

ISSN 1592-1638

Vol. 10 • N. 4 • December 2008

# Heroin Addiction and Related Clinical Problems



Periodico trimestrale - Spec. in Abb. Post. - D.L. 353/2003 conv. in L. 27/02/2004 n° 46 art. 1, comma 1, DCB PISA - Aut. trib. di Pisa n.5 del 9-3-2000

the official journal of

***Europad***  
European Opiate Addiction Treatment Association

PACINIeditore  
MEDICINA

AU-CNS

# Europad

## EUROPEAN OPIATE ADDICTION TREATMENT ASSOCIATION

EUROPAD, formerly EUMA, was founded in Geneva (Switzerland) on September 26, 1994. It shall remain independent of political parties and of any government.

### The vision

EUROPAD exists to improve the lives of opiate misusers and their families and to reduce the impact of illicit drug use on society as a whole. The Association works to develop opiate addiction treatment in Europe but also aims to make a major contribution to the knowledge of, and attitudes to, addiction treatment worldwide.

## BOARD OF DIRECTORS

Icro Maremmani	President	Pisa, <i>Italy</i>
Marc Reisinger	Vice-President	Bruxelles, <i>Belgium</i>
Andrej Kastelic	General Secretary	Lubiana, <i>Slovenia</i>
Rainer Schmid	Vienna, <i>Austria</i>	
Gabriele Fischer	Vienna, <i>Austria</i>	
Oleg Aizberg	Minsk, <i>Belarus</i>	
Nermana Mehic-Basara	Sarajevo, <i>Bosnia and Herzegovina</i>	
Alexander Kantchelov	Sofia, <i>Bulgaria</i>	
Ante Ivancic	Porec, <i>Croatia</i>	
Didier Touzeau	Paris, <i>France</i>	
Marc Auriacombe	Bordeaux, <i>France</i>	
Albrecht Ulmer	Stuttgard, <i>Germany</i>	
Stephan Walcher	Munich, <i>Germany</i>	
Paul Quigley	Dublin, <i>Ireland</i>	
Matteo Pacini	Pisa, <i>Italy</i>	
Pier Paolo Pani	Cagliari, <i>Italy</i>	
Michael Arieli	Jerusalem, <i>Israel</i>	
Haim Mell	Jerusalem, <i>Israel</i>	
Emilis Subata	Vilnius, <i>Lithuania</i>	
Helge Waal	Oslo, <i>Norway</i>	
Luis Patricio	Lisbon, <i>Portugal</i>	
Wojciech Rudalski	Warsaw, <i>Poland</i>	
Karina Stainbarth-Chmielewska	Warsaw, <i>Poland</i>	
Sergey Koren	Moscow, <i>Russia</i>	
Alexander Kozlov	Moscow, <i>Russia</i>	
Nikola Vuckovic	Novi Sad, <i>Serbia</i>	
Marta Torrens	Barcelona, <i>Spain</i>	
Mercedes Lovrecic	Lubiana, <i>Slovenia</i>	
Lubomir Okruhlica	Bratislava, <i>Slovak Republic</i>	
Olof Blix	Jönköping, <i>Sweden</i>	
Marlene Stenbacka	Stockholm, <i>Sweden</i>	
Jean Jacques Deglon	Geneva, <i>Switzerland</i>	
Peter Vossenber	Deventer, <i>The Netherlands</i>	
Sergey Dvoryak	Kiev, <i>Ukraine</i>	
Michael Farrell	London, <i>United Kingdom</i>	
Colin Brewer	London, <i>United Kingdom</i>	

---

## Editorial Board

### Editor

Icro Maremmani "Santa Chiara" University Hospital, Department of Psychiatry, University of Pisa, Italy, EU

### Associate Editor

Pier Paolo Pani Social-health Intregation Service, Sardinia Health and Social Administration  
Cagliari, Italy, EU

### International Advisory Board

Hannu Alho National Public Health Institute (KTL), University of Helsinki, Finland, EU  
Marc Auriacombe Université Victor Segalen, Bordeaux 2, France, EU  
James Bell Langton Centre, Sydney, Australia  
Olof Blix County Hospital Ryhov, Jönköping, Sweden, EU  
Barbara Broers University Hospital of Geneva, Switzerland  
Miguel Casas University Hospital of "Vall d'Hebron" - University of Barcelona, Spain, EU  
Michael Farrell King's College, University of London, UK, EU  
Loretta Finnegan National Institutes of Health, Bethesda, ML, USA, [Retired]  
Gabriele Fischer University of Vienna, Vienna, Austria, EU  
Gilberto Gerra United Nations Office on Drugs and Crime, Vienna  
Gian Luigi Gessa University of Cagliari, Italy, EU, [Emeritus]  
Michael Gossop King's College, University of London, UK, EU  
Leift Grönbladh University Hospital of Uppsala, Sweden, EU  
Lars Gunne University of Uppsala, Sweden, EU, [Emeritus]  
Andrej Kastelic Center for Treatment of Drug Addiction, University Hospital, Lubiana, Slovenia  
Michael Krausz St.Paul's Hospital, University of British Columbia, Canada  
Mary Jane Kreek The Rockefeller University, New York, USA  
Mercedes Lovrecic Institute of Public Health of the Republic of Slovenia, Lubiana, Slovenia, EU  
Joyce Lowinson Albert Einstein College of Medicine, The Rockefeller University, New York, USA, [Emeritus]  
Robert Newman Baron de Rothschild Chemical Dependency Institute, Beth Israel Medical Center, New York, NY, USA  
Charles P. O'Brien University of Pennsylvania, Philadelphia, USA  
Lubomir Okruhlica Centre for Treatment of Drug Dependencies, Bratislava, Slovak Republic, EU  
Mark Parrino American Association for the Treatment of Opioid Dependence, New York, USA  
Giulio Perugi Department of Psychiatry, University of Pisa, Italy, EU  
Marc Reisinger European Opiate Addiction Treatment Association, Brussels, Belgium, EU  
Marlene Stenbacka Karolinska Institute, Stockholm, Sweden, EU  
Alessandro Tagliamonte University of Siena, Italy, EU  
Marta Torrens University of Barcelona, Spain, EU  
Ambros Uchtenhagen Research Foundation on Public Health and Addiction, Zurich University, Switzerland  
Helge Waal Center for Addiction Research (SERAF), University of Oslo, Norway  
George Woody University of Pennsylvania, Philadelphia, USA

---

## **Editorial Coordinators**

Marilena Guareschi

Association for the Application of Neuroscientific Knowledge to Social Aims, AU-CNS,  
Pietrasanta, Lucca, Italy, EU

Matteo Pacini

"G. De Lisio" Institute of Behavioural Sciences, Pisa, Italy, EU

## **Publishers**

Association for the Application of Neuroscientific Knowledge to Social Aims, AU-CNS  
Not for profit Agency

*"From science to public policy"*

Via XX Settembre, 83 - 55045 Pietrasanta, Lucca, Italy, EU

Phone +39 0584 790073 - Fax +39 0584 72081 - E-mail: info@aucns.org

Pacini Editore

Via A. Gherardesca - 56121 Ospedaletto, Pisa, Italy, EU

Phone +39 050 313011 - Fax +39 050 3130300 - E-mail: Pacini.Editore@pacinieditore.it

Internet:[http:// www.pacinieditore.it](http://www.pacinieditore.it)

*Cited in:*

*EMBASE Excerpta Medica Database*

*SCOPUS*

*EMCave*

**Free download at:**

*<http://www.atforum.com/europad.html>*

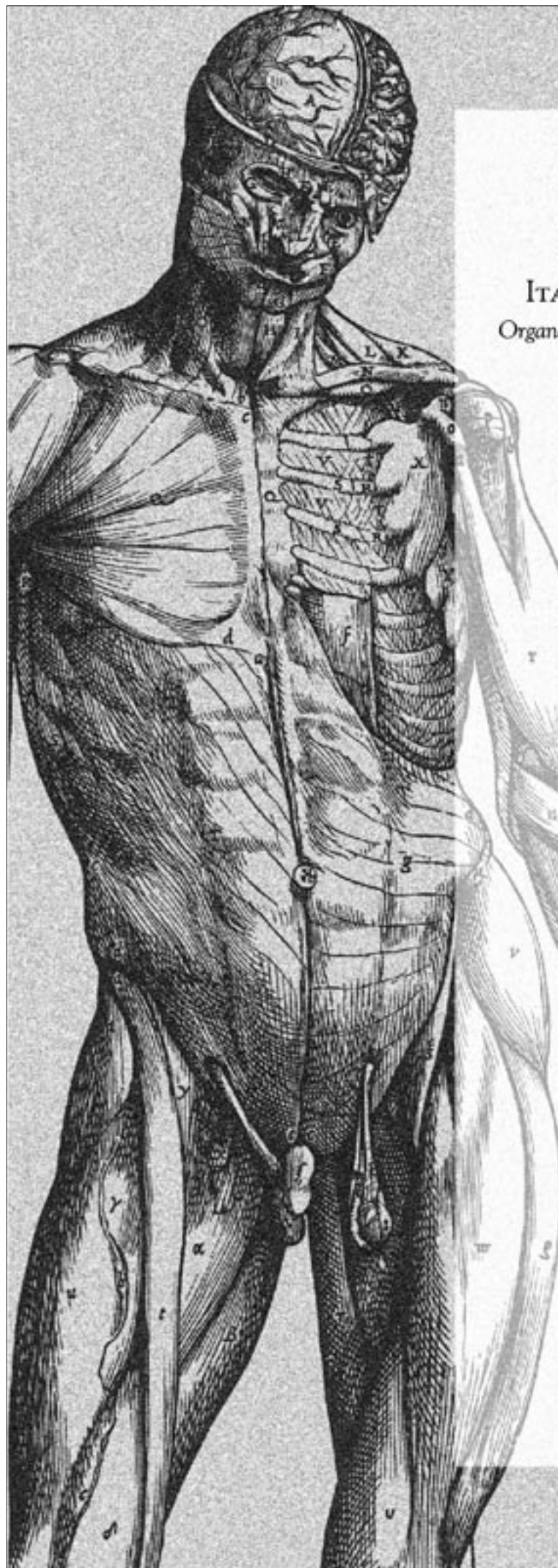
*[http://pain-topics.org/opioid\\_rx/europad.php](http://pain-topics.org/opioid_rx/europad.php)*

**Open Access at:**

*<http://www.europad.org>*

## CONTENTS

<b>Buprenorphine-Naloxone Versus Methadone Maintenance Therapy: A Randomised Double-Blind Trial With Opioid-Dependent Patients</b>	5-18
Jonathan B. Kamien, Steven A. Branstetter, and Leslie Amass	
<b>Predictors for Non-Relapsing Status in Methadone Maintained Heroin Addicts. A Long Term Perspective Study</b>	19-28
Iero Maremmani, Matteo Pacini, Francesco Lamanna, Pier Paolo Pani, Manuela Trogu, Giulio Perugi, Joseph Deltito, and Gilberto Gerra	
<b>Unintentional and Intentional Injuries Due to Opiate Abuse</b>	29-32
Marlene Stenbacka	
<b>Scientific Evidence and Practical Experience with Methadone-Assisted Withdrawal of Heroin-Dependent Pregnant Patients</b>	33-38
Hendree Jones	
<b>Opioid Therapy and Restoration of the Immune Function in Heroin-Addicted Patients</b>	39-44
Lorenzo Somaini, Cristina Giaroni and Gilberto Gerra	
<b>Major Policy and Clinical Developments in the Use of Methadone and Buprenorphine Treatment in the U.S.</b>	45-48
Mark W. Parrino	



# Medicina delle Tossicodipendenze

ITALIAN JOURNAL OF THE ADDICTIONS

*Organo ufficiale della Società Italiana Tossicodipendenze*

## Comitato Scientifico

Vittorino Andreoli  
Antonio Argiolas  
Ustik Avico  
Giovanni Biggio  
Giovanni Battista Cassano  
Paolo Castrogiovanni  
Pietro Corsi  
Gaetano Di Chiara  
Davide S. Ferrara  
Walter Fratta  
Luigi Gallimberti  
Enzo Gori  
Gian Paolo Guelfi  
Pier Francesco Mannaioni  
Icro Maremmani  
Alberto Oliverio  
Eugenio Paroli  
Zvani Rossetti  
Emilio Sternieri  
Alessandro Tagliamonte  
Enrico Tempesta

## Società Italiana Tossico Dipendenze

### Presidente

Pier Paolo Pani

### Segretario

Icro Maremmani

### Tesoriere

Augusto Consoli

### Consiglieri

Augusto Consoli  
Marina Davoli  
Gaetano Di Chiara  
Andrea Flego  
Giulberto Gerri  
Paola Iure  
Enrico Nocera  
Luigi Stella  
Manuela Trogu  
Andrea Ventramini



Pacini Editore & AU CNS

## Buprenorphine-Naloxone Versus Methadone Maintenance Therapy: A Randomised Double-Blind Trial With Opioid-Dependent Patients

Jonathan B. Kamien<sup>1,2</sup>, Steven A. Branstetter<sup>1,3</sup>, and Leslie Amass<sup>1</sup>

<sup>1</sup> Vine Street Center, Addiction Research and Treatment Services, Department of Psychiatry, University of Colorado School of Medicine, Denver, Colorado, USA

<sup>2</sup> BioPsych Consulting, Califon, New Jersey, USA

<sup>3</sup> Department of Psychology, West Virginia University, Morgantown, West Virginia, USA

### Summary

This is the first randomised study comparing buprenorphine-naloxone with methadone for maintenance treatment of opioid dependence. A 17-week, double-blind, double-dummy trial of daily dosing compared buprenorphine-naloxone (8/2 mg and 16/4 mg) with methadone (45 mg and 90 mg) in 268 participants. The percentage of opioid-free urine samples over time did not differ by drug or dosage. The percentage of patients with  $\geq 12$  consecutive opioid-negative urine samples did not differ by drug and was significantly greater for patients receiving higher doses of either agent. Induction success, compliance, nonopioid drug use, retention and Addiction Severity Index scores did not differ among groups. Buprenorphine-naloxone is a viable alternative to methadone in clinical practice.

**Key Words:** Buprenorphine; Buprenorphine-naloxone (Suboxone®); Methadone; Opioid dependence; Treatment outcome.

### 1. Introduction

Opioid dependence is a chronic medical condition and serious international public health problem. An estimated 13 million injection drug users worldwide are dependent on opioids [1], but more than 70% of injection drug users remain untreated in Europe [24] and the United States [52, 53]. Untreated injection drug users are exposed to the significant adverse medical, social and psychological consequences of drug misuse, including heightened risk for human immunodeficiency virus (HIV) and hepatitis viral infection from using contaminated syringes and needles.

Methadone maintenance therapy has been the

mainstay of medication-assisted treatment for opioid dependence; such therapy reduces illicit opioid use and substantially reduces morbidity and mortality rates associated with opioid dependence [11, 46]. However, limited access to methadone treatment in many countries, high numbers of untreated injection drug users, increased health service costs for treatment of addiction-related diseases and cost to society of drug-abuse-related behaviour have prompted international interest in additional medications for managing opioid dependence [15, 54].

Buprenorphine, a  $\mu$ -opioid receptor partial agonist and a kappa-opioid receptor antagonist, has been useful in expanding access to effective opioid-dependence

treatment [15, 37]. The partial  $\mu$ -agonist pharmacology of buprenorphine is unique and its clinical pharmacology and application for managing opioid dependence has been reviewed comprehensively [13, 37]. The clinical efficacy of buprenorphine for maintenance treatment also is well established [29, 35, 39, 43, 45].

The sublingual tablet formulation of buprenorphine (Subutex®) is a maintenance treatment for opioid dependence approved for this indication within a framework of medical, social and psychological treatment. The global availability of buprenorphine has steadily increased, and its successful use as a treatment for opioid dependence has warranted its inclusion in the 15th World Health Organization Model List of Essential Medicines [65]. Subutex is available in Europe, the United States and more than 30 other countries worldwide.

A combination tablet containing buprenorphine and naloxone in a 4:1 ratio (Suboxone®) was developed to mitigate abuse and diversion of buprenorphine [16, 17, 30]. Because injection of the opioid antagonist naloxone will precipitate withdrawal in individuals who are opioid dependent, naloxone in the combination tablet is expected to reduce, but not entirely eliminate, parenteral abuse associated with buprenorphine [18, 19, 30, 33, 48, 50, 58, 61]. Clinical and laboratory-based studies of the buprenorphine-naloxone combination formulation have supported its efficacy and safety [29] and reduced abuse potential [4, 9, 58] relative to buprenorphine alone. Features of the buprenorphine-naloxone combination tablet that make it attractive for treating opioid dependence include its efficacy during less-than-daily dosing [7, 8], safety in direct dose induction [10, 25, 39], usefulness for short-term opioid

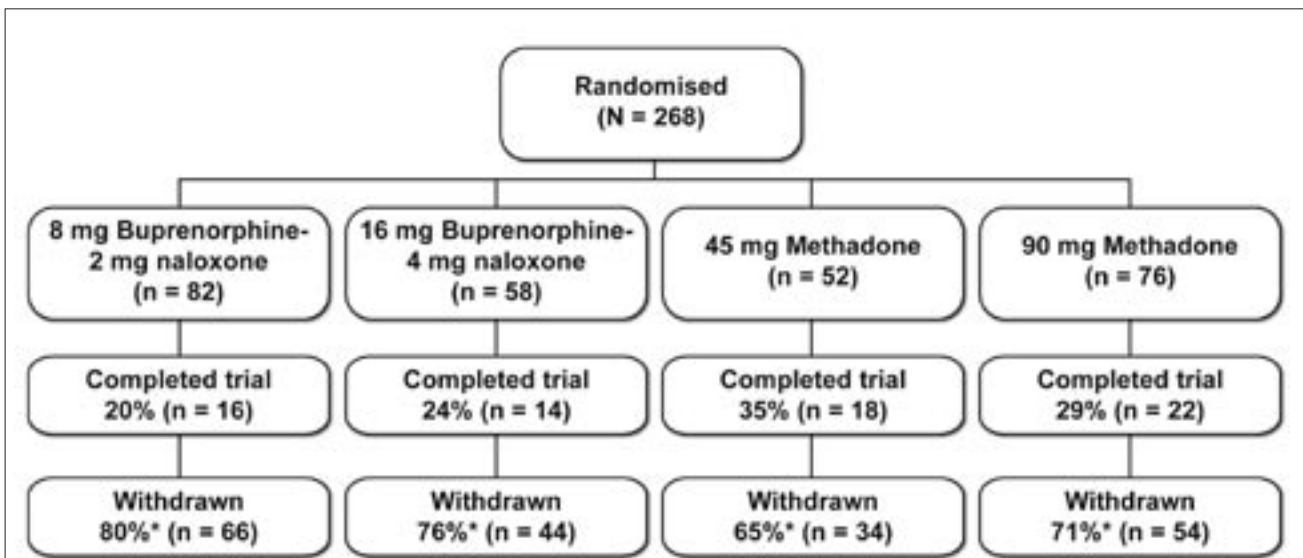
withdrawal [10, 42], use as a take-home therapy [12, 25, 29], use as a frontline primary care therapy [25, 39], promise as a medication that can attract new patients to treatment [63] and ability to be integrated with care for HIV infection [62]. Additionally, health economic studies have shown comparable cost-effectiveness among buprenorphine-naloxone, buprenorphine alone and methadone [21]. Suboxone is available in Europe, the United States, Canada, Australia and several other countries worldwide.

The efficacy of buprenorphine and of methadone has been compared directly several times. These comparative evaluations used the sublingual liquid formulation (studied during the earlier stages of the therapeutic development of buprenorphine) or the buprenorphine-only tablet subsequently developed for clinical use. Although numerous methodologic differences exist across studies, buprenorphine has generally had comparable efficacy [43] and cost-effectiveness [22] to methadone. The current study is the first to directly compare the efficacy of the buprenorphine-naloxone sublingual tablet with that of methadone for maintenance treatment of opioid dependence.

**2. Methods**

*2.1 Participants*

The study was conducted at the Vine Street Center in Denver, Colorado, a licensed, outpatient opioid-treatment facility for adults aged 18 years and older. The clinic offered a range of pharmacotherapies for the treatment of opioid dependence, including methadone,



\*Missed 3 consecutive doses.

Figure 1. Patient disposition during the trial.

levo-alpha acetyl methadol and naltrexone, along with comprehensive counselling services. Participants were recruited through newspaper and poster advertisements and referred from local treatment programmes. Two hundred sixty-eight individuals participated in this trial (Figure 1).

To be included in the study, participants were at least 18 years old, were in good health and met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for opioid dependence and the Food and Drug Administration (FDA) criteria for methadone maintenance treatment and were using heroin or prescription opioids or receiving methadone maintenance treatment. Exclusion criteria included evidence of active psychosis, manic-depressive illness, organic psychiatric disorders or serious medical illness (e.g. liver or cardiovascular disease). Codependence on other drugs (e.g. cocaine, ethanol or sedative-hypnotics) did not exclude participation. The study was approved by the Colorado Multiple Institution Review Board for human research. Before enrolment, participants provided written informed consent after receiving a full explanation of the procedures. After enrolment, participants completed a comprehensive intake interview to determine study eligibility.

The intake interview included online computerised versions of the psychoactive substance abuse disorder sections of the modified DSM-IV Criteria Checklist [34] and the fifth edition of the Addiction Severity Index [47]. Urine samples were obtained under observation and analysed for opioids, cocaine metabolites, amphetamines, benzodiazepines, barbiturates and cannabinoids using the enzyme-multiplied immunoassay technique (Behring Corporation, San Jose, California, United States). Additional questionnaires were completed to provide information about demographics and drug history. Health status was determined by medical history, physical examination and laboratory evaluation (including complete blood count, clinical chemistry profiles and urinalysis).

Participants were enrolled from 17 July 1997 to 3 September 1999. The study was stopped before achieving the targeted enrolment of 300 participants due to a university-wide mandate to discontinue enrolment of new participants in any experimental drug trial, resulting from sanctions imposed by the FDA on the University of Colorado Health Sciences Center.

## 2.2 Design

The study was a 17-week, double-blind, double-dummy, randomised clinical trial comparing 4 groups: 8 mg buprenorphine-2 mg naloxone (8 mg buprenorphine-naloxone), 16 mg buprenorphine-4 mg naloxone (16 mg buprenorphine-naloxone), 45

mg methadone and 90 mg methadone. Doses were selected based on relative potency comparisons from controlled trials that compared oral methadone with sublingual buprenorphine available at the time of the study [36, 44, 59]. The methadone doses were chosen to be representative of or higher than those typical of US methadone programmes at the time of the study [11]. Minimum likelihood allocation was used to randomly assign the participants sequentially to 1 of the 4 groups [3] while controlling for sex, methadone and/or Vine Street Center treatment history and duration of regular opioid use (< or  $\geq$  15 years).

