır Olma ve Tedavi İsteği Ölçeği (DHOTİÖ-SOCRATES) uygulandı.
Bulgular: Üç yüz doksan iki hastadan 287'sinde (%73.21) depreşme ya da tedaviden ayrılma görülürken, 105 hasta (%26.79) BN idame tedavi programına uyumlu olarak değerlendirildi. Birinci derece akrabalarda madde kötüye kullanımı, denetimli serbestlik ve intihar öyküsü oranı depreşme/tedaviden ayrılma grubunda (DTA) daha yüksekti. Bunlar dışında sosyodemografik veriler açısından iki grup arasında bir fark saptanmadı. BOYÖ ve MAÖ ortalama değerleri DTA grubunda idame tedavisine uyumlu gruba göre daha yüksekken, DUDIT, DAST-10, SOCRATES puanları ve BN ortalama dozu gruplar arasında farklılık göstermedi. Aşerme şiddetinin 6. ayın sonunda denetimli serbestlik kararı ve intihar öyküsü ile birlikte olumsuz seyirle ilişkili olduğu bulundu. MAÖ'nin 5 itemi arasından "aşermenin şiddeti" denetimli serbestlik kararı ve intihar öyküsü ile birlikte olumsuz seyrin belirleyicisiydi. Regresyon analizlerine tedavi tipi dahil edildiğinde ayaktan BN idame tedavisi uygulanıyor olması denetimli serbestlik kararı ve intihar öyküsü ile birlikte olumsuz gidişin belirleyicisi oldu.
Sonuç: DTA ile idame tedavisine uyumlu hastalar arasında BN dozu açısından farklılık saptanmadığından bu çalışma, yoğun yoksunluk ya da aşerme belirtileri olanların, özellikle de şiddetli aşerme yaşayanların daha yüksek BN dozuna ihtiyacı olabileceğini düşündürmektedir. Özkıyım girişimi öyküsü ve denetimli serbestlik kararının bulunması özellikle ayaktan tedavi altında olanlarda olumsuz seyir için yüksek risk etkenleridir. Bu yüzden yatarak tedavide olduğu gibi ayaktan idame tedavisinde de tedavinin ilk iki haftasında BN tedavisinin daha yakından gözlenmesi, özellikle de daha şiddetli aşerme yaşayanlarda, daha iyi bir seyir sağlayabilir.

Anahtar sözcükler: buprenorfin, tedaviden ayrılma, depreşme, eroin bağımlılığı, idame, nalokson, depreşme

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ABSTRACT:

Predictors of outcome during a 6-month follow-up among heroin dependent patients receiving buprenorphine/naloxone maintenance treatment

Objective: The aim of this study was to evaluate the predictors of outcome during a 6-month follow-up among heroin dependent patients receiving buprenorphine/ naloxone (BN) maintenance treatment.
Methods: Three hundred and ninety-two heroin dependent patients, who were consecutively admitted to the clinic (n=106, 27.04%) or accepted as outpatients for BN maintenance treatment (n=286, 72.96%) were included in the study. Patients were investigated with the Bakirkoy Opioid Withdrawal Scale (BOWS), the Substance Craving Scale (SCS), the Drug Use Disorders Identification Test (DUDIT), the Drug Abuse Screening Test (DAST-10) and the Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES) at baseline evaluation.
Results: Among 392 heroin dependent patients, 287 (73.21%) were considered to have relapsed to substance use or to have dropped out of treatment, whereas 105 (26.79%) were considered to be compliant to the BN maintenance treatment. Rates of having a first degree relative with substance abuse, being under probation and having a history of suicide attempts were higher in relapsed/dropout group (RDG) when compared with the maintenance group. Other sociodemographic variables did not differ between these two groups. Mean scores on the BOWS and SCS were higher in the RDG than the maintenance group at the first month, whereas the DUDIT, DAST-10, SOCRATES scores and mean dose of BN did not differ between the groups. Among items of the SCS, "severity of craving" predicted a negative outcome. When type of treatment was included in these regression analyses as an independent variable, outpatient treatment predicted negative outcome together with history of suicide attempt and being under probation.
Conclusions: Since the dose of BN did not differ between the RDG and those retained in maintenance treatment, the present study suggests that those with severe withdrawal symptoms, particulary those with a high severity of craving, may need a higher dose of BN. A history of suicide attempt and being under probation are high risks for a negative outcome, particularly among those in outpatient treatment. Thus, more observed (supervised) use of BN in the first two weeks, which is more available during inpatient treatment, may improve outcome in outpatient maintenance treatment.

