

# Predictors of long term opioid withdrawal outcome after short-term stabilization with buprenorphine

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**Abstract. – OBJECTIVE:** We aim to examine predictors of opiate abstinence status 3 months after the end of buprenorphine/naloxone treatment for opioid-dependent participants.

**PATIENTS AND METHODS:** Participants (n= 516, age > 15 years) received buprenorphine/naloxone treatment for 4 weeks and then randomly assigned to undergo dose tapering over either 7 days or 28 days. Bivariate analysis was performed to identify possible predictors of successful opiate abstinence outcome ( $p$ -value < 0.10). Logistic regression analysis with backward stepwise selection was, then, performed to produce final model containing independent predictors at  $p$ -value < 0.05.

**RESULTS:** Bivariate analysis identified several possible predictors including: opioid and drug urine tests result at the end taper; employment status, family problems, and alcohol use domains of addiction severity index (ASI) score; and clinical opiate withdrawal scale (COWS) at the end of stabilization. Final predictor list identified by logistic regression include: ASI score for family and alcohol problems, COWS at the end of stabilization and opiate urine test at the end of taper.

**CONCLUSIONS:** Participants presenting with a negative urine test for opiate, more severe alcohol, more severe family problems, or more symptoms of opiate withdrawal at the end of stabilization were more likely to have a successful opiate abstinence.

*Key Words:*

Opioid, Predictors, Buprenorphine, Abstinence, Long-term.

## Introduction

The use and abuse of opioids, including heroin and prescription pain medication, are an enduring public health problem. For example, in 2010, 24-35 million adults aged between 15 and 64 years used an illicit opiate worldwide<sup>1</sup>. In the

United States, results of the 2011 National Survey on Drug Use and Health (NSDUH) showed that an estimated 22.5 million Americans aged 12 or older were current or past month illicit drug users. The survey showed that 281,000 Americans aged 12 or older used heroin in 2011<sup>2</sup>.

One of the frequently used FDA-approved pharmacotherapies for opioid dependence, second to methadone, is buprenorphine<sup>3</sup>. Buprenorphine has many features that make it an excellent agent to facilitate detoxification from illicit opioids and abused prescription opioids. Since buprenorphine is a partial mu opiate receptor agonist, it is associated with a low frequency of respiratory depression when increased doses of buprenorphine are used<sup>4</sup>. Second, using buprenorphine does not usually result in overdose<sup>4</sup>. Finally, interdosing interval of buprenorphine can be extended by doubling or tripling the dose without causing toxicity. This feature can be attributed to the fact that larger doses do not enhance buprenorphine's agonist activity, but they do extend its duration of action<sup>5</sup>.

Studies of predictors of outcome for buprenorphine treatment evaluated outcome at various endpoints. Dreifuss et al<sup>6</sup> examined several participants characteristics as possible predictors of successful outcome at the end of a 12 week buprenorphine/naloxone treatment. Another research group<sup>7</sup> explored various predictors of successful outcome at the end of a 13 day buprenorphine/naloxone or clonidine regimen. Recently, Hillhouse et al<sup>8</sup> examined participant characteristics associated with success at the end of a 4 week stabilization with buprenorphine. Despite the fact that these investigations identified several participant characteristics as possible predictors for a successful opiate abstinence outcome, they examined the outcome immediately the end of the treatment. These studies did not explore possible predictors for long term outcome.

It has been demonstrated that stopping buprenorphine had negative effects on the success rate of opiate abstinence<sup>9</sup>. In other words, a significant proportion of participants with a successful opiate outcome at the end of buprenorphine treatment had an opioid-positive urine test results at a subsequent follow-up visit. Ling et al<sup>9</sup> reported a percentage of 37% having an opioid-negative test result at the end of taper (after a 4-week stabilization with buprenorphine) compared to 13% at 3-month post taper follow-up visit.

Given the risk of opiate abstinence failure after stopping buprenorphine treatment, there is a need to consider opiate abstinence status at subsequent follow-up visits as a part of successful treatment outcome. The current work, thus, examined data from Clinical Trials Network (CTN, a branch of the US National Institute on Drug Abuse) to identify participant characteristics associated with successful opiate abstinence at 3-month post taper (after a 4-week stabilization with buprenorphine).