## 2.3 Medication supplies and preparation

Buprenorphine-alone, buprenorphine-naloxone and placebo tablets were manufactured by Reckitt Benckiser Pharmaceuticals (Hull, United Kingdom) and supplied free of charge through the National Institute on Drug Abuse and Research Triangle Institute. Buprenorphine-alone tablets containing 2 mg buprenorphine or 8 mg buprenorphine and matching placebo tablets were used during dose induction. Buprenorphine-naloxone tablets containing 8 mg buprenorphine and 2 mg naloxone and matching placebo tablets were used during maintenance.

Methadone solution was purchased from Roxane Laboratories (Columbus, Ohio, United States) in 946-ml bottles at a concentration of 10 mg/ml. Doses less than 90 mg were prepared in 9-ml volumes by diluting methadone solution with sterile water. Undiluted 9-ml methadone solution comprised the 90-mg doses. Methadone doses were placed in break-resistant, amber, 15-ml plastic unit-dose vials and masked for taste with 2 drops of peppermint spirits and a Bitrix granule solution (6  $\mu$ g/ml; Macfarlan-Smith Ltd., Edinburgh, United Kingdom) and sealed with tamper-evident caps. Placebo solutions were prepared as 9-ml sterile water for irrigation (Baxter Healthcare, Deerville, Illinois, United States) and masked for taste in the same manner as the methadone. Both the methadone and the placebo solutions were coloured with 5 drops of blue food colouring per 946-ml methadone solution or 1000-ml sterile water.

## 2.4 Medication administration

Participants were required to attend the clinic 7 days per week for medication; take-home medication was not provided. Before receiving the first day's dose, all participants were required to be experiencing mild abstinence signs and to provide a urine sample in which methadone was undetectable, unless the participant was transferring directly from a methadone treatment programme. Participants transferring directly from

methadone treatment were required to wait at least 24 hours from the time of their last verified methadone dose. Mild abstinence signs were assessed by the dispensing nurse using an observer rating scale [5–7, 14]. Specific procedures for buprenorphine and methadone induction follow.

Double-blind and double-dummy dosing conditions were applied. All participants received an oral solution first, followed by the tablets. Masking agents in the liquids were designed to also mask the taste of the tablets [5, 6, 8]. The dispensing nurse gave the participants the day's methadone or placebo solution to drink, then the day's tablets in a plastic cup. Patients were instructed to place the tablets under their tongue and hold them there until the tablets dissolved.

To assess the adequacy of the double-blind and double-dummy procedure, on the last study day participants were asked, "Which medication do you think you were taking during the last 17 weeks?" Most participants responded that they had been taking methadone (buprenorphine-naloxone: 81.5%; methadone: 70.3%;  $p=NS$ ), which suggested that the double-blind and double-dummy procedures were adequate to keep the participants from knowing which drug they were receiving. To the best of our knowledge, neither the counselling nor the dispensing staff had any knowledge of the study blind and neither was able to discern dosing assignments.

### 2.5 Buprenorphine induction and maintenance

A 2-day, rapid-induction procedure used buprenorphine alone [7, 8]. On the first day, the buprenorphine-naloxone groups received 2 sublingual tablets that each contained 2 mg buprenorphine, for a total dose of 4 mg buprenorphine. On the second day, the buprenorphine-naloxone groups received 1 tablet containing 8 mg buprenorphine. On the third and all subsequent days, the 8-mg buprenorphine-naloxone group received 1 placebo tablet and 1 sublingual tablet that contained 8 mg buprenorphine and 2 mg naloxone, whereas the 16-mg buprenorphine-naloxone group received 2 sublingual tablets that each contained 8 mg buprenorphine and 2 mg naloxone, for a total dose of 16 mg buprenorphine-naloxone.

### 2.6 Methadone induction and maintenance

On the first day, the methadone groups received 15 mg methadone. Doses of methadone were then increased daily by 15 mg until the target dose of 45 mg or 90 mg was reached on day 3 or day 6, respectively. On all subsequent days, the methadone groups received either 45 mg or 90 mg methadone.

### 2.7 Urine sample collection and analysis

Urine samples were collected 3 times weekly under observation (Mondays, Wednesdays and Fridays) before administering medication and were analysed on site for the presence of opioids using the enzyme multiplied immunoassay technique. Urine samples also were analysed for the presence of cocaine metabolites, amphetamines, benzodiazepines, barbiturates and cannabinoids on 1 randomly chosen day per week using the same method. Cut-off calibration concentrations of 300 ng/ml were used for testing for opioid and cocaine metabolites, 200 ng/ml for benzodiazepines and barbiturates, 50 ng/ml for cannabinoids and 1000 ng/ml for amphetamines. The percentage of missing samples was similar in all 4 groups (12% [8 mg buprenorphine-naloxone], 14% [16 mg buprenorphine-naloxone], 12% [45 mg methadone] and 16% [90 mg methadone]). Breath alcohol samples were collected on urine testing days as part of routine clinical procedure; participants were not permitted to attend the clinic intoxicated.

### 2.8 Counselling

Participants received 1 hour of individual, manualised behavioural counselling with a trained therapist every other week for the duration of the study. Therapy sessions focused primarily on helping participants make lifestyle changes in regard to drug use, employment, family interactions and social/recreational activities. Participants also received AIDS education. Strong oversight and mandated counselling (enforced by withholding doses until a patient saw his or her counsellor) ensured that the amount and quality of counselling did not differ across groups.

### 2.9 Safety monitoring

Before dosing each day, the dispensing nurse conducted a brief assessment to determine whether adverse events had occurred. Complaints were noted in the participant's chart but were not systematically recorded for data collection purposes because this study was not a formal safety evaluation. All serious adverse events were immediately reported to the project investigator.

### 2.10 Study withdrawal and post-study treatment options

If participants failed to obtain their medication for 3 consecutive days or did not provide urine samples on 5 consecutive occasions, they were withdrawn from the study and offered alternative treatment in the centre's clinical programme or referred to other local treatment agencies. Because buprenorphine was not

available outside of research parameters at the time of this trial, participants who completed the study were offered continued care under a compassionate extension of treatment [40]. Participants who elected this alternative agreed to remain blind to the medication and dose until the randomised clinical trial was complete. All participants were evaluated for progress and evidence of clinical stability before being transferred to the compassionate extension phase. Doses for participants who consistently provided opioid-positive urine samples during the study were increased in a blind fashion to either 16 mg buprenorphine-naloxone or 90 mg methadone at entry to the compassionate extension phase. Participants in the compassionate extension phase were also offered take-home medication for Tuesdays, Thursdays and weekends if opioids were undetectable in their 3 previous consecutive urine samples. Only descriptive data (percentage of participants entering and average duration of participation) for this phase are described in this report.

### *2.11 Participant debriefing*

When the study ended, investigators met with each remaining participant, revealed the participant's study drug and dose and made arrangements for continued care. Letters offering to meet for debriefing purposes were sent to enrollees no longer participating in the study or receiving services in the clinic.

### *2.12 Outcome measures*

The primary outcome measure was the amount of opioid abstinence achieved over time. On average, each participant was scheduled for a total of 51 urine tests for the presence of opioids (thrice weekly for 17 weeks). Missed samples were considered positive for the purposes of analysis. The secondary outcomes included the proportion of participants who achieved 12 consecutive opioid-negative samples, the proportion of participants with successful inductions, medication compliance, nonopioid illicit drug use, treatment retention and changes in overall functioning. A successful induction was defined as at least 1 dose of medication on the sixth day of the study or later. Medication compliance was measured by the number of medication doses ingested by each participant. Retention time was measured by the percentage of participants active in the study over time, calculated from the day of first dose to the day of the last dose actually received. Functioning in several psychosocial domains was assessed by examining Addiction Severity Index (ASI) scores at the end of treatment, controlling for intake ASI scores.

### *2.13 Statistical analysis*

To examine baseline differences among the groups, we used analysis of variance (ANOVA) or chi-square tests. Given the nature of the longitudinal data and multiple data points, hierarchical linear modelling (HLM) was used to examine opioid abstinence and use of nonopioid drugs over time [51]. HLM has increasingly been used in studies of interventions and clinical trials and has been advocated as an important tool in examining complex relationships between outcomes and their covariates [66].

To estimate retention time, the Kaplan-Meier statistic was used with 95% confidence intervals. Log rank chi-square test was used to determine if there were significant group differences in retention time.

## **3. Results**

### *3.1 Demographic characteristics*

Two-hundred sixty-eight (268) participants were randomly assigned to receive medication. Selected baseline characteristics are shown in Table 1. A malfunction of the minimum-likelihood-allocation computer software used for stratifying subject assignments resulted in uneven numbers being assigned to the 4 groups. Treatment groups did not differ according to gender, previous history of methadone treatment, history of treatment at the Vine Street Center, ethnicity, age, years of opioid use or years of education. Participants primarily used heroin daily, and approximately two thirds had a history of methadone maintenance treatment. Ten participants transferred directly from a methadone maintenance programme into the study (methadone dose range, 30–85 mg/day). Fifty-three participants received treatment at the Vine Street Center previously.

### *3.2 Opioid abstinence*

Two-level HLM analyses demonstrated that the percentage of opioid-free urine samples over time among drug groups ( $p=0.81$ ) or among drug doses ( $p=0.46$ ) did not differ significantly (Figure 2). Overall, the results of the HLM analyses demonstrate that whereas, in general, study participants increased their percentage of opioid-negative urine samples over the course of the trial, this increase was not predicted by drug type or drug dose.

### *3.3 Consecutive opioid-negative urine samples*

Ten percent (10%) of the 8-mg buprenorphine-naloxone group, 17% of the 16-mg buprenorphine-naloxone group, 12% of the 45-mg methadone group

Table 1. Demographic characteristics.

Characteristic	Buprenorphine-Naloxone		Methadone	
	8 mg (n=82)	16 mg (n=58)	45 mg (n=52)	90 mg (n=76)
Male, n (%)	58 (70.7)	41 (70.7)	42 (80.8)	50 (65.8)
Age, years*	37.2 ± 1.2	38.9 ± 1.4	40.3 ± 1.5	38.1 ± 1.2
Race, n (%)				
White, non-Hispanic	41 (50.0)	30 (51.7)	25 (48.1)	35 (46.0)
Black, non-Hispanic	14 (17.1)	9 (15.5)	12 (23.1)	15 (19.7)
Hispanic	26 (31.7)	16 (27.6)	13 (25.0)	26 (34.2)
Asian	0	1 (1.7)	1 (1.9)	0
Other	1 (1.2)	2 (3.4)	1 (1.9)	0
Education, years*	11.7 ± 0.2	12.6 ± 0.3	12.1 ± 0.3	12.1 ± 0.2
History of methadone treatment, n (%)	50 (61.0)	39 (67.2)	35 (67.3)	49 (64.5)
Transferred from methadone maintenance, n (%)	4 (4.8)	2 (3.4)	1 (1.9)	3 (3.9)
Methadone maintenance dose at time of transfer, mg/d*	54.5 ± 12.3	40.0 ± 0.0	30 ± 0.0	44 ± 10.2
History of Vine Street Center treatment, n (%)	10 (12.2)	10 (17.2)	14 (26.9)	9 (11.8)
Years of regular opioid use*	9.2 ± 1.1	10.2 ± 1.3	12.4 ± 1.4	10.0 ± 1.2
Days of using heroin in the last 30 days*	26.9 ± 0.9	26.3 ± 1.1	26.7 ± 1.1	26.3 ± 0.9
DSM-IV abuse or dependence, n (%)				
Cocaine	22 (26.8)	17 (29.3)	19 (36.5)	17 (22.4)
Cannabis	16 (19.5)	12 (20.7)	5 (9.6)	10 (13.6)
Amphetamines	7 (8.5)	8 (13.8)	4 (7.7)	10 (13.1)
Sedatives	4 (4.9)	4 (6.9)	3 (5.8)	1 (1.3)
Nicotine	37 (45.1)	21 (36.2)	26 (50.0)	37 (48.7)
Alcohol	20 (24.4)	16 (27.6)	14 (26.9)	24 (31.6)
Hallucinogens	2 (2.4)	3 (5.2)	0	1 (1.3)
Inhalants	3 (3.7)	2 (3.4)	1 (1.9)	0
PCP	4 (4.9)	4 (6.9)	3 (5.8)	1 (1.3)

\*Mean ± the standard error of the mean. There were no significant differences across groups by drug or by dose

and 16% of the 90-mg methadone group had at least 12 consecutive opioid-negative urine samples. Results of the homogeneity of proportions test found that the percentage of participants with at least 12 consecutive opioid-negative urine samples differed by dose (8 mg vs. 16 mg buprenorphine-naloxone,  $p < 0.001$ ; 45 mg vs. 90 mg methadone,  $p = 0.02$ ), but not by drug (8 mg buprenorphine-naloxone vs. 45 mg methadone,  $p = 0.18$ ; 16 mg buprenorphine-naloxone vs. 90 mg methadone,  $p = 0.22$ ). Those receiving higher doses of methadone or buprenorphine-naloxone were more likely to have at least 12 consecutive opioid-negative urine samples than those receiving lower doses.

### 3.4 Induction

The homogeneity of proportions test was used to determine if the percentage of participants who had successful induction differed significantly among the 4 groups. Successful inductions occurred in 80.5%, 81.0%, 82.7% and 82.9% of the participants receiving 8 mg buprenorphine-naloxone, 16 mg buprenorphine-naloxone, 45 mg methadone and 90 mg methadone, respectively. No significant differences were detected between any 2 treatment groups ( $p = 0.22-0.98$ ).

### 3.5 Medication compliance

To determine if groups differed in the amount of

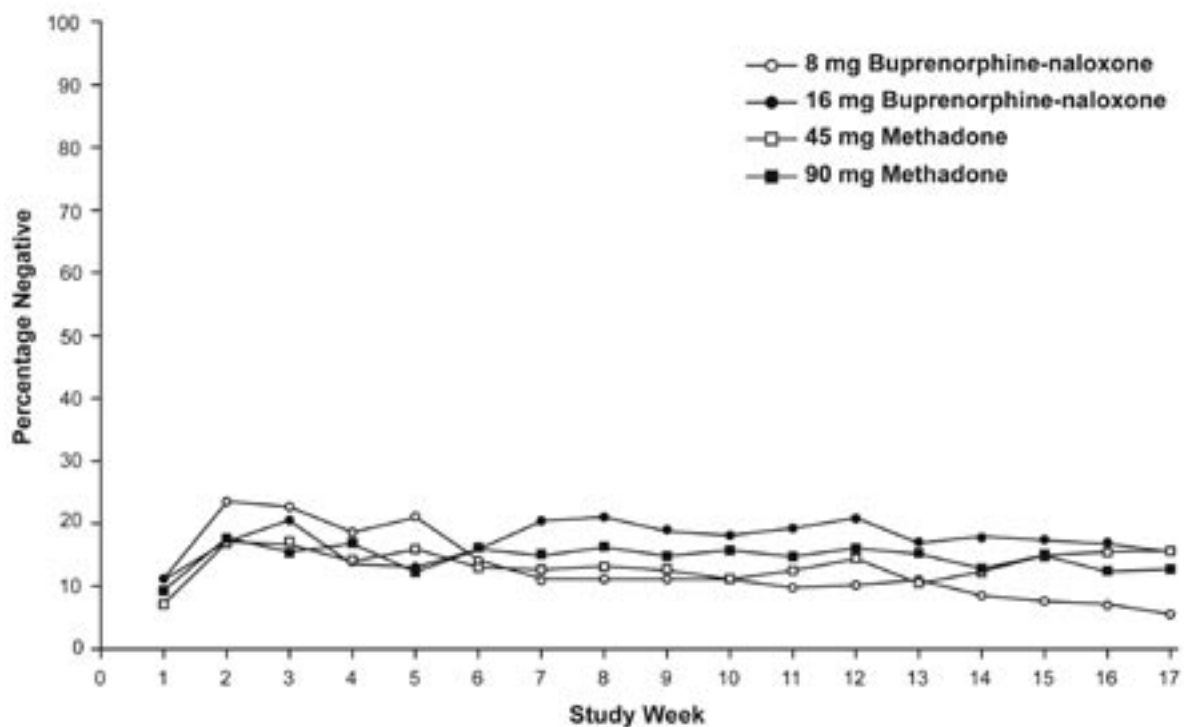


Figure 2. Percentage of opioid-negative urine test results in the 4 treatment groups. Each point represents the percentage of patients with negative urine test results at the end of each week.

medication ingested, ANOVAs were conducted. Of the 119 total possible doses to be ingested, mean  $\pm$  standard error of mean (SEM) numbers of doses ingested by each group were  $38.1 \pm 4.7$ ,  $37.5 \pm 5.6$ ,  $48.9 \pm 5.9$  and  $44.3 \pm 4.9$  for the 8-mg buprenorphine-naloxone, 16-mg buprenorphine-naloxone, 45-mg methadone and 90-mg methadone groups, respectively. Results of the ANOVAs demonstrate that medication compliance did not differ significantly according to drug or dose ( $p=0.41$ ).

### 3.6 Nonopioid drug use

Unconditional level 1 HLM models showed that nonopioid drug use neither changed significantly over time nor differed significantly across groups ( $p=0.32-0.83$ ). The most commonly used drugs other than opioids were cocaine and cannabinoids. The percentage of patients with positive urine samples ranged from 69.8% to 77.6% for cocaine and 65.6% to 77.5% for cannabinoids. Mean percentages of participants with positive urine samples ranged from 57.3% to 68.0% for barbiturates, 57.8% to 68.5% for amphetamines and 62.5% to 69.0% for benzodiazepines.

### 3.7 Retention

To estimate retention time, Kaplan-Meier survival analyses using 95% confidence intervals and log rank chi-square tests to determine significant group differences were generated (Table 2). Additionally, Kaplan-Meier graphs show that cumulative retention by low dose in Figure 3 with the log rank test ( $p=0.09$ ), and high dose in Figure 4 with the log rank test ( $p=0.28$ ) did not differ significantly by drug.

### 3.8 Overall functioning

To evaluate whether participants differed in psychosocial functioning by group, univariate general linear models were conducted. For these analyses, ASI scores at the end of the trial were the outcome, and intake scores on the ASI were entered as covariates to control for initial levels of functioning. Participants did not vary significantly by group on ASI Alcohol, Cocaine, Drug, Employment, Family, Legal, Medical, Opioid or Psychiatric scales ( $p= 0.08-0.84$ ). Table 3 shows the self-reported number of days of heroin use in the past 30 days, and the opiate and drug composite scores from the ASI collected at baseline, at week 8 and at week 16.

Table 2. Mean and median retention based on Kaplan-Meier survival analyses

	Mean Retention (Weeks)	SE	95% Confidence Interval		Median Retention (Weeks)	SE	95% Confidence Interval	
			Lower Bounds	Upper Bounds			Lower Bounds	Upper Bounds
Low Dose								
8 mg buprenorphine-naloxone	12.125	0.178	11.776	12.1473	13	0.294	12.419	13.584
45 mg methadone	13.214	0.199	12.824	13.604	15	0.470	13.591	15.652
Overall	12.588	0.133	12.327	12.588	14	0.167	13.672	14.605
High Dose								
16 mg buprenorphine-naloxone	12.504	0.196	12.120	12.888	13	0.347	12.319	13.681
90 mg methadone	12.277	0.182	11.919	12.634	13	0.316	12.381	13.619
Overall	12.379	0.134	12.117	12.641	13	0.234	12.542	13.458
Total Trial Retention	12.482	0.094	12.297	12.666	14	0.167	13.672	14.328

SE = standard error

Table 3. Self-reported heroin use and Addiction Severity Index opiate and drug composite scores over time

	Buprenorphine-Naloxone		Methadone	
	8 mg	16 mg	45 mg	90 mg
Self-reported days of heroin use in the past 30 days*				
Intake	26.9 ± 0.8	26.3 ± 1.1	26.7 ± 1.2	26.3 ± 0.9
Week 8	7.0 ± 2.0	1.3 ± 0.8	12.1 ± 2.7	5.7 ± 1.6
Week 16 <sup>a</sup>	5.8 ± 2.4 <sup>a</sup>	3.1 ± 1.7 <sup>a</sup>	9.0 ± 2.5	4.3 ± 1.6
Addiction Severity Index Opiate Composite Score* <sup>c</sup>				
Intake	0.70 ± 0.02	0.70 ± 0.02	0.70 ± 0.02	0.68 ± 0.02
Week 8	0.33 ± 0.05 <sup>b</sup>	0.16 ± 0.05 <sup>b</sup>	0.37 ± 0.07 <sup>b</sup>	0.34 ± 0.04 <sup>b</sup>
Week 16	0.28 ± 0.06 <sup>b</sup>	0.23 ± 0.06 <sup>b</sup>	0.34 ± 0.06 <sup>b</sup>	0.34 ± 0.04 <sup>b</sup>
Addiction Severity Index Drug Composite Score*				
Intake	0.24 ± 0.01	0.26 ± 0.01	0.34 ± 0.07	0.27 ± 0.01
Week 8	0.11 ± 0.02 <sup>b</sup>	0.11 ± 0.03 <sup>b</sup>	0.13 ± 0.03 <sup>b</sup>	0.12 ± 0.02 <sup>b</sup>
Week 16	0.09 ± 0.02 <sup>b</sup>	0.14 ± 0.03 <sup>b</sup>	0.11 ± 0.02 <sup>b</sup>	0.12 ± 0.02 <sup>b</sup>

\*Mean ± the standard error of the mean

<sup>a</sup>The combined buprenorphine-naloxone groups reported significantly less heroin use than the combined methadone groups,  $p=0.05$ <sup>b</sup>Significantly different from intake,  $p<0.00001$ <sup>c</sup>The Opiate Composite Score is derived from the drug scale

### 3.9 Safety monitoring

Five serious adverse events were reported during the trial. All events resulted in hospitalisation and were not related to the study drug. Three hospitalisations were

related to treatment for abscesses associated with illicit injection heroin use, 1 was related to high blood pressure and 1 was for a lung mass and shoulder infection. Four events occurred in participants assigned to receive methadone and 1 in a participant assigned to receive buprenorphine-naloxone.