Keywords: buprenorphine, drop-out, heroin dependence, maintenance, naloxone, relapse

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INTRODUCTION

Although rates of opioid abuse found in Turkey are lower than North America and Europe[1], opioid abuse is an increasing public health problem in Turkey, both due to the use of heroin and to an increasing number of individuals developing dependence on prescription opioids[2,3]. Illicit use of opioids has been associated with considerable societal costs, including increased rates of emergency department visits, drug overdoses, criminal activity, lost work days and general medical and psychiatric consequences[4-7]. Similar to the trend in North America and Europe[2], treatment admissions for opioid abuse and dependence in Turkey have increased dramatically in recent years.

Buprenorphine is a partial opioid agonist of the mu receptor, with antagonistic properties at the kappa receptor[8]. To prevent buprenorphine abuse, buprenorphine is typically packaged with naloxone (buprenorphine/naloxone - BN, Suboxone®), which yields no effect when administered sublingually but exerts antagonist properties when injected[8,9]. Opioid maintanence treatment (OMT) for opioid dependence such as BN, is effective in reducing mortality, HIV transmission, crime, and other drug use[10,11]. BN has also been shown to be a safe and effective treatment of opioid dependence in non-specialized, outpatient, office-based settings[12-14].

Abstinence-oriented symptomatic treatment was the most commonly offered treatment option in Turkey until the end of 2009. Starting from beginning of 2010, the BN combination was approved for opioid dependence treatment as a detoxification or a maintenance treatment by the Turkish Ministry of Health[15] which served as an opportunity to increase the number of patients with opioid dependence receiving treatment. The number of prescriptions for BN has increased steadily since its approval and BN has been associated with bringing new users into treatment. Prescribing BN is restricted to hospitals that have a state-approved specialized clinic for treatment of substance dependency. Consistent with this, physician adoption has been primarily among addiction specialists who make up all the prescribers in Turkey. After approval of treatment by authorized bodies, the Alcohol and Drug Research, Treatment and Training Center (AMATEM) in Istanbul started providing BN OMT to the hospitalized patients only. Thus due to limited resources, there was a long waiting list to get into this maintenance program. At the beginning of 2011 AMATEM wrote a guideline[16] and started implementation of BN maintenance treatment on an outpatient basis.

The central problem in the treatment of heroin dependency is high rates of relapse to drug use after periods of forced or self-imposed abstinence[17]. Retention in OMT has been associated with improved outcomes in adults[18-20], and discontinuation of therapy has been associated with relapse[21], overdose death[22], and worse HIV treatment outcomes[23]. Retention rates for BN maintenance treatment at 6 months ranged from 35% to 59%[12,14,24], and a 38% retention was reported in one study that followed patients for 2 years[25]. In another study the overall retention rate was recorded as 56.9% (64.7% of their months were opioid-negative) for 1 year, with about half of the dropouts occurring in the first month[26]. Pinto et al.[27] reported that among 134 opioid dependent patients, 61.2% were retained in treatment at 3 months and 42.5% were retained in treatment at 6 months. Finally in a recent study Schwarz et al.[28] reported that over one third (37.2%) of the sample discontinued BN maintenance treatment within the first month following induction, while 25% of the sample stayed for at least 43 months in treatment[28].

