

Heroin Addiction and Related Clinical Problems



Periodico trimestrale - Sped. 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

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, Italy
Marc Reisinger	Vice-President	Brussels, Belgium
Andrej Kastelic	General Secretary	Ljubljana, Slovenia

Oleg Aizberg, Minsk, Belarus	Haim Mell, Jerusalem, Israel
Michael Arieli, Jerusalem, Israel	Vladimir Mendelevich, Kazan, Russia
Marc Auriacombe, Bordeaux, France	Genci Mucullari, Tirana, Albania
Safet Blakaj, Pristina, Kosovo	Lubomir Okruhlica, Bratislava, Slovak Republic
Olof Blix, Jönköping, Sweden	Matteo Pacini, Pisa, Italy
Colin Brewer, London, UK	Pier Paolo Pani, Cagliari, Italy
Jean Jacques Deglon, Geneva, Switzerland	Luis Patricio, Lisbon, Portugal
Sergey Dvoryak, Kiev, Ukraine	Tijana Pavicevic, Podgorica, Montenegro
Michael Farrell, London, UK	Paul Quigley, Dublin, Ireland
Gabriele Fischer, Vienna, Austria	Marina Roganovic, Kotor, Montenegro
Milazim Gjocaj, Pristina, Kosovo	Rainer Schmid, Vienna, Austria
Martin Haraldsen, Sandefjord, Norway	Aneta Spasovska Trajanovska, Skopje, Macedonia
Liljana Ignjatova, Skopje, Macedonia	Karina Stainbarth-Chmielewska, Warsaw, Poland
Ante Ivancic, Porec, Croatia	Marlene Stenbacka, Stockholm, Sweden
Nikola Jelovac, Split, Croatia	Emilis Subata, Vilnius, Lithuania
Minja Jovanovic, Kragujevac, Serbia	Marta Torrens, Barcelona, Spain
Euangelos Kafetzopoulos, Athens, Greece	Didier Touzeau, Paris, France
Alexander Kantchelov, Sofia, Bulgaria	Albrecht Ulmer, Stuttgart, Germany
Sergey Koren, Moscow, Russia	Peter Vossenbergh, Deventer, The Netherlands
Alexander Kozlov, Moscow, Russia	Nikola Vuckovic, Novi Sad, Serbia
Gunnar Kristiansen, Oslo, Norway	Helge Waal, Oslo, Norway
Mercedes Lovrecic, Ljubljana, Slovenia	Stephan Walcher, Munich, Germany
Nermana Mehic-Basara, Sarajevo, Bosnia and Herzegovina	Wojciech Rudalski, Warsaw, Poland

Editorial Board

Editor

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

Associate Editor

Pier Paolo Pani Sardinian Regional Dependence Coordination Unit, 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 South London and Maudsley NHS Foundation Trust, London, UK, EU
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, Ljubljana, 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, Ljubljana, 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

Internet: <http://www.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>

Cited in:

EMBASE Excerpta Medica Database

SCOPUS

EMCave

Social Sciences Citation Index (SSCI) - Thomson Reuters

Free download at:

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

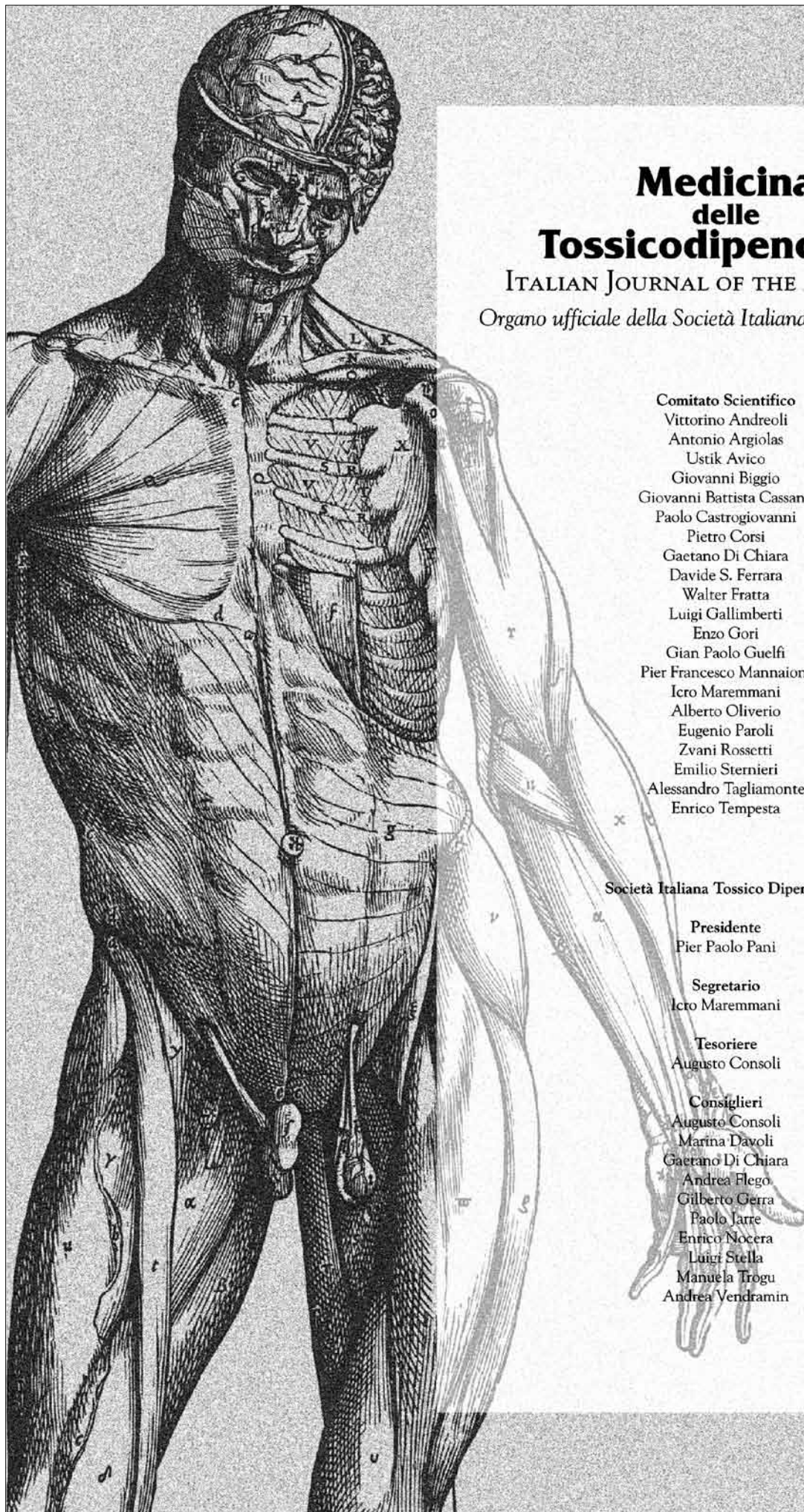
http://pain-topics.org/opioid_rx/europad.php

Open Access at:

<http://www.europad.org>

CONTENTS

Evaluation of Opioid-Dependent Prisoners in Oral Opioid Maintenance Therapy	5
Verena Metz, Christian Matzenauer, Karin Kammerer, Bernadette Winklbaaur, Nina Ebner, Dunja Radler and Gabriele Fischer	
Dose Determination in Dual Diagnosed Heroin Addicts during Methadone Treatment	17
Icro Maremmani, Matteo Pacini, Stefania Canoniero, Joseph Deltito, Angelo G.I. Maremmani and Alessandro Tagliamonte	
Urine Labelling Marker System for Drug Testing Improves Patient Compliance	25
Kaarlo Simojoki and Hannu Alho	
Quality of Life as a Means of Assessing Outcome in Opioid Dependence Treatment	33
Marta Torrens	
Why There Has Been an Excess of Overdoses in Norway Since 1990	37
Martin Haraldsen	



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
Gilberto Gerri
Paolo Jarre
Enrico Nocera
Luigi Stella
Manuela Trogu
Andrea Vendramin



Pacini Editore & AU CNS

Regular article

Heroin Addict Relat Clin Probl 2010; 12(1): 5-16

HEROIN ADDICTION &
RELATED CLINICAL
PROBLEMS

www.europad.org

Evaluation of Opioid-Dependent Prisoners in Oral Opioid Maintenance Therapy

Verena Metz¹, Christian Matzenauer¹, Karin Kammerer¹, Bernadette Winklbaaur¹,
Nina Ebner², Dunja Radler¹ and Gabriele Fischer¹

¹Medical University of Vienna, Department of Psychiatry and Psychotherapy, Waehringer Guertel 18-20, 1090 Vienna, Austria

²Medical University of Vienna, Department of Child and Adolescent Psychiatry, Waehringer Guertel 18-20, 1090 Vienna, Austria

Summary

Background: Opioid maintenance treatment is available in prison in many countries, but without a specific methodology or homogeneity. The aim of our study was to investigate characteristics and differences among opioid-dependent prisoners in an Austrian penitentiary. **Methods:** Structured assessments were obtained from 57 (78.1%) of 73 opioid-maintained prisoners on their demographic data, imprisonment terms, health status and quality of life. **Results:** From 1996 until 2007, the number of opioid-maintained detainees increased by 444%. Prisoners treated with methadone had significantly more convictions ($p=0.036$) and a longer duration of poly-drug abuse ($p=0.093$) and opioid consumption ($p=0.05$) than patients maintained on slow-release morphine. **Conclusions:** There is a strong need for a diversification of opioid maintenance treatments, as well as the development of a specific methodology for the use of therapeutic opioids in prison.

Key Words: Buprenorphine; Methadone; Opioid Addiction; Opioid maintenance therapy; Oral slow-release morphines; Prisoners; Substance dependence

1. Introduction

A substantial part of the population in prison is known to be substance-dependent [6, 9, 21]. Fazel et al. [27] report a prevalence of substance use disorders of 30-60% in female prisoners, and 10-48% in male prisoners. Gunter et al. [36] reported a prevalence of substance abuse/dependence in prison of 55% for women and 63% for men. In the United States, over 60% of arrested persons test positive for at least one illicit substance [12]. In Europe, as well as the United States, as many as four out of five detainees are believed to have a history of substance abuse [12, 21]. Reasons for this high prevalence of substance abuse in prison vary; many of these prisoners are sentenced for drug-related crimes (possession or trading of drugs) and crime in the pursuit of drug acquisition, suggesting that these prisoners could have been substance-dependent before detainment, while others become

dependent during their time in prison. Boys et al. [6] found that 26% of prisoners in England and Wales began using heroin while in prison. A study by Strang et al. [62] showed that the continuation of heroin use in prison occurred more frequently (70%) than the initiation of cocaine (20%) or amphetamine use (15%). In addition, previous terms of imprisonment turn out to be correlated with heroin use in prison among male prisoners and cocaine use among female ones.