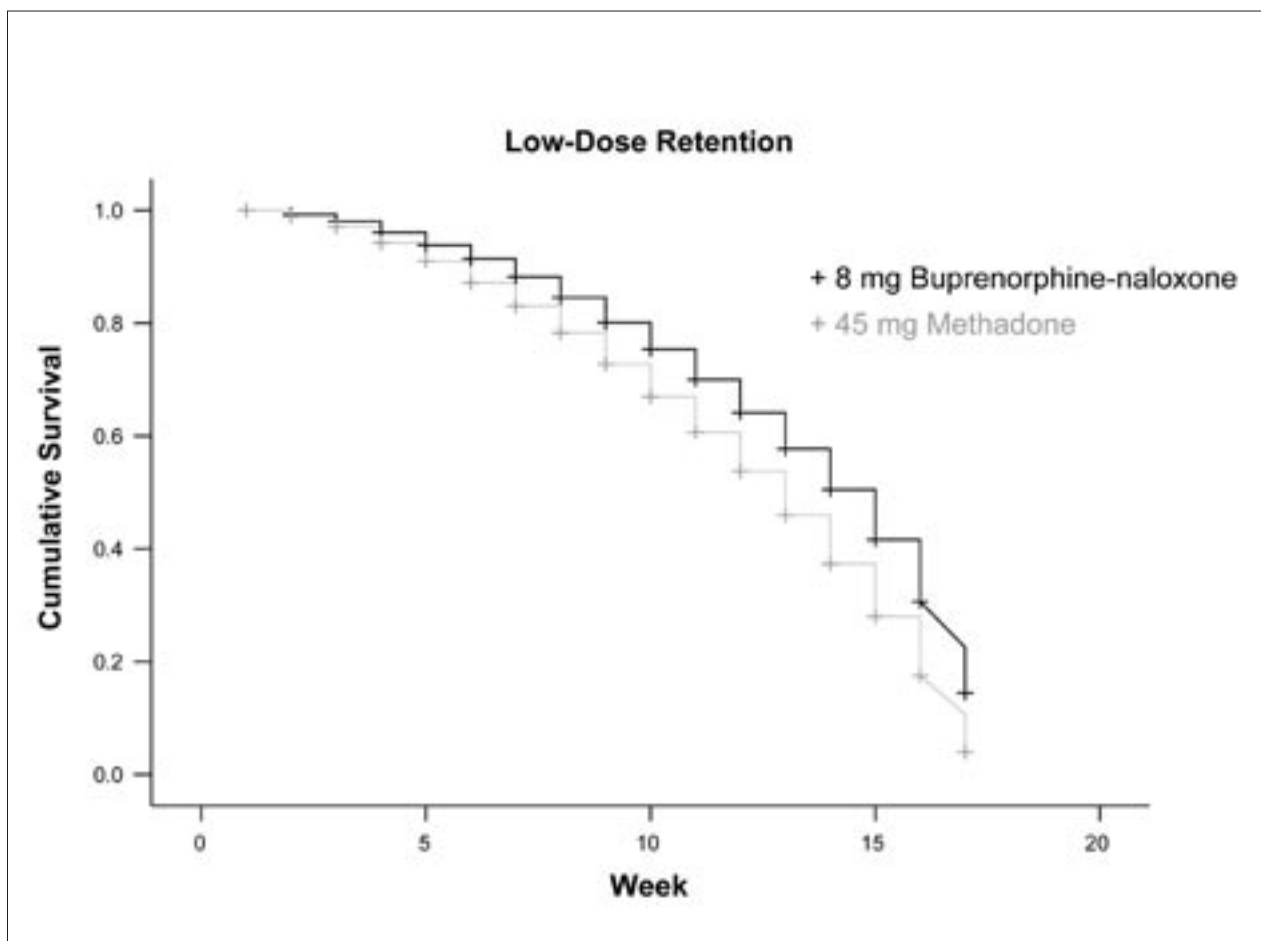


Figure 3. Low-dose retention Kaplan-Meier survival graphs, demonstrating cumulative survival by dose level at each week.

### 3.10 Poststudy treatment

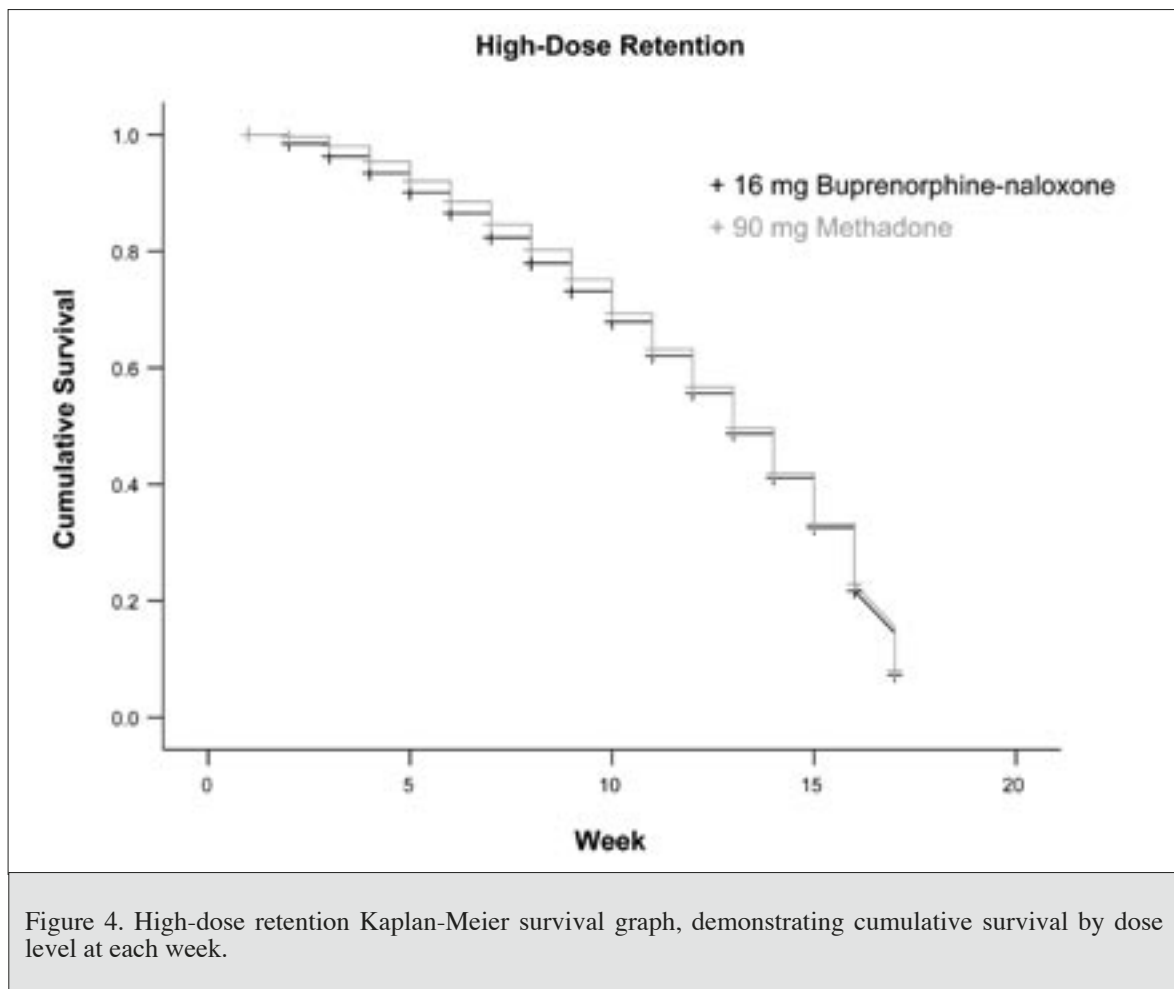
Ninety percent (63/70) of participants who completed the study elected to continue treatment under the compassionate extension of treatment programme. Similar percentages of participants in each treatment group decided to continue treatment (94%, 79%, 94% and 91% of the 8-mg buprenorphine/naloxone, 16-mg buprenorphine/naloxone, 45-mg methadone and 90-mg methadone groups, respectively). Overall, participants received treatment in this phase for about half a year (mean  $\pm$  SEM, 184 days  $\pm$  19). Medication and doses received during the study did not significantly affect the duration of time participants continued to receive treatment after the study ended. Of the 7 participants who declined to participate in the compassionate extension phase, 6 elected to withdraw from the study during a 30-day dose taper and 1 transferred to methadone maintenance at another facility.

## 4. Discussion

In the current study, maintenance with buprenorphine-

naloxone resulted in opioid abstinence similar to that achieved with maintenance using methadone. In particular, 16 mg buprenorphine-naloxone was noninferior to 90 mg methadone, highlighting the usefulness of this medication for the management of opioid dependence. To our knowledge, no other study has directly compared the marketed buprenorphine-naloxone sublingual tablet to methadone for maintenance treatment of opioid dependence. One study compared these 2 agents in a stepped-care model in which patients began treatment with buprenorphine-naloxone but were transferred to methadone (90–111 mg/day) if 32 mg/day buprenorphine-naloxone resulted in missed visits, reports of craving or withdrawal or illicit opioid use. In that study, the use of methadone and buprenorphine-naloxone similarly retained patients and suppressed illicit opioid use [39]. Both studies used relatively high doses of methadone for comparison, increasing confidence in the suggestion that buprenorphine-naloxone is a viable alternative to methadone for opioid dependence treatment.

Many studies have compared maintenance with sublingual liquid or tablet buprenorphine alone versus maintenance with methadone. Most studies report



that buprenorphine and methadone have similar efficacy in reducing illicit opioid use [23, 35, 36, 56, 59, 64], although some studies report better efficacy for buprenorphine [28, 31, 32] or for methadone [41, 44, 55]. In cases in which 1 drug seemed to be superior to the other, procedural variables, such as an insufficiently rapid buprenorphine induction procedure or inadequate buprenorphine doses, may have influenced the results [20]. A review of 3 meta-analyses comparing buprenorphine and methadone emphasised that induction to buprenorphine should proceed more rapidly than what is safe for methadone induction and should reach maintenance doses within 2 to 3 days [20]. The same review also emphasised that buprenorphine dosing should be flexible and variable according to clinical need. The current study, which used a rapid buprenorphine induction procedure and clinically relevant buprenorphine doses, provides further evidence for the equivalence of buprenorphine to methadone. This finding is of particular importance when considering circumstances in which an alternative to methadone is preferred or necessary because of medical or regulatory restrictions on the patient or limited access to methadone.

That higher maintenance doses of methadone and buprenorphine-naloxone produced greater opioid abstinence than lower doses of these drugs in the current

study is not surprising. Greater efficacy of higher doses is supported by other studies of methadone [11, 44, 60] and buprenorphine maintenance [2, 37, 56], but the current study is the first to show that this finding holds true for buprenorphine-naloxone as well. The finding that 16 mg buprenorphine-naloxone produces greater abstinence than 8 mg buprenorphine-naloxone underscores the need for appropriate dose selection and should provide important guidance for countries where maintenance doses for buprenorphine-naloxone average 8 mg or less.

Buprenorphine-naloxone and methadone also had similar effects on other outcome measures. More than 80% of patients were inducted successfully with maintenance drug and dose, regardless of the group assignment. Similarly, high percentages have been successfully inducted with buprenorphine-naloxone using similar procedures [26] and have reached the second week of treatment in other comparisons of buprenorphine and methadone [27, 36, 44, 55, 59]. Medication compliance and retention rates, although low, did not differ by group and are comparable to those found in earlier studies using a similar methodology [27, 36, 44]. Nonetheless, 90% of the patients who completed the current study expressed a desire to continue treatment. In studies where buprenorphine has been made available using

flexible dosing or less stringent attendance requirements, retention rates were substantially higher [26, 35, 39, 49, 59]. Retention rates as high as 75% have been reported over a 1-year period [38].

Buprenorphine-naloxone and methadone produced comparable results for other aspects of treatment performance. Neither drug significantly affected nonopioid drug use, and overall addiction severity decreased over time, paralleling findings in other controlled evaluations of buprenorphine and methadone [29, 39]. Although the current study was not designed to monitor safety per se, very few serious adverse events occurred and none were related to methadone or buprenorphine-naloxone. Therefore, the current results add to the evidence that buprenorphine-naloxone is safe for extended maintenance therapy [57].

The current randomised controlled trial has several strengths that extend the generality of previous research. First, the conservative analytical procedure used in this study, wherein all missing values of urine testing results were extrapolated as positive, controlled for early dropouts and participants who were using opioids and may have decided to be absent for screening. Second, a rapid buprenorphine dose induction procedure and therapeutic maintenance doses of each study medication were used. These features permitted testing the efficacy of buprenorphine-naloxone relative to methadone under best practice induction procedures for buprenorphine, using comparison doses that allowed a fair comparison with methadone. Third, patient participation included those patients previously undergoing maintenance therapy with methadone, those dependent on prescription opioids and those engaging in polysubstance abuse. This demography increases the generality of the findings to the larger international population of opioid-dependent persons seeking treatment with buprenorphine [33, 39]. Finally, the study was conducted in a licensed, community-based opioid treatment programme and exposed patients to buprenorphine-naloxone for a longer period than did most previous efficacy trials (up to 10 months for patients who elected to continue treatment under the compassionate extension phase). These environmental aspects increase the ecological validity of the study and generally underscore buprenorphine-naloxone versatility for use in a multitude of treatment settings [10], for extended maintenance therapy [29] and with a variety of counselling platforms [25] and treatment approaches [39].

Limitations of this study include the uneven numbers assigned to the 4 treatment groups, which potentially decreased the power to detect differences, and the steadily decreasing numbers of patients due to study dropout. The rigorous design of this controlled clinical trial, strict attendance criteria and use of fixed doses naturally contributed to continuous attrition. The find-

ing that buprenorphine-naloxone was not inferior to methadone under these conditions attests to the value of buprenorphine-naloxone as a treatment for opioid dependence and as an alternative to methadone treatment.

## 5. Conclusions

Maintenance treatment with 16 mg buprenorphine-naloxone reduced opioid use at a rate equivalent to that achieved with 90 mg methadone. Other treatment outcomes were comparable for buprenorphine-naloxone and methadone, including completion of dose induction, treatment retention, greater reductions in illicit opioid use in response to higher doses, low incidence of adverse events and similar decreases in addiction severity. Overall, the comparability of buprenorphine-naloxone with methadone, the lower overdose risk and growing availability should help to significantly expand patient access to safe and effective treatment and reduce the harms associated with untreated opioid dependence.

## Role of funding source

The National Institute on Drug Abuse was not involved in designing the study, collecting the data, preparing the manuscript or the decision to submit the manuscript for publication.

## Contributors

The authors contributed equally to this work.

## Conflict of Interest

Dr. Amass is currently employed by Schering-Plough Corporation, a distributor of buprenorphine. Drs. Kamien and Branstetter report no conflicts of interest.

## References

1. ACEIJAS C., STIMSON G.V., HICKMAN M., RHODES T., UNITED NATIONS REFERENCE GROUP ON HIV/AIDS PREVENTION AND CARE AMONG IDU IN DEVELOPING AND TRANSITIONAL COUNTRIES. (2004): Global overview of injecting drug use and HIV infection among injecting drug users. *AIDS* 18(17): 2295-2303.
2. AHAMADI J., BABAEI-BEIGI M., ALISHAHI M., MAANY I., HIDARI T. (2004): Twelve-month maintenance treatment of opium-dependent patients. *J Subst Abuse Treat* 26(1): 363-366.
3. AIKEN M. (1982): A program for balancing the allocation of subjects in a clinical trial. *Comput Biomed Res* 15(6): 519-524.
4. ALHOH., SINCLAIR D., VUROIE., HOLOPANINEN A. (2007): Abuse liability of buprenorphine-naloxone

- tablets in untreated IV drug users. *Drug Alcohol Depend* 88(1): 75-78.
5. AMASS L., BICKEL W.K., CREAN J.P., BLAKE J., HIGGINS S.T. (1998): Alternate-day buprenorphine dosing is preferred to daily dosing by opiate-dependent humans. *Psychopharmacology (Berl)* 136(3): 217-225.
  6. AMASS L., BICKEL W.K., HIGGINS S.T., HUGHES J.R. (1994): A preliminary investigation of outcome following gradual or rapid buprenorphine detoxification. *J Addict Dis* 13(3): 33-45.
  7. AMASS L., KAMIEN J.B., MIKULICH S.K. (2001): Thrice-weekly supervised dosing with the combination buprenorphine-naloxone tablet is preferred to daily supervised dosing by opioid-dependent humans. *Drug Alcohol Depend* 61(2): 173-181.
  8. AMASS L., KAMIEN J.B., MIKULICH S.K. (2000): Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet. *Drug Alcohol Depend* 58(1-2): 143-152.
  9. AMASS L., KAMIEN J.B., REIBER C., BRANSTETTER S. (2000): Abuse liability of IV buprenorphine-naloxone, buprenorphine and hydromorphone in buprenorphine-naloxone maintained volunteers. *Drug Alcohol Depend* 60(suppl 1): S6.
  10. AMASS L., LING W., FREESE T.E., REIBER C., ANNON J.J., COHEN A.J., MCCARTY D., REID M.S., BROWN L.S., CLARK C., ZIEDONIS D.M., KREJCI J., STINE S., WINHUSEN T., BRIGHAM G., BABCOCK D., MUIR J.A., BUCHAN B.J., HORTON T. (2004): Bringing buprenorphine-naloxone detoxification to community treatment providers: the NIDA Clinical Trials Network field experience. *Am J Addict* 13(suppl 1): S42-S66.
  11. BALL J.C., ROSS A (1991): *The Effectiveness of Methadone Maintenance Treatment*. Springer-Verlag, New York.
  12. BELL J., BYRONG G., GIBSON A., MORRIS A. (2004): A pilot study of buprenorphine-naloxone combination tablet (Suboxone®) in treatment of opioid dependence. *Drug Alcohol Rev* 23(3): 311-317.
  13. BICKEL W.K., AMASS L. (1995): Buprenorphine treatment of opiate dependence: a review. *Exp Clin Psychopharmacol (Berl)* 3(4): 477-489.
  14. BICKEL W.K., AMASS L., CREAN J.P., BADGER G.J. (1999): Buprenorphine dosing every 1, 2, or 3 days in opioid-dependent patients. *Psychopharmacology (Berl)* 146(2): 111-118.
  15. CARRIERI M.P., AMASS L., LUCAS G.M., VLAHOV D., WODAK A., WOODY G.E. (2006): Buprenorphine use: the international experience. *Clin Infect Dis* 43(suppl 4): S197-S215.
  16. CHIANG C.N., BRIDGE P., HAWKS R.L., HERBERT S., HILL J., MAGHRABLIAN L., et al. (1996): The development of buprenorphine-naloxone products for treating opiate dependence. In: Harris LS, editor. *Problems of Drug Dependence 1995: Proceedings of the 57th Annual Scientific Meeting of the College on Problems of Drug Dependence, Inc.* NIDA Research Monograph No. 162; National Institute on Drug Abuse: Rockville, Maryland, p. 117.
  17. CHIANG C.N., HAWKS R. (1994): Development of a buprenorphine-naloxone combination drug for the treatment of drug addiction. In: Harris LS, editor. *Problems of Drug Dependence 1993: Proceedings of the 55th Annual Scientific Meeting of the College on Problems of Drug Dependence, Inc.* NIDA Research Monograph No. 141; National Institute on Drug Abuse: Rockville, Maryland, p. 458.
  18. COMER S.D., COLLINS E.D. (2002a): Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. *J Pharmacol Exp Ther* 303(2): 695-703.
  19. COMER S.D., COLLINS E.D., FISCHMAN M.W. (2002b): Intravenous buprenorphine self-administration by detoxified heroin abusers. *J Pharmacol Exp Ther* 301(1): 266-276.
  20. DORAN C., HOLMES J., LADEWIG D., LING W. (2005): Buprenorphine induction and stabilisation in the treatment of opiate dependence. *Heroin Addict Rel Clin Probl* 7(1): 7-18.
  21. DORAN C.M. (2005): Buprenorphine, buprenorphine-naloxone, and methadone maintenance: a cost-effectiveness analysis. *Expert Rev Pharmacoeconomics Outcomes Res* 5: 583-591.
  22. DORAN C.M., SHANAHAN M., MATTICK R.P., ALI R., WHITE J., BELL J. (2003): Buprenorphine versus methadone maintenance: a cost-effectiveness analysis. *Drug Alcohol Depend* 71(3): 295-302.
  23. EDER H., FISCHER G., GOMBAS W., JAGSCH R., STÜHLINGER G., KASPER S. (1998): Comparison of buprenorphine and methadone maintenance in opiate addicts. *Eur Addict Res* 4(suppl 1): 3-7.
  24. EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). (2006): The state of the Drugs problem in Europe. Lisbon: EMCDDA.
  25. FIELLIN D.A., PANTALON M.V., CHAWARSKI M.C., MOORE B.A., SULLIVAN L.E., O'CONNOR P.G., SCHOTTENFELD R.S. (2006): Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med* 355(4): 365-374.
  26. FINCH J.W., KAMIEN J.B., AMASS L. (2007): Two-year experience with buprenorphine-naloxone (Suboxone®) for maintenance treatment of opioid-dependence within a private practice setting. *J Addict Med* 1(2): 104-110.
  27. FISCHER G., GOMBAS W., EDER H., JAGSCH R., PETERNELL A., STÜHLINGER G., PEZAWAS L., ASCHAUER H.N., KASPER S. (1999): Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction* 94(9): 1337-1347.
  28. FISCHER G., ORTNER R., ROHRMEISTER K., JAGSCH R., BAEWERTA., LANGERM., ASCHAUER H. (2006): Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. *Addiction* 101(2): 275-281.
  29. FUDALA P.J., BRIDGE T.P., HERBERT S., WILLIFORD W.O., CHIANG C.N., JONES K., COLLINS J., RAISCH D., CASADONTE P., GOLDSMITH R.J., LING W., MALKERNEKER U., MCNICHOLAS L., RENNER J., STINE S.,