There are few studies of OMT outcomes that consider what factors might be associated with treatment dropout or what might be done to improve dropout rates. Pre-treatment characteristics, most consistently associated with poorer outcome among heroin dependent patients in BN maintenance treatment, include; male gender, lack of employment, younger age at onset of opioid use, more continuous and longer opioid use, use of heroin rather than other opioids

as the primary drug, higher levels of psychiatric symptoms, lower levels of general functioning, poorer psychosocial functioning and more severe legal problems[14,29-36]. However, depression was associated with treatment retention in two studies[34,37]. During treatment, predictors of negative outcomes in heroin dependents 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[10,14,35,38].

This is the first report of early treatment characteristics associated with treatment outcomes among Turkish heroin dependents in BN maintenance treatment, which is the only agent that is used for maintenance treatment in Turkey. Thus, the aim of this study was to evaluate the outcomes of patients, who were prescribed sublingual BN as a maintenance treatment during a 6-month follow-up and to identify early treatment characteristics associated with outcomes in heroin dependent patients.

METHODS

Settings and Sample

The study was conducted in the Bakirkoy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, Alcohol and Drug Research Treatment and Training Center (AMATEM) in Istanbul. The patient's written informed consent was obtained after the study protocol was thoroughly explained.

The decision with respect to treatment type, i.e. outpatient or inpatient, was determined by the written AMATEM guideline[16]. According to this guideline, patients who have been diagnosed as being opioid dependent for at least two years, who abuse depressants such as alcohol or benzodiazepine, who use polysubstances and those who have dropped-out of outpatient OMT twice in a year are given BN maintenance treatment as an inpatient.

The induction and stabilization phase ends after one to two weeks. Baseline interviews with the patients were done before induction of the BN. Both outpatients and inpatients (after being discharged from the hospital) were advised to participate to the Outpatient Treatment Program (OTP) once a week for at least one year, whereas they were obligated to come to the outpatient treatment unit every month to have BN prescribed. The prescribed BN doses ranged from 2 to 24 mg per day, with most patients receiving 8 to 12 mg per day.

The primary outcome measure was abstinence from heroine and other drugs, as documented by urine toxicology and self-reports, at consecutive 6-month intervals after induction of maintenance treatment. Thus, the proportion of patients remaining in maintenance treatment (the percentage of patients who were given prescriptions for BN maintenance treatment, who did not use heroine or other drugs, who did not miss their medication for 7 days, or did not miss psychiatric evaluations each month) was used. Urinalyses were conducted with the use of a semiquantitative homogeneous enzyme immunoassay for buprenorphine, opioids, cocaine, marijuana, amphetamine, ecstacy, benzodiazepines and alcohol.

Evaluation

Baseline evaluation was conducted between March 2012 and July 2012. Four hundred and twenty consecutive heroin-dependent patients were considered for participation in the study. All participants met the DSM-IV diagnostic criteria for heroin dependence. The exclusion criteria were illiteracy, mental retardation or cognitive impairment and comorbid psychotic disorder. Thus, six patients were excluded due to illiteracy and four patients due to cognitive deficits. Although none of the patients refused to participate in the study, 18 patients were excluded as they left some parts of the scales unfilled, did not give the forms back or left the treatment program prematurely; i.e. before completing the forms. Therefore, a total of 392 heroin-dependent inpatients participated in the study. Onset of the

follow-up was defined as initiation of BN for outpatientsand being discharged from the hospital for inpatients.

Measures

All patients were assessed by using a semi-structured socio-demographic form. The diagnosis of heroin dependence in each participating patient was based on the clinical examination, a screening interview based on the Structured Clinical Interview for DSM-IV (SCID-I)[39] Turkish version[40], conducted by a trained interviewer (CE) at the baseline.