Illicit substances are generally known to be easily available in prisons [21]. Due to the high frequency of violent acts committed by other detainees and a hopeless atmosphere, prisons represent a high-risk milieu for those people prone to addiction.

Prison terms could be used to stabilize prisoners' health and prevent any relapse into crime or drug consumption after release. Detoxification is often followed by a rapid relapse into criminal activities and/or the consumption of illegal

substances [34, 47, 58], eventually leading to a return to prison. Oral opioid maintenance therapy has been shown to reduce relapse rates after release from prison [42, 59], and maintenance therapy is known to generally increase quality of life as well as stabilizing patients' health by contributing significantly to a reduction of illicit consumption, and also of HIV and HCV infections, by preventing intravenous consumption and sexual risk behaviours, so reducing mortality [20, 48]. Haig refers to the effectiveness of methadone maintenance treatment in prison in reducing drug use and injection behaviour, and therefore recommends the introduction or expansion of prison-based methadone programmes [37].

Sharp differences can be found between prison populations in different countries, in terms of the crimes inmates are detained for. In Austria, there are virtually no prison sentences for the possession of small amounts of illicit substances considered to be for personal consumption only; in these cases, the principle of "therapy instead of punishment" is applied. Thus, most substance-dependent prisoners in Austria are offenders against property or have been judged guilty of acts of violence; by contrast, in the United States mandatory sentencing requirements for drug-related crimes have been introduced under what is known as the "war on drugs" policy, which has led to a more than tenfold increase in drug-related imprisonments over the last 20 years [10, 18].

Opioid maintenance therapy has been offered in prisons for almost 40 years, with the first project initiated in the United States in 1968 [17]. Nowadays, opioid maintenance therapy is available in most countries, but mainly in selected prisons [1, 15, 42]. In European countries, methadone or buprenorphine are usually offered in prison therapy regimens, with most of the regimens being detoxification- rather than maintenance-based [38]. With methadone, however, the maintenance treatment approach leads to significantly greater reductions of illicit consumption than detoxification programmes, and is therefore generally chosen for cases of long-term therapies designed to treat opioid dependence [50].

A few countries have introduced needle-exchange programmes in selected prisons; these include the United States, Switzerland, Germany, Spain, Moldova, Belarus, and Kyrgyzstan [11]; Iran introduced a needle-exchange programme in 2002 in response to an HIV epidemic in prisons [23, 64]. Needle-exchange programmes, along with opioid maintenance therapy, have been shown to reduce risk behaviours and the transmission of infectious diseases, while increasing staff and prisoner safety [14, 60].

In Austria, opioid maintenance treatment has been available since 1987 [31]. Unlike most other countries, in Austria oral slow-release morphines (SROM), in addition to methadone and buprenorphine, are registered for use in opioid maintenance therapy. Methadone, an orally administered solution, has been used to treat opioid addiction since 1965 [16]. Possible side-effects include heavy sweating, mood

swings, depression, listlessness, and weight gain [46].

The typical side-effects of methadone were observed to be weaker with SROM treatment [19], which is registered for use in opioid maintenance therapy in Austria, Slovenia and Bulgaria. In Austria, SROM is available in two different forms: a capsule filled with small wax-coated balls of morphine (Substitol® retard) and a morphine tablet with a retard surface (Compensan® retard).

Buprenorphine is considered relatively safe, due to the low level of its potential for respiratory depression [45, 51]. One of its main advantages is that dose reductions in patients treated with buprenorphine lead to fewer side-effects than dose reductions of methadone or SROM [33]. Buprenorphine is widely registered for use in opioid maintenance therapy in most Western countries. Recently, a formula comprising both buprenorphine and naloxone, an opioid receptor antagonist, has been introduced.

Opioid maintenance therapy is available in all of Austria's 28 prisons. In most countries prisoners are kept on less expensive medications (methadone, for example), whereas the prescriptions given to patients in Austria are usually for the same medication that was being used prior to detainment. The percentage of prisoners undergoing opioid-maintenance therapy rose from 7.5% in February 2002 to 8.8% in July 2008 [2, 29]. Needle-exchange programmes have not yet been introduced in Austrian prisons, although a study by Boys et al. [6] reported that 16% of IDUs initiated their intravenous use of illicit substances in prison.

1.1 Costs

The public expenditures related to substance use disorders can be split into those associated with prevention, research, treatment, rehabilitation, law enforcement and cost-of-illness [22]. The direct costs are public costs sustained for prevention and medical treatment, and those for the purchase of illicit substances, court fees, legal advice, assistance and material damage. The costs arising from indirect consequences are those due to loss of productivity, earnings, tax revenues and social insurance contributions, together with those needed to pay for social assistance. The costs of intangible consequences include the loss of well-being caused by drug addiction, i.e. disease, premature death and/or imprisonment. In Austria, public expenditures on substance-related issues have been estimated to amount to 0.08% of the gross domestic product [22].

1.2 Drug-related deaths after release from prison

A study by Farrell & Marsden [26] showed a high rate of substance-related deaths among newly released prisoners in England and Wales. Of 48,777 released prisoners, 442 died within a year, and in 68% of those cases, death was due to substance-related causes. The study also showed that the

mortality rate for women within the first week after release was 69 times higher and for men 29 times higher than that of the general population. Psycho-education on the risk of overdoses after losing tolerance, and on opioid maintenance therapy instead of detoxification, as well as on referrals to local treatment centres after release would help to decrease the mortality risk among newly released prisoners. Opioids were associated with 95% of the substance-related deaths, cocaine with 21%, benzodiazepines with 20%, and antidepressants were involved in 10% of the cases. Similarly, Pratt et al. [53] reported a high prevalence of suicides among newly released prisoners. One year after release, 382 suicides were reported; of these, 21% occurred within the first month and 51% within 4 months after release from prison. The mortality rate for women is 35.8 times higher and for men 8.3 times higher than that for the general population.

1.3 Study aims

The aim of our study was to evaluate prisoners in maintenance therapy with respect to their current oral opioid maintenance therapy, their history of substance abuse, and their previous criminal activities. Furthermore, we wanted to assess additional prescriptions for psychotropic medications, and quality of life of the participants to permit comparisons between participants who were being maintained on different oral opioids; additionally, a focus was on aspects of different groups, as hardly any data on social insurance contributions are available in reviewing the question of the diversification of opioid maintenance in prison.

2. Methods

Our investigation was approved by the Federal Ministry of Justice, and the assessment took place in February 2002. All the prisoners who participated gave written informed consent before taking part in the investigation.

2.1 Frame of Investigation/ Setting

“Justizanstalt Stein” is the largest prison for males in Austria and is located in Krems an der Donau, 74 km west of Vienna in Lower Austria. It is a males-only penitentiary with a maximum capacity of 730 prisoners. The prison is not used for pre-trial confinement.

At the time of our study, there were 719 detainees in the “Stein” prison; of these, 73 were undergoing maintenance treatment, and 57 (78.1%) agreed to participate in this survey. Three men were excluded for safety reasons, one patient was in hospital, one had insufficient knowledge of the German language, and 11 refused to participate due to lack of interest or fear of negative consequences.

The detainees work in over 30 prison-operated factories. For detainees already facing release, there are three outposts

for loose detainment.

Four psychologists, four social workers and three psychiatrists work at the penitentiary. Ward V3 is a special ward for the accommodation of opioid-dependent prisoners undergoing maintenance therapy. Due to shortage of space and for safety reasons, only 44 patients can be accommodated in the ward. If more than 44 prisoners are in treatment, some will be transferred to another ward within the prison.

Before prisoners can start treatment, illegal opiate consumption or an opioid maintenance treatment already initiated prior to detainment must be verified by urinalysis and psychiatric and clinical assessment. Weekly urinalyses are conducted during the course of treatment.

Medication intake is supervised by a nurse and two prison officers at the penitentiary.

2.2 Instruments

Patients were assessed on a standardized basis using the European Addiction Severity Index (EuropASI), the German version of the Lancashire Quality of Life Profile (Berliner Lebensqualitätsprofil, BeLP), and personal and medical records in prison.

The European Addiction Severity Index [35] is an adaptation of the fifth version of the Addiction Severity Index. It is a short semi-standardized interview for gathering information about somatic status, employment and living status, alcohol and drug abuse, legal status, family background, social network, and psychological status. The interview usually lasts between 30 and 60 minutes.

The German version of the Lancashire Quality of Life Profile (BeLP) [52, 54] is a structured interview for assessment of subjective quality of life and well-being of persons suffering from mental illnesses. The questionnaire is structured in 11 parts and usually takes between 15 to 30 minutes. Not all the items in the BeLP are applicable to patients in prison, so only selected items have been analyzed.

The medical files at the penitentiary contain information about the prisoners’ prescribed and administered medications and about any infectious diseases they may have, as well as data on psychiatric assessments (information on psychiatric comorbidities such as severe stress and anxiety disorders).

2.3 Outcome variables and cluster characteristics

Frequency and mean duration of imprisonment were registered, as well as the number and kind of crimes the participants had been convicted of. Furthermore, duration of intravenous drug use, age at onset of intravenous consumption, consumption of other drugs, prior treatment approaches, mean dosage of the maintenance medication, and concomitant medications were all recorded.

To allow comparisons between two groups in our population, it was split along the median of the appropriate char-

acteristic. The median age was 36 years. For comparisons referring to the daily dosage, the groups were split along 80 mg of methadone and 520 mg of SROM. For those referring to the age when the individuals first tried heroin, the group was split along the 19th birthday.

2.4 Data Analysis

Data were analyzed using SPSS® (Statistical Package for the Social Sciences®), version 10.0. The influence of patient age on the outcome was assessed by means of a covariance analysis. For normally distributed variables, differences in mean values of independent groups were assessed using t-tests for independent samples (e.g. differences in subgroup characteristics of medication groups), and Mann-Whitney U-tests for skew distributions. For comparisons in regard to frequency, chi-square tests, Bravais-Pearson product-moment correlations and descriptive statistics for main variables characterizing the study sample (e.g. substance abuse history and number of previous treatment approaches) were computed.