- TUSEL D., BUPRENORPHINE/NALOXONE COLLABORATIVE STUDY GROUP. (2003): Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 349(10): 949-958.
30. FUDALAP.J., YUE., MACFADDEN W., BOARDMAN C., CHAING N.C. (1998): Effects of buprenorphine and naloxone in morphine-stabilized opiate addicts. *Drug Alcohol Depend* 50(1): 1-8.
31. GERRA G., BORELLA F., ZAIMOVIC A., MOI G., BUSSANDRI M., BUBICI C., BERTACCA S. (2004): Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. *Drug Alcohol Depend* 75(1): 37-45.
32. GIACOMUZZI S.M., RIEMER Y., ERTL M., KEMMLER G., ROSSLER H., HINTERHUBER H., KURZ H. (2003): Buprenorphine versus methadone maintenance treatment in an ambulant setting: a health-related quality of life assessment. *Addiction* 98(5): 693-702.
33. HARRIS D.S., JINES R.T., WELM S., UPTON R.A., LIN E., MENDELSON J. (2000): Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. *Drug Alcohol Depend* 61(1): 85-94.
34. HUDZIAK J.J., HELZER J.E., WETZEL M.W., KESSEL K.B., MCGEE B., JANCA A., PRZYBECK T. (1993): The use of the DSM-III-R checklist for initial diagnostic assessments. *Compr Psychiatry* 34(6): 375-383.
35. JOHNSON R.E., CHUTUAPE M.A., STRAIN E.C., WALSH S.L., STITZER M.L., BIGELOW G.E. (2000): A comparison of levomethadyl acetate, buprenorphine and methadone for opioid dependence. *N Engl J Med* 343(18): 1290-1297.
36. JOHNSON R.E., JAFFE J.H., FUDALAP.J. (1992): A controlled trial of buprenorphine treatment for opiate dependence. *JAMA* 267(20): 2750-2755.
37. JOHNSON R.E., STRAIN E.C., AMASS L. (2003): Buprenorphine: how to use it right. *Drug Alcohol Depend* 70 (2 suppl): S59-S77.
38. KAKKO J., SVANBORG K.D., KREEK M.J., HEILIG M. (2003): 1-Year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. *Lancet* 361(9358): 662-668.
39. KAKKO J., GRÖNBLADH L., SVANBORG K.D., VON WACHENFELDT J., RÜCK C., RAWLING B., NILSSON L.H., HEILIG M. (2007): A stepped care strategy utilizing buprenorphine and methadone vs. conventional methadone maintenance in heroin dependence: a randomized controlled trial. *Am J Psychiatry* 164(5): 797-803.
40. KAMIEN J.B., BRANSTETTER S.A., MIKULICH S.K., AMASS L. (2000): Impact of contingent take-homes and blind dose increases during buprenorphine-naloxone tablet and methadone maintenance treatment. In: Harris LS, editor. *Problems of Drug Dependence 1999: Proceedings of the 61st Annual Scientific Meeting of the College on Problems of Drug Dependence, Inc.* NIDA Research Monograph 180; U.S. Government Printing Office, Washington, DC.
41. KOSTEN T.R., SCHOTTENFELD R., ZIEDONIS D., FALCIONI J. (1993): Buprenorphine versus methadone maintenance for opiate dependence. *J Nerv Ment Dis* 181(6): 358-364.
42. LING W., AMASS L., SHOPTAW S., ANNON J.A., BABCOCK D., BRIGHAM, G., HARRER J., REID M., MUIR J., BUCHAN B., ORR D., WOODY G., KREJCI J., ZIEDONIS D., BUPRENORPHINE STUDY PROTOCOL GROUP. (2005): A multi-center randomized trial of buprenorphine-naloxone and clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction* 100(8): 1090-1100.
43. LING W., WESSON D.R. (2003): Clinical efficacy of buprenorphine: comparisons to methadone and placebo. *Drug Alcohol Depend* 70(2 suppl): S49-S57.
44. LING W., WESSON D.R., CHARUVA STRA C., KLETT C.J. (1996): A controlled trial comparing buprenorphine and methadone maintenance in opiate dependence. *Arch Gen Psychiatry* 53(5): 401-407.
45. MAREMMANI I., PANI P.P., PACINI M., PERUGI G. (2007): Substance abuse and quality of life over 12 months among buprenorphine maintenance-treated and methadone maintenance-treated heroin-addicted patients. *J Subst Abuse Treat* 33(1): 91-98.
46. MATTICK R.P., BREEN C., KIMBER J., DAVOLI M. (2003): Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database Syst Rev* 2: CD002209.
47. MCLELLAN A.T., LUBORSKY L., CACCIOLA J., GRIFFITH J., EVANS F., BARR H.L., O'BRIEN C.P. (1985): New data from the Addiction Severity Index: reliability and validity in three centers. *J Nerv Ment Dis* 173(7): 412-423.
48. MENDELSON J., JONES R.T., FERNANDEZ I., WELM S., MELBY A.K., BAGGOTT M.J. (1996): Buprenorphine and naloxone interactions in opiate-dependent volunteers. *Clin Pharmacol Ther* 60(1): 105-114.
49. PETITJEANS., STOHLER R., DÉGLON J.J., LIVOTI S., WALDVOGEL D., UEHLINGER C., LADEWIG D. (2001): Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug Alcohol Depend* 62(1): 97-104.
50. PICKWORTH W.B., JOHNSON R.E., HOLICKY B.A., CONE E.J. (1993): Subjective and physiologic effects of intravenous buprenorphine in humans. *Clin Pharmacol Ther* 53(5): 570-576.
51. RAUDENBUSH S.W., XIAO-FENG L. (2001): Effects of study duration, frequency of distribution and sample size on power in studies of group differences in polynomial change. *Psychol Methods* 6(4): 387-401.
52. SAMHSA (Substance Abuse and Mental Health Services Administration). (2004a): *Overview of Findings from the 2003 National Survey on Drug Use and Health*. Office of Applied Studies, NSDUH Series H-24, DHHS Publication No. SMA 04-3963; Rockville, Maryland.
53. SAMHSA (Substance Abuse and Mental Health Services Administration), Office of Applied Studies. (2004b): *Treatment Episode Data Set (TEDS): 1992-2002*.

- National Admissions to Substance Abuse Treatment Services, DASIS Series: S-23, DHHS Publication No. (SMA) 04-3965; Rockville, Maryland.
54. SCHOTTENFELD R.S., CHAWARSKI M.C., PAKES J.R., PANTALON M.V., CARROLL K.M., KOSTEN T.R. (2005): Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *Am J Psychiatry* 162(2): 340-349.
  55. SCHOTTENFELD R.S., CHAWARSKI M.C., MAZLAN M. (2008): Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. *Lancet* 371(9631): 2192-200.
  56. SCHOTTENFELD R.S., PAKES J.R., OLIVETO A., ZIEDONIS D., KOSTEN T.R. (1997): Buprenorphine versus methadone maintenance for concurrent opiate dependence and cocaine abuse. *Arch Gen Psychiatry* 54(8): 713-720.
  57. STANTON A., MCLEOD C., KISSIN W., SONNENFELD J., LUCKEY J. (2006): Evaluation of the Buprenorphine Waiver Program: results from SAMHSA/CSAT's evaluation of the Buprenorphine Waiver Program. In: Harris LS, editor. *Problems of Drug Dependence 2005: Proceedings of the 67th Annual Scientific Meeting of the College on Problems of Drug Dependence, Inc.* NIDA Research Monograph 186; National Institute on Drug Abuse; Rockville, Maryland.
  58. STOLLER K.B., BIGELOW G.E., WALSH S.L., STRAINE.C. (2001): Effects of buprenorphine/naloxone in opioid-dependent humans. *Psychopharmacology (Berl)* 154(3): 230-242.
  59. STRAIN E.C., STITZER M.L., LIEBSON I.A., BIGELOW G.E. (1994): Comparison of buprenorphine and methadone in the treatment of opiate dependence. *Am J Psychiatry* 151(7): 1025-1030.
  60. STRAIN E.C., STITZER M.L., LIEBSON I.A., BIGELOW G.E. (1993): Methadone dose and treatment outcome. *Drug Alcohol Depend* 33(2): 105-117.
  61. STRAIN E.C., STOLLER K., WALSH, S.L., BIGELOW G.E. (2000): Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers. *Psychopharmacology (Berl)* 148(4): 374-383.
  62. SULLIVAN L.E., BARRY D., MOORE B.A., CHAWARSKI M.C., TETRAULT J.M., PANTELON M.V., SCHOTTENFELD R.S., FIELLIN D.A. (2006): A trial of integrated buprenorphine/naloxone and HIV clinical care. *Clin Infect Dis* 43(suppl 4): S184-S190.
  63. SULLIVAN L.E., CHAWARSKI M., O'CONNOR P.G., SCHOTTENFELD R.S., FIELLIN D.A. (2005): The practice of office-based buprenorphine treatment of opioid dependence: is it associated with new patients entering treatment? *Drug Alcohol Depend* 79(1): 113-116.
  64. UEHLINGER C., DÉGLON J., LIVOTIS., PETITJEAN S., WALDVOGEL D., LADEWING D. (1998): Comparison of buprenorphine and methadone in the treatment of opioid dependence. Swiss Multicentre Study. *Eur Addict Res* 4(suppl 1): 13-18.
  65. WORLD HEALTH ORGANIZATION. (2007): WHO Model List of Essential Medicines 15th Edition [Online]. [www.who.int/entity/medicines/publications/EML15.pdf](http://www.who.int/entity/medicines/publications/EML15.pdf).
  66. YEH P.H., GAZDZINSKI S., DURAZZO T.C., SJÖSTRAND K., MEYERHOFF D.J. (2007): Hierarchical linear modeling (HLM) of longitudinal brain structures and cognitive changes in alcohol-dependent individuals during sobriety. *Drug Alcohol Depend* 91(2-3): 195-204.

#### Acknowledgements

This project was supported by Grant R01 DA11160 from the National Institute on Drug Abuse. Preliminary data were presented at the 61st Annual Scientific Meeting of the College on Problems of Drug Dependence, Inc., June 1999; Acapulco, Mexico. Final data were presented at the 3rd Annual European Association of Addiction Therapy Conference, September 2007; Vienna, Austria. The authors thank Robert Willard, MD, Mori Krantz, MD, Lisa Kosmiski, MD, Margery Johnson, RN, and Janet Robinson, LPN, for medical support; Connie Miles, CPT, for pharmacy services; Chris Reiber, PhD, MPH, and Susan K. Mikulich, PhD, for statistical analyses; the patients and clinical staff at the Vine Street Center; and Eric Ennis, LCSW, and Tom Brewster, LCSW, of the Addiction Research and Treatment Services for assisting with post-study patient care. The authors thank Reckitt Benckiser for providing buprenorphine, buprenorphine-naloxone and placebo tablets to support this study.

Received September 22, 2008 - Accepted December 3, 2008



Pacini Editore & AU CNS

## Predictors for Non-Relapsing Status in Methadone-Maintained Heroin Addicts. A Long-Term Perspective Study

Icro Maremmani<sup>1,2,3</sup>, Matteo Pacini<sup>1,3</sup>, Francesco Lamanna<sup>1</sup>,  
Pier Paolo Pani<sup>4</sup>, Manuela Trogu<sup>4</sup>, Giulio Perugi<sup>1,3</sup>, Joseph Deltito<sup>3,5</sup>  
and Gilberto Gerra<sup>6</sup>

<sup>1</sup>Vincent P. Dole Dual Diagnosis Group, Santa Chiara University Hospital,  
Department of Psychiatry, NPB, University of Pisa, Italy

<sup>2</sup>AU-CNS, "From Science to Public Policy" Association, Pietrasanta, Lucca, Italy

<sup>3</sup>Institute of Behavioural Sciences "G. De Lisio", Pisa, Italy

<sup>4</sup>Social-Health Integration Service, Office of Social Policies, Sardinia Health and Social Administration,  
Sardinia Autonomous Region, Cagliari, Italy

<sup>5</sup>Department of Psychiatry and Behavioural Science, New York Medical College, Valhalla, New York, USA.

<sup>6</sup>Global Challenges Section, Human Security Branch, Division for Operations,  
United Nations Office on Drugs and Crime, Vienna

### Summary

Despite the established effectiveness of Methadone Maintenance Therapy (MMT), specific evidence regarding factors influencing the prognosis of enrolled patients is quite limited. This study aims to ascertain which patient- or treatment-related features, assessed in a standardized way at the beginning of the program, do have an influence on whom is retained for long-term compliance with retention in treatment. 129 patients (94 male and 35 female) were treated in a methadone maintenance treatment program for 6 years on average. Retention in treatment was compared (survival analysis and Leu-Desu statistics) among groups of patients selected on the basis of socio-demographic and clinical variables. The variables that showed statistically significant differences ( $p < 0.05$ ) for an association regarding retention rate were included in separate logistic backward regression analyses comprising outcomes as dependent variables. Results show that dual diagnosis, defined by concurrent psychiatric disorders in evidence before the onset of heroin use, is the strongest negative predictor of relapse throughout a six year's average observation period, regardless of other clinical and socio demographic variables. Such a finding should be read in the context of a high-threshold setting, and accounts only for those patients, who had been retained in treatment over the first year.

**Key Words:** Methadone Treatment; Response Predictors to Treatment Outcome; Retention; Psychiatric Comorbidity.

### 1. Background

The effectiveness of methadone maintenance treatment for heroin addiction is widely accepted and supported by the existing scientific literature. A body of research, both experimental (including a number of

randomized and/or controlled trials) and observational (mostly perspective and retrospective cohort studies) have shown that MMT patients demonstrate relevant improvement while retained within a successful program: reduction of opiate use (possibly to cessation), extinction of craving, decreased or stopped criminal

activities, somatic well-being and social adjustment [1, 5, 7, 20, 50, 51].

Despite the robust body of evidence supporting the effectiveness of MMT, knowledge about the factors influencing the prognoses of enrolled patients is quite limited.

On theoretical grounds, MMT can be successful due to issues related to either i) the patient, ii) the therapeutic setting, iii) the treatment procedure. Factors associated to other spheres (sociodemographic features, clinical features, management skills, treatment philosophy and policy, combined medical and psychosocial facilities, methadone dosing, the duration of programs). These may have an impact on treatment outcome and be regarded as prognostic predictors.

Each of the above spheres has already been investigated in previous studies. Among patient-related features, age, non-white race, earlier age of addiction onset, cocaine use, and engagement in illegal activities, have been linked to a negative or less satisfactory outcome [2, 19]. Also, the presence and severity of psychiatric comorbidity is a possible reason for treatment failure or limited improvement [24, 32, 42-45, 52].

As far as setting-related variables are concerned, some treatment features (availability of counselling, staff direction by a physician who is directly in charge of cases, a maintenance-oriented attitude, the availability of other medical facilities in the same environment) have been associated with a better outcome [2, 28], although higher psychological distress levels at baseline and poorer health (as indicated by lower SF (Short Form) 12 global mental health Score) are predictive of continuous abstinence from heroin [6].

Among treatment-related variables, let alone methadone dosage, other important predictors have been identified, such as skipping doses (negative predictor) and the availability of take-home Methadone (positive predictor) [2]. Both these variables are significantly related, in a negative and positive way, respectively, to compliance of a program's rules. Individualized treatment and take-away doses are both associated with increased retention rates [4, 37]. Recently, provider-related variable of retention was evaluated: patient treatment satisfaction. It is important to note that "patient satisfaction" becomes salient and predicts higher retention rates (81% vs 41% at one year) only if methadone dosage is appropriate [54].

An important aspect in predicting outcome, is the length of treatment. Research on this issue indicates that the longer there is treatment compliance, the less likely there is a negative outcome, suggesting that the early results tend to consolidate through time spent while under treatment [47-49]. Nevertheless, no clear individual characteristics have been found that can be relied upon as predictors of outcome and retention for

different term lengths.

The present study aimed to ascertain which patient- or treatment-related related features, assessed in a standardized way at the beginning of the program, do have an influence on retention in long term treatment. In particular, we decided to investigate the possible role of psychiatric comorbidity on the outcome of successful methadone treatment. On the basis of previous evidence [31] the hypothesis of the study was that concomitant psychiatric disorders may not consistently influence retention in long-term treatment.

## 2. Methods

### 2.1 Design of the study

A prospective cohort study was designed in order to evaluate treatment outcomes (in terms of retention in treatment, substance use, clinical improvement and general social adjustment) of patients included in a methadone program.

All 129 consecutive patients were admitted to the program over a 8 year time period (from January 1993 to May 2001) and followed for up to 9 years. The length of the prospective observation was 6 years on average, (min 1, max 9); follow-up evaluation was carried out monthly, from the beginning of treatment.

The study was conducted according to the principles of the Helsinki Pact and Good Clinical Practice Consolidate Guidelines (CPMP/ICH/135/1995). All patients included in the study signed informed consent. Both the consent form and the experimental procedures were approved by the competent ethics committees in accordance with internationally accepted criteria for ethical research.

### 2.2 Setting

Since 1993, the Pisa-MMTP has been using a clinical protocol that has the characteristics of a high-threshold treatment facility for opioid addiction focusing on pharmacological maintenance. After patients at the PISA-MMTP have been safely inducted into treatment with methadone, their doses are gradually increased until the point is reached where there is no more than one urine drug screen which is positive for illicit opiates, cocaine, or benzodiazepines in the previous sixty-day's period.

Once this requirement is fulfilled, the patient is defined as having being "stabilized" and the dose at which this goal has been accomplished is referred to as the "stabilization dose". No upper limit for dosage exists. Nevertheless, one time limitation is present in this setting: patients who cannot achieve stabilization within one year are terminated, to be transferred to

local treatment units. The dosage is increased as indicated by the results of urinalyses, while evidence of improvement on social grounds does not alone justify dose stability as long as urine tests stay positive for illicit opiates. Patients are not allowed to raise or lower the dose by themselves. Take-home doses, without limitations, at most for a 7-day's period, are allowed, once patients have shown complete compliance with the rules of the program. Urine samples for toxicology analyses are collected randomly approximately once a month, to evaluate for metabolites of illicit drugs and benzodiazepines.

In our program patients are required to be actively involved in treatment by attending the clinic whenever it is scheduled, participating in the development of their treatment plan, working towards treatment goals, meeting with medical and case management staff, and attending groups when indicated.

Patients with psychiatric comorbidity are also treated with psychoactive drugs (neuroleptics, mood stabilizers, antidepressants) and psychotherapy, as needed. All physicians working in the PISA-Methadone Programmes are psychiatrists who have been trained for at least two-years in the treatment of addictive disorders.

### 2.3 Subjects

All patients referred to Pisa Methadone Maintenance Treatment Program (PISA-MMT) during the January 1993-May 2001 period (N=129) were consecutively enrolled in the study.

To be referred to the PISA-MMT program patients had to:

- 1 Fulfill the various DSM criteria for opioid dependence;
- 2 Have a history of heroin addiction of a least 2 years;
- 3 Be between the ages of 18 and 40.

Patients were excluded if they had any serious medical condition which made participation in the study risky (e.g. active tuberculosis, acute hepatitis, renal or cardiovascular illness, unstable diabetes or AIDS).

Patients could withdraw their participation at any time and be transferred to an other treatment.

The baseline characteristics of the sample were: average age  $29.5 \pm 6$ ; mostly male (n=94; 72.8%), never married (n=85; 65.8%), and currently unemployed (n=67; 51.9%), with a low educational level ( $9.1 \pm 2.3$  years). For details see table 1.

Sixty-six of them (51.2%) had at least one additional psychiatric diagnosis. Most of the dual diagnosis patients were affected by type 1 (N = 25, 37.9%) or type 2 bipolar disorder (n=13, 19.7%). Some of them had adjunctive psychiatric comorbidities of the anxiety cluster (n=8, 12.1%) and a history of alcohol and/or

benzodiazepine abuse (n=7, 10.6%). The second most frequent diagnosis was depressive disorder (n=9, 13.6%), usually complicated by severe anxiety disorders, such as panic disorder with severe agoraphobia, obsessive-compulsive disorder or alcohol abuse. The 7 subjects diagnosed as alcoholics or benzodiazepine-addicts had all a clear history of social phobia or panic disorder. Schizophrenia was the least frequent diagnosis (n=4, 6.1%). Patients with dual diagnosis received the same intensity in treatment regarding counselling, medications and previous treatments. Sometimes they were treated with neuroleptics and antidepressant but not contemporaneously.

### 2.4 Instruments

The following instruments were used to collect data on the variables to be studied:

#### 2.4.1. Drug Addiction History Rating Scale (DAH-RS)

The DAH-RS [29]. is a multi-scale questionnaire comprising the following categories: sociodemographic information, physical health, mental health, substance abuse, treatment history, social adjustment and environmental factors. The questionnaire rates 10 items: physical problems, mental problems, substance abuse, previous treatment, associated treatments, employment status, family situation, sexual problems, socialization and leisure time, legal problems. (The specific clinical variables addressed are: hepatic, vascular, haemo-lymphatic, gastrointestinal, sexual, dental pathology, HIV serum status; memory disorders, anxiety disorders, mood disorders, aggression, thought disorders, perception disorders, awareness of illness; employment, family, sex, socialization and leisure time, legal problems; use of alcohol, opiates, CNS depressants, CNS stimulants, hallucinogens, phencyclidine, cannabis, inhalants, polysubstance abuse; frequency of drug use, pattern of use, previous treatments; current treatments). Items have been constructed in order to obtain dichotomous answers (yes/no).

#### 2.4.2. Psychiatric Diagnostic Evaluation.

Psychiatric disorders were investigated on the basis of the DSM-IV Decision Trees for Differential Diagnosis. Each decision tree starts with a set of clinical features. When one of these features is a prominent item of the current clinical picture, the clinician will ask a series of questions to rule in or rule out a number of disorders. The questions are just approximations to the diagnostic criteria and are not meant to replace them. Three decision trees have been used: "Differential Diagnosis

Table 1. Demographic characteristics and drug addiction history of the sample		
Age	M±s	30±6
Sex (male)	N (%)	94 (72.9)
Civil status: (Never married)	N (%)	85 (65.9)
Education (< 8 years)	N (%)	91 (70.5)
Work:		
White collar		31 (24.0)
Blue collar	N (%)	29 (22.5)
Unemployed		69 (53.5)
Presence of physical concerns	N (%)	103 (79.8)
HIV positive	N (%)	14 (10.9)
Work concerns	N (%)	81 (62.8)
Household concerns	N (%)	69 (53.5)
Romantic concerns	N (%)	48 (37.2)
Social/leisure concerns	N (%)	69 (53.5)
Legal concerns	N (%)	63 (48.8)
Polyabuse (more than 3)	N (%)	90 (69.8)
Heroin daily intake	N (%)	106 (82.2)
Age at first use of heroin	M±s	19±4
Heroin dependence: Age of onset	M±s	21±5
Dependence duration (mos)	M±s	94±70
Age at first treatment	M±s	27±6
Dual Diagnosis	N (%)	66 (51.2)

of Psychotic Disorders” (initial clinical features: delusions, hallucinations, disorganized speech, or grossly disorganized behaviour); “Differential Diagnosis of Mood Disorders” (initial clinical features: depressed, elevated, expansive or irritable mood; two separate items record the presence of depression and/or any tendency towards the bipolar spectrum as testified by an elevated, expansive or irritable mood); “Differential Diagnosis of Anxiety Disorders” (initial clinical features: symptoms of anxiety, fear, avoidance, or increased arousal). Personality disorders were not considered in the analyses, due to the higher rate of overlap between different pictures and the low inter-rater reliability. Moreover, the most frequent personality pictures in substance abusers and addicts are diagnosed in ways that include substance abuse among diagnostic items and do not exclude the secondary nature of sociopathic and oppositional behavior as due to addictive drives.

We considered there to be a “dual diagnosis” when we have determined the presence of both heroin dependence and an autonomous psychiatric disorder.

#### 2.4.3. Urine analyses

Toxicological urine analyses were carried out randomly every week during the induction phase and

approximately every month during the stabilization phase. The enzyme-linked multiplied immunoassay for opiates was used.

#### 2.5. Data analysis

We assessed DAH-RS at the baseline. Criteria for the outcome were assessed monthly. Regarding the psychiatric evaluation patients were evaluated while free of an acute phase, for which hospitalization was required, so to reduce the diagnostic ambiguity between intoxication related symptoms and spontaneous mental disorders. In case where further relevant clinical information emerged from subsequent interviewing, diagnoses were reassessed.