## Patients and Methods

### *Main Study Objectives and Design*

The primary objectives of this clinical study was to compare the relative advantage of two rates of buprenorphine/naloxone tapering following a four week of flexible dose stabilization, as reflected by the proportion of participants providing opiate free urines at the end of the taper regimen. Following brief buprenorphine/naloxone treatment, consisting of 3 days of induction, 25 days stabilization, and patients were randomized to undergo dose tapering over either 7 days or 28 days. After completing dose tapering, participants were followed for 3 months. The primary objective was addressed by Ling et al<sup>9</sup>. The author concluded that tapering buprenorphine dose tapering over 28 days did not provide apparent advantages compared to tapering over 7 days.

### *Study Population*

Patients met DSM-IV criteria for current opioid dependence, were at least 15 years old and seeking treatment for opioid dependence. Key exclusion criteria included any of the following: having a medical condition that would make participation medically hazardous; having a known allergy or sensitivity to buprenorphine or nalox-

one; having an acute severe psychiatric condition in need of immediate treatment; having dependence on alcohol, other depressants, or stimulants, requiring immediate medical attention; having a current pattern of benzodiazepine use; having participated in an investigational drug study, including buprenorphine, within the past 30 days prior to screening; have had methadone or levo-alpha acetyl methadol (LAAM) maintenance or detoxification within 30 days of enrollment; having a pending legal action that could prohibit or interfere with participation; being unable to remain in area for the duration of treatment; being pregnant, lactating, or planning to become pregnant; having a positive urine sample for methadone and benzodiazepine immediately preceding buprenorphine/naloxone induction; or seeking long-term (greater than 2 months) opiate maintenance treatment (see Ling et al, 2009 for further details).

### *Treatments*

After screening and baseline assessments, patients received a three-day buprenorphine/naloxone induction and a 25-day buprenorphine/naloxone stabilization, (total 28 day stabilization phase). During the first three weeks of stabilization phase the dosing was flexible. The study physician may adjust the participant's buprenorphine dose in increments of 8 mg. The maximum allowable buprenorphine dose was 24 mg per day, and the minimum allowable buprenorphine dose was 8 mg per day. In the final week of the stabilization phase, participants were on a stable dose of 8 mg, 16 mg, or 24 mg of buprenorphine.

Following stabilization phase, participants were randomly assigned in a 1:1 ratio to one of two buprenorphine/naloxone tapering regimens: the 7-day or 28-day taper schedule. For each tapering group, the dose taper schedule was determined by the dose stratification on the last day of stabilization phase.

### *Measures*

The Addiction Severity Index (ASI) is a standardized to evaluate severity profiles in several areas commonly affected by substance abuse<sup>10</sup>. The ASI covers the following domains: medical, family/social employment/support, drug and alcohol use, legal, and psychiatric. In the present analysis, the score of each domain of ASI was tested as a possible predictor separately. ASI scores were calculated as described previously<sup>11</sup>.

The data obtained to calculate the ASI were about problem behavior within the previous 30 days. ASI was administered at screening.

The Clinical Opiate Withdrawal Scale (COWS) is an 11-item interviewer administered questionnaire of observable signs and symptoms opiate withdrawal<sup>12</sup>. COWS was evaluated at screening, at the end of stabilization phase, and at the end of dose tapering phase.

The Adjective Rating Scale for Withdrawal (ARSW) is a 16-item questionnaire of signs and symptoms opiate withdrawal<sup>13,14</sup>. Each item is rated from 0 (none) to 9 (severe) by the study subject, and is based on his or her subjective withdrawal discomfort<sup>15</sup>. ARSW questionnaire was completed by the participant at screening, at the end of stabilization phase, and at the end of dose tapering phase.

Visual Analog Scales (VAS) is a 3-item self-report measure that assesses the degree to which the participant experiences any craving for opiates, the severity of withdrawal symptoms, and the extent to which the study medication helps to alleviate cravings (if applicable). Each item is rated from 0 (not at all) to 100 (extremely) by the participant. In the present analysis, the average score of the 3 items was examined as a predictor of the outcome. VAS questionnaire was completed by the participant at screening, at the end of stabilization phase, and at the end of dose tapering phase.