3. Results

3.1 Sample characteristics

The mean age of the 57 participating men was 35.47 years (SD=6.8 years, range 23 to 49 years). Forty prisoners (70.2%) were unmarried, four (7.0%) were married, 11 (19.3%) were divorced, and 2 (3.5%) had separated from their spouses. Forty-eight (84.2%) of the participants had completed nine years of education, one (1.8%) had a general qualification for university entrance, one (1.8%) had completed vocational school education, and seven (12.3%) had not completed any education. All the participants (98.2%), except one person who was ill, were working during their detainment.

At the time of our investigation, the mean duration of imprisonment of the participants was 86.47 months (SD=50.22, range 16 to 286 months). On average, the prisoners had been convicted 10.72 times (SD=7.06, range 3 to 40), mostly for crimes related to drug acquisition (mean=4.93 times, SD=6.11, range 0 to 28) and to drug possession or trading

(mean=3.65 times, SD=3.63, range 0 to 17) (Table 1). One individual had been sentenced to life imprisonment for committing a serious offence.

Forty-four participants (77.2%) had a hepatitis C virus infection, ten (17.5%) were uninfected, and the status of three (5.3%) was unknown. Nine participants (15.8%) were HIV positive, 46 (80.7%) were HIV negative, and the infection status of two (3.5%) was unknown.

All the participants had administered drugs intravenously at least once in their life. The mean age when they first consumed drugs intravenously was 20.95 years (SD=6.13 years, range 12 to 41 years). The duration of intravenous drug use ranged from 0 to 30 years, with a mean duration of 8.81 years (SD=7.56 years). In the six months prior to study initiation, 11 participants (19.3%) had administered drugs intravenously; all eleven reported that they had used their own needles.

Table 2 shows the participants' history of substance use. The mean duration of heroin abuse was 7.23 years (SD=6.79), with a range from 0 to 30 years. Cocaine was used for an average of 5.00 years (SD=6.42 years, range 0 to 24 years).

In Table 3, the treatment data are displayed; on average, the participants underwent 10.09 treatment approaches for their substance dependence (SD=15.29, range 0 to 74), showing a range for their current therapy between the first and the 75th therapy in their lives.

Table 4 shows the participants' satisfaction with their lives. Most patients (16; 28.1%) declared themselves to be "alternately satisfied and unsatisfied". Most of the participants (30; 52.6%) were satisfied with their somatic health status (ranging from "rather satisfied" to "completely satisfied"), compared to 20 (35.1%) participants who were dissatisfied (ranging from "completely unsatisfied" to "rather unsatisfied"); 7 (12.3%) were "alternately satisfied and unsatisfied". Twenty-five participants (43.9%) were satisfied with their mental health status, 13 (22.8%) were "alternately satisfied and unsatisfied", and 19 (33.3%) were unsatisfied.

At the time of our investigation, twenty-three study participants (40.4%) were maintained on methadone, while 34 (59.6%) were maintained on SROM (none of them were being maintained on buprenorphine).

Table 1: Number of charges, convictions, and months in prisons (n=57)

	Average	SD	Minimum	Maximum
Charges for drug crime	3.65	3.63	0	17
Charges for crime in the pursuit of drug acquisition	4.93	6.11	0	28
Charges for violent crime	2.46	3.64	0	16
Convictions	10.72	7.06	3	40
Months in prison	86.47	50.22	16	268

Table 2: Substance abuse history, in years (n=57).

Substance	Average	SD	Minimum	Maximum
Heroin	7,23	6,79	0	30
Methadone	3,07	4,39	0	22
Other opioids and analgesics	5,23	6,91	0	30
Benzodiazepines	6,12	7,42	0	24
Cocaine	5,00	6,42	0	24
Amphetamines	1,54	3,80	0	20
Cannabinoids	14,61	9,45	0	36
Hallucinogens	0,35	1,08	0	07
More than one substance per day	11,95	7,90	0	30

Table 3. Number of previous treatment approaches (n=57)

Pre-treatment	Average	SD	Minimum	Maximum
Outpatient detoxification	1,33	2,86	0	17
Inpatient detoxification	2,18	4,64	0	23
Maintenance treatment	1,88	1,05	1	7
Outpatient treatment	2,46	10,09	0	72
Inpatient treatment	0,95	2,89	0	20
Day care unit	0,40	2,65	0	20
Psychiatric clinic	0,88	4,65	0	35
Total number of treatments	10,09	15,29	1	75

Table 4: Satisfaction according to BeLP, in % (n=57)

	Completely unsatisfied	Unsatisfied	Rather unsatisfied	Alternately satisfied and unsatisfied	Rather satisfied	Satisfied	Completely satisfied
Satisfaction with life	12,3	12,3	14,0	28,1	15,8	14,0	3,5
Satisfaction with somatic health status	5,3	19,3	10,5	12,3	15,8	24,6	12,3
Satisfaction with mental health status	8,8	8,8	15,8	22,8	15,8	19,3	8,8

On average, the initial methadone dose was 69.86 mg (SD=39.68 mg, range 10 mg to 200 mg), and the SROM dose was 312.50 mg (SD=169.79 mg, range 200 mg to 720 mg). After an average of 13.35 months (SD=8.49 months, range 1 to 39 months) from the start of the study, the mean doses had changed to 78.04 mg methadone (SD=28.99 mg, range 20 mg to 120 mg) and 486.47 mg SROM (SD=201.87 mg, range 90 mg to 800 mg). Only 11 participants (19.3%) were maintained on the same amount of medication they were taking at the beginning of their therapy; 21 participants (36.8%) had a higher dose, while 8 participants (14.0%) were on a lower dose. Seventeen participants (29.8%) had changed their opioid medication.

Only nine participants (15.8%) did not receive any other prescription medicine; twenty-one participants (36.8%) had a prescription of one additional medication, and one person (1.8%) was receiving six additional medications. Most of the participants (37 participants; 64.9%) had a prescription for benzodiazepines, of which Anxiolit®, a sedative containing oxazepam, was the one prescribed most frequently

3.162, df=41.32, p=0.003) and a markedly shorter history of intravenous use (mean=7.00 years, SD=6.66 vs. 10.34 years, SD=8.05, t=-1.743, df=55, p=0.087). Patients maintained on low doses were less likely to suffer from severe depression than patients maintained on high medication doses ($\chi^2=5.009$, df=1, p=0.025). In addition, patients on low doses were markedly less likely to be in debt ($\chi^2=2.818$, df=1, p=0.093) and also considerably less likely to have experienced severe stress and anxiety disorders during the previous 30 days ($\chi^2=3.499$, df=1, p=0.061). Patients maintained on low doses tended to spend their leisure time with friends, while patients on high doses tended to spend their free time alone ($\chi^2=2.850$, df=1, p=0.091). The duration of methadone consumption (mean=1.74 years, SD=3.08 vs. 4.27 years, SD=5.05, U=230.000, Z=-2.869, p=0.004) and benzodiazepine consumption (mean=4.37 years, SD=6.37 vs. 7.70 years, SD=8.03, U=297.500, Z=-1.758, p=0.079) were shorter in patients who were taking low doses than in those who were receiving high doses.

Patients who first tried heroin before their 19th birthday

Table 5: Differences between persons maintained on methadone and persons maintained on slow-release oral morphines (SROM)

	Persons maintained on methadone N=23	Persons maintained on SROM N=34
Mean age (in years)	37.35	34.21
Average number of convictions	13.09	9.12
Mean duration of opiate consumption	5.3	1.56
Mean duration of multiple drug abuse	14.09	10.50

(24 participants; 42.1%). Twenty participants (35.1%) had a prescription for antidepressants, fourteen (24.6%) were receiving neuroleptics, and two (3.5%) were taking anticonvulsants (see Figure 1).

3.2 Differences between medication groups and clustered subgroups

Patients maintained on methadone were markedly older than patients maintained on SROM (mean age 37.35 years (SD=6.85) vs. 34.21 years (SD=6.56), t=1.743, df=55, p=0.087). Additionally, patients on methadone had a record of significantly more convictions (mean=13.09, SD=8.63 vs. 9.12, SD=5.32, t=2.150, df=55, p=0.036) and showed a considerably longer duration of opiate consumption (5.3 years vs. 1.56 years, t=3.028, df=55, p=0.005), as well as multiple drug abuse (14.09 years vs. 10.50 years, t=1.709, df=55, p=0.093).

Patients maintained on low doses of opioids (less than 80 mg methadone per day or less than 520 mg SROM per day) had a significantly shorter history of opiate abuse (mean=2.84 years, SD=3.69 vs. 7.70 years, SD=8.16, t=-

had a shorter education than those who tried heroin for the first time after their 19th birthday (mean=8.79 years, SD=1.93 vs. 9.64 years, SD=1.45, U=316.500, Z=-1.704, p=0.088).

For assessment of quality of life, participants were divided into two groups according to their scores in the Lancashire Quality of Life Profile: those whose reply was “completely satisfied”, “satisfied”, “rather satisfied” or “alternately satisfied and unsatisfied” constituted the group with high satisfaction, and those who replied “rather unsatisfied”, “unsatisfied” or “completely unsatisfied” constituted the group with low satisfaction.

Participants who were satisfied with their lives experienced significantly less psychological problems during the previous 30 days (t=2.142, df=31.14, p=0.040), were more likely to be HIV-negative ($\chi^2=3.742$, df=1, p=0.070), and had more friends they could rely on in case of need or emergency ($\chi^2=5.370$, df=2, p=0.068) compared to those who were unsatisfied with their lives.