Patients who stayed in treatment were assessed at the end of treatment. Among patients with negative outcomes, those who dropped out of treatment were assessed at time of treatment interruption, this being the last regular assessment, and not the previous month's.

Retention in treatment was compared (survival analysis and Leu-Desu statistics) between groups of patients selected on the basis of DHA-RS socio-demographic and clinical variables.

For the purpose of this analysis, the term “com-

pleted observations” refers to patients who left the treatment as a “not stabilized patient” (see the section appearing above entitled “Setting” for details), while “censored observations” refers to patients who are still in treatment at the end-point or leaving treatment for reasons unrelated to the treatment itself (e.g. patients moving to other towns and periods of imprisonment for past criminal activities) or patients detoxified after the maintenance period. In other words, we consider 2 kinds of positive outcome: the first when a patient left the program after successful detoxification (after the maintenance period) or was referred, as a “stabilized” patient, to other programs; the second when a patient was still in treatment, at the end-point, as a “stabilized” patient. We consider it to be a negative outcome when a patient has failed to achieve stabilization within a year or has relapsed into addictive behaviour after a period of stabilization.

The variables that showed statistically significant differences ( $p < 0.05$ ) for an association with retention rate were included in separate logistic backward regression analyses comprising outcome as dependent variables. Statistical analyses were carried out using the SPSS package. Since this is an exploratory study, statistical tests were considered significant at the  $p < 0.05$  level.

### **3. Results**

#### *3.1 Retention in treatment*

129 patients were observed for 1 year; 86 for 2 years; 67 for 3 years; 56 for 4 years; 43 for 5 years; 36 for 6 years; 27 for 7 years; 21 for 8 years; 1 for 9 years.

33 patients (26.61%) didn't achieve the stabilization phase in 1 year; 12 (14.55%) relapsed during the second year of treatment; 3 (4.76%) relapsed during the third year; 4 (7.77%) during the fourth. No patients relapsed into addictive behaviour after 4 years of treatment. The cumulative proportion of patients survived at the end of the observational period was 0.55. A positive outcome was observed in 77 patients (59.68%).

#### *3.2. Predictors of response to treatment*

Table 2 reported the association of survival in treatment, as a stabilized patient, with baseline socio-demographic characteristics, social adjustment, drug addiction history and psychiatric comorbidity. The stereotype of a good response to a long-term methadone treatment appears to be unrelated to age and sex. The major proportion of patients not relapsing in heroin use is observed for patients who remained in treatment for more than 3 years. They were mainly blue collar employees with adequate income, having family minor/no

concerns, with no baseline concurrent use of un-prescribed benzodiazepines, and with a stable addictive mode at the start of the treatment. A stable addictive mode refers to a particular lifestyle while using heroin. “Stable” signifies that the patient maintains productivity and that he is not engaged in street crime despite major individual and relational impairment. Generally non relapsing patients, when entering treatment, are in the early stages of their illness. The early stage is opposite to late stage of the natural course of addiction, which is called the “revolving door stage”, where patients undergo a series of relapses and repeatedly fail to maintain a drug-free condition after detoxification. Before heroin (ab)use it is possible to identify, in non relapsing patients psychiatric symptoms. Their age of first use of heroin is more than 17 years and the age of onset of the dependence (continuous use) is later ( $> 20$  years). During the treatment, non-relapsing patients have a stabilization dosage of methadone of more than 120 mg/daily and the time to achieve the stabilization is longer than 6 months. Generally relapsing patients were previously treated in therapeutic communities. Finally dual diagnosed heroin addicts show better retention in treatment than heroin addicts without psychiatric comorbidity.

Age, sex, education, marital status, some social adjustment areas (leisure-time, social and legal issues), the substance abuse at baseline (alcohol, stimulants, cannabinoids, amphetamines, inhalant and hallucinogenic) show no significant impact on relapsing risk.

Table 3 shows how the most important predictors of non relapsing, during a long-term methadone treatment, is the time spent in treatment. Patients treated for more than 3 years have 5.55 time (min 4.73, max 6.37) the possibility of having a good outcome in comparison to patients treated for less than 1 year. Patients with dual diagnosis show an odds ratio of 2.01 (min 1.46, max 2.56) compared with patients without psychiatric comorbidity. The presence of psychiatric symptoms in the patient's history before heroin use shows an odd ratio of 0.49 (min -0.14, max 1.12). So, the most important predictors of non relapsing are time spent in treatment and the presence of a psychiatric comorbidity (dual diagnosis).

### **4. Discussion**

By a univariate analysis, a number of variables appears to be related to retention in our methadone maintenance treatment program.

#### *4.1 Sociodemographic data*

Age, sex and marital status do not appear to influence the likelihood of relapse. Other studies indicate a

Table 2. Methadone treatment: association of survival in treatment with baseline socio-demographic characteristics, social adjustment, drug addiction history and psychiatric comorbidity. Only significant differences are reported.

	N	Survived N (%)	Lee desu statistics	P
Work:				
Unemployed	69	32 (46.38)a		
White collar	31	22 (70.97)		
Blue collar	29	23 (79.31)a	9.04	0.010
Income:				
Lower	22	7 (31.82)		
Adequate	107	70 (65.42)	9.52	0.002
Social Adjustment:				
Family:				
Minor/no concerns	85	62 (72.94)		
Major concerns	44	15 (34.09)	18.39	0.000
Baseline concurrent use of non-prescription BDZs:				
Yes	64	32 (50.00)		
No	65	45 (69.00)	6.33	0.011
Addictive mode*:				
Stable	49	39 (79.59)		
Unstable	80	38 (47.50)	10.71	0.001
Clinical stage:				
Late stage**	101	55 (54.46)		
Early stage	28	22 (78.57)	5.24	0.022
Stressors before heroin (ab)use				
Social/familiar stressors	19	15 (78.95)		
Psychiatric symptoms	19	16 (84.21)		
No stressors	91	46 (50.55)	11.47	0.003
Time spent in treatment				
< 1 year	43	10 (23.26)b,c,e		
1-2 years	19	7 (36.84)b,d,f		
2-3 years	11	8 (72.73)c,d,g		
>3 years	56	52 (92.86)e,f,g	86.41	0.0000
Stabilisation dosage				
< 80 mg/daily	27	14 (51.85)		
>120 mg/daily	62	39 (62.90)	4.38	0.03
Time to achieve stabilisation				
< 3 months	23	11 (47.83)		
3-6 months	56	30 (53.57)		
> 6 months	50	36 (72.00)	16.08	0.000
Age of 1st heroin use				
Early (<17 yrs)	49	22 (44.90)		
Late (>17 yrs)	80	55 (68.75)	5.93	0.014
Onset of dependence:				
Earlier (<20 yrs)	73	38 (52.02)		
Later (>20 yrs)	56	39 (69.64)	4.17	0.041
Previous treatment in therapeutic community				
Yes	49	22 (44.90)		
No	80	55 (68.75)	4.61	0.031

Dual Diagnosis:				
Absence	63	31 (49.21)		
Presence	66	46 (69.70)	8.57	0.003
*kind of lifestyle while using heroin. Stable signifies that the patient maintains productivity and that he is not engaged in street crime despite major individual and relational impairment. ** So called “revolving door stage”. The patient underwent a series of relapses and repeatedly failed to maintain abstinence.				
a,b,c,d,e,f,g = p<0.05				

protective effect of an older age with respect to relapse during methadone treatment [27, 52]:

Constructive family relationships, employment and a satisfactory income level are positive predictors for our sample, in agreement with what has been reported by other authors for global adjustment [14], family ties [23], parental role [39] and income levels [25]. The favourable effect of family ties is not specific for methadone treatment, but of any treatment, including buprenorphine [12] and no-agonist drugs [34]. Literature data also indicate that criminality is a negative predictor of retention in methadone maintenance programs [27]: otherwise, we found no similar relationships.

Some authors have reported no influence of social variables upon the outcome of methadone treatment [46] and therefore is not a valid baseline predictor for matching patients to either naltrexone- or / and methadone-based treatment options [35].

#### 4.2 Clinical features

In an univariate view, a number of clinical features also influence the likelihood of relapse.

Substance use, especially within a social network has a substantial negative impact on treatment outcome [15]. Baseline cocaine and alcohol use were reported as negative prognostic factors [11, 41], the latter for subjects entering buprenorphine-maintenance programs [40].

In our sample, benzodiazepine use is the only substance-use status bearing a negative influence on relapse. Baseline consumption of alcohol, stimulants, cannab-

inoids, amphetamines, inhalant and hallucinogenic drugs had no significant impact. A similar finding was reported for cannabinoids in a previous study. [9].

Relapse is less likely for addicts, who maintain some level of social adjustment and working capacity (so called “stables”) and those in an early stage, i.e. without a history of several treatment failures. A lower age of first heroin use (>17 years old) and a later onset of addiction (>20 years old) are also negative predictors of relapse during treatment. Such data probably indicate that higher grades of disease severity increases the rate of treatment resistance.

Stress levels may favour relapse [18]. On the other hand, higher psychological distress levels at baseline (as indicated by lower SF12 global mental health Score) are predictive of continuous abstinence from heroin [6]. In our study a history of heroin without either a stress-buffering dynamic or a self-medication mechanism is positively linked with the likelihood of relapse.

Being in treatment for a longer time, especially if over three years, has a positive prognostic value, this agrees with other literature reports [47, 48]. The importance of higher dosages to optimize retention in treatment is also documented [26, 30]. As regarding the time to achieve a stabilization phase and the impact of previous treatment in an Italian “therapeutic community” little data is available.

The role of dual diagnosis as a prognostic factor is still controversial. Older studies link dual diagnosis with poorer outcomes in methadone maintenance programs [3, 32]. Otherwise, later studies refute such impressions [13, 14, 17, 38]. The present study finds a positive

Table 3. Most important predictors of non relapsing in 129 methadone maintained heroin addicts.			
Predictors	Odds ratio	Min	Max
Dual Diagnosis	2.01	1.46	2.56
Psychiatric symptoms (stressors) before heroin (ab)use	0.49	-0.14	1.12
Time spent in treatment			
<1year vs >3 years	5.55	4.73	6.37
1-2 vs >3 years	3.56	2.58	4.54
2-3 vs >3 years	0.55	-0.63	1.73
Statistic: chi square 74.80 df 25 p<0.001			

impact of dual diagnosis upon the risk of relapse. A robust finding from our multivariate analysis, shows dual diagnosis as a predictor of relapse-free survival in treatment, coming just second to time spent in treatment in importance. In order to avoid dual diagnosis overrating, our definition is limited to patients who had been clearly mentally ill in times before the onset of habitual heroin use. Thus, in a high threshold methadone maintenance treatment program, as that considered in this work, autonomous, primary psychiatric comorbidity is the best clinical predictor of long-term treatment retention (6 years of observation on average). Such a finding is not easy to interpret, indeed. The better therapeutic response of dual diagnosis heroin addicts may be due, beyond the use of higher methadone dosages, to the concurrent employment of psychotropic treatment regimens. However, it may also be hypothesized that higher-dose methadone maintenance itself exerts a therapeutic action upon autonomous mental disorders, as is reported in the literature for a variety of psychopathological symptoms [8, 10, 16, 33, 53]. Since patients had started suffering from mental disturbances previous to engaging into regular heroin use, the therapeutic action of methadone maintenance may mirror self-medicating dynamics originally leading to addiction [21, 22, 55].

## 5. Limitations

We have arrived at an interesting conclusion that to many may seem paradoxical, that is that subjects with certain co-morbid psychiatric conditions (Psychotic, Depressive, Bipolar Spectrum and Anxiety Disorders) tend to respond better to MMT than those without evidence of these disorders prior to consistent heroin abuse. One would expect such patients to at least in some global sense to be "sicker"; that in itself would lead most to predict for a negative and not a positive outcome in this group. Unfortunately we did not ascertain the effect of MMT on all psychiatric disorders. We particularly regret not assessing subjects for DSM IV Cluster B personality Disorders (Particularly Sociopathic and Borderline Personality Disorder.) One might expect that the dually diagnosed patients to have received more care in general, yet this was not the case. Strangely our dually diagnosed patients required less psychoactive medications while in treatment with methadone, as we already have observed in another previous study [36]. Although our main hypothesis as to why this may be is that methadone itself has a positive effect on the above mentioned psychiatric illnesses, our study was not designed to specifically give a definite answer to this conjecture. One can generate many hypotheses which should be the substrate for further research. We also feel that the structure imposed by the study may

be beneficial in itself to those of whom without it may have poorer aspects of social integration (because of their Psychiatric Disorders). In short, for them active participation forms a significant portion of a rehabilitative process.

## 5. Conclusions

In a high threshold methadone maintenance treatment program, the presence of dual diagnoses, as defined as psychiatric comorbidity preceding the onset of regular heroin use, is the best predictor of relapse-free survival in treatment for as long as six year's average observation period, regardless of other sociodemographic and clinical features. Such a finding is limited to patients who stay in treatment for at least one year.

## Role of funding source

This study was supported by internal funds.

## Contributors

The authors contributed equally to this work.

## Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present study.

## References

1. BALL J. C., LANGE W. R., MYERS C. P., FRIEDMAN S. R. (1988): Reducing the risk of AIDS through methadone maintenance treatment. *J Health Soc Behavior.* 29 214-226.
2. BALL J. C., ROSS C. A. (1991): The Effectiveness of Methadone Maintenance Treatment. Springer-Verlag, New York.
3. CACCIOLA S. J., ALTERMAN A. I., RUTHERFORD M. J., MCKAY J. R., MULVANEY F. D. (2001): The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. *Drug Alcohol Depend.* 61 271-280.
4. CONDELLI W. S. (1993): Strategies for increasing retention in methadone programs. *J Psychoactive Drugs.* 25 143-147.
5. COOPER J. R. (1989): Methadone treatment and acquired immuno-deficiency syndrome. *JAMA.* 262 1664-1668.
6. DARKE S., ROSS J., MILLS K. L., WILLIAMSON A., HAVARD A., TEESSON M. (2007): Patterns of sustained heroin abstinence amongst long-term, dependent heroin users: 36 months findings from the Australian Treatment Outcome Study (ATOS). *Addict Behav.* 32:(9) 1897-1906.
7. DOLE V. P., NYSWANDER M. E., DE JERLAIS D., JOSEPH H. (1982): Sounding board: Performance-

- based rating of methadone maintenance programs. *N Engl J Med.* 306 169-172.
8. EMRICH H. M., VOGT P., HERZ A. (1982): Possible antidepressive effects of opioids: action of buprenorphine. *Ann N Y Acad Sci.* 398 108-112.
  9. EPSTEIN D. H., PRESTON K. L. (2003): Does cannabis use predict poor outcome for heroin-dependent patients on maintenance treatment? Past findings and more evidence against. *Addiction.* 98:(3) 269-279.
  10. EXTEIN I., POTTASH A. L. C., GOLD M. S. (1982): A possible opioid receptor dysfunction in some depressive disorders. *Ann N Y Acad Sci.* 398 113-119.
  11. FARLEY T. A., CARTTER M. L., WASSELL J. T., HADLER J. L. (1994): Predictors of outcome in methadone programs: effect of HIV counseling and testing. *Conn Med.* 58:(3) 165-171.
  12. GASQUET I., LANCON C., PARQUET P. (1999): Predictive factors for patient maintenance on buprenorphine high dosage treatment: a naturalistic study in primary care. *Encephale.* 25:(6) 645-651.
  13. GELKOPF M., WEIZMAN T., MELAMED Y., ADELSON M., BLEICH A. (2006): Does psychiatric comorbidity affect drug abuse treatment outcome? A prospective assessment of drug abuse, treatment tenure and infectious diseases in an Israeli methadone maintenance clinic. *Isr J Psychiatry Relat Sci.* 43:(2) 126-136.
  14. GERRA G., BORELLA F., ZAIMOVIC A., MOI G., BUSSANDRI M., BUBICI C., BERTACCA S. (2004): Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. *Drug Alcohol Depend.* 75:(1) 37-45.
  15. GOEHL L., NUNES E., QUITKIN F., HILTONI. (1993): Social networks and methadone treatment outcome: the costs and benefits of social ties. *Am J Drug Alcohol Abuse.* 19:(3) 251-262.
  16. GOLD M. S., POTTASH A. L. C., SWEENEY D. R., MARTIN D., EXTEIN I. (1982): Antimanic, antidepressant, and antipanic effects of opiate: clinical, neuro-anatomical, and biochemical evidence. *Ann N Y Acad Sci.* 398 140-150.
  17. GOSSOP M., MARSDEN J., STEWART D. (2006): Remission of psychiatric symptoms among drug misusers after drug dependence treatment. *J Nerv Ment Dis.* 194:(11) 826-832.
  18. HIEN D. A., NUNES E., LEVIN F. R., FRASER D. (2000): Posttraumatic stress disorder and short-term outcome in early methadone treatment. *J Subst Abuse Treat.* 19:(1) 31-37.
  19. HSER Y. I., ANGLIN M. D., FLETCHER B. (1998): Comparative treatment effectiveness. Effects of program modality and client drug dependence history on drug use reduction. *J Subst Abuse Treat.* 15:(6) 513-523.
  20. HUBBARD R. L., MARSDEN M. E., RACHAL J. V., HARWOOD H. J., CAVANAUGH E. R., GINZBURG H. M. (1989): Drug abuse treatment: A national study of effectiveness. The University of North Carolina, Chapel Hill.
  21. KHANTZIAN E. J. (1980): An ego/self theory of substance dependence: a contemporary psychoanalytic perspective. *Nida Res Monogr.* 30 184-191.
  22. KHANTZIAN E. J. (1982): Psychological (structural) Vulnerabilities and the Specific Appeal of Narcotics. *Ann N Y Acad Sci.* 398 24-32.
  23. KIDORF M., KING V. L., NEUFELD K., STOLLER K. B., PEIRCE J., BROONER R. K. (2005): Involving significant others in the care of opioid-dependent patients receiving methadone. *J Subst Abuse Treat.* 29:(1) 19-27.
  24. KOSTEN T. R., ROUNSAVILLE B. J., KLEBER H. D. (1986): A 2.5 year follow-up of depression, life crises, and treatment effects on abstinence among opioid addicts. *Arch Gen Psychiatry.* 43 733-738.
  25. KOSTEN T. R., ROUNSAVILLE B. J., KLEBER H. D. (1987): Predictors of 2.5-year outcome in opioid addicts: pretreatment source of income. *Am J Drug Alcohol Abuse.* 13:(1-2) 19-32.
  26. LEAVITT S. B., SHINDERMAN M., MAXWELL S., EAP C. B., PARIS P. (2000): When "enough" is not enough: new perspectives on optimal methadone maintenance dose. *Mt Sinai J Med.* 67:(5-6) 404-411.
  27. MAGURA S., NWAKEZE P. C., DEMSKY S. Y. (1998): Pre- and in-treatment predictors of retention in methadone treatment using survival analysis. *Addiction.* 93:(1) 51-60.
  28. MAGURAS., NWAKEZE P. C., KANG S. Y., DEMSKY S. (1999): Program quality effects on patients outcomes during methadone maintenance: a study of 17 clinics. *J Subst Use Misuse.* 34:(9) 1299-1324.
  29. MAREMMANI I., CASTROGIOVANNI P. (1989): DAH-RS: Drug Addiction History Rating Scale. University Press, Pisa.
  30. MAREMMANI I., PACINI M., LUBRANO S., LOVRECIC M. (2003): When 'enough' is still not 'enough'. Effectiveness of high-dose methadone in the treatment of heroin addiction. *Heroin Addict Relat Clin Probl.* 5:(1) 17-32.
  31. MAREMMANI I., ZOLESI O., AGLIETTI M., MARINI G., TAGLIAMONTE A., SHINDERMAN M. S., MAXWELL S. (2000): Methadone Dose and Retention in Treatment of Heroin Addicts with Axis I Psychiatric Comorbidity. *J Addict Dis.* 19:(2) 29-41.
  32. MASON B. J., KOCSIS J. H., MELIA D., KHURI E. T., SWEENEY J., WELLS A., BORG L., MILLMAN R. B., KREEK M. J. (1998): Psychiatric comorbidity in methadone maintained patients. *J Addict Dis.* 17:(3) 75-89.
  33. MCKENNA G. J. (1982): Methadone and opiate drugs: psychotropic effects and self medication. *Ann N Y Acad Sci.* 398 44-55.
  34. MCLELLAN A. T., ALTERMAN A. I., METZGER D. S., GRISSOM G. R., WOODY G. E., LUBORSKY L., O'BRIEN C. P. (1994): Similarity of outcome predictors across opiate, cocaine, and alcohol treatments: role of treatment services. *J Consult Clin Psychol.* 62:(6) 1141-1158.
  35. OSBORN E., GREY C., REZNIKOFF M. (1986): Psychosocial adjustment, modality choice, and outcome in naltrexone versus methadone treatment. *Am J Drug Alcohol Abuse.* 12:(4) 383-388.
  36. PACINI M., MAREMMANI I. (2005): Methadone reduces the need for antipsychotic and antimanic agents

- in heroin addicts hospitalized for manic and/or acute psychotic episodes. *Heroin Addict Relat Clin Probl.* 7:(4) 43-48.
37. PANI P. P., PIRASTU R., RICCI A., GESSA G. L. (1996): Prohibition of take-home dosages: negative consequences on methadone maintenance treatment. *Drug Alcohol Depend.* 41 81-84.
  38. PANI P. P., TROGU E., CONTU P., AGUS A., GESSA G. L. (1997): Psychiatric severity and treatment response in a comprehensive methadone maintenance treatment program. *Drug Alcohol Depend.* 48 119-126.
  39. PELES E., SCHREIBER S., ADELSON M. (2006): Factors predicting retention in treatment: 10-year experience of a methadone maintenance treatment (MMT) clinic in Israel. *Drug Alcohol Depend.* 82:(3) 211-217.
  40. POIRIER M. F., LAQUEILLE X., JALFRE V., WILLARD D., BOURDEL M. C., FERMANIAN J., OLIE J. P. (2004): Clinical profile of responders to buprenorphine as a substitution treatment in heroin addicts: results of a multicenter study of 73 patients. *Prog Neuropsychopharmacol Biol Psychiatry.* 28:(2) 267-272.
  41. PRESTON K. L., SILVERMAN K., HIGGINS S. T., BROONER R. K., MONTOYA I., SCHUSTER C. R., CONE E. J. (1998): Cocaine use early in treatment predicts outcome in a behavioral treatment program. *J Consult Clin Psychol.* 66:(4) 691-696.
  42. ROUNSAVILLE B. J., KOSTEN T. R., KLEBER H. D. (1986): Long-term changes in current psychiatric diagnoses of treated opiate addicts. *Compr Psychiatry.* 27 480-498.
  43. ROUNSAVILLE B. J., KOSTEN T. R., WEISSMAN M. M., KLEBER H. D. (1986): Prognostic significance of psychopathology in treated opioid addicts: a 2.5-year follow-up study. *Arch Gen Psychiatry.* 43 379-345.
  44. ROUNSAVILLE B. J., TIERNEY T., CRITS-CHRISTOPH K., WEISSMAN M. M., KLEBER H. B. (1982): Predictors of outcome in treatment of opiate addicts: Evidence for the multidimensional nature of addicts' problems. *Compr Psychiatry.* 23 462-478.
  45. ROUNSAVILLE B. J., WEISSMAN M. M., CRITS-CHRISTOPH K., WILBER C., KLEBER H. (1982): Diagnosis and symptoms of depression in opiate addicts. Course and relationship to treatment outcome. *Arch Gen Psychiatry.* 39:(2) 151-156.
  46. RUTHERFORD M. J., CACCIOLAJ S., ALTERMAN A. I., COOK T. G. (1997): Social competence in opiate-addicted individuals: gender differences, relationship to psychiatric diagnoses, and treatment response. *Addict Behav.* 22:(3) 419-425.
  47. SIMPSON D. D. (1979): The relation of time spent in drug abuse treatment to posttreatment outcome. *Am J Psychiatry.* 136:(11) 1449-1453.
  48. SIMPSON D. D. (1981): Treatment for drug abuse. Follow-up outcomes and length of time spent. *Arch Gen Psychiatry.* 38:(8) 875-880.
  49. SIMPSON D. D., JOE G. W., ROWAN-SZAL G. A. (1997): Drug abuse treatment retention and process effects on follow-up outcomes. *Drug Alcohol Depend.* 47:(3) 227-235.
  50. STRAIN E. C., STITZER M. L., LIEBSON I. A., BIGELOW G. E. (1993): Dose-response effects of methadone in the treatment of opioid dependence. *Ann Intern Med.* 119:(1) 23-27.
  51. STRAIN E. C., STITZER M. L., LIEBSON I. A., BIGELOW G. E. (1993): Methadone dose and treatment outcome. *Drug Alcohol Depend.* 33:(2) 105-117.
  52. TORRENS M., CASTILLO C., PEREZ-SOLA V. (1996): Retention in a low-threshold methadone maintenance program. *Drug Alcohol Depend.* 41:(1) 55-59.
  53. VEREBEY K. E. (1982): Opioids in mental illness: theories, clinical observations and treatment possibilities. *Ann N Y Acad Sci.* 398.
  54. VILLAFRANCAS W., MCKELLAR J. D., TRAFTON J. A., HUMPHREYS K. (2006): Predictor of retention in methadone programs: A signal detection analysis. *Drug Alcohol Depend.* 83 218-224.
  55. WURMSER L. (1974): Psychoanalytic considerations of the etiology of compulsive drug use. *J Am Psychoanal Assoc.* 22:(4) 820-843.