Bakirkoy Opioid Witdrawal Scale (BOWS): The Bakirkoy Opioid Withdrawal Scale (BOWS) is a clinician rated scale that has been used since 1995 in Bakirkoy AMATEM. The BOWS includes 13 symptoms of opioid withdrawal which are simply rated as present or absent. Each "present" answer scores as 1, thus the total score of the scale is 13, which shows the most severe withdrawal. Two components on the BOWS reached the criterion of an Eigenvalue greater than one (3.98 and 1.40) and the variance accounted for by these components were 30.61% and 10.76% respectively. The first factor consisted of general withdrawal symptoms (GWS - dysphoric mood, muscle aches, lacrimation, rhinorrhea, dilated pupils, piloerection, sweating, excessive yawning, fever) and the second factor consisted of gastro-intestinal symptoms (GIS - nausea, vomiting, stomachache, diarrhea). All item-component loadings were in the "good" to "excellent" range. Internal consistency reliability for the BOWS, examined by Cronbach's alpha, was also high (coefficient α=0.81)[41].

Substance Craving Scale (SCS): Craving for substance use was evaluated using SCS. SCS is a version of the Penn Alcohol Craving Scale (PACS), which is a 5-item questionnaire developed to evaluate the desire for alcohol use during the previous week (frequency, severity, duration, resistance, and general craving)[42,43]. Each item is scored between 0 and 6, and the maximum craving score is 30. SCS is the version of the PACS for evaluating craving in substance use disorders. Cronbach's alpha value for the SCS is 0.84. The overall item-total correlation values corrected for each item varies between 0.75 and 0.82[44].

The Drug Use Disorders Identification Test (DUDIT): The DUDIT is frequently used in the drug abuse field and has demonstrated sound psychometric properties[45]. The DUDIT is an 11-item self-report questionnaire that was developed as an analogous instrument to the Alcohol Use Disorders Identification Test (AUDIT)[46] to screen individuals for drug problems. In their initial investigation of the psychometric properties of the DUDIT, Berman et al.[47] used both general and clinical population samples. The first nine questions are scored on 5-point scales ranging from 0 to 4, and last two are scored on 3-point scales with values of 0, 2, and 4. Thus, total scores range from 0 to 44, with higher scores suggestive of a more severe drug problem. The Turkish version of the DUDIT has a Cronbach's alpha of 0.93 and a single component accounted for 58.65% of total variance. Additionally, the DUDIT showed good discriminant validity as it significantly differentiated patients with drug use disorder from alcohol dependents[48].

The Drug Abuse Screening Test (DAST-10): The DAST-10 is frequently used in the field of drug abuse, and has demonstrated sound psychometric properties[49]. The DAST assesses drug consequences and problem severity in the past year[50]. The original 28-item DAST, modeled after the Michigan Alcoholism Screening Test[51], has a unidimensional construct when factor analyzed[50]. All versions of the DAST (28-, 20- and 10-item) have been found to have moderate to high levels of validity, sensitivity, and specificity[49]. Since the 10-item version of the DAST (DAST-10) has comparable sensitivity and specificity to its 28- and 20-item counterparts[49], the former was used in the present study. For the DAST-10, scores range from 0 to 10. The Turkish version has a Cronbach's

alpha of 0.90 and a single component accounted for 59.35% of total variance. Additionally, the DAST-10 showed good discriminant validity as it significantly differentiated patients with drug use disorder from alcohol dependents[52].

The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES): The SOCRATES is a 19-item self-report questionnaire developed by Miller and Tonigan[53] for evaluating the level of readiness for change and motivation to change in individuals with a substance use disorder. Factor analysis of the original scale indicated that the form measures three domains: recognition, ambivalence, and taking steps. The factorial structure of the 16-item Turkish version was reported to be compatible with the original version of the scale[54]. When its 16-item Turkish version (Cronbach's alpha=0.85), which was reported to be valid and reliable in Turkish alcohol-dependent individuals, was administered to drug-dependent individuals its Cronbach's alpha value was 0.84 for the total scale[55].