Patients whose reply was “completely satisfied”, “satisfied” or “rather satisfied” in the Lancashire Quality of Life Profile had a history of 9.52 years of heroin abuse (SD=8.37), which is significantly longer than patients whose indication

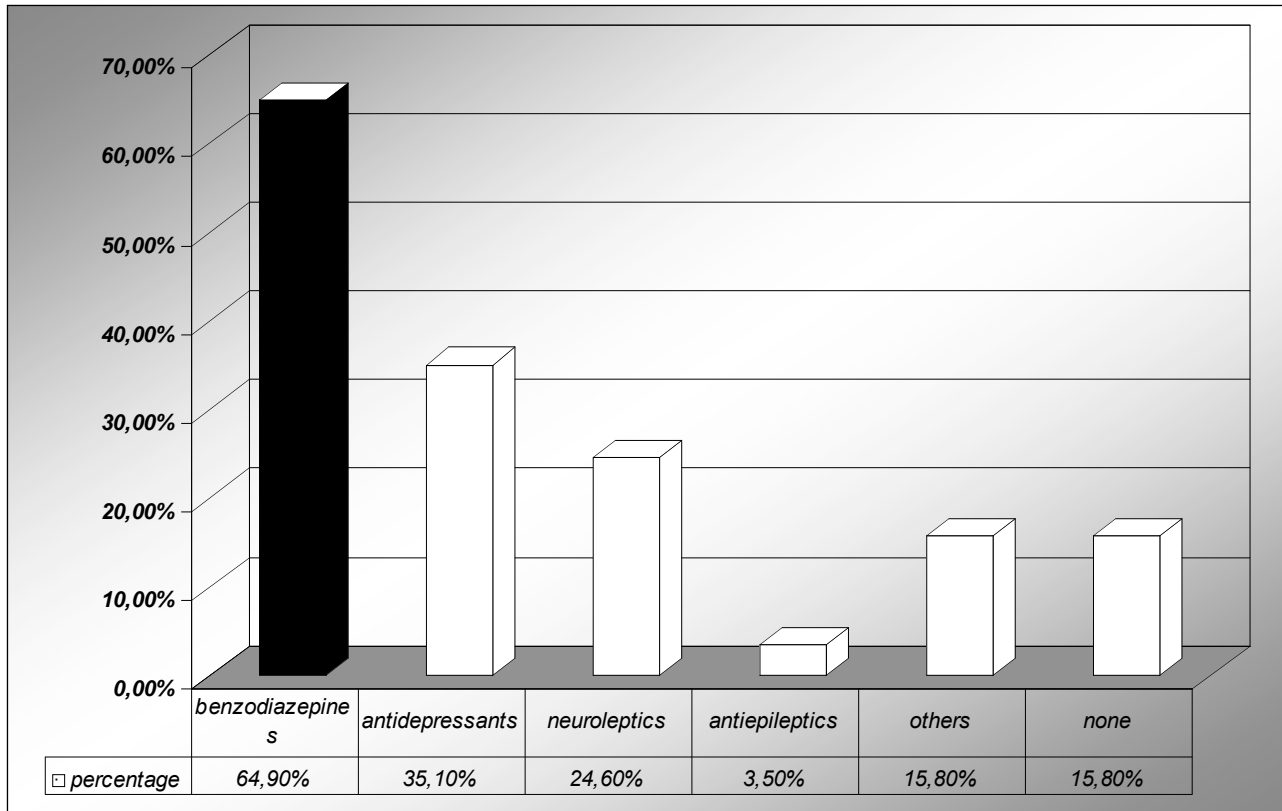


Figure 1. Number of patients prescribed additional medications (n=57).

was “alternately satisfied and unsatisfied”, “rather unsatisfied”, “unsatisfied” and “completely unsatisfied”; this second group had a mean history of 5.44 years of heroin abuse (SD=4.65) ($t=-2.190$, $df=25.28$, $p=0.035$). Participants who were satisfied had suffered from withdrawal symptoms on significantly fewer days during the previous 30 days ($\chi^2=6.502$, $df=2$, $p=0.039$) and had had fewer consultations due to mental health problems during the previous year ($\chi^2=3.792$, $df=1$, $p=0.051$) than unsatisfied participants.

3.3 Development at “Stein” penitentiary

We examined the number of substance-maintained individuals in the “Stein” prison, and found a constant increase in this sub-population over time. At the end of 1996, 18 detainees were in maintenance treatment. At the end of 2000, this population had doubled, and by the end of 2002 had quadrupled, with 89 patients undergoing therapy. The total number of detainees fluctuated between 630 and 719 over these years.

During preparation of this article, we found that by the end of 2007, 98 prisoners were in maintenance treatment. Twenty-six (26.5%) were receiving methadone, 43 (43.9%) SROM, and 29 (29.6%) were being maintained on buprenor-

phine. Twelve (12.2%) were HIV-positive, and 74 (75.5%) were HCV-positive. Ninety-one patients (92.9%) had a prescription for benzodiazepines.

4. Discussion

At the time of this study, only a few reports investigating patient and treatment characteristics of opioid-dependent detainees and evaluating their quality of life in this setting were available; thus, despite the small size of our group, our study constituted a rather innovative approach.

The educational status of the participants in this study seems to be extraordinarily high, as 87.7% of the participants had completed nine or more years of education, but this is consistent with the generally high educational standards in Austria due to the relatively long obligation to attend school [28]. Prison populations in other European countries show a similar level of education [39].

As detainees in Austria (§44 and §48 Strafvollzugsgesetz) as well as in Germany (§37 and §38 Strafvollzugsgesetz) are obliged either to work or to attend classes, our study had an extremely high prevalence of working patients (98.2%). Although opioid dependence constitutes a severe somatic disease, patients seem to be able to work if they do not suffer

from withdrawal symptoms or take illicit substances.

Most of our participants had been convicted for drug-related crimes, which is consistent with findings from other studies [27]. Our study did not evaluate how many participants initiated their drug use during previous detainments, as heroin use has been shown to be strongly related to the total time spent in prison [6].

A high frequency of previous treatments was observed in the participants in this study, while Kinlock et al. found a greater variation regarding the number of previous therapies in US prisoners [41]. This difference may be accounted for by the high treatment availability for opioid dependence in Austria.

In Austria, arrestees are routinely assessed for opioid dependence, and treatment is provided if needed, whereas assessment and therapeutic intervention is not part of the standard care provided in many Western countries, e.g. in the USA only approximately half of all jails assess arrestees for opioid dependence; and although most US prisons report using standardized detoxification protocols, very few offer opioid medication for detoxification treatment [30]; in a UK study, nearly a quarter of substance dependent prisoners claimed to have experienced withdrawal symptoms after they were arrested [8].

The diversification of administration of opioid medications in our study population can be explained by the common Austrian practice of prescribing the same medications in prison that the patients had been using prior to imprisonment. As with any other disease, diversification is a necessary procedure in choosing the best treatment option according to the characteristics of patients. In 2002, patients were all maintained on methadone or SROM; no patients were maintained on buprenorphine. By 2007, most of the patients were maintained on SROM, while methadone ranked only third, surpassed by buprenorphine. This does not exactly reflect opioid maintenance treatment approaches outside prison [55], but as prisoners in Austria usually receive prescriptions for the same medications they used before imprisonment, our data do not necessarily reflect prison doctors' choices. The difference in prescribed medications may result from the fact that our participants constitute a population with more serious health problems than the average opioid-maintained population, as they had, on average, undergone more than 10 treatment approaches.

Opioid maintenance treatment has been shown to reduce risk behaviour, although this only occurs if patients with these problems have an opportunity of avoiding risk behaviour. Sarang et al. [57] describe needle-sharing as a routine consequence of unavailable needle-exchange programmes in a Russian prison. The prevalences of HCV and HIV infections in our population were consistent with those in opioid-dependent patients in Austria [32]. Due to the relatively long duration of treatment and the low compliance with treatment in the outside world, detainment in prison might provide an ideal

environment for treating chronic hepatitis C virus infection. Independently of this, Article 3 of the European Convention on Human Rights bans denying adequate medical treatment for prisoners. Treatment of chronic hepatitis C virus infection with interferon and ribavirin has been introduced in selected prisons in Canada [24, 25], USA [61] and Italy [56]. Tan et al. [63] showed that the treatment of HCV infection is cost-effective not only in the general population, but also in prison populations; in addition, treatment has been shown to increase quality of life in prison.

As most of our participants have been convicted for drug-related crimes, imprisonment might be an ideal environment for stabilizing patients, either by optimizing their existing maintenance treatment or by initiating maintenance therapy. This might lead to fewer drug-related crimes and fewer lethal overdoses after release, as substance-dependent persons are at high risk of drug overdose after release from prison [4, 26, 40]. Farrell & Marsden [26] found that benzodiazepines were involved in 20% of drug-related deaths among newly released prisoners. Recent investigations show the benefits of aftercare following release from prison with reference to the consumption of illicit substances [43, 44]. Opioid maintenance therapy has been shown to possess a preventive function against drug-related deaths following release from prison [26].

Our population showed a high level of concomitant benzodiazepine intake (64.9%). As the concomitant consumption of benzodiazepines is a strong indicator for high-risk behaviour and poor retention in treatment programmes [5, 7, 13], and it increases the potentially lethal effects of opioids by depressing the sensitivity of the respiratory center in the brain stem for carbon dioxide, while being associated with a high risk of overdose [3, 49], this observation in our study population should not be overlooked. Benzodiazepines may be necessary in particular environments such as prisons due to a high incidence of anxiety, sleep disorders, aggressive behaviour against oneself and others, but this treatment might hinder social attachment and ability to work after release, and have fatal effects. The high number of benzodiazepine prescriptions and the rise of prescriptions from 64.9% to 92.9% highlight the potentially high level of unawareness in doctors without a specialization in addiction medicine of the risks of benzodiazepine use.

In conclusion, the present study showed that opioid maintenance therapy can be safely offered in prison, regardless of which substance is used; thus, there is no reason for avoiding diversification, although it would probably be appropriate to design a specific methodology for the use of the different substances.

Prisoners maintained on methadone were older and had a longer history of criminal behaviour, opiate consumption and polydrug abuse, but they showed no difference in well-being and quality of life compared to the prisoners maintained on SROM. In a randomized controlled double-blind

double-dummy study conducted by Eder et al (2005), patients receiving SROM did not show any significant demographic differences, but had significantly lower depression and anxiety scores and fewer physical complaints compared to subjects maintained on methadone [19]. The differences revealed in these samples will be related to the different availability of medically prescribed opioids; methadone was introduced in Austria in 1992, while SROM has been slowly introduced in the past decade. The long-term consequences should be investigated in a prison setting.

Quality of life generally seems to be high, as virtually all patients were working 8 hours a day, mostly in skilled trades. Those who were satisfied with their lives experienced fewer psychological problems, fewer withdrawal symptoms and had a more reliable social network, and thus seemed to comprise a group with better health, but, surprisingly, they had a markedly longer history of heroin abuse. No explanation for this fact could be found.

Patients maintained on lower doses of methadone or SROM seemed to be less ill than those maintained on higher doses, in terms of their history of drug abuse, depression and anxiety disorders.