Received January 15, 2008 - Accepted May 1, 2008



Pacini Editore & AU CNS

**HEROIN ADDICTION &  
RELATED CLINICAL  
PROBLEMS**

www.europad.org

Regular article

Heroin Addict Relat Clin Probl 2008; 10(4): 29-32

# Unintentional and Intentional Injuries Due to Opiate Abuse

Marlene Stenbacka

*Stockholm Dependency Centre*

*Karolinska Institute, Department of Public Health Sciences, Stockholm, Sweden, EU*

## *Summary*

Alcohol and drug abuse runs a generally higher risk of fatal and non-fatal injury risk. But the overall injury pattern in relation to opiate abuse is not well known. *Aim.* The aim of the study is to analyse intentional and unintentional injuries –in the forms of accidents and suicides, as reported in the case histories of opiate abusers compared to the general population in Stockholm. *Method:* The analyses are based on a cohort of 1700 drug abusers identified in 1967 and followed until 2003 and 2005 with respect to causes of death, and inpatient care stays. *Results:* The results show that 817 (48%) subjects took opiate as their primary drug and nearly one third of these had died due to an intentional or an unintentional injury. Nearly 60 percent of the opiate abusers had been treated, at least once, in hospital for an injury. On average, the total cohort had been treated in hospital for an injury 1.6 times (range, 0-40 times), while the opiate abusers who had been treated in hospital for a drug-related diagnosis at least once had, on average, also been treated for an injury diagnosis 2.8 times (0-20 times) during the follow-up period. *Conclusion:* Societal support and injury prevention need to be improved in this vulnerable group.

*Key Words:* Drug Addiction; Opioid Dependence; Injury Risk.

## 1. Introduction

There is evidence that opiate abusers are at higher risk for mortality compared to the general population. Tunving [8] studied 524 young drug addicts treated at hospital and followed these by keeping registers for about 10 years. A total of 62 were found to have died of drug-related deaths at an average age of 28 years; 19 of them had committed suicide: male opiate addicts died 5.4 times, as often as expected. The males were exposed to greater risk than the females. A critical period seems to be at 26-28 years of age, a period when abuse of this type seems to take its most compulsive form.

Studies on opiate abusers in maintenance treatment have shown a higher mortality rate for those outside treatment than for those in treatment [2, 7]. That was

also shown in a 15-year follow-up study of 188 people with a history of intravenous opiate abuse. Of these, 32% had died during the entire follow-up period [1]. Stable abstinence from opiate abuse is associated with a lower risk of premature death than in patients who continue to use drugs [1]. In a 33-year follow-up study of 581 male heroin addicts admitted to the California Civil Addict Program (CAP) during the years 1962-1964, nearly one third had died during the follow-up period. Nearly 20 percent of the deceased had died because of homicide, suicide or an unintentional accident [4].

Many studies on mortality among drug abusers have focused on opiate abusers in clinical settings. Few studies, by contrast, have focused on a more general cohort of registered opiate abusers. In this study we were able to follow a cohort of opiate abusers in relation to mor-

tality and morbidity over a 37-year follow-up period. Opiate abuse in combination with central stimulants or alcohol was studied, too.

## 2. Aims

The main aim of the study was to analyse unintentional and intentional injuries in two large cohorts of male and female opiate abusers longitudinally.

## 3. Material and Methods

### 3.1 The Case-finding Study

This study is based on two data sets: (1) A case-finding study of drug users in Stockholm in 1967 [8]. The reporting sources were hospitals, prisons, the social welfare committee, psychiatric hospitals and units and other hospitals, penal services, the police, temperance committees, schools, an injection mark survey at a prison in Stockholm, and others. Altogether, 1,949 cases with drug use were identified, of which 98% were Swedish citizens. Of these, 1,616 were intravenous drug users.

In this study, we included 1,705 drug users (1,288 men and 417 women) who had no missing values on personal identifications or other important variables. Three hundred and seventy-four (287 men and 87 women) had only used opiates (Op). Four hundred and forty-three (360 men and 83 women) had used both opiates and central stimulants (Op+Cs) and 89 patients opiates and alcohol (Op+Alc). In all, 477 of the opiate users had died during the follow-up period.

### 3.2 Conscription study

(2) We also analysed data from the 'conscription study', which included about 50,000 18-year-old young men conscripted for military service in 1969-70 in the whole of Sweden. The study has been described in detail elsewhere [6].

The questions on drug use were: "Have you ever tried drugs without the doctor's prescription?" (yes/no); "Which drugs have you used most frequently?" (cannabis, central stimulants, opiates and others); "Have you also tried the following drugs?" (cannabis, central stimulants, opiates and others); "Have you ever used intravenous drugs?" (yes, once, several times /no).

### 3.3 Follow-up

The Case-finding Study implemented follow-up in terms of mortality and cause of death, starting in 1997; these patients had been identified in the Case-finding Survey up to Dec 2003, or their date of death was

recorded. Data about cause of death were linked with the study cohort after permission from the Karolinska Ethical Committee. The conscription study was followed up in terms of mortality, causes of death, and inpatient care up to 2005.

All cases were linked with the national cause-of-death register to determine the date and cause of death, using the national registration number. The Cause of Death Register in Sweden covers all cases of death throughout Sweden. The cause-of-death register is based on death certificates. Deaths were classified into different groups according to the "Classification of Causes of Death in Swedish Statistics", which is compiled from the International Classification of Diseases, Injuries, and Causes of Death (ICD). ICD-8 was used for the period 1967-1986, ICD-9 was used for 1987-1996, and ICD-10 was used for 1997 onwards. On each certificate there is one underlying cause of death and it is possible to add contributing causes. For patients who die in hospital, the death certificate is made by the physician in charge, and for deaths not occurring in hospital, the physician in charge of the patient certifies the cause of death. When the cause of death is unclear, an autopsy is performed. In undetermined deaths, there is always a forensic autopsy. If an autopsy is performed, the death certificate is considered preliminary until the information gathered from the autopsy is included, too. From 1973 to 1995, the frequency of autopsy for natural causes of death was 86% in those aged 15 to 49 years, 68% in those aged 50 to 69 years, and 45% in those who were 70 or over, but the autopsy frequency then declined. For unnatural causes of death, the autopsy frequency was 90% in those aged 15 to 49 years, 88% in those aged 50 to 69 years, and 53% in those who were 70 years or over. The cause-of-death register covers more than 99% of all deaths occurring in Sweden (Statistics Sweden [Federal Agency for National Statistics], 1998).

### 3.4 Statistical Analyses

The Standard Mortality Ratio (SMR) was calculated as the observed number of deaths divided by the expected number of deaths, with 95% confidence intervals. The cohort was standardized according to age and gender. We were, however, unable to standardize the female Op+Alc users according to gender because of the small size of this sample.

## 4. Results

In all three categories of opiate abuse (opiate abuse alone, opiate abuse + central stimulants, opiate abuse and alcohol) the female users were younger at baseline and this was especially true for those who had used opiates alone: 26.7 years for men and 22.1 years for

women. Age at death was about 47-49 years in all these three categories. Among opiate users, especially, the women were younger than the men, 41.7 vs. 49 years of age.

4.1 Causes of death

A high number of opiate abusers in all three categories (477 (58%) out of 817) had died during the follow-up period, 1967 to 2003. We found that nearly one third in each of the three categories had died of an alcohol-related diagnoses, and nearly one fifth of a drug-related diagnosis. Nearly 40% of the female and 30% of the male opiate users had died of an alcohol-related diagnosis.

When analyzing primary causes of deaths it was found that, irrespective of drug use, the most common cause of death was accidents (n=73), which mostly included transport accidents, homicide, injuries from falls. Forty-nine people had committed suicide (24 persons from intoxication, and 11 from smothering). Thirty-one had died of unclear suicide; of these, a majority, 21 (67.8%) had died of intoxication. A total of 64 (13%) people had died because of intoxication.

Table 1 shows causes of deaths in different age categories at death: 15-34, 35-54 and 55+. Irrespective of drug use (Op, Op+Cs and Op+Alc use), a common

cause of death among the youngest (15-34 years) was accidents (41%), followed by suicide (18%).

A higher percentage of women than men died because of suicide; while death because of an accident was more frequent among men (16% vs 12%).

Those who had been treated or died of an opiate-related diagnosis had much higher percentages, especially for (any) accident, and for suicide (not shown in any table). Table 2 shows that death because of accidents was evident for 15% of the total opiate group followed by suicide (10%) and undetermined suicide (7%).

At conscription, 5,494 (about 11%) had tried at least one kind of drug, 3,320 (6%) cannabis, 674 (1%) central stimulants, and 984 (2%) any opiate. One hundred and seventy-two people had been treated or died during the follow-up period because of an opiate-related diagnosis (not shown in table).

5. Discussion

The aim of the present study was to analyze unintentional and intentional injuries due to the abuse of opiates. We found a high mortality in the Case-finding Survey. Nearly 60% of the whole cohort had died during the long follow-up period.

An explanation for the high mortality in this cohort may be the limited number of places available in the

Table 1. Suicides and accidents among 477 deaths cases (392 men and 85 women) identified as opiate users in 1967, divided into men and women and different age categories. Follow-up 1967-2003

Causes	Opiates			OP+CS			OP+Alc *)		
	15-34 (n=39) %	35-54 (n=105) %	55+ (n=66) %	15-34 (n=48) %	35-54 (n=136) %	55+ (n=83) %	15-34 (n=9) %	35-54 (n=32) %	55+ (n=15) %
Unclear suicides	10 %	5 %	3 %	8 %	7 %	8 %	11 %	9 %	20.0
Suicide	18 %	12 %	3 %	21 %	12 %	1 %	33 %	16 %	-
Accidents	41 %	11 %	6 %	35 %	17 %	2 %	11 %	13 %	7 %

\*) This group is a part of the two other groups ( Op or Op+Cs.)

Table 2. Suicides and accidents among 477 deaths in different categories of opiate abusers Follow-up 1967-2003 . Numbers and percentages.

Causes of death	Total Opiate only (n=210)	Total Opiates + CS (n=267)	Total *) Opiates + Alcohol (n=56)	Total Opiate use only + OP+CS (n=477)
Undetermined suicides	11(5.2%)	20(7.5%)	7(12.5%)	31(6.5%)
Suicides	22(10.5%)	27(10.1%)	8(14.3%)	49(10.3%)
Accidents	31(14.8%)	42(15.7%)	6(10.7%)	73(15.3%)

\*) This group is a part of the other two groups (Op or Op+Cs.)

Swedish methadone programme [3]. It was not until 1988 that the methadone programmes started to expand, and the number of opiate abusers in maintenance treatment started to rise. In order to prevent an HIV-epidemic among intravenous drug abusers, and especially among intravenous opiate abusers, the Swedish National Board of Health and Welfare decided to increase the number of places available to patients.

The female opiate users died at a younger age (about 43 years) than their male counterparts (48 years).

Suicide and accidents were the most common cause of deaths in the youngest age category (15-34 years). A similar pattern was found in a 20-year follow-up study of 9,491 teenage addicts in relation to mortality in the United Kingdom: it was found that, of 301 deaths, 68.6% were due to an overdose or to accidental poisoning [5]. The most common causes of death among those aged 35-54 years were cirrhoses and circulatory diseases, accidents and suicide.

The causes of deaths were quite similar among men and women. However, death due to accidents was more common among men than women – 16% and 12%, respectively.

In the conscription survey, a close association was found between opiate abuse during the follow-up period, and accident and suicide, compared with conscripts with no use. One explanation for this strong association is that, as a rule, opiate abusers are burdened with other risk factors such as psychiatric problems, early behavioural risk factors and benefit from few protective factors.

## 6. Conclusion

In this study, opiate abuse has been shown to be associated with high mortality. The high incidence of suicides and accidents was especially evident among the youngest age category. These two causes of deaths could have been prevented. This knowledge could make an important contribution to the efforts being made to prevent opiate abuse in society.

## Role of funding source

This study was supported by Co-ordination of the Swedish Drug Policy (2003:45).

## Conflict of Interest

The author has no relevant conflict of interest to report in relation to the present study.

## References

1. DAVSTADI., STENBACKAM., LEIFMANA., BECK O., KORKMAZ S., ROMELSJO A. (2007): Patterns of illicit drug use and retention in a methadone program: a longitudinal study. *J Opioid Manag.* 3:(1) 27-34.
2. FUGELSTAD A., STENBACKA M., LEIFMAN A., NYLANDER M., THIBLIN I. (2007): Methadone maintenance treatment: the balance between life-saving treatment and fatal poisonings. *Addiction.* 102:(3) 406-412.
3. GRONBLADH L., OHLUND L. S., GUNNE L. M. (1990): Mortality in heroin addiction: impact of methadone treatment. *Acta Psychiatr Scand.* 82:(3) 223-227.
4. OSLER M., NORDENTOFT M., ANDERSEN A. M. (2006): Childhood social environment and risk of drug and alcohol abuse in a cohort of Danish men born in 1953. *Am J Epidemiol.* 163:(7) 654-661.
5. OYEFESOA., GHODSEH., CLANCYC., CORKERY J., GOLDFINCH R. (1999): Drug abuse-related mortality: a study of teenage addicts over a 20-year period. *Soc Psychiatry Psychiatr Epidemiol.* 34:(8) 437-441.
6. STENBACKA M. (2000): The role of competence factors in reducing the future risk of drug use among young Swedish men. *Addiction.* 95:(10) 1573-1581.
7. STENBACKA M., LEIFMAN A., ROMELSJO A. (1998): The impact of methadone on consumption of inpatient care and mortality, with special reference to HIV status. *Subst Use Misuse.* 33:(14) 2819-2834.
8. TUNVING K. (1988): Fatal outcome in drug addiction. *Acta Psychiatr Scand.* 77:(5) 551-566.

Received May 26, 2008 - Accepted October 20, 2008



Pacini Editore & AU CNS

## Scientific Evidence and Practical Experience with Methadone-Assisted Withdrawal of Heroin-Dependent Pregnant Patients

Hendree Jones

*Johns Hopkins University, School of Medicine,  
Department of Psychiatry and Behavioral Sciences, Baltimore, MD, USA*

### *Summary*

Opioid dependence during pregnancy is a complex multi-faceted medical challenge that, if untreated, places the mother and child at risk for life threatening consequences. While methadone maintenance is the accepted standard of care for opioid dependent patients who are pregnant, there are limited circumstances when this life saving medication may not be an immediate option. Thus, this paper first highlights the data supporting the current USA clinical guidelines regarding medication-assisted withdrawal during pregnancy in opioid-dependent patients. Next, the results of a retrospective study comparing the maternal and neonatal consequences of methadone-assisted withdrawal to methadone maintenance in pregnant opioid-dependent patients are summarized. Given the generally poorer maternal outcomes of the medication-assisted withdrawal patients, these data provide renewed and current support for methadone-maintenance as the first-line treatment approach for opioid-dependent pregnant women.

*Key Words:* Opioid Addiction; pregnancy; maternal outcomes; medication-assisted withdrawal; methadone treatment

Opioid dependence during pregnancy represents both a complex medical challenge and an opportunity for the patient to initiate life fulfilling improvements. Two modalities of treatment are commonly used in the United States for approaching the treatment of pregnant opioid addicted patients: the use of agonist therapy (e.g., methadone) and the use of medically-assisted withdrawal followed by an intense psychosocial treatment. The term medication-assisted withdrawal will be used through out this paper and is defined as the use of a therapeutic medication, methadone, to take a patient from an opioid-dependent state to a medication-free state. Medication-assisted withdrawal is also known as medically-assisted withdrawal or medication-supervised withdrawal. In contrast, tapering, for this paper, is defined as a slow methadone dose decrease following

a period of methadone stabilization. The term that will not be used in this paper is detoxification. This term is avoided for several reasons. First, detoxification can be a stigmatizing term since it can be defined as the removal of a toxic substance from the body. Clearly, in the case of decreasing the dose of methadone over time in methadone stabilized patients, this life-saving medication should not be viewed as a toxin. Second, detoxification can also be defined as a biological process in which the liver employs enzyme pathways to reduce the toxicity of compounds making them easier for the body to excrete. As the focus of this paper is on patients entering treatment to overcome their dependence on heroin, methadone-assisted withdrawal will be the most frequent term employed.

For opioid-dependent pregnant patients, the ad-

vantages of methadone maintenance, the standard of treatment, over no treatment or medication-assisted withdrawal followed by medication-free treatment include: reductions in maternal non-prescribed opioid use and subsequent fetal exposure, enhanced compliance with obstetrical care, and enhanced neonatal outcomes (i.e., heavier birth weight [13]). Although medication-assisted withdrawal is clearly less optimal than methadone maintenance, there are occasions when monitored withdrawal may be medically indicated [14]. These situations include refusal of any treatment unless the patient is free of medication by the time of delivery, [17] or the inability to receive agonist maintenance in her community (due to long waiting lists for treatment or the lack of a clinic) or receipt of a medical treatment for which methadone is a contraindication. If medication-assisted withdrawal is initiated, further treatment is imperative for maintaining and sustaining abstinence from illicit opioids [3].

Current recommendations in the USA for medication-assisted withdrawal are based on descriptive data and case studies [1, 18, 20] as well as on sound clinical experience and judgment. These recommendations include withdrawing patients between 14 and 32 weeks gestation in order to reduce the risks of miscarriage, withdrawal-induced fetal stress and premature labor, respectively [6]. If medication-assisted withdrawal is unavoidable in the third trimester, weekly non-stress testing is recommended to monitor fetal well-being [10]. Specific methadone dosing recommendations range from reducing the dose 2 mg to 2.5 mg every 7-10 days [2, 3] or 5 mg every two weeks [6]. More rapid inpatient or outpatient withdrawal schedules have recommended a reduction of 2-2.5 mg each day or > 10 mg/week, respectively [6, 11].

Although more recent reports with larger sample sizes have reported that rates of spontaneous abortion and premature delivery in this population were similar to rates found in the general population, these results should be interpreted with caution as they are based on quite small sample sizes [15, 16]. The most striking conclusion from these studies is that the opioid use relapse rates are (41%-96%) quite high in these women, [15, 16] especially compared to the relapse rate of 13% reported in a pregnant population who were adequately maintained on methadone [9]. Not surprisingly, this high rate of opioid relapse is similar to that of a general patient population at one month (65-80%) [4, 7] and six months (over 90%) following medication-assisted withdrawal [19].

Given the gaps in the literature including the lack of a systematic comparison between medication-assisted withdrawal to a methadone maintenance control group, this retrospective chart review attempted to address three questions. Firstly, does methadone maintenance

provide better maternal treatment and neonatal outcomes compared to methadone-assisted withdrawal? Secondly, do maternal and neonatal outcome differences exist between groups receiving methadone maintenance and groups first receiving methadone-assisted withdrawal and subsequently transferred to methadone maintenance? Thirdly, is the length of methadone-assisted withdrawal related to maternal or neonatal outcome? Answers to these questions may provide additional evidence to treatment providers and policy makers to determine the best treatment approaches for pregnant opioid-dependent patients.

This retrospective record review was conducted using the patients at the Center for Addiction and Pregnancy (CAP), a comprehensive care setting for pregnant drug addicted patients in Baltimore, Maryland. The full methods and complete results have been published [12]. All data were abstracted from the respective maternal and neonatal hospital charts of the patients. This study was approved by the Johns Hopkins School of Medicine Institutional Review Board.

For the medication-assisted withdrawal sample, patients were selected from one of two regimens: A three day methadone-assisted withdrawal consisting in providing methadone 20 mg, 10 mg, and 10 mg on days 1-3, respectively, or a 7-day methadone-assisted withdrawal that began with methadone 40 mg (all patients received 30 mg and an additional 10 mg was available on the first day), 30 mg, 25 mg, 20 mg, 15 mg, 10 mg and 5 mg per consecutive day from days 1-7, respectively. These patients were then compared to medication-maintenance sample who received 30 mg (with an additional 10 mg available on the first day), 40 mg, 50 mg and 60 mg per consecutive day from days 1-4, respectively. Additional increases in 5 mg or 10 mg doses were provided based upon clinical indication. Both methadone stabilization, and withdrawal were completed on the residential unit of the CAP.