Statistical Methods

The statistical package SPSS 11.5 for Windows was used for all the analyses. Categorical variables were compared by means of chi-square statistics. We used the Student t test to compare the groups on continuous variables, since these variables were normally distributed. In addition, a One-way Anova was used to compare three groups, namely relapsed, maintenance and dropout, on continuous variables. Logistic Regression models (Forward) were performed to evaluate variables that predict negative outcome (relapse/drop-out) in first and sixth months. In both of these models, the independent variables were having a first-degree relative with substance abuse, history of suicide attempts, being under probation, severity of withdrawal and craving. Moreover, Logistic Regression models were conducted where the independent variables were items of the SCS. In the second step of both of these models, treatment type (inpatient-outpatient) was added as an independent variable into the analyses. Since this study was cross-sectional, results of these regression analyses should be interpreted with caution. The term 'predictors' in the present study is used as a more general term to classify all independent variables in regression analyses, rather than describing causal relationships.

RESULTS

Among 392 heroin dependent patients, 287 (73.21%) were considered to be RDG, whereas 105 (26.79%) were considered to be those who were retained in BN maintenance (BNM) treatment. The rates and means of some sociodemographic and clinical variables for the total sample and the comparison between the RD and BNM groups are shown in Table 1. The rates of having a first-degree relative with substance abuse, being under probation and history of suicide attempts were higher in the relapsed group. Other than these, the sociodemographic variables did not differ between groups (Table 1).

Mean scores of the BOWS and SCS were higher in the RDG than the maintenance group, whereas the DUDIT, DAST-10, SOCRATES scores and the mean dose of BN did not differ between the groups (Table 2).

We also compared variables according to four groups, namely relapsed to heroin use relapsed to other substance use, maintenance and dropout groups. Table 3 compares inpatient and outpatient groups according to the status of retention in the treatment. The rate of not attending the outpatient treatment unit at the end of the first month was 27.3% (24.5% for inpatients, 28.3% for outpatients). At the end of the 6th month, 105 patients (26.79%) had been retained in the treatment. This rate was 22.4% for outpatients, whereas it was 38.7% for inpatients (Table 3). The rates of retention in the treatment (those who received prescriptions for BN maintenance treatment) were higher among the inpatient group than the outpatient group in both the first (Odds Ratio=2.74) and sixth months (Odds Ratio=1.92) (Table 3).

Table 1: Sociodemographic characteristics

	Total sample n=392		Maintenance group n=105		Relapsed/dropout group n=287			
	Mean	SD	Mean	SD	Mean	SD	t	p
Age	28.73	9.06	29.82	10.62	28.33	8.40	1.30	0.20
Duration of education	8.54	2.80	8.89	3.18	8.41	2.64	1.49	0.14
Onset of substance use	17.25	4.39	17.72	4.66	17.07	4.28	1.30	0.19
Onset of heroin use	21.38	5.05	21.99	5.52	21.16	4.86	1.44	0.15
Age at first treatment	24.27	6.37	24.85	7.19	24.05	6.03	1.09	0.28
	n	%	n	%	n	%	χ^2	p
Substance abuse among 1st degree relatives	69	17.7	12	11.4	57	20.1	3.92	0.048
Male	369	94.1	100	95.2	269	93.7	0.32	0.57
Probation*	191	49.4	42	40.4	149	52.7	4.58	0.032
Prison							2.80	0.25
Related with substance	69	17.6	13	12.4	56	19.6		
Not related with substance	55	14.1	15	14.3	40	14.0		
Suicide**	111	28.5	22	21.0	89	31.3	4.06	0.044
Self-mutilation	240	61.9	65	61.9	175	61.8	0.00	0.99
IV use of heroin	168	43.1	40	38.1	128	45.2	1.59	0.21
Other substances							2.92	0.40
Cannabis	65	31.4	22	21.0	43	15.0		
Other (cocaine, pills, ecstacy etc.)	36	17.4	7	6.7	29	10.1		
Polysubstance	106	51.2	26	24.8	80	27.9		

There were no differences between groups according to marital and employment status, previous treatment, previous maintenance treatment (not shown).
Odds ratio (95% CI) *1.64 (1.04-2.59) **1.72 (1.01-2.93)