Offering opioid maintenance therapy in prison may lead to a fall in reincarceration rates after release due to stabilization and easier reintegration into society, and thus may help to limit public spending on social welfare. Oral opioid maintenance therapy has been shown to be safe with respect to abuse and passing on the medication to other detainees if offered under standardized circumstances and supervised intake. Despite this, there is still a strong need for the development of a specific methodology for opioid administration in penitentiaries worldwide.

References

1. AFSHARP.(2007): *Efficacy of harm reduction measures in prisons of Islamic Republic of Iran*. Presentation at the 18th International Conference on the Reduction of Drug Related Harm, Warsaw, Poland.
2. AUSTRIA PRESSE AGENTUR (2008). In: Der Standard: „Schwitzen statt sitzen“ scheint sich zu bewähren. Available at <http://derstandard.at/Text/Wii/?id=1216917909574>. Accessed on January 14th, 2009.
3. BAUER S.M., LOIPL R., JAGSCH R., GRUBER D., RISSER D., THAU K., FISCHER G. (2008): Mortality in opioid-maintained patients after release from an addiction clinic. *Eur Addict Res* 14(2): 82-91.
4. BINSWANGER I.A., STERN M.F., DEYO R.A., HEAGERTY P.J., CHEADLE A., ELMORE J.G., KOEPESELL T.D. (2007): Release from prison – a high risk of death for former inmates. *N Engl J Med* 356(2): 157-165.
5. BLEICHA., GELKOPFM., SCHMIDTV., HAYWARD R., BODNER G., ADELSON M. (1999): Correlates of benzodiazepine abuse in methadone maintenance treatment. A 1 year prospective study in an Israeli clinic. *Addiction* 94(10): 1533-1540.
6. BOYSA., FARRELLM., BEBBINGTON P., BRUGHA T., COID J., JENKINS R., LEWIS G., MARSDEN J., MELTZER H., SINGLETON N., TAYLOR C. (2002): Drug use and initiation in prison: results from a national prison survey in England and Wales. *Addiction* 97: 1551-1560.
7. BRAMNESS J.G., KORNØR H. (2007): Benzodiazepine prescriptions for patients in opioid maintenance treatment in Norway. *Drug Alcohol Depend* 90(2-3): 203-209.
8. BROOKE D., TAYLOR C., GUNN J., MADEN A. (1998): Substance misusers remanded to prison – a treatment opportunity? *Addiction* 93(12): 1851-1856.
9. BUREAU OF JUSTICE STATISTICS (2007): Criminal Offenders Statistics. Available at <http://www.ojp.usdoj.gov/bjs/crimoff.htm>, last revised August 8, 2007. Accessed January 21st, 2008.
10. BUREAU OF JUSTICE STATISTICS (2007): Federal Justice Statistics. Available at <http://www.ojp.usdoj.gov/bjs/fed.htm>, last revised December 20, 2007. Accessed January 21st, 2008.
11. CANADIAN HIV/AIDS LEGAL NETWORK (2004): Prison needle exchange: lessons from a comprehensive review of international evidence and experience.
12. CDC (2001): Drug Use, HIV, and the Criminal Justice System. Available at <http://www.cdc.gov/idu/facts/druguse.htm>, last modified December 26th, 2007. Accessed January 21st, 2008.
13. DEMARIA P.A. Jr., STERLING R., WEINSTEIN S.P. (2000): The effect of stimulant and sedative use on treatment outcome of patients admitted to methadone maintenance treatment. *Am J Addict* 9(2): 145-153.
14. DOLAN K., RUTTER S., WODAK A.D. (2003): Prison-based syringe exchange programmes: a review of international research and development. *Addiction* 98(2): 153-158.
15. DOLAN K., WODAK A. (1996): An international review of methadone provision in prisons. *Addiction Res* 4(1): 85-97.
16. DOLE V.P., NYSWANDER M. (1965): A medical treatment for diacetylmorphine (heroin) addiction. *JAMA* 193: 80-84.
17. DOLE V.P., ROBINSON J.W., ORRACA J., TOWNS E., SEARCYP., CAINE E. (1969): Methadone treatment of randomly selected criminal addicts. *N Engl J Med* 280(25): 1372-1375.
18. DRUCKER E. (1999): Drug prohibition and public health: 25 years of evidence. *Public Health Rep* 114(1): 14-29.
19. EDER H, JAGSCH R., KRAIGHER D., PRIMORAC

- A., EBNER N., FISCHER G. (2005): Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. *Addiction* 100(8): 1101-1109.
20. EMCDDA (2001): *Annual report on the state of the drugs problem in the European Union*. Office for Official Publications of the European Communities, Luxembourg.
 21. EMCDDA (2002): *Annual report on the state of the drugs problem in the European Union and Norway*. Office for Official Publications of the European Communities, Luxembourg.
 22. EMCDDA (2004): *Public expenditure on drugs in the European Union*. Office for Official Publications of the European Communities, Luxembourg.
 23. ESHRATI B., ASL R.T., DELL C.A., AFSHAR P., MILLSON P.M., KAMALI M., WEEKES J. (2008): Preventing HIV transmission among Iranian prisoners: Initial support for providing education on the benefits of harm reduction practices. *Harm Reduct J* 5: 21.
 24. FARLEY J., VASDEV S., FISCHER B., HAYDON E., REHM J., FARLEY T.A. (2005): Feasibility and outcome of HCV treatment in a Canadian federal prison population. *Am J Public Health* 95(10): 1737-1739.
 25. FARLEY J.D., WONG V.K., CHUNG H.V., LIM E., WALTERS G., FARLEY T.A., YOSHIDA E.M. (2005): Treatment of chronic hepatitis C in Canadian prison inmates. *Can J Gastroenterol* 19(3): 153-156.
 26. FARRELL M., MARSDEN J. (2007): Acute risk of drug-related death among newly released prisoners in England and Wales. *Addiction* 103: 251-255.
 27. FAZEL S., BAINS P., DOLL H. (2006): Substance abuse and dependence in prisoners: a systematic review. *Addiction* 101(2): 181-191.
 28. FEDERAL MINISTRY OF EDUCATION, ARTS AND CULTURE (2008): *Grunddaten des österreichischen Schulwesens – Zahlenspiegel 2008*. Available at http://www.bmukk.gv.at/medienpool/17604/zahlenspiegel_2008.pdf. Accessed on February 18th, 2009.
 29. FEDERAL MINISTRY OF JUSTICE OF THE REPUBLIC OF AUSTRIA (2008): *Anfragebeantwortung der Bundesministerin für Justiz 4606/AB (XXIII. GP)*. Available at http://www.parlinkom.gv.at/PG/DE/XXIII/AB/AB_04606/imfname_121563.pdf. Accessed on January 14th, 2009.
 30. FISCELLA K., MOORE A., ENGERMAN J., MELDRUM S. (2005): Management of opiate detoxification in jails. *J Addict Dis* 24(1): 61-71.
 31. FISCHER G., PETERNELLA A., BALDINI A., BREZA A., EDER H., NIEDERMAYER I., TOPITZ A., HABERLER A., KRAIGHER D., KASPER S. (1998): *Behandlung der Abhängigkeit von psychotropen Substanzen* (Tätigkeitsprofil der Drogenambulanz). Allgemeines Krankenhaus der Stadt Wien, Wien.
 32. GOMBAS W., FISCHER G., JAGSCH R., EDER H., OKAMOTO I., SCHINDLER S., MÜLLER C., FERENCI P., KASPER S. (2000): Prevalence and distribution of hepatitis C subtypes in patients with opioid dependence. *Eur Addict Res* 6(4): 198-204.
 33. GOWING L., ALIR., WHITE J. (2006): Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev* 2006(2): CD002025.
 34. GRUBER V.A., DELUCCHI K.L., KIELSTEIN A., BATKI S.L. (2008): A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug Alcohol Depend* 94(1-3): 199-206.
 35. GSELLHOFER B., KÜFNER H., VOGT M., WEILER D. (1999): *European Addiction Severity Index: EuropASI*. Nach der 5. Auflage der amerikanischen Version von McLellan und Baltmannsweiler. Schneider Verlag, Hohengehren.
 36. GUNTER T.D., ARNDT S., WENMAN G., ALLEN J., LOVELESS P., SIELENI B., BLACK D.W. (2008): Frequency of mental and addictive disorders among 320 men and women entering the Iowa prison system: use of the MINI-Plus. *J Am Acad Psychiatry Law* 36(1): 27-34.
 37. HAIG T. (2003): Randomized controlled trial proves effectiveness of methadone maintenance treatment in prison. *Can HIV AIDS Policy Law Rev* 8(3): 48.
 38. HENNEBEL L.C., STÖVER H., CASSELMAN J. (2005): Substitution treatment in European prisons. A study of policies and practices of substitution treatment in prison in 18 European countries. *Heroin Add & Rel Clin Prob* 7(2): 31-36.
 39. HETLAND H., EIKELAND O.J., MANGER T., DISETH A., ASBJØRNSEN A. (2007): Educational background in a prison population. *Journal of Correctional Education* 58(2): 145-156.
 40. KARIMINIA A., LAW M.G., BUTLER T.G., CORBEN S.P., LEVY M.H., KALDOR J.M., GRANT L. (2007): Factors associated with mortality in a cohort of Australian prisoners. *Eur J Epidemiol* 22: 417-428.
 41. KINLOCK T.W., BATTJES R.J., SCHWARTZ R.P., THE MTC PROJECT TEAM (2002): A novel opioid maintenance program for prisoners: preliminary findings. *J Subst Abuse Treat* 22: 141-147.
 42. KINLOCK T.W., BATTJES R.J., SCHWARTZ R.P.; MTC PROJECT TEAM (2005): A novel opioid maintenance program for prisoners: report of post-release outcomes. *Am J Drug Alcohol Abuse* 31(3): 433-454.
 43. KINLOCK T.W., GORDON M.S., SCHWARTZ R.P., O'GRADY K., FITZGERALD T.T., WILSON M. (2007): A randomized clinical trial of methadone maintenance for prisoners: results at 1-month post-release. *Drug Alcohol Depend* 91(2-3): 220-227.