*Dosing information.* Buprenorphine dose at the end of stabilization phase was evaluated as potential predictors of response.

*Demographic characteristics.* Demographic information assembled included age, gender, ethnicity, employment, and marital status. Demographic characteristics were collected at screening.

*Toxicology testing* was conducted qualitatively for the following: morphine, methadone, oxycodone, cocaine, amphetamines, barbiturates, benzodiazepines, methamphetamines, phencyclidine (PCP), marijuana, and tri-cyclic antidepressants. The results of urine drug toxicology at the end of taper were investigated as a predictor of the outcome.

### **Outcome Measure**

Opiate abstinence was the primary treatment outcome and was defined based on opiate urine test result and participant retention. Successful abstinence outcome defined as being “present” at 3 months post taper follow-up visit and the absence of opioids according to the urine toxicology

assessment. Based on these criteria, participants who did not attend the 3 months post taper visit or had a positive urine test for opiates were not considered successful abstinence outcome.

### **Statistical Analysis**

To identify subject characteristics associated with successful abstinence outcome, the relationship between subject characteristics and opiate abstinence status at 3-month post taper was explored. First, bivariate analyses compared patients who with successful abstinence outcome to those who were not successful. Continuous variables were assessed with independent t-tests, and categorical variables with chi-square tests. Second, participant characteristics identified in the first step as being statistically significant ( $p < 0.10$ ) were included in a logistic model. Backward stepwise selection was used to refine the model with a threshold  $p$  value of 0.05 for including variables in the final predictive model. The statistical analysis was conducted by using R software (version 2.15.2; <http://cran.r-project.org>).

### **Data Source**

The information reported here results from secondary analyses of data from clinical trials conducted as part of the National Drug Abuse Treatment Clinical Trials Network (CTN) sponsored by National Institute on Drug Abuse (NI-DA). Specifically, data from CTN-0003 (Study title: Suboxone (Buprenorphine/Naloxone) Taper: A Comparison of Two Schedules) were included. CTN databases and information are available at “[www.ctndatashare.org](http://www.ctndatashare.org)”.

## **Results**

### **Study Sample Characteristics**

The age range was 18.3 to 71.1 years with a sample mean of 35.9 years (standard deviation [SD], 10.5); 70% were White, 11% were African American, 7% were Hispanic, 9% were Multiracial, and 3% were of another race; 33% were females, and 67% were males. Regarding the marital status, 24% were married, 51% were never married, 17% were divorced, 6% were separated, and 2% were widowed.

### **Dosing and Dose Tapering Summary**

During the last week of stabilization phase, 8% of participants received a buprenorphine dose of 8 mg, 29% of patients received a buprenor-

phine dose of 16 mg, and 63% of participants received a buprenorphine dose of 24 mg. Regarding buprenorphine dose tapering schedule, buprenorphine dose was tapered over 7 days in 49% of participants and over 28 days in 51% of participants.

### **Predictors of Successful Outcome: Bivariate Analysis**

Preliminary tests of associations between various patients' characteristics and abstinence outcome were summarized in Tables I and II. Table I summarized the results of test of association (i.e. chi-squared) for categorical participant characteristics. There was no apparent association between gender, race or marital status and abstinence outcome. Neither study taper group (7 vs. 28 days taper) nor stabilization dose of buprenorphine was associated with abstinence outcome. However, opioid and drug urine tests at the end of taper were correlated with outcome. Having opioid positive urine at the end of taper ( $p < 0.001$ ) and having drug positive urine at the end of taper ( $p = 0.042$ ) were associated with lower rates of successful abstinence outcome.

The results of test of association (i.e. Student's  $t$  test) for continuous participant characteristics were summarized in Table II. There was no apparent correlation ( $p = 0.306$ ) between age and abstinence outcome. Among the examined ASI domains (at screening) the following items were associated with outcome: employment ( $p$ -value = 0.085), alcohol use ( $p$ -value = 0.032) and Family/social ( $p$ -value = 0.098). Visual analog scales were not associated with outcome at any of the examined time points: screening, end of stabilization, and end of taper. Among the explored COWS values, COWS at the end of stabilization showed a significant correlation ( $p \leq 0.001$ ) with abstinence outcome. However, COWS result at screening and end of taper were not associated with outcome. ARSW was also examined at three time points: screening, end of stabilization and end of taper. The values of ARSW at the three explored time points were not correlated with abstinence outcome.