Table 2: Comparing scale scores according to outcome at the 6th month

	Maintenance group (n=105)		Relapsed/dropout group (n=287)			
	Mean	SD	Mean	SD	t	p
BOWS	3.85	3.17	4.62	3.05	-2.20	0.028
Substance Craving Scale	18.26	8.39	20.84	6.90	-2.82	0.005
DUDIT	33.56	5.14	33.45	5.58	0.19	0.852
DAST-10	7.14	1.33	7.40	1.52	-1.56	0.120
SOCRATES	68.29	10.79	69.07	8.39	-0.75	0.452
BN stabilization dose	9.16	2.05	9.25	1.74	-0.41	0.68

BOWS: Bakirkoy Opioid Withdrawal Scale, DUDIT: Drug Use Disorders Identification Test, DAST-10: Drug Abuse Screening Test, SOCRATES: Stages of Change Readiness and Treatment Eagerness Scale, BN: buprenorphine/naloxone

In the first month the mean craving score was higher in the group relapsed to heroin use (n=60, 23.13±5.32) than the maintenance group (n=205, 18.87±7.96), whereas the other groups showed no difference (other substance use: n=20, 20.65±7.24; dropout: n=107, 20.82±6.82). There were no differences between the 4 groups according to the other scale scores. Also the mean dose of BN did not differ between groups (maintenance group: 9.31±1.89, relapsed to heroin use: 9.57±2.21, other substance use: 8.70±1.49, drop-out: 8.97±1.44, F=2.10, df=3, 388, p=1.00) (not shown).

The mean score of the BOWS, particularly the GIS factor of the BOWS, and the SCS were higher in the group relapsed to heroin or other substance use (n=80, 5.14±2.80, 1.35±1.15, 22.51±5.90, respectively) than the maintenance group (n=205, 4.13±3.25, 1.01±1.12, 18.87±7.96, respectively), whereas the dropout group showed no difference (n=107, 4.42±2.94, 1.00±0.95, 20.82±6.82, respectively). There were no differences between the 3 groups according to the other scale scores (not shown).

Table 3: Comparison of inpatient and outpatient groups according to the status of retention in treatment

	Type of the treatment					
	Inpatient		Outpatient			
	n=106	%	n=286	%		
1st month						
BN maintenance	74	69.8	131	45.8	25.18	<0.001
Relapse to heroin use	3	2.8	57	19.9		
Relapse to other substance use	3	2.8	17	5.9		
Dropout	26	24.5	81	28.3		
6th month						
BN maintenance	41	38.7	64	22.4	12.21	0.007
Relapse to heroin	6	5.7	12	4.2		
Relapse to other substance use	3	2.8	6	2.1		
Dropout	56	52.8	204	71.3		

BN: buprenorphine/naloxone, Odds Ratios are for being an inpatient and retention in the maintenance treatment;
Odds ratio (95% CI): 1st month: 2.74 (1.70-4.40), 6th month: 1.92 (1.20-3.07)

Table 4: Predictors of negative outcome (relapse/dropout group) in the 6th month

							95% C.I.		
1st month	**B**	**S.E.**	**Wald**	**df**	**p**	**Odds Ratio**	**Lower**	**Upper**	**Nagelkerke R^2**
Model 1A									0.061
Suicide attempt	-0.562	0.280	4.023	1	0.045	0.570	0.329	0.987	
Probation	-0.495	0.237	4.366	1	0.037	0.610	0.383	0.970	
SCS (Craving Score)	0.041	0.015	7.038	1	0.008	1.042	1.011	1.073	
Model 1B									0.073
Suicide attempt	-0.635	0.281	5.088	1	0.024	0.530	0.305	0.920	
Probation	-0.581	0.240	5.842	1	0.016	0.560	0.349	0.896	
Outpatient	0.818	0.254	10.368	1	0.001	2.265	1.377	3.727	
Model 2A									0.065
Suicide attempt	-0.561	0.280	4.008	1	0.045	0.570	0.329	0.988	
Probation	-0.508	0.238	4.581	1	0.032	0.601	0.378	0.958	
SCS item 2 (severity)	0.209	0.073	8.104	1	0.004	1.233	1.067	1.424	
Model 2B									0.073
Suicide attempt	-0.635	0.281	5.088	1	0.024	0.530	0.305	0.920	
Probation	-0.581	0.240	5.842	1	0.016	0.560	0.349	0.896	
Outpatient	0.818	0.254	10.368	1	0.001	2.265	1.377	3.727	