44. KINLOCK T.W., GORDON M.S., SCHWARTZ R.P., O'GRADY K.E. (2008): A study of methadone maintenance for male prisoners: 3-month postrelease outcomes. *Crim Justice Behav* 35(1): 34-47.
45. LAI S.H., YAO Y.J., LO D.S. (2006): A survey of buprenorphine related deaths in Singapore. *Forensic Sci Int* 162(1-3): 80-86.
46. LANGROD J., LOWINSON J., RUIZ P. (1981): Methadone treatment and physical complaints: a clinical analysis. *Int J Addict* 16(5): 947-952.
47. MAGURA S., ROSENBLUM A. (2001): Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. *Mt Sinai J Med* 68(1): 62-74.
48. MAREMMANI I., PANI P.P., PACINI M., PERUGI G. (2007): Substance use 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.
49. MARTYRES R.F., CLODE D., BURNS J.M. (2004): Seeking drugs or seeking help? Escalating "doctor shopping" by young heroin users before fatal overdose. *Med J Aust* 180(5): 211-214.
50. MASSON C.L., BARNETT P.G., SEES K.L., DELUCCHI K.L., ROSEN A., WONG W., HALL S.M. (2004): Cost and cost-effectiveness of standard methadone maintenance treatment compared to enriched 180-day methadone detoxification. *Addiction* 99(6): 718-26.
51. MEGARBANE B., HREICHER., PIRNAYS S., MARIE N., BAUD F.J. (2006): Does high-dose buprenorphine cause respiratory depression?: possible mechanisms and therapeutic consequences. *Toxicol Rev* 25(2): 79-85.
52. OLIVER J. (1991): The social care directive: development of a quality of life profile for use in community services for the mentally ill. *Soc Work Soc Sci Rev* 3: 5-45.
53. PRATT D., PIPER M., APPLEBY L., WEBB R., SHAW J. (2006): Suicide in recently released prisoners: a population-based cohort study. *Lancet* 368(9530): 119-123.
54. PRIEBE S., OLIVER J., KAISER W. (eds.) (1991): *Quality of life and mental health care*. Wrightson Biomedical Publishing, Petersfield UK.
55. REITOX NATIONAL FOCAL POINT (2005) Austria Drug Situation 2005. Report to the EMCDDA. Available at <http://www.emcdda.europa.eu/html.cfm/index435EN.html>. Accessed on July 27th, 2007.
56. SABBATINIS., GIULIANIR., MANFREDIR. (2006): Combined pegylated interferon and ribavirin for the management of chronic hepatitis C in a prison setting. *Braz J Infect Dis* 10(4): 274-278.
57. SARANGA., RHODEST., PLATTL., KIRZHANOVA V., SHELKOVNIKOVA O., VOLNOVV., BLAGOVO D., RYLKOVA. (2006): Drug injecting and syringe use in the HIV risk environment of Russian penitentiary institutions: qualitative study. *Addiction* 101(12): 1787-1796.
58. SEES K.L., DELUCCHI K.L., MASSON C., ROSEN A., CLARK H.W., ROBILLARDH., BANYS P., HALL S.M. (2000): Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *JAMA* 283(10): 1303-1310.
59. STALLWITZ A., STÖVER H. (2007): The impact of substitution treatment in prisons – a literature review. *Int J Drug Policy* 18(6): 464-474.
60. STARK K., HERRMANN U., EHRHARDT S., BIENZLE U. (2006): A syringe exchange programme in prison as prevention strategy against HIV infection and hepatitis B and C in Berlin, Germany. *Epidemiol Infect* 134(4): 814-819.
61. STERLING R.K., HOFMANN C.M., LUKETIC V.A., SANYAL A.J., CONTOS M.J., MILLS A.S., SHIFFMAN M.L. (2004): Treatment of chronic hepatitis C virus in the Virginia Department of Corrections: can compliance overcome racial differences to response? *Am J Gastroenterol* 99(5): 866-872.
62. STRANG J., GOSSOP M., HEUSTON J., GREEN J., WHITELEY C., MADEN A. (2006): Persistence of drug use during imprisonment: relationship of drug type, recency of use and severity of dependence to use of heroin, cocaine, and amphetamine in prison. *Addiction* 101(8): 1125-1132.
63. TAN J.A., JOSEPH T.A., SAAB S. (2008): Treating hepatitis C in the prison population is cost-saving. *Hepatology* 48(5): 1387-1395.
64. WHO (2004): *Best Practice in HIV/AIDS Prevention and Care for Injecting Drug Abusers: The Triangular Clinic in Kermanshah, Islamic Republic of Iran*. World Health Organization, Geneva.

Role of funding source

No funds for this study

Contributors:

Mrs. Kammerer collected the data; Mrs. Ebner & Mrs. Winklbaaur analyzed and interpreted the data, and assisted Mr. Matzenauer who wrote the major part of the first version of the article, in writing. Mrs. Metz and Mrs. Radler wrote equally on the first version of the paper, did literature search, corrected the paper regarding content and spelling and Mrs. Metz conducted the journal submission, as well as the major revision of the article before resubmitting it to "Heroin Addiction and Related Clinical Problems". Mrs. Fischer supervised all contributing authors.

Conflict of Interest:

There is no conflict of interest.

Acknowledgements

We would like to thank all inmates of “Justizanstalt Stein” who participated in our evaluation.

Furthermore, we would like to thank the prison officers,

the administrative officers, the psychological and medical team, the social workers at “Justizanstalt Stein”, and its head Friedrich Nowak.

Walter Kahl at the Prison Service Department (Vollzugsdirektion) of the Austrian Federal Ministry of Justice provided essential data about the number of detainees currently in opioid maintenance therapy.

Received July 30, 2009 - Accepted November 30, 2009



Pacini Editore & AU CNS

Regular article

Heroin Addict Relat Clin Probl 2010; 12(1): 17-24

HEROIN ADDICTION &
RELATED CLINICAL
PROBLEMS

www.europad.org

Dose Determination in Dual Diagnosed Heroin Addicts during Methadone Treatment

Icro Maremmani^{1,2,3}, Matteo Pacini³, Stefania Canoniero⁴, Joseph Deltito^{3,6},
Angelo G.I. Maremmani^{2,3} and Alessandro Tagliamonte⁵

1. "Vincent P. Dole" Dual Diagnosis Unit, Santa Chiara University Hospital, Department of Psychiatry, NPB, University of Pisa, Italy

2. AU-CNS, "From Science to Public Policy" Association, Pietrasanta, Lucca, Italy

3. "G. De Lisio", Institute of Behavioral Sciences Pisa, Italy

4. Department of Drug Dependence, La Spezia, Italy

5. Department of Neuroscience, Section of Pharmacology, University of Siena, Italy

6. Department of Psychiatry and Behavioural Science, New York Medical College, Valhalla, New York, USA.

Summary

Ninety-nine consecutive responders to treatment for heroin addiction (54 with one or more Axis I psychiatric diagnosis (DD-patients), and 45 without psychiatric comorbidity (NDD-patients), were monitored prospectively (20 months on average, min.1, max. 51), in order to achieve some useful clinical information pertaining to effective methadone dose determination for double diagnosed heroin addicts. First day and first month dosages do not differ between the two groups. Stabilization dosages are higher in DD patients than in NDD patients. The time to reach stabilization phase is longer in DD patients than in NDD patients. Tapering of methadone follows a similar trend in both groups. DD patients need more attention from clinicians, especially when stabilization dosage has to be established.

Key Words: Methadone Maintenance; Psychiatric Comorbidity; Methadone Dose Determination

1. Introduction

Methadone is a long-acting opioid analgesic with well-characterized pharmacological properties that make it suitable for the treatment of heroin addicts on a maintenance protocol. The development of methadone maintenance treatment programs (MMTPs) started in New York in the mid-sixties, and since then it became the most widely prescribed treatment for heroin addiction worldwide. In the first study, the initial dose was around 35 milligrams a day, and it was gradually increased to standard doses of approximately 100 mgs/d [1]. However, several decades later, there is not yet complete agreement on the doses of methadone to be prescribed in a maintenance program, and the doses used in randomized clinical trials are often higher than those currently used in routine clinical practice [7]. These differences may explain recurring claims for alleged low methadone effectiveness,

since the response to methadone treatment (in terms of retention into therapy, negative urinalysis for illicit drugs, and socialization) is dose-dependent.

An outpatient treatment service for drug addicts (Dual Diagnosis Unit) has been established many years at the "Santa Chiara" University Hospital, Department of Psychiatry, University of Pisa, Italy, EU.

The service was initiated with the aim to treat drug abusers, in particular heroin addicts, with a double diagnosis; that is, subjects with one or more DSM-IV-TR Axis I psychiatric diagnoses in addition to that of Opioid Dependence. In order to assess the existence of possible peculiarities in the treatment protocols used in these patients, an equal number of heroin addicts with no additional Axis I mental disorders were enrolled in the program. Some recent publications report the main outcomes of this study and show that, when a proper stabilization level is attained in the long-term, du-

ally diagnosed opioid dependent patients who survive early attrition tend to stay in treatment longer than those without psychiatric co-morbidity [3, 6]. Retention in the program is one of the hard-core endpoints that validates treatment for heroin addiction.

The aim of this study was that of describing and discussing in detail the differences observed between the treatment participants in the two groups and stress their relevance in various treatment phases.

2. Methods

2.1 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 "stabilized" and the maintenance dose reached is referred to as the "stabilization dose". No upper limit for dosage exists. Nevertheless, a time limit has been imposed in this setting: patients who cannot achieve stabilization within one year stop the program and are transferred to local treatment units. The dosage is increased on the basis of the results of urinalyses, and other criteria such as improvement in social parameters does not effect dose stability as long as urine samples stay positive for opiates. Patients are not allowed to raise or lower their doses by themselves. Take-home doses, for at most a 7-day period are allowed, once patients have shown complete compliance with the rules of the programme. Urine samples for analyses are collected randomly almost once a month, to evaluate the metabolites of illicit drugs and benzodiazepines.

2.1 Sample

The sample included in this study consisted of 99 consecutive stabilized patients followed during treatment for an average of 592 ± 417 days (min 365 max 1536). During the follow-up period we excluded patients with a negative outcome. We considered a "negative outcome" when a patient has failed to achieve "stabilization" within a year (see above) or has relapsed into addictive behaviour after a period of stabilization. We are aware that this limit precludes an intention to treat analysis. On the other hand, we are forced to operate within a rigid number of slots.