### **Predictors of Successful Outcome: Logistic Regression Analysis**

Logistic regression determined the predictors of abstinence status 3 months post taper. Opioid

**Table I.** Bivariate comparisons of categorical predictors with opiate urine tests results 3 months post taper.

Variable	Subclass	Urine negative at 3 months post taper n (%)	Urine positive at 3 months post taper n (%)	$p$ value <sup>1,2</sup>
Race	White	55 (74.3%)	311 (70.5%)	0.655
	African American	9 (12.2%)	47 (10.7%)	
	Hispanic	5 (6.8%)	30 (6.8%)	
	Multiracial	3 (9.5%)	42 (9.5%)	
	Another race	2 (2.5%)	11 (2.5%)	
Marital status	Married	22 (29.3%)	103 (23.4%)	0.282
	Never married	33 (44.0%)	233 (52.8%)	
	Divorced	14 (18.7%)	73 (16.6%)	
	Separated	3 (4.0%)	26 (5.9%)	
	Widowed	3 (4.0%)	6 (1.4%)	
Gender	Female	27 (36.0%)	142 (32.2%)	0.606
	Male	48 (64.0%)	299 (67.8%)	
Taper group	7 days taper	34 (45.3%)	221 (50.1%)	0.523
	28 days taper	41 (54.7%)	220 (49.9%)	
Stabilization buprenorphine dose	8 mg	7 (9.6%)	33 (7.6%)	0.116
	16 mg	28 (38.4%)	121 (27.8%)	
	24 mg	38 (52.1%)	282 (64.7%)	
Opioid urine test result at the end taper	Positive	25 (33.3%)	301 (68.3%)	<b>&lt; 0.001</b>
	Negative	50 (66.7%)	140 (31.7%)	
Drug urine test result at the end taper	Positive	52 (69.3%)	355 (80.5%)	<b>0.042</b>
	Negative	23 (30.7%)	86 (19.5%)	

<sup>1</sup> $p$ -value was calculated using chi-squared test; <sup>2</sup> $p$ -value in bold indicate statistical significance ( $\alpha < 0.1$ ).

Predictors of long term opioid withdrawal outcome

**Table II.** Bivariate comparisons of continuous predictors with opiate urine tests results 3 months post taper.

Variable	Subclass	Urine negative at 3 months post taper mean (SD)	Urine positive at 3 months post taper mean (SD)	p value <sup>1,2</sup>
Age		37.0 (9.7)	35.7 (10.6)	0.306
The Addiction Severity Index (ASI) at screening <sup>3</sup>	Medical	0.202 (0.33)	0.149 (0.15)	0.188
	Employment	0.435 (0.34)	0.507 (0.30)	<b>0.085</b>
	Drug use	0.308 (0.04)	0.304 (0.05)	0.462
	Alcohol use	0.087 (0.13)	0.053 (0.10)	<b>0.032</b>
	Legal	0.037 (0.11)	0.053 (0.14)	0.251
	Family/social	0.180 (0.22)	0.135 (0.20)	<b>0.098</b>
	Psychiatric	0.204 (0.21)	0.182 (0.20)	0.389
Visual Analog Scales (VAS) <sup>4</sup>	Screening	56.7 (23)	58.3 (21)	0.560
	End of stabilization	34.3 (9.4)	35.3 (10)	0.389
	End of taper	36.3 (19)	39.3 (19)	0.252
Clinical Opiate Withdrawal Scale (COWS) <sup>5</sup>	Screening	8.71 (4.2)	8.62 (3.7)	0.873
	End of stabilization	0.560 (0.83)	1.03 (1.4)	<b>&lt; 0.001</b>
	End of taper	2.81 (4.0)	2.62 (3.1)	0.717
Adjective Rating Scale for Withdrawal (ARSW) <sup>6</sup>	Screening	64.5 (31)	62.3 (32)	0.573
	End of stabilization	8.52 (11)	11.0 (16)	0.105
	End of taper	21.1 (29)	19.9 (25)	0.762

<sup>1</sup>p-value was calculated using Student t test; <sup>2</sup>p-value in bold indicate statistical significance ( $\alpha < 0.1$ ); <sup>3</sup>Maximum possible total score for ASI is 1 for each subclass; <sup>4</sup>Maximum possible total score for VAS is 100; <sup>5</sup>Maximum possible total score for COWS is 48; <sup>6</sup>Maximum possible total score for ARSW is 144.

urine test result at the end of taper, alcohol use status (ASI score) at screening, family/social status (ASI score) at screening, and COWS score at the end of stabilization were significant predictors of abstinence outcome. The results are summarized in Table III.