Model 1A: Independent variables are having first degree relative with substance abuse, history of suicide attempt, being under probation, severity of withdrawal and craving; Model 1B: Treatment type (inpatient-outpatient) is added as an independent variable to Model 1A; Model 2A: Independent variables are items of Substance Craving Scale (SCS); Model 2B: Treatment type is added as an independent variable.

At the end of the 6th month, severity of craving predicted a patient falling into the RDG, together with a history of suicide attempts and being under probation. When type of treatment was included in the regression analyses as an independent variable, outpatient treatment predicted a negative outcome, together with history of suicide attempts and being under probation. Among the 5 items of the craving scale, item 2 (which is "severity of craving"), predicted a negative outcome even when type of treatment was entered into the analysis as an independent variable (Table 4).

DISCUSSION

The present study examined patients' pretreatment characteristics associated with the outcome of 6-month BN maintenance treatment plus medical management, with or without adjunctive drug counseling, in a large sample of heroin dependent patients. In bivariate analyses, patients that relapsed to substance use or those considered as dropouts from treatment had (1) higher rates of substance abuse among first-degree relatives, (2) a higher likelihood of being under

probation, (3) a history of suicide attempts, (4) higher severity of withdrawal, and (5) craving. In regression analysis, craving was associated with a negative outcome (relapse/dropout) together with history of suicide attempts and being under probation. When type of treatment (inpatient/outpatient) was also taken as an independent variable, outpatient treatment predicted a negative outcome instead of craving, together with history of suicide attempts and being under probation. This suggests that although the severity of craving is an important risk factor dropping out of treatment, two weeks of supervised treatment with additional educational programs in the stabilization phase may be helpful to these patients to continue maintenance treatment. Finally, history of a suicide attempts and being under probation are two risk factors for a negative outcome, independent from both craving and the type of the treatment.

The rate of not attending the outpatient treatment unit at the end of the first month was 47.7% (30.2% for inpatients, 54.2% for outpatients). Previous studies conducted in different settings have reported that the rates of discontinuation of BN maintenance treatment within the first month following induction ranged between 37.2% and 50.0%[26,28]. Thus the rate found in the present study is lower for inpatients but higher for outpatients than previous studies conducted in different countries and different settings. A common finding in the substance abuse treatment literature is that patients who stay in treatment longer have better outcomes[20,24]. Retention rates for BN maintenance treatment at the 6th month ranged from 35% to 59% in previous studies[12,14,24,27]. Studies considering predictors of treatment outcome in opioid dependence have employed various measures, including treatment retention, rates of positive urine drug screenings, and continuous opioid abstinence. The main goal of treatment was retention in these previous studies. Although many patients report reductions in use in these studies, the only objective measure they had was urine toxicology testing; i.e. while Soeffing and Martin[26] reported that the overall retention rate was 56.9% for 1 year, they also stated that 64.7% of their months were opioid-negative. However, in the present study the main goal of treatment was continuous abstinence from both heroin and other illicit drugs, and retention in the treatment. This may be considered as "abstinent retention". Thus at the end of the 6th month, 26.8% were abstinent and were still in the BN maintenance treatment. This rate was higher among inpatients (38.7%) than outpatients (22.4%), and was even consistent with rates found in the previous studies that considered retention in the treatment as the main goal.

Severe psychiatric problems[30,32], poorer psychosocial functioning[29,32], and more severe legal problems[31] are some of the characteristics consistently associated with poorer outcome among heroin dependent patients in BN maintenance treatment. Consistent with these findings, having a first-degree relative with substance abuse, being under probation and a history of suicide attempts were higher in the RDG with a negative outcome. Being under probation and history of suicide attempts were also predictors of RDG, both with severity of craving and outpatient treatment, when treatment type was added in the analyses as an independent variable.