Most of the patients were male ($n=76$; 76.8%), single ($n=69$; 69.7%) and unemployed ($n=58$; 59.8%), and had less than 13 years of formal education ($n=67$; 69.8%). Age ranged

between 19 and 46 years (mean = 30 sd 6). The age of the first use was 18 ± 4 (min 13 max 31). The age of the continued use was 20 ± 4 (min 14 max 31). The mean duration of drug addiction was 8.6 years (sd 5.9 (min 1 month max 22 yrs)). The age of the first therapeutic contact was 27 ± 6 (min 16 max 45). 85 (85.9%) patients showed physical complications, 92 (92.9%) had an abnormal mental status at treatment entry. Social adjustment was problematic in 60 (60.9%) patients regarding their family life; 66 (66.7%) regarding their job, 29 (29.3) regarding their romantic involvement and in 57 (57.6%) regarding their social contacts and or their leisure time activities. 53 (53.5%) had legal problems, 68 (68.7%) were polyabusers, 88 (88.9%) had been unsuccessfully treated in the past.

Forty-five subjects had one or more DSM-IV-TR Axis I psychiatric diagnoses in addition to Opioid Dependence and are defined as Dual Diagnosed Patients (or "DD-patients"). Fifty-four subjects did not have any additional Axis I mental disorder diagnosed, and are defined as not having a Dual Diagnosis (or "NDD-patients").

Heroin Addicts with and without Dual Diagnosis do not differ with regard to physical complications, abnormal mental status at study entry, social adjustment (family, job, romantic involvement, social/leisure and legal problems), polyabuse, unsuccessful treatments in the past, age of first use and age of continuous use.

Subjects with psychiatric comorbidity (DD-patients) showed significant differences (after Buonferroni's correction) regarding the duration of addiction, which is less than that reported by N-DD patients (Mean Rank: NDD=58.22 Vs DD=38.80 Mann-Whitney z test= -3.36 p=.0008). According to the literature DD patients are seeking for help earlier (NDD=28±7 yrs Vs DD=25±5 yrs T-test=-2.68 p=0.009).

All patients gave their written informed consent to the study after the procedure had been fully explained.

2.3 Assessment

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

2.3.1 Drug Addiction History Rating Scale (DAH-RS)

The DAH-RS, (administered at the beginning of treatment) [4] 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, haemolympathic, 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).

2.3.2 Psychiatric Diagnostic Evaluation. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version.

This user-friendly instrument [2] will help clinicians make standardized, reliable, and accurate diagnoses and avoid the common problem of “premature closure”- the premature focus on one diagnostic possibility. Specifically adapted from the research standard for Axis I structured clinical interviewing for use in clinical settings, the SCID-I covers those DSM-IV diagnoses most commonly seen by clinicians and includes the diagnostic criteria for these disorders with corresponding interview questions. The SCID-I is divided into six self-contained modules that can be administered in sequence: mood episodes; psychotic symptoms; psychotic disorders; mood disorders; substance use disorders; and anxiety, adjustment, and other disorders

The criteria for a “dual diagnosis” are satisfied when clearly distinct symptoms of heroin dependence and of an autonomous psychiatric disorder have been identified.

Axis II comorbidity was excluded when our sample was clustered. Axis I and Axis II disorders are two related but separate dimensions of psychopathology. In addition, a wide range of personality disorders are present among substances abusers, so it is very difficult to identify subgroups on the basis of Axis II disorders. In this study the Axis I-diagnosed heroin addict group served as a “psychiatric” control group; the non-Axis I diagnosis group served as a traditional “normal” control group. NDD patients were excluded from this study when an Axis II disorder was present.

2.4 Statistical analysis

We report the dosage of the first day, the weekly dosage for the first month, the every four-month dosage for the entire duration of the study (comparing these dosages between heroin addicts with and without dual diagnosis). We also compared the stabilization dose and the time required to achieve it. We used the routines of SPSS 4.0. The statistical tests were considered significant at the level of $p < 0.05$.

3. Results

Table 1 compares first-day dosages in heroin addicts with

and without dual diagnosis.

The first day mean dosage was 46 ± 37 for NDD-patients and 40 ± 22 for DD-patients respectively. The most frequent dosage (mode) was 30 mg for NDD-patients and 40 for DD-patients respectively. The median (the dose which splits the sample in halves) dose was 37.5 mg for NDD-patients and 40 for DD-patients respectively. One third of the sample was treated with dosages above 40mg. The highest dosages in NDD-patients were 130 mg for one patient and 200 mg for two patients. Those in DD-patients were 80 mg for two patients and 100 mg for two patients. These differences were not statistically significant (Mann-Whitney U - Wilcoxon Rank Sum W Test $z = -0.41$ 2-tailed $p = 0.67$).

Table 2 reports the weekly dosages within the first month. During the first week dosages increased by 139.5%. In the following three weeks dosages increased by 120.0%, 112.5% and 104.9%, respectively. No significant differences were found with the exception of day-7 dosages that were higher in NDD than DD-patients.

Table 3 reports the dosage variation for the first month of treatment in Heroin Addicts with and without dual diagnosis. Only at the end of the first week are variations statistically different according to groups with and without dual diagnosis. No patients with dual diagnosis reduced dosages, but a great percentage of these patients did not increase first day dosage during the first week. No differences between groups have been shown during the second, the third and the fourth week.

Considering the follow-up period, the methadone mean stabilization dosage (highest dose taken for at least 4 weeks, related to “positive outcome”) was 119 ± 70 mg/day (min 22 max 400). The mode and the median were 80 mg/day and 100 mg/day respectively. Seventeen patients (17.2%) were treated with dosages of 60 mg/day or less. Thirty-six patients (35.4%) received a dosage greater than 120 mg/day. DD-patients need a stabilization dosage higher than NDD-patients (136 ± 85 Vs 105 ± 51 ; T-test = 2.12 $p = .03$).

The time to reach the stabilization dose (months) was 5 ± 5 (min 1 max 31). The mode was 3 and the median was 3. Only 7 patients (7.1%) needed a time longer than 9 months. It takes longer to stabilize DD-patients than NDD-patients (7 ± 6 Vs 3 ± 2 ; T-test = 4.34 $p < .001$).

Table 4 displays the trends of dosage over time, separately for DD and NDD-patients, and for the whole sample. Time is divided into four-month intervals, and mean dosages for correspondent intervals are reported. NDD-subjects need higher methadone doses than DD subjects at the beginning of the program (interval 1), but the relationship reverses soon after in interval two, when DD-patients are the ones who require higher dosages. The latter relationship is maintained all through the study period, despite later changes in dose-trend in the single groups. Nevertheless, the course of stabilization appears to be similar in NDD and DD-patients, since both groups show a trend towards an increase of methadone dose in interval 1 and 2, with peak mean-dose reached at the end

Table 1. First day methadone dosage in 99 responders to treatment heroin addicts with and without dual diagnosis at the start of methadone maintenance

Dosage (mg)	Total sample N=99	NDD N=54	DD N=45
	N (%)	N (%)	N (%)
10	7 (7.1)	2 (3.7)	5 (11.1)
15	3 (3.0)	1 (1.9)	2 (4.4)
20	11 (11.1)	7 (13.0)	4 (8.9)
30	25 (25.3)	16 (29.6)	9 (20.0)
35	1 (1.0)	1 (1.9)	
40	19 (19.2)	8 (14.8)	11 (24.4)
45	1 (1.0)	1 (1.9)	
50	11 (11.1)	6 (11.1)	5 (11.1)
60	8 (8.1)	4 (7.4)	4 (8.9)
70	3 (3.0)	2 (3.7)	1 (2.2)
80	4 (4.0)	2 (3.7)	2 (4.4)
90	1 (1.0)	1 (1.9)	
100	2 (2.0)		2 (4.4)
130	1 (1.0)	1 (1.9)	
200	2 (2.0)	2 (3.7)	

Table 2. Weekly dosage for the first month of treatment in heroin addicts with and without dual diagnosis

	Total sample N=99	NDD patients N=54	DD patients N=45
	M±s	M±s	M±s
Day1	43±31	46±37	40±22
Day 7	60±35	66±38*	53±31*
Day 14	72±41	76±40	67±43
Day 21	81±48	85±42	77±54
Day 28	85±49	89±44	80±55

* Mann-Whitney U - Wilcoxon Rank Sum W p<0.05

of interval 2 for both groups. From interval 3 on, a trend towards lowering of dosage is seen, which temporarily inverts in interval 5 for DD-subjects., and in interval 7 for NDD ones. Dose values tend to raise for DD, but not for NDD-patients, as late as at interval 9.

The retention in treatment of patients with and without psychiatric comorbidity is not different, In DD-patients, 93.36% are censored, in comparison with 88.89% of NDD patients. At the start of treatment the attrition sample is similar for the two groups. In the first four months period no NDD-

patients leave the treatment whereas DD-patients show the greatest rate of attrition. After the 8th month of treatment no DD-patient leaves treatment for reasons related to treatment failure. Among NDD patients it is possible to find cases of unsuccessful treatment for as long as twelve months. After this period no NDD-patient leaves the treatment. Leu-Desu Statistics (F = 1.36; p = 0.24) demonstrates that the retention rates of the two groups are similar.