Adjusting for other predictors included in the final logistic regression model, the odds of having a successful outcome for a participant with a negative opioid urine test result at the end of taper is 4.3 times that of a participant who had a positive opioid urine test result at the end of taper.

A one unit increase in the value of alcohol use status (ASI score) is associated with 11.3 fold in-

crease in the odds of having a successful opiate abstinence outcome. Similarly, a one unit increase in the value of family/social status (ASI score) at screening is associated with a 3.3 fold increase in the odds having a negative urine test result 3 months post taper. These values were calculated after adjusting for other significant predictors in the final logistic regression model.

Finally, controlling for opioid urine test result at the end of taper, alcohol use status (ASI score) at screening, and family/social status (ASI score) at screening, a one unite increase in COWS score at the end of stabilization results in 1.48 increase in the odds having a positive opioid urine test result 3 months post taper.

**Table III.** Logistic regression results: predictors of opiate abstinence outcome 3 months post taper.

Predictor	Odds ratio	95% confidence interval
Opioid negative urine test result at the end taper	4.29	2.55-7.41
ASI: Alcohol use status at screening <sup>1</sup>	11.3	1.39-80.7
ASI: Family/social status at screening <sup>1</sup>	3.29	1.002-10.6
COWS score at the end of stabilization <sup>1</sup>	0.677	0.498-0.880

<sup>1</sup>The odds ratio for ASI-acohol use status, ASI-employment status, and COWS score at screening were adjusted to show the increased likelihood of success for an increase of there value of 1 unit; <sup>2</sup>The exact lower limit of the odds ratio is more than one (1.001).

## Discussion

This report presents new information on opioid-dependent patients characteristics associated with successful abstinence 3-month post taper (after a 4-week stabilization with buprenorphine). For example, the results show the deleterious effect of having opioid positive urine at the end of taper on opioid abstinence status 3 months post taper. The present analysis also illuminates the importance of monitoring addiction severity and opioid withdrawal intensity. In other words, two measures of ASI (alcohol use and family/social status) at screening and one measure of opiate withdrawal (COWS) at stabilization phase were identified as predictors of opiate abstinence status 3 months post taper.

Comparing opiate long term abstinence status to the opiate abstinence status at the end of buprenorphine treatment shed some light on two observations. First, the rate of abstinence (measured by opioid urine test) declined from 37% at the end of taper to 15% three months post taper. This illuminates the motivation behind the present analysis that is about 74% (Table II) of participants with successful opiate abstinence status at the end of taper have been classified as unsuccessful opiate abstinence 3 month later. Second, opioid urine test result (at the end of dose taper) was identified as a strong predictor of outcome 3 months post taper. Previous drug use in general, and opiate use in particular, have previously been associated with poorer opioid withdrawal outcome<sup>8</sup>.

In contrary to previous studies<sup>16,17</sup>, patients with more severe alcohol and/or family problems have higher likelihood of successful opiate abstinence outcome. Several trials demonstrated that individuals with more severe alcohol and/or family problems at screening were associated with poorer opiate abstinence outcome at follow-up visits<sup>16,17</sup>. However, others reported that there was no association between alcohol use and opiate use<sup>6,7</sup>. The disagreement about the impact of family and alcohol problems on opiate abstinence may be due to inconsistent opiate detoxification protocols and/or inter-patient variability in responsiveness to opiate withdrawal.

Patients with more severe withdrawal symptoms at the end of stabilization were less likely to have a successful opiate abstinence outcome. A speculative explanation of this observation is that participants with more severe withdrawal symptoms would drop out of treatment and have worse

outcomes compared to participants with lower levels of withdrawal. This result is consistent with previous reports. For example, Rounsaville et al<sup>18</sup> reported that participants with more severe withdrawal had worse clinical outcomes in opioid dependence treatment than those with less severe withdrawal.