BN maintenance treatment for opioid dependence consists of three phases: (a) induction, (b) stabilization, and (c) maintenance[16]. Of the three phases of BN treatment, induction, the initiation of BN treatment, is a key to treatment success. In fact, a substantial proportion of BN treatment failures occur during the first 7 days of treatment[57-59]. One reason for limited BN treatment is the challenge patients and providers face with BN induction[60,61]. During this time, patients are typically expected to present to a healthcare setting in active opioid withdrawal, and physicians will manage the induction process by repeatedly assessing patients' signs and symptoms of withdrawal while titrating the BN dose. Results of the present study suggest that inpatients were retained in the treatment more at the end of the first month and following months. The first two weeks of the treatment, comprising induction and stabilization phases, seems to yield better results if conducted under supervision.

Receiving educational programs during this period may also have supported the abstinence of these inpatients. These factors may explain the finding of better outcomes for inpatients, who received a structured educational program and were given BN under supervision in the present study. Thus it is essential that new induction and stabilization strategies, based on existing models or theories in other countries, should be conducted with our outpatients when including them in BN maintenance treatment.

Both the induction and stabilization phases include the determination of the appropriate dose of BN to reduce and eliminate craving and signs and symptoms of withdrawal, which is essential to eliminate the use of other opioids and substances. One of the important findings of the present study was that, while craving and withdrawal were higher in the group with a negative outcome, the mean dose of BN for stabilization did not differ between the groups. The mean dose of BN in the first 2 weeks was not associated with outcome, similar to the findings in patients treated with comparable mean daily doses of 9-12 mg[35,37,62]. In one observational study, initial induction doses of 16 mg were associated with better retention[38]. In a meta-analysis, Mattick et al.[63] reported that higher doses of BN might suppress heroin use better than higher doses of methadone, although treatment retention may be poorer. The authors noted that slow BN induction in some studies might be associated with poorer retention. It is important to note that the doses of BN used in some of these clinical trials were lower than doses of BN currently recommended[64]. A review that evaluated primary treatment outcomes as a function of taper duration of BN suggested that taper duration was associated with opioid abstinence achieved during detoxification but not with other markers of treatment outcome[65].

Unfortunately the results of the present study suggest better effectiveness of observed versus unobserved (inpatient versus outpatient) BN induction and stabilization. Hopefully, the development and validation of the unobserved BN induction method will lead to increased availability of effective opioid dependence treatment[66]. Continuing education of clinicians beyond their initial training through conferences, articles, or formal mentoring is a strategy to reduce any perceived concerns and promote good practices[67]. Previous findings also support the need for clinicians to assess and address comorbid conditions, such as mood disorders and other substance use, which are prevalent among patients seeking treatment for heroin dependency[68,69]. Other predictors of treatment outcome may also exist that were not examined in this trial, including genetic predictors, which have been found to be associated with pharmacotherapeutic treatment outcome in other populations of substance abusers[70,71]. Different from the previous studies, the severity of craving, withdrawal, motivation, dependency and problems related with dependency were evaluated as pretreatment variables that may be related with outcome in the present study. It is hoped that knowledge about patient characteristics associated with successful (and unsuccessful) outcomes from the current study will be used to develop more effective treatments for this patient population. Since the dose of BN did not differ between the two groups, the present study suggests that those with high withdrawal symptoms or craving, particulary those with high frequency and severity of craving, may need a higher dose of BN. In addition, more observed (supervised) use of BN in the first two weeks may improve the outcome in outpatient maintenance treatment, particularly for those with a higher severity of problems related to dependency. At a minimum, the findings of the present study may suggest that clinics should review their dosing and monitoring methods. A re-assessment of treatment efficacy through a possible dosage increase or supportive psychosocial programs could potentially increase adherence to BN maintenance treatment[72,73].

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