Table 3. Dosage variation for the first month of treatment in Heroin Addicts with and without dual diagnosis

Methadone dosage variation	Total sample N=99	NDD patients N=54	DD patients N=45	Chi
Day1-Day7 period				
Decreased dosages	3	3 (100)	0 (0)	9.59**
Increased dosages	68	42 (61.8)	26 (38.2)	
No variations	28	9 (32.1)	19 (67.9)	
Day7-Day14 period				
Decreased dosages	5	4 (80.0)	1 (20.0)	1.62
Increased dosages	66	34 (51.5)	32 (48.5)	
No variations	28	16 (57.1)	12 (42.9)	
Day14-Day21 period				
Decreased dosages	3	1 (33.3)	2 (66.7)	0.56
Increased dosages	56	31 (55.4)	25 (44.6)	
No variations	40	22 (55.0)	18 (45.0)	
Day21-Day28 period				
Decreased dosages	3	3 (100)	0 (0)	4.27
Increased dosages	32	20 (62.5)	12 (37.5)	
No variations	64	31 (48.4)	33 (51.6)	

*p<0.01 **p<0.001

Dosages increase, in the two groups, during all periods in a statistically significant way (Mann-Whitney U - Wilcoxon Rank Sum W p<0.01)

Table 4. Four monthly period mean dosage in heroin addicts with and without psychiatric comorbidity

	Total sample		NDD patients		NDD patients	
	N	M±s	N	M±s	N	M±s
1st Quarter	94	89±53	49	91±44	45	87±61
2st Quarter	76	106±70	37	102±53	39	111±83
3st Quarter	66	93±59	31	81±49	35	102±67
4st Quarter	56	81±57	25	70±44	31	90±64
5st Quarter	48	77±57	23	63±41	25	92±66
6st Quarter	42	72±53	21	58±38	21	87±62
7st Quarter	37	69±46	20	60±35	18	77±54
8st Quarter	33	61±37	17	55±30	16	67±43
9st Quarter	20	63±36	10	51±24	10	71±42
10st Quarter	11	69±40	5	50±21	6	84±47

4. Discussion

The first day methadone dosage aims to eliminate the opioid withdrawal syndrome. This dosage is generally comprised between 20 and 40 mg [8]. Although our data demonstrate that 6.1% of our sample need a methadone dose greater than 80 mg. In a few cases this dosage was raised to over 100 mg. Undermedication of a patient can result in a rapid termination from therapy as patients will “escape” and not return for follow up. So it is crucial to have a safe methodology to increase a methadone dosage over 20-40 mg the same day. We give the first 20 mg to the patients and we re-evaluate withdrawal symptoms after 2 hours. If symptoms are still present an additional dose of 20 mg is provided, followed by a 2-hour period of clinical observation. This procedure should be repeated until withdrawal symptoms are extinguished. The dosage so established is the daily dose for the earlier induction phase and must be repeated until a pharmacological steady state is reached (3-4 days). We used the exceptional dosage (200 mg) in two treatment seeking pushers without psychiatric comorbidity. DD-patients do not need a greater first-day dosage than NDD-patients. This trend is maintained throughout the first month of treatment. Summarizing, we can state that there is no difference either in treating withdrawal symptoms or in methadone dosage required during the first month of treatment between patients with and without psychiatric comorbidity.

As we previously demonstrated [3, 5, 6], the stabilization dosage is higher in DD-patients than in NDD-patients. Psychiatric comorbidity does not differently affect the opioid tolerance in DD compared to NDD-patients, as demonstrated by the first day methadone dosage which is required. On the other hand, psychiatric illness influences therapeutic maintenance dose: more methadone is needed in DD-patients to improve their formerly dysfunctional behaviors. On clinical grounds, the presence of psychiatric illness is not to be considered as a drawback when adequate methadone doses have to be administered. On the contrary, undermedicated DD-patients may be mistaken for non-responders to the treatment if the attitude of the treating clinician is to be too limiting with dosages. The time to reach the stabilization dose appears to be longer in our patients than what is frequently reported in the literature (5 months Vs 1 month). This time is longer in DD than in NDD-patients (7 months Vs 3 months). From the clinical point of view, these data suggest the importance of prolonged medical surveillance while on the stabilization dosage. This is true especially for DD-patients, who take longer to reach their stabilization dosage. Such an attitude can avoid mistaking undermedicated patients for non-responders, particularly when psychiatric illness is present. It follows that, as far as DD-patients are properly managed, and their therapeutic plan adjusted according to their clinical state, the stabilization can be reached as successfully as for

NDD-patients. After the stabilization phase, lasting 8 months on average, methadone tapering can start. Methadone doses administered to DD-patients becomes higher than NDD-patients' as late as in the 8th month. From then on to the end of observation, dosage stays higher for DD-patients, but show the same trend toward decrease as for NDD patients. On the whole, it is advisable to start DD-patients on dosages equal or slightly lower than those administered to NDD-patients, in the first month of treatment. Stabilization dosage must be aimed at for rather a long time (around 5 months); stabilization dosage is expected to be higher (around 140 mg/day) than for NDD-patients. The tapering phase proceeds similarly for both groups. Social adjustment is not likely to be impaired when methadone is being tapered. Data concerning the retention rate corroborate the statement that DD and NDD-patients can equally benefit from MMTP.

5. Conclusions

A third to a half of opiate users may suffer from mental health illnesses, including anxiety, mood disorders, psychotic disorders. Entry into an MM treatment has a significant positive impact in their psychological well-being. These patients may have equivalent outcomes, yet need more attention from clinicians regarding the issue of adequate dosages (lower before the 2nd quarter and higher after the 2nd quarter of treatment). Particular attention is needed when stabilization dosage is to be established, which is expected to take longer in DD than in NDD-patients.

References

1. Dole V.P., Nyswander M.E. (1965): A medical treatment for diacetylmorphine (heroin) addiction: A clinical trial with methadone hydrochloride. *JAMA*. 193 80-84.
2. First M. B., Spitzer R. L., Gibbon M., Williams J. B. W. (1997): Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version. American Psychiatric Publishing, Inc, Arlington, VA, USA.
3. Maremmani I., Canoniero S., Pacini M. (2000): Methadone dose and retention in treatment of heroin addicts with Bipolar I Disorder comorbidity. Preliminary Results. *Heroin Addict Relat Clin Probl*. 2:(1) 39-46.
4. Maremmani I., Castrogiovanni P. (1989): DAH-RS: Drug Addiction History Rating Scale. University Press, Pisa.
5. Maremmani I., Pacini M., Lubrano S., Perugi G., Tagliamonte A., Pani P.P., Gerra G., Shinderman M. S. (2008): The long term outcomes of treatment-resistant heroin addicts with and without Axis 1 psychiatric comorbidity (dual diagnosis). *Eur Addict Res*. 14:(3) 134-142.
6. 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.

7. Mattick R. P., Breen C., Kimber J., Davoli M. (2002): Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence (Cochrane Review). *The Cochrane Library, issue n 4.* Oxford: Update Software,
8. Payte J. T., Khuri E. T. (1993): Principles of Methadone dose determination. In: Parrino M. (Ed.) *State Methadone Treatment Guidelines.* U.S. Department of Health & Human Services, Rockville, MD. pp. 47-58.

Contributors

The authors contributed equally to this paper.

Conflict of Interest

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

Role of funding source

This paper was supported by internal funds

Received February 24, 2009 - Accepted June 28, 2009



Pacini Editore & AU CNS

Regular article

Heroin Addict Relat Clin Probl 2010; 12(1): 25-32

HEROIN ADDICTION &
RELATED CLINICAL
PROBLEMS

www.europad.org

Urine Labelling Marker System for Drug Testing Improves Patient Compliance

Kaarlo Simojoki¹ and Hannu Alho^{2,3}

¹*Espoo Treatment and Rehabilitation Center, A-clinic Foundation, Espoo, Finland;*

²*National Institute for Health and Welfare, Helsinki, Finland;*

³*Unit of Substance Abuse Medicine, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland*

Summary

Urine drug testing plays an important role in substance abuse treatments. When strictly controlled, as it often is, urine sampling creates a humiliating situation and ties up resources. A new sample labelling method has been developed to make supervision unnecessary. This innovation is achieved by labelling the urine with polyethylene glycols. In this study, 57 patients who required urine sampling were randomized into two groups, the traditional supervised (TS) group and the new marker (NM) group. The urine test return rate was 98.3% in the NM group and 100% in the TS group. Attempts to manipulate the urine samples were discovered in 2% of the NM group and 0% of the TS group. Most patients preferred the NM testing method. The personnel too preferred the NM system, and estimated that it reduced their workload dedicated to drug screening by 50%. We conclude that the NM method is more acceptable to patients and personnel, and may increase compliance as a result.

Key Words: Drug Testing; Urine Samples; Drug Addiction; Marker System

1. Background

Urine drug testing, performed regularly or randomly, plays an important role in substance abuse treatments [1-3]. Drug testing can be used to measure compliance or treatment outcome, and can also ensure the safe administration of medication. Drug testing is also used in many other areas, such as child welfare [4], occupational health care, and imprisonment. In every case, the major challenge is to ensure that the urine being analysed can undoubtedly be connected to the correct person [5, 6]. To ensure this, urine sampling is often strictly controlled, which can be a humiliating situation and ties up human resources [7, 8]. This strict control may have a negative impact on mutual trust and reduce patient compliance.

Recently, a new marker method that makes supervision unnecessary for urine sample labelling was introduced [9, 10]. This outcome can be achieved by labelling the urine with modified polyethylene glycols, which are taken orally, quickly excreted through the kidneys, and do not occur in

natural urine. The different molecular weight marker solutions can be identified and linked to the person to whom it was given. In this procedure, only the consumption of the marker solution must be supervised. Drug testing is performed using normal, standard methods. In earlier studies [11] NM urine testing had a significantly higher sensitivity for the detection of concomitant drug use, and a high prevalence of urine manipulation in conventional urine screening methods was also observed. The most used manipulation method is dilution or mixing of the urine with other liquids, for example, water, for which attempts at manipulation can be checked by determining the urine creatinine concentration. When the urine labelling method is used, the marker concentration normally drops below the limit of detection before the drug reaches this limit. Screening tests with marker solutions can themselves be manipulated, most commonly by spitting a marker solution into clean urine from a different person. This, however, can be avoided by giving the marker together with sucrose, which never occurs in normal urine. Patients have also tried adding acids, alkalines and other chemical

substances to their urine samples. Such manipulations affecting the enzymatic drug analysis can be detected by applying CEDIA sample checks.

The aim of this study was to compare two different urine screening methods, the traditional sampling (TS) method and the new marker (NM) method, with respect to compliance, patient satisfaction, unfulfilled samples, and estimated time spent on sampling.

2. Methods

2.1 Subjects

The study began on November 10, 2008 and ended on January 19, 2009. It included volunteer patients undergoing treatment at the Espoo Treatment and Rehabilitation Centre, A-clinic Foundation. Subjects were from the opioid dependence maintenance treatment unit, the detox department, and outpatient department. They were asked if they would like to become volunteer participants in the study if urine testing was part of their treatment programme. Prior to participation, the procedures, benefits, and shortcomings of the methods were carefully explained to them. The patients in maintenance treatment were required to have a history of treatment for at least 1 month prior to the study. Patients were excluded if they were disabled, less than 18 years of age, pregnant, nursing women, or prisoners, or if they had a record of kidney disease. In total, 57 subjects were included, of which 29 were in maintenance treatment, 26 were in detox, and 2 were outpatients.

2.2 Randomization

The study subjects were randomized into two groups, the NM and the TS group. Randomization was conducted by a computer programme (Vassar Statistics).

2.3 Urine testing

Following urine testing, subjects in both groups completed a questionnaire. The information gathered included when the urine test was