There are several limitations of the present analysis<sup>19</sup>. The first is that, the definition of a successful outcome is being present at the end of the study (i.e. three months post taper) and providing a urine sample negative for opiates. This implies that individuals who failed to attend the last office visit were not considered as successful outcome<sup>20,22</sup>. One could argue that participants who failed to finish the study should be excluded from the study. However, this could result in different findings and conclusions. Additionally, the present criteria for successful outcome are consistent with several previous reports that presented several possible predictors of opiate abstinence<sup>7,8,23</sup>. As a result, it would be more intuitive to compare the results of the present analysis to earlier reports.

Another potential limitation is the narrow range of observed continuous predictors. For example, COWS values at the end of stabilization. COWS values at the end of stabilization ranged between 0 and 8 and the difference between subjects with successful abstinence outcome and those without successful abstinence outcome is 0.47 (Table II). This finding makes the validity of extrapolation to the maximum range of COWS of 100 questionable.

The primary study investigated the effects of tapering duration after buprenorphine stabilization<sup>9</sup>. The comparison between 7 and 28 days taper regimen revealed that there was no significant difference in opioid-free urine test at the end of taper<sup>9</sup>. Further analysis of subject characteristics identified several predictors of opiate abstinence outcome at the end of stabilization period including: non-daily opioid use for the past 30 days at baseline, previous drug abuse treatment, and marital status<sup>8</sup>.

## Conclusions

The present study has contributed new and important clinical informations on participant characteristics that were linked to lower rates of opiate abstinence 3 months post taper. Patients pre-

senting with a negative urine test for opiate were more likely to have a successful opiate abstinence. Those who presented with alcohol or family problems at screening were more likely to have better opiate abstinence outcome. Finally, participants with higher values of COWS score at the end of stabilization had lower rates of opiate abstinence compared to participants with low COWS values.

### Conflict of Interest

The Authors declare that there are no conflicts of interest.