For this paper two primary outcome measures were presented: 1) number of days in CAP treatment; and the 2) number of obstetrical visits. The secondary measures presented for the mother included maternal urine toxicology at delivery (tested positive for opioids, cocaine, barbiturates and/or benzodiazepines) and, for the three groups in methadone treatment, total daily prescribed methadone dose in milligrams at delivery. Secondary outcomes for the neonate, included head circumference and length in centimeters, weight in grams, Apgar 1 and 5 minute scores, number of days in the hospital, gestational age at delivery and whether or not the neonate was treated with medication for neonatal abstinence syndrome (NAS). The analytic approach to the data is available upon request to author, HE Jones.

As a whole, the total sample of 175 participants, at treatment entry were, on average, in their 20's, a

mean of 20.3 weeks pregnant, predominantly Black (86%), typically single, often with less than a high school education, only occasionally employed, generally legally unencumbered, frequently multiparous with an average of 1.3 previous substance addiction treatment episodes.

Since the treatment variables were primary interest in this study, and since some patients in both the 3 and 7-day methadone-assisted withdrawal regimens transferred to methadone maintenance later, it was necessary to compare five defined treatment groups: (1) patients prescribed a 3-day methadone-assisted withdrawal who received no additional methadone for the remainder of their pregnancy (3-day withdrawal-only) (n=67); (2) patients first prescribed a 3-day methadone-assisted withdrawal who were subsequently prescribed methadone-maintenance during their pregnancy (3-day withdrawal + maintenance) (n=8); (3) patients prescribed a 7-day methadone-assisted withdrawal who received no additional methadone for the remainder of their pregnancy (7-day withdrawal-only) (n=28); (4) patients first prescribed a 7-day methadone-assisted withdrawal who were subsequently prescribed methadone-maintenance during their pregnancy (7-day withdrawal + maintenance) (n=20); or, (5) Patients who were prescribed methadone-maintenance from treatment entry (maintenance) (n=52). The 3- and 7-day methadone-assisted withdrawal + methadone groups were included in the study, despite their relatively small sizes, in order to examine the effects that initial withdrawal and subsequent methadone maintenance may have on maternal and neonatal outcomes, a question which has not been previously examined in the literature. The maternal results are shown in table 1.

Three results are highlighted for maternal retention

in treatment. First, a comparison between the three methadone-maintained groups and the two medication-assisted withdrawal only group was significant,  $\chi^2(1) = 134.8, p < .0001, R^2 = .22$ . The comparison between the 3-day medication-assisted withdrawal only and the 7-day medication-assisted withdrawal only was likewise significant,  $\chi^2(1) = 14.8, p < .0001, R^2 = .02$ . In contrast, the three groups whose members at some point entered methadone treatment were not different from one another,  $\chi^2(2) = 2.8, p > .2$ .

The results for the number of obstetrical visits closely paralleled the results for number of days in CAP treatment, with the three methadone-maintained groups attending obstetrical clinic on 8.3 (SE = 1.3) occasions, on average, while the two medication-free groups averaged only 2.3 (SE = .4) obstetrical visits,  $\chi^2(1) = 84.6, p < .0001, R^2 = .17$ .

Although none of the three planned contrasts were significant (all ps > .09) for the maternal urine test results, all three methadone maintenance groups had lowest rates of illicit drug use detected at delivery of the five groups. The average doses of methadone received at delivery were similar across the three methadone maintenance groups.

No statistically significant differences were noted on the neonatal outcome measures of birth weight, APGAR scores, requiring medication to treat neonatal abstinence syndrome, length of hospital stay or estimated gestational age at delivery.

Taken together, these results support the ability of methadone to serve as a strong, positive reinforcer for facilitating treatment retention that can, in turn, lead to more comprehensive medical treatment, mental health, and social service care for patients thus creating an opportunity for improved health and well-being

Table 1. Effects of initial withdrawal and subsequent methadone maintenance on maternal outcomes

	3-day Methadone-assisted withdrawal	3-day Methadone-assisted withdrawal + maintenance	7-day Methadone-assisted withdrawal	7-day Methadone-assisted withdrawal + maintenance	Methadone maintenance
Measure	N=67	N=8	N=28	N=20	N=52
Mean methadone dose at delivery		58.1		54.8	61.9
Mean obstetrical visits	2	6	4	10	10
Mean days retained in treatment	14	104	30	95	122
n (%) urine toxicology tests positive for illicit drugs	53.0	33.3	57.14	15	23.1

of mothers, children and potentially families. It is also noteworthy that 41.6% of patients placed on 7-day methadone-assisted withdrawal were transferred to methadone-maintenance whereas only 10.6% of those patients receiving 3 days of methadone-assisted withdrawal subsequently received methadone-maintenance. Thus, the biggest benefit of a longer methadone-assisted withdrawal period may be the opportunity to help patients reconsider methadone treatment, the best approach for their illness.

Clearly, length of time retained in treatment has been reported to be associated with improved longer-term treatment outcomes including drug abstinence improved maternal child relationships and employment [5, 8]. The dramatically shorter treatment retention in the methadone-assisted withdrawal groups and the impressive length of retention in the methadone-maintained groups provide the first systematic comparison of these two treatment modalities and affirm the critical importance of placing opioid-dependent patients on methadone-maintenance as part of a comprehensive treatment program. These data also suggest that patients who at first demand medication-assisted withdrawal and are later stabilized on methadone can have optimal maternal and neonatal outcomes similar to the outcomes of those patients who are consistently maintained on methadone through out their pregnancy.

The fact that both methadone-assisted withdrawal groups had rates of greater than 50% positive illicit drug urine tests compared to 15-33% for the methadone-maintained groups further supports the need for methadone maintenance to assist in reducing drug use during pregnancy.

Although the initial birth outcomes did not show statistically significant differences between groups of interest, what remains unknown are the potential longer-term effects of the premature loss of patients to treatment and the impact this loss may have both on the mothers and their children. For example, patients lost to treatment during pregnancy rarely return to a pediatric clinic which provides immunizations, specialized care and developmental assessments and interventions. These patients may also miss out on other valuable aspects of comprehensive treatment. Finally, the lack of observed differences in the present planned comparison of methadone-maintenance versus methadone-assisted withdrawal may be due to a lack of statistical power to detect a relatively small effect size. It could be argued that because the differences in treatment outcome between methadone-maintenance and methadone-assisted withdrawal are small, research focused on examining the possibility of such differences is unnecessary. However, small effect sizes are not necessarily inconsequential, as small differences may reflect a profound, long-term impact that occurs

infrequently – such as seen in low birth weight.

The limitations of this study include the retrospective chart review design collected over many years and the modest and unequal sample sizes of the groups transferring to methadone following methadone-assisted withdrawal.

The current results suggest that, while all medication-assisted withdrawal can be conducted during any pregnancy trimester without significant obstetrical or fetal consequences, this is not in the best interest of the mother or child since, as a group, medication-free patients had poorer maternal outcomes than did methadone-maintained patients. These poorer maternal outcomes may place the mother-child dyad at risk for long-term negative consequences. Thus, methadone-maintenance should be strongly considered as the primary treatment approach for opioid-dependent pregnant women.

### Role of funding source

This research was supported by National Institute on Drug Abuse grant R01 DA-14979. Co-Investigators on full study, Kevin E. O'Grady, Debra Malfi and Michelle Tuten.

### Conflict of Interest

No conflicts of interest declared.

### References

1. BLINICK G., WALLACH R. C., JEREZ E. (1969): Pregnancy in narcotics addicts treated by medical withdrawal: The methadone detoxification program. *Am J Obstet Gynecol.* 105: 997-1003.
2. CENTER FOR SUBSTANCE ABUSE TREATMENT (1993): State methadone treatment guidelines. (Treatment Improvement Protocol Series, 1). US Department of Health and Human Services, Rockville, MD.
3. CENTER FOR SUBSTANCE ABUSE TREATMENT (2006): Detoxification and Substance Abuse Treatment. (Treatment Improvement Protocol Series 45). US Department of Health and Human Services, Rockville, MD.
4. CHUTUAPE M. A., JASINSKI D. R., FINGERHOOD M. I., STITZER M. L. (2001): One, three, and six month outcomes following brief inpatient opioid detoxification *Am J Drug Alcohol Abuse.* 27: 19-44.
5. DAHLGREN L., WILLANDER A. (1989): Are special treatment facilities for female alcoholics needed? A controlled 2-year follow-up from a specialized female unit (EWA) versus a mixed male/female treatment facility. *Alcohol Exp Clin Res.* 13: 399-405.
6. FINNEGAN L. P., WAPNER R. J. (1987): Drug use in

- 
- Pregnancy. In: NEIBYL J. R. (Ed.) *Narcotic Addiction in Pregnancy*. Lea and Febiger, Philadelphia.
7. GOSSOP M., GREEN L., PHILLIPS G., BRADLEY B. (1989): Lapse, relapse, and survival among opiate addicts immediately after treatment: A prospective follow-up study. *Br J Psychiatry*. 154: 348-353.
  8. GRELLA C. E., JOSHI V., HSER Y. I. (2000): Program variation in treatment outcomes among women in residential drug treatment. *Eval Rev*. 24: 364-383.
  9. JANSSON L., SVIKIS D. S., VELEZ M., JONES H. E. (2007): The Impact of managed care on drug-dependent pregnant and postpartum women and their children. *Substance Use Misuse*. 42: 1-14.
  10. JARVIS M. A. E., SCHNOLLS H. (1994): Methadone treatment during pregnancy. *J Psychoactive Drugs*. 26: 155-161.
  11. JARVIS M. A. E., SCHNOLLS H. (1995): Methadone maintenance and withdrawal in pregnant opioid addicts. In: CHIANG C. N., FINNEGAN L. P. (Eds.): *Medication development of the treatment of pregnant addicts and their infants NIDA Res Monogr 149*. US DHHS, Washington DC. pp. 58-77.
  12. JONES H.E., O'GRADY K.E., MALFID., TUTEN M. (2008): Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. *Am J Add*. 17: 372-386.
  13. KALTENBACH K., BERGHELLA V., FINNEGAN L. (1998): Opioid dependence during pregnancy: Effects and management. *Obstet Gynecol Clinics North Am*. 25: 139-151.
  14. KANDALL S. R., DOBERCZAK T. M., JANTUNEN M., STEIN J. (1999): The methadone-maintained pregnancy. *Clin Perinatol*. 26: 173-183.
  15. LUTY J., NIKOLAOU V., BEARN J. (2003): Is opiate detoxification unsafe in pregnancy? *J Subst Abuse Treat*. 24: 363-367.
  16. MAAS U., KATTNER E., WEINGART J., SCHAFER A., OBLADEN M. (1990): Infrequent neonatal opioid withdrawal following maternal methadone detoxification during pregnancy. *J Perinatal Med*. 18: 111-118.
  17. MARTIN J., PAYTE J., ZWEBEN J. E. (1991): Methadone maintenance treatment: a primer for physicians. *J Psychoactive Drugs*. 23: 165-176.
  18. REMENTERIA J. L., NUNAG N. N. (1973): Narcotic withdrawal in pregnancy: Stillbirth incidence with a case report. *Am J Obstet Gynecol*. 116: 1152-1156.
  19. SILSBY H., TENNANT F. S. J. (1974): Short-term, ambulatory detoxification of opiate addicts using methadone. *Int J Addict*. 9: 167-170.
  20. ZUSPAN F., P., GUMPEL J., A., MEJIA-ZELAYA A. (1975): Fetal stress from methadone withdrawal. *Am J Obstet Gynecol*. 122: 43.

Received June 16, 2008 - Accepted October 25, 2008



**Europad**

European Opiate Addiction Treatment Association

**FORUM**

## Pre-Conference Sessions

**Sunday, April 26, 2007**

**EUROPEAN OPIATE ADDICTION TREATMENT ASSOCIATION (EUROPAD) -  
HEROIN ADDICTION AND RELATED CLINICAL PROBLEMS**

**TIME: 1:00 PM - 5:00 PM**

**Chairmen: Icro Maremmani, MD**  
Pisa, Italy, EU

**Marc Reisinger, MD**  
Brussels, Belgium, EU

- 1:00 PM** *Efficacy of Opioid Agonist Therapy on Psychopathological Symptoms: Methadone vs Buprenorphine*  
Icro Maremmani (Pisa, Italy, EU)
- 1:20 PM** *Repressive Strategy Against Liberal Strategy in Treating Heroin Addicts in Russia*  
Vladimir Mendeleovich (Kazan, Russia)
- 1:40 PM** *Economic Evaluation of Interventions To Treat Opiate Dependence: A Review of the Evidence*  
Christopher M. Doran (Sydney, Australia)
- 2:00 PM** *The European Experience Delivering Buprenorphine and Methadone. Comparison Between France and Portugal (regulations, clinical experience, practice)*  
Pascal Courty (Clermont-Ferrand, France, EU), Luis Patricio (Lisbon, Portugal, EU) and Didier Touzeau (Paris, France, EU)
- 2:20 PM** *Foundamental Principles and Rules in Treating Heroin Addicts at "Fondation Phenix" in Geneve, Switzerland*  
Michel Bourquin and Jean-Marie Rossier (Geneve, Switzerland)
- 2:40 PM** *Screening and Treatment of Viral Hepatitis B and C in Inmates With and Without Opioid Agonist Therapy. Results of Four French National Surveys (2000-2005)*  
Andre-Jean Remy (Perpignan, France, EU)
- 3:00 PM** *What Treatment is Good Treatment? Clinician's Reflections on Patient Perspectives*  
Alexander Kantchelov, Tsvetana Stoykova, Orlin Todorov and Alexander Belchev (Sofia, Bulgaria, EU)
- 3:20 PM** *Heroin Addiction and Mortality*  
Barbara Lovrecic and Mercedes Lovrecic (Lubiana, Slovenia, EU)
- 3:40 PM** *Does a Specific Psychopathology of Heroin Addiction Exist?*  
Pier Paolo Pani (Cagliari, Italy, EU)
- 4:00 PM** *Treating Heroin Addicts in Jail*  
Andrej Kastelic (Lubiana, Slovenia, EU)
- 4:20 PM** *Opiates and Alcohol. Important Clinical Connections*  
Albrecht Ulmer (Stuttgart, Germany, EU)
- 4:40 PM** *Discussion*
- 5:00 PM** *End of Forum*

**In collaboration with EUROPAD-Italia and Italian Society of Addiction Medicine (SITD)**



Pacini Editore & AU CNS

## Opioid Therapy and Restoration of the Immune Function in Heroin-Addicted Patients

Lorenzo Somaini<sup>1</sup>, Cristina Giaroni<sup>2</sup> and Gilberto Gerra<sup>3</sup>

<sup>1</sup>Addiction Treatment Centre, Local Health Unit, ASL BI, Biella, Italy, EU

<sup>2</sup>Department of Clinical Medicine, Section of Experimental and Clinical Pharmacology,  
University of Insubria, Varese, Italy, EU

<sup>3</sup>Global Challenges Section, Human Security Branch, Division for Operations,  
United Nations Office on Drugs and Crime, Vienna

### Summary

There are several reports suggesting that opioid compounds may influence the immune response. Studies carried out in experimental animals and in humans have shown that both innate and acquired immunity are significantly affected by opioids. From a molecular viewpoint, opioids behave like cytokines, modulating the immune response by interacting with their receptors both in the central nervous system and in the periphery. One of the main features of opioid-mediated modulation of the immune function is the development of immunosuppression, which has been documented in injecting heroin abusers. Over the last few years, however, evidence has been provided to suggest that various opioid drugs may have distinctive effects on the immune function. Data obtained from animal studies have demonstrated, for instance, that long-acting opioids, such as methadone and buprenorphine, are devoid of any intrinsic immunosuppressive activity. In this connection, the hypothesis, which was first put forward some years ago, that the normalization of altered cellular immunity can, in injecting heroin abusers, be achieved through long-term methadone or buprenorphine treatment, has been positively re-evaluated in recent times. Our group has recently investigated the immune response in heroin-addicted patients currently under methadone or buprenorphine maintenance treatment, comparing them with untreated heroin addicts and healthy controls. In agreement with the data obtained by other groups, our study has provided evidence confirming the 'immunoprotective' effect of long-acting opioid drugs. From a pathophysiological viewpoint, the ability of opioids to modulate the immune function may have some bearing on the development of the infectious diseases that are often associated with drug abuse. The high percentage of infections among injecting drug users is partly related to injection methods and life-style practices, but it is now accepted that heroin-induced immunosuppression may contribute as a co-factor in the contraction of several microbial and viral infections, such as Hepatitis C virus (HCV) infection. Conversely, in view of the 'immunoprotective' action of some opioids, such as buprenorphine, it has now been proposed that the administration of these latter compounds may improve the outcome of chronic HCV virus infections.

*Key Words:* Opioid Therapy; Immune Function; Retention, Heroin Addicted Patients.

Opioid drugs are potent analgesic compounds, but they carry a potential risk of inducing several adverse effects, such as physical dependence, and, as has been recently suggested, of altering the immune function (1,2,3). One of the first demonstrations indicating that

activation of opioid receptors within the central nervous system was able to modulate the peripheral immune system was presented by Shavit and colleagues about ten years ago (4). Since then, several studies, carried out both in experimental animals and in humans, have

shown that innate and acquired immunity are both significantly affected by opioids (5,6,7). In particular, it is now widely acknowledged that drugs of abuse, such as morphine and heroin, have a significant negative effect on the immune system (2).

When considering the impact of opioids on the immune system, however, a distinction must be drawn between the physiological role exerted by endogenous opioids, such as beta-endorphine, met-enkephalin and dynorphine, and the effect of exogenous opioids, whether they are taken for therapeutic purposes, such as methadone and buprenorphine, or as drugs of abuse, such as heroin and morphine. The balance between T-helper 1 cells (Th1), which are linked with cellular immune responses and tissue injury, and T-helper 2 cells (Th2), which are responsible for humoral responses and allergy, is normally needed for a correct homeostasis of the immune system (8,9). Endogenous opioids seem to have a physiological role in modulating the Th1/Th2 balance, by reducing Th1 and enhancing Th2 representative cytokines. Exogenous opioids, on the other hand, seem to display various different modulatory profiles on the immune function, according to the drug considered. In this connection, evidence has been provided to show that, while morphine and heroin are liable to attenuate the immune response, long-acting opioids that are used in withdrawal treatment, such as methadone and buprenorphine, are devoid of any immunosuppressive activity. In experimental animals, morphine, but not buprenorphine, has been shown to induce alterations of immunological parameters, including, for instance, decreased natural killer (NK) cell cytolytic activity and blood lymphocyte proliferation responses to mitogen. In particular, the injection of morphine in the periaqueductal gray (PAG) rat, dose-dependently suppressed T cell proliferation induced by the mitogen agent, concanavalin A, and influenced splenic NK cell cytotoxic activity (10). However, the administration of buprenorphine in the same brain region was unable to influence either parameter. In the same way, morphine and buprenorphine appear to show different behaviours in their modulation of the macrophage function. So too, morphine, but not buprenorphine, negatively modulated nitric oxide and tumor necrosis factor alpha (TNF- $\alpha$ ) production, as well as the phagocytosis of *Candida albicans* (10).

The possible mechanism(s) of morphine-mediated immunosuppression may derive from the drug's ability to regulate the immune system either directly, by activating mu opioid receptors located on immune cells, or through an indirect central pathway, by activating mu opioid receptors in the central nervous system (CNS) (3). The significant fall in NK cell activity observed after administering morphine directly into the right lateral ventricle of the rat was blocked by the central

administration of the opioid antagonist, naltrexone, suggesting that the opioid agonist suppressed the NK cell function primarily through opioid receptors located in the CNS (11). In addition, the suppression of mitogen-induced whole blood lymphocyte proliferation in rats was demonstrated when morphine was present, but not in the case of its analogue, N-methyl-morphine, which does not readily cross the blood-brain barrier (11).

Another mechanism underlying the opioid-mediated modulation of the immune system is revealed by the ability of these compounds to influence immunocompetent cell production, as shown by the dose-dependent reduction of T- and B-lymphocyte, NK and monocyte/macrophage numbers observed in the presence of morphine (2).

Opioids may also influence the immune function through the activation of the descending pathways of the hypothalamus-pituitary axis (HPA) and the sympathetic nervous system (12). Activation of the HPA axis elicits the production of immunosuppressive glucocorticoids in the periphery, while activation of the sympathetic nervous system induces the release of epinephrine, norepinephrine and dopamine from the adrenal medulla, as well as from sympathetic nerve terminals innervating primary and secondary lymphoid organs (13-14). Norepinephrine and glucocorticoids both act as negative modulators of the immune function by acting on leukocytes. The ability of a centrally administered acute dose of morphine to inhibit lymphocyte proliferation, or otherwise NK cell activity, appears to be primarily mediated by the sympathetic nervous system, whereas a more prolonged exposure to opioids alters the immune system predominantly by activating the HPA axis.

A further variety of changes induced by chronic exposure to opioids have been observed in the human immune system by means of studies carried out in heroin addicts and in heroin withdrawal subjects. Gavitrpong and colleagues documented a decrease in the immune system function both of heroin addicts and of subjects undergoing a short period of heroin withdrawal (lasting between 15 to 21 days and 6 to 24 months). Longer withdrawal periods, lasting over two years, were, however, associated with a gradual return of some immunological parameters, such as the CD4/CD8 ratio and the absolute numbers of the NK cell count, to normal levels (15).

In agreement with the data obtained in experimental animals, clinical studies appear to indicate that not all opioid agonists share the same immunosuppressive properties (3). The hypothesis that significant abnormalities of cellular immunity in heroin abusers can be normalized by switching to a long-term methadone treatment was formulated many years ago (16,17). More recently, additional studies have been addressed to evaluating whether the strengthening of the immune

response observed with long-acting opioid drugs was dependent on the drug profile or, rather, on life-style changes associated with maintenance treatment. Randomized clinical trials have shown that both methadone and buprenorphine are able to activate the immune system, even when this had previously been inhibited in heroin-addicted individuals, by increasing cytokine concentrations (18,19). Accordingly, alterations in the production of various cytokines, such as those observed in heroin addicts, were partly or completely rectified in patients maintained on methadone (20). Recently, our group has investigated the immune system function in former heroin-addicted patients in maintenance therapy with methadone and buprenorphine for at least six months, by comparing them both with untreated heroin addicts who are still injecting heroin, and with healthy controls (21). The proliferation rate of peripheral blood monocytes induced by phytohemagglutinin in untreated heroin addicts was significantly lower than that observed in patients treated with methadone and buprenorphine. Besides this, alterations in the Th1/Th2 balance and reduced levels of IL-4, TNF- $\alpha$ , interferon- $\gamma$  were documented in untreated heroin-addicted subjects with respect to buprenorphine- and methadone-treated patients. A possible limitation of this kind of study is attributable to significant socio-demographic variations between different groups. In our study, however, no significant differences in terms of extent of heroin exposure, previous treatment programmes, employment status, highest school grade completed, quality of interpersonal relationships, marital status, legal problems and stressful events were found among the different groups studied. Thus, while the role of small changes in life-style cannot be excluded, they probably made only a minor contribution to the normalization of the immune system.

Similarly to what has been observed in preclinical studies, the neuroendocrine function may significantly change in individuals receiving short-acting opioid drugs on a chronic basis. Indeed, a significant alteration of the endogenous opioid system and stress responsiveness has been observed in heroin addicts (22,23,24). Treatment with long-acting opioids normalizes changes in the HPA axis induced by heroin abuse (25,26). The administration of buprenorphine is followed by the development of appropriate responses to both the adrenocorticotrophic hormone and cortisol, as well as by the normalization of HPA axis reactivity in response to experimental stress (27). These effects could play an additional role in the improvement of the altered immune function observed in heroin-addicted patients. A recent study was carried out in rats to evaluate the ability of buprenorphine to prevent the effects of experimental surgery on HPA activation, by the group of Paola Sacerdote. Surgical stress// is associated with increased

corticosterone levels, decreased NK cell activity and the enhancement of tumour metastasis. Among the various opioids studied, only buprenorphine was able to prevent neuroendocrine and immune system changes and lessen the increase in tumor metastasis induced by surgical stress (28).

From a pathophysiological viewpoint, the ability of heroin to induce immunosuppression may have some bearing on the higher rates of infectious diseases, such as hepatitis C and AIDS, that are observed in heroin addicts, although the high percentage of infections among injecting drug users is probably related to drug injection procedures and life-style practices (29,30). In this connection, one interesting issue is the relationship between the ability of long-acting opioids to restore the immune system, and the development of chronic hepatitis C virus infection. Hepatitis C virus is widely present among drug users. In this pathological condition cellular immune mechanisms, including the activation of T cell responses, take part in virus eradication in the liver, lymphatic organs and peripheral blood. Long-acting opioids seem to //improve/ ameliorate// the outcome of the viral infection, as suggested by the ability of methadone to significantly reduce the relapse rate in patients undergoing interferon and ribavirin treatment (31).

In conclusion, several different studies have confirmed that long-acting opioid drugs, such as methadone and buprenorphine, are able to progressively restore the immune function; this may partly depend on their ability to restore the HPA axis function. Alternatively, the ‘immunoprotective’ effect of both drugs may depend on a constant, and long-lasting activation of opioid receptors both in the central nervous system and on leukocytes. Further investigations are, however, needed to definitively assess the relationship between long-acting opioid drugs and the immune system, and to elucidate the brain-immune system communication pathways.

#### **Role of funding source**

This paper was supported by internal funds.

#### **Contributors**

The authors contributed equally to this work.

#### **Conflict of Interest**

The authors have no relevant conflict of interest to report in relation to the present paper.

## References

1. VALLEJOR., de LEON-CASASOLAO., BENJAMIN R. (2004): Opioid therapy and immunosuppression. *Am. J. Therapeut.* 11: 354-365.
2. SACERDOTE P., LIMIROLI E., GASPANI L. (2001) Experimental evidence for immunomodulatory effect of opioids. In H. Machelska and C. Stein Eds: *Immune Mechanism of Pain and Analgesia, advances in Experimental Medicine and Biology*. Kluwer Academic, New York 521, pp. 106-112.
3. SACERDOTE P. (2006): Opioids and the immune system. *Palliative Med.* 20: s9-s15.
4. SHAVIT Y., DEPAULIS A., MARTIN FC., TERMAN GW., PECHNICK RN., ZANE CJ., GALE RP., LIEBENSKIND JC. (1986): Involvement of brain opiate receptors in the immune-suppressive effect of morphine. *Prot Natl Acad Sci. USA* 83. pp. 7114-7117.
5. EINSENSTEIN TK., HILBURGER ME. (1998): Opioids modulation of immune responses: effects on phagocyte and lymphoid cell populations. *J Neuroimmunol.* 83: 36-44.
6. YEAGER MP., COLACCHIO TA., YU CT., HILDEBRANDT L., HOWELL AL., WEISS J., GUYRE M. (1996): Morphine inhibits spontaneous and cytokine enhanced natural killer cell cytotoxicity in volunteers. *Anesthesiology.* 83: 500-508.
7. YOKOTA T., UEHARA K., NOMOTO Y. (2000): Intrathecal morphine suppresses NK activity following abdominal surgery. *Can J Anaesth.* 47: 303-308.
8. MOSMANTR., SADS. (1996): The expanding universe of T-cell subsets; Th1, Th2 and more. *Immunol Today.* 17: 138-146.
9. ROMAGNANI S. (1994): Lymphokine production by human T cell in disease states. *Annu Rev. Immunol.* 12: 227-257.
10. GOMES-FLORES R., WEBER RJ. (2000): Differential effects of buprenorphine and morphine on immune and neuroendocrine functions following acute administration in the rat mesencephalon periaqueductal gray. *Immunopharmacology.* 48: 145-156.
11. HERNANDEZ MC., FLORES LR., BAYER BM. (1993): Immunosuppression by morphine is mediated by central pathways. *J Pharmacol Exp Ther.* 267: 1336-1341.
12. VALLEJOR., de LEON-CASASOLAO., BENYAMIN R. (2004): Opioid therapy and immunosuppression. *Am. J Ther.* 11: 354-65.
13. BUDD K. (2004): The immune system and opioimmunotoxicity. *Rev Analgesia.* 8: 1-10.
14. FECHO K., MASLONEK KA., DYKSTRA LA. (1995): Assessment of the involvement of central nervous system and peripheral opioid receptors in the immunomodulatory effects of acute morphine treatment in rats. *Anesthesiology* 83: 500-508.
15. GAVITRAPONG P., SUTTITUM TUNDA., KOTCHABHAKDI N., UNEKLABH T. (1998): Alteration of immune functions in heroin addicts and heroin withdrawal subjects. *J Pharmacol Exp Ther.* 286(2): 883-889.
16. MADDEN JJ., FALEK A., SHAFER DA., GLICK JH. (1979): In: Effects of opiates and demographic factors on DNA repair synthesis in human leukocytes. *Prot Natl Acad Sci. USA* 76: 5769-5773.
17. FALEK A., HOLLINGSWORTH F. (1980): Opiate and human chromosome alterations. *Int J Addict.* 15: 155-163.
18. NERI S., BRUNO CM., PULVIRENTI D., MALAGUERRA M., ITALIANO C., MAUCERI B., ABATE G., CILIO D., CALVAGNO S., TSAMI A., INTERLANDI D., PRESTIANNI L., RICCHENAM., NOTOR. (2005): Randomized clinical trial to compare the effects of methadone and buprenorphine on the immune system in drug abusers. *Psychopharmacology.* 179: 700-704.
19. PRESTON KL. (2005): Buprenorphine for opioid dependence. In: Budd, K., Raffa R. (Eds). *Buprenorphine the unique opioid analgesic*. Georg Thieme Verlag, Stuttgart.
20. ZAJICOVA A., WILCZEK H., HOLAN V. (2004): The alteration of immunological reactivity in heroin addicts and their normalization in patients maintained on methadone. *Folia Biol (Praha).* 50(1): 24-8.
21. SACERDOTE P., FRANCHIS., GERRAG., LECCESE V., PANERAIAE., SOMAINIL. (2008): Buprenorphine and methadone maintenance treatment of heroin addicts preserves immune function. *Brain Behav & Immunity.* 22: 606-613.
22. GERRAG., ZAIMOVICA., MOIG., BUSSANDRIM., BUBICIC., MOSSINIM., RAGGIMA., BRAMBILLA F. (2004): Aggressive responding in abstinent heroin addicts: neuroendocrine and personality correlates. *Prog. Neuropsychopharmacol. Biol Psychiatr.* 28(1): 129-39
23. GARLAND EJ., ZIS AP. (1989): Effect of codeine and oxazepam on afternoon cortisol secretion in men. *Psychoneuroendocrinology.* 14(5):397-402.
24. FACCHINETTIF., VOLPEA, NAPPIG, PETRAGLIA F., GENAZZANIAR. (1985): Impairment of adrenergic-induced proopiomelanocortin-related peptide release in heroin addicts. *Acta Endocrinol (Copenh).* 108(1): 1-5.
25. KREEK MJ. (1992): Rational for maintenance pharmacotherapy of opiate dependence. In: O'Brein CP., Jaffe JH. (Eds). *Addictive States*. Raven Press. Ltd., New York, pp 205-230.
26. KREEK MJ. (2001): Drug addictions: molecular and cellular endpoints. *Ann NY Acad. Sci.* 937: 27-49.
27. GERRA G., ZAIMOVIC A., RAGGI MA., MOI G., BRANCHI B., MORONI M., BRAMBILLA F. (2007): Experimentally induced aggressiveness in heroin-dependent patients treated with buprenorphine comparison of patients receiving methadone and healthy subjects. *Psychiatry Res.* 149(1-3): 201-13.
28. FRANCHIS., PANERAIAE., SACERDOTE P. (2007): Buprenorphine ameliorates the effect of surgery on hypothalamus-pituitary-adrenal axis, natural killer cell activity and metastatic colonization in rats in comparison with morphine or fentanyl treatment. *Brain Behav & Immunity.* 21(6):767-74.
29. FRIEDMAN H., NEWTON C., KLEIN TW. (2003): Microbial infections, immunomodulation and drug of

- abuse. *Clin. Microbiol. Rev.* 16: 209-219.
30. UGEN KE., NYLAND SB. (2007): Injecting drugs of abuse and immunity: implication for HIV vaccine testing and efficacy. *Springer Semin Immun.* 28: 281-287.
31. NERI S., TRAVALI S., BERTINO G., PULVIRENTI D., ITALIANO C., LIBBRA M., MAUCERI B., ABATE G., CALVAGNO S., CILIO D., TSAMI A., IGANCCOLO L., CALLARID., CARUSO L. (2007): Immune response in addicts with chronic hepatitis C treated with interferon and ribavirine. *J Gastroenterol Hepatol.* 22: 74-79.

*Received July 7, 2008 - Accepted November 10, 2008*

International Meeting

# EUROPAD ITALIA 4

Heroin Addiction. The Clinical and Therapeutic Aspects.  
8th Italian National Conference



**Comune di Pietrasanta**  
Città d'arte • Città nobile dal 1841



Gruppo SIMS



## Chairmen

Icro Maremmani

*(Pisa, Italy, EU)*

Marc Reisinger

*(Bruxels, Belgium, EU)*

Andrej Kastelic

*(Liubiana, Slovenia, EU)*

Roberto Nardini

*(Pietrasanta, Italy, EU)*

Matteo Pacini

*(Pisa, Italy, EU)*

Pier Paolo Pani

*(Cagliari, Italy, EU)*

Alessandro Tagliamonte

*(Siena, Italy, EU)*

# SAVE THE DATE



AU CNS



Pietrasanta, (Lucca), Italy, EU

"Sala dell'Annunziata"

"Luigi Russo" Cultural Centre

Piazza del Duomo

October 29-31, 2009

PIETRASANTA  
*Pietrasanta is Erice like*

For more information: [www.europad.org](http://www.europad.org)



Pacini Editore & AU CNS

**HEROIN ADDICTION &  
RELATED CLINICAL  
PROBLEMS**

www.europad.org

Letter to the Editor

Heroin Addict Relat Clin Probl 2008; 10(4): 45-48

## Major Policy and Clinical Developments in the Use of Methadone and Buprenorphine Treatment in the U.S.

Mark W. Parrino

*American Association for the Treatment of Opioid Dependence - AATOD*

TO THE EDITOR: One of the most significant and recent trends over the past eight years, involving the use of methadone in the United States, has been the prescription of methadone to treat chronic pain in private medical practice settings. This phenomenon continues to have a profound effect on treating pain management but also a negative effect on the public's perception concerning the safe use of methadone to treat chronic opioid addiction. The IMS Health Prescription Audit has been tracking the number of prescriptions dispensed for methadone for pain in the United States. Approximately 500,000 prescriptions for methadone were written for pain management patients in 1998 and this has increased to more than 4 million prescriptions written to treat pain in 2006. This does not include the use of this medication to treat chronic opioid addiction in the nation's network of 1,203 opioid treatment programs (OTPs), which treat 260,000 patients on any given day.

There have been increases in the number of prescriptions for other opioids as well, including hydrocodone and oxycodone medications in addition to methadone. Compared to the increases in hydrocodone and oxycodone, methadone has increased to a lesser degree when compared to the larger landscape of using such Schedule II prescription opioids for pain management.

There has been an increase in emergency room visits with regard to the prescription of methadone for pain, which has increased past 50,000 visits in 2005.

There have been more calls to US-based Poison Control Centers, increasing from approximately 2,000 calls in 2002 to more than 3,000 calls in 2005. Methadone has also been an increasing factor in reports of poisoning deaths in the United States as well.

The most alarming data to emerge from this increased use of methadone for pain has also been reported by the American Association of Poison Control Centers based on its data for 2005. Methadone ranks the highest compared to hydrocodone and oxycodone products in addition to morphine, when evaluating the ratio of deaths per 100 exposure. Methadone accounts for 1.8 deaths per 100 people exposed to the medication.

Methadone has also increased as an expression of the percent of all reported poisoning deaths for the Center for Disease Control and Prevention (CDCP) rising from 4% in 1999 to approximately 13% in 2004.

This alarming increase in emergency room visits, increasing calls to Poison Control centers and increasing numbers of deaths reported by coroners and medical examiners has prompted more media reports of these deaths through print media and television journalism in addition to government reports.

It has prompted a new group of “advocates” to call for the safer use of methadone in pain management settings, which has also unfortunately been linked to proposed increases in the regulation of methadone programs in different states, in spite of the fact that such deaths are not connected to OTP patient practices.

The Drug Abuse Treatment Act (DATA) was passed by Congress in 2000 and allowed physicians in the United States, for the first time in more than 80 years, to use federally approved opioids to treat chronic opioid addiction in their private medical practice settings. There has been a consistent rise in the distribution of buprenorphine through pharmacies based on the Drug Enforcement Administration ARCOS data. The increase has been quite remarkable with 10 million units of buprenorphine being used to treat chronic opioid addiction in 2004 to more than 50 million units of the medication being used in 2007.

There has also been an increasing use of buprenorphine to treat chronic opioid addiction in the nation’s opioid treatment programs, increasing from approximately 23,000 units in 2003 to approximately 450,000 units in 2007.

This use of buprenorphine in OTPs would have been more significant had federal regulations changed to permit the use of this valuable medication in the OTP setting as it had in the private medical practice setting.

The original Congressional legislation, as referenced above (DATA 2000), approved the use of this medication in private medical practice settings but did not include opioid treatment programs as well. Separate regulations, which govern OTPs, have existed since 1974 and limit how buprenorphine can be used in opioid treatment programs.

As of September 30, 2007, the Substance Abuse and Mental Health Services Administration (SAMHSA) through the Center for Substance Abuse Treatment (CSAT) has certified almost 12,000 physicians to use buprenorphine in their office-based treatment practices. This is double in number when compared to similar data in 2005.

Each physician, who is approved by the federal agencies, must participate in an 8-hour training course by one of the federally approved courses, such as the American Society of Addiction Medicine (ASAM) or the American Academy of Addiction Psychiatry (AAAP) as an example of such approved entities.

A great deal has been learned about the specialties reported through such physicians. According to a federal survey conducted by SAMHSA, approximately 56% of the physicians involved in using buprenorphine to treat chronic opioid addiction in the United States are part of a non-addiction specialty. Approximately 25% of such participating physicians have specialties in addiction

medicine and approximately 14% have a specialty in addiction psychiatry. The federal government has also found through its surveys that approximately 43% of the participating physicians have had no prior experience in providing medication-assisted treatment.

We have also learned a great deal about the characteristics of patients, who are treated through buprenorphine treatment and the aforementioned federally approved waiver program. Approximately 60% of the patients, who are being treated in private medical practice with buprenorphine, are new to medication-assisted treatment. Less than 20% of the patients being treated in such physician practice settings have transitioned from methadone treatment programs. These patients are predominantly white, younger and employed with fewer comorbidities.

Through similar studies at the federal level, it has also been determined that the majority of patients, approximately 40%, have approximately two visits with the physician during the first 30 days of treatment.

While the use of buprenorphine to treat chronic opioid addiction has been a great success in the United States, especially in having more patients enter treatment for their addiction, there are concerns about the limited use of this medication through the nation’s network of opioid treatment programs based on tight regulatory control. It is anticipated that these controls will be lifted in the coming year so that patients will also be able to gain access to such treatment services as part of the comprehensive opioid treatment program experience.

It is anticipated that the expanding use of such medications to treat chronic opioid addiction will generally lead to an improved public perception about the legitimate use of such medications to treat chronic opioid addiction a part of the public health initiative. AATOD will continue to work with its partners in addiction medicine and the federal government to advance this policy.

Major new legislation has recently passed in the United States, which will provide access to patients in need of addiction treatment services through better insurance coverage. This may have a profound effect on increasing access to care but it is too soon to determine how insurance companies will react.

In summary, we are on the verge of increasing access to treatment for chronic opioid addiction in the United States, but it is critically important that the public be properly educated about the value of treating opioid addiction for its citizens to benefit families and the surrounding communities. When all is said and done, the one thing that ties one civilization to the next and one nation to the next is the desire that our citizens, our families and the people we care for get access to the best addiction treatment services available.

**Conflict of Interest**

**Role of funding source**

This report was supported by internal funds.

The author has no relevant conflict of interest to report in relation to the present report.

*Received and Accepted October 18, 2008*



Pacini Editore & AU CNS

Subscribe to our Journal!  
Join EUROPAD!  
Support our activities!

**HEROIN ADDICTION &  
RELATED CLINICAL  
PROBLEMS**

www.europad.org

**“Heroin Addiction and Related Clinical Problems”, the official journal of EUROPAD.** This is the journal for professionals who wish to keep in touch with research and opinion on opiate misuse treatments in Europe and around the world. It is also for contributors who wish to share their research with a group of professionals committed to the development of effective opiate addiction treatments. “Heroin Addiction and Related Clinical Problems” is an international free-of-charge, peer review publication. Subscription to the Journal includes free membership in EUROPAD.

**The EUROPAD Conference:** Every two years the Association organises a conference in a major European centre. The most recent of these attracted 400 delegates, an impressive collection of international speakers and a wide range of original papers. Next appointment is in Helsinki, Finland, in the last week of May 2010.

**The EUROPAD Italian Conference:** The association arranges a regular ‘Italian Conference’ in years that alternate with those of the main conference. Next appointment is in Pietrasanta, Italy, in the last week of October 2009.

**The EUROPAD International Conferences:** The association arranges regular ‘International Conferences’, which may be located in any part of the world. Next appointment is in Bergen, Norway, May 2009.

**The Europad “Chimera” Award:** The society makes an award to individuals who have made an outstanding contribution to the effective treatment of drug addiction in general, and heroin addiction in particular. Visit <http://www.europad.org/> for more information and award recipients.

**EUROPAD and the American Association for the Treatment of Opioid Dependence (AATOD):** At each AATOD conference EUROPAD holds its own one-day seminar where European papers are presented. Next appointment is in New York, NY, USA, April 2009.

**A subscription to the journal costs €70,00 (or €30,00 for Eastern European citizens)**

Please complete this form in capital letters, then FAX it to +39 0584 72081 or e-mail a scanned copy to: [info@aucns.org](mailto:info@aucns.org)

All EUROPAD Members will receive a printed copy of the journal, together with a discount of 20% off the standard cost of participating in EUROPAD activities.

Family Name _____	<b>Δ Charge my Credit Card</b>
First Name _____	Δ Master Card Δ Eurocard Δ VISA Δ CartaSi (Italy only)
Agency _____	Card Number _____
Mailing Address:	Expiration date _____
Street/Road _____	CCV _____
Postcode _____	
City _____	
Country _____	
Phone _____ Fax _____	Date _____
E-mail _____	Signature _____

## INFORMATION FOR CONTRIBUTORS

**The Editor** of *Heroin Addiction & Related Clinical Problems* welcomes contributions of original manuscripts that are not under consideration for publication elsewhere. The *Journal* publishes research reports, proposals, letters to editor.

**Peer Review:** All manuscripts, including those written at the invitation of the editor, are subject to peer review by at least two experts to determine the originality, validity, and significance of the submitted material. Authors will usually be advised within eight weeks on the decision on their manuscript. All reviewers will remain anonymous.

**Manuscript Specifications:** Manuscript must be typed double-spaced with one-inch margins on A4 paper (Max 29.952 characters). The cover page must contain the article title, authors' names and affiliations, and address for correspondence and telephone number of corresponding author. Please, submit your paper only by E-mail in Rich Text Format Saved File. Please provide figures in .pdf or .tiff, .jpeg format or as Microsoft Power Point Presentation. Each article must include an abstract (100-word maximum) and a reference list.

Bibliography must be ordered by authors' names alphabetically. Start each reference with bibliography number; use these numbers, in parentheses, for in-text citations. Personal communications, unpublished manuscripts, manuscripts submitted but not yet accepted, and similar unpublished items should not appear in the reference list. Such citations may be noted in the text.

Please use the following guidelines for arranging references:

Journal article:

1. DOLE V.P., NYSWANDER M.E., WARNER A. (1968): Successful treatment of 750 criminal addicts. *JAMA* 206: 2708-2711.

Book:

1. TAGLIAMONTE A., MAREMMANI I. (1995): *Drug Addiction and Related Clinical Problems*. Springer-Verlag, Wien, New York.

Book Chapter:

1. DOLE V.P. (1995): Methadone Maintenance. Comes of Age. In A. Tagliamonte and I. Maremmani Eds: *Drug Addiction and Related Clinical Problems*. Springer-Verlag, Wien New York. pp. 45-49.

Journal names should be abbreviated as they appear in *Index Medicus*, journals not currently indexed there should not be abbreviated.

**Submission Procedure:** Submit the files to Icro Maremmani, MD, Editor, <maremman@med.unipi.it> and a Cc copy to <info@aucns.org>

Submissions should be accompanied by a cover letter indicating that the paper is intended for publication and specifying for which section of the journal it is being submitted (Regular Article, Preliminary Communications, Reports, Proposals, Letters to the Editor);

### Author Disclosure

**Role of Funding Source.** Authors are kindly requested to briefly describe the role of the study sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. If the funding source(s) had no such involvement, authors should so state.

Following the Role of the Funding Source text, authors are required to declare their individual contribution to the manuscript under a subheading *Contributors*.

**Conflict of Interest.** ALL authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, authors should state that there are none.

**Acknowledgements,** before the reference list and not as a footnote on the title page.

**Ethics of Experimentations:** Authors must declare in the cover letter that their studies submitted to *Heroin Addiction & Related Clinical Problems* have been conducted in accordance with Declaration of Helsinki.



© Icro Marammani

The Flourmill of Dreams, Liens, Austria, 1998