### References

- 1) UNITED NATIONS OFFICE ON DRUGS AND CRIME. World Drug Report, 2011.
- 2) SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION. Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings. 2012. In: NSDUH Series H-44, HHS Publication No (SMA) 12-4713 [Internet]. Rockville, MD: Substance Abuse and Mental Health Services Administration; [1 online resource].
- 3) CENTER FOR SUBSTANCE ABUSE TREATMENT. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Pharmacology of Medications Used To Treat Opioid Addiction. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. SAMHSA/CSAT Treatment Improvement Protocols. Rockville (MD), 2005.
- 4) WALSH SL, PRESTON KL, STITZER ML, CONE EJ, BIGELOW GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther* 1994; 55: 569-580.
- 5) CHAWARSKI MC, SCHOTTENFELD RS, O'CONNOR PG, PAKES J. Plasma concentrations of buprenorphine 24 to 72 hours after dosing. *Drug Alcohol Depend* 1999; 55: 157-163.
- 6) DREIFUSS JA, GRIFFIN ML, FROST K, FITZMAURICE GM, POTTER JS, FIELLIN DA, SELZER J, HATCH-MAILLETTE M, SONNE SC, WEISS RD. Patient characteristics associated with buprenorphine/naloxone treatment outcome for prescription opioid dependence: Results from a multisite study. *Drug Alcohol Depend* 2013; 131: 112-118.
- 7) ZIEDONIS DM, AMASS L, STEINBERG M, WOODY G, KREJCI J, ANNON JJ, COHEN AJ, WAITE-O'BRIEN N, STINE SM, MCCARTY D, REID MS, BROWN LS, JR., MASLANSKY R, WINHUSEN T, BABCOCK D, BRIGHAM G, MUIR J, ORR D, BUCHAN BJ, HORTON T, LING W. Predictors of outcome for short-term medically supervised opioid withdrawal during a randomized, multicenter trial of buprenorphine-naloxone and clonidine in the NIDA clinical trials network drug and alcohol dependence. *Drug Alcohol Depend* 2009; 99: 28-36.
- 8) HILLHOUSE M, CANAMAR CP, LING W. Predictors of outcome after short-term stabilization with buprenorphine. *J Subst Abuse Treat* 2013;44: 336-342.
- 9) LING W, HILLHOUSE M, DOMIER C, DORAIMANI G, HUNTER J, THOMAS C, JENKINS J, HASSON A, ANNON J, SAXON A, SELZER J, BOVERMAN J, BILANGI R. Buprenorphine tapering schedule and illicit opioid use. *Addiction* 2009; 104: 256-265.
- 10) McLELLAN AT, KUSHNER H, METZGER D, PETERS R, SMITH I, GRISSOM G, PETTINATI H, ARGERIOU M. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat* 1992; 9: 199-213.
- 11) MCGAHAN P, GRIFFITH J, PARENTE R, McLELLAN AT. *Addiction Severity Index: composite scores manual*. Philadelphia, PA: Veterans Administration Press., 1986.
- 12) WESSON DR, LING W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs* 2003; 35: 253-259.
- 13) AMASS L, KAMIEN JB, MIKULICH SK. Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet. *Drug Alcohol Depend* 2000; 58: 143-152.
- 14) BICKEL WK, STITZER ML, BIGELOW GE, LIEBSON IA, JASINSKI DR, JOHNSON RE. A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. *Clin Pharmacol Ther* 1988; 43: 72-78.
- 15) ORESKOVICH MR, SAXON AJ, ELLIS ML, MALTE CA, REOUX JP, KNOX PC. A double-blind, double-dummy, randomized, prospective pilot study of the partial mu opiate agonist, buprenorphine, for acute detoxification from heroin. *Drug Alcohol Depend* 2005; 77: 71-79.
- 16) SIGMON SC, DUNN KE, BADGER GJ, HEIL SH, HIGGINS ST. Brief buprenorphine detoxification for the treatment of prescription opioid dependence: a pilot study. *Addict Behav* 2009; 34: 304-311.
- 17) McLELLAN AT, ALTERMAN AI, METZGER DS, GRISSOM GR, WOODY GE, LUBORSKY L, O'BRIEN CP. Similarity of outcome predictors across opiate, cocaine, and alcohol treatments: role of treatment services. *J Consult Clin Psychol* 1994; 62: 1141-1158.
- 18) ROUNSAVILLE BJ, KOSTEN T, KLEBER H. Success and failure at outpatient opioid detoxification. Evaluating the process of clonidine- and methadone-assisted withdrawal. *J Nerv Ment Dis* 1985; 173: 103-110.
- 19) SALEH MI. Modeling longitudinal changes in buprenorphine treatment outcome for opioid dependence. *Pharmacopsychiatry* 2014; 47: 251-258.
- 20) CURCIO F, FRANCO T, TOPA M, BALDASSARRE C, GRUPPO RESPONSABILI UOST. Buprenorphine/naloxone ver-

- sus metadone in opioid dependences: a longitudinal survey. *Eur Rev Med Pharmacol Sci* 2011; 15: 871-874.
- 21) F. FRANCESCHI F, IACOMINI P, MARSILIANI D, CORDISCHI C, FORTE E, ANTONIMI S, ALESI A, GIACOBELLI D, ZUCCALÀ G. Safety and efficacy of the combination Acetaminophen-Codeine in the treatment of pain of different origin *Eur Rev Med Pharmacol Sci* 2013; 17: 2129-2135.
- 22) MAMMUCARI M, LAZZARI M, MAGGIORI E, GAFFORIO P, TUFARO G, S. BAFFINI, MAGGIORI S, PALOMBO E, DE MEO B, SABATO AF; ON BEHALF OF THE STEERING COMMITTEE OF ITALIAN SOCIETY OF MESOTHERAPY. Role of the informed consent, from mesotherapy to opioid therapy. *Eur Rev Med Pharmacol Sci* 2014; 18: 566-574.
- 23) SZALEK E, KARBOWNIK A, MURAWA D, POŁOM K, TEZYK A, GRACZ J, GRABOWSKI T, GRZESKOWIAK E, BICZYSKO-MURAWA A, MURAWA P. The pharmacokinetics of oral oxycodone in patients after total gastric resection. *Eur Rev Med Pharmacol Sci* 2014; 18: 3126-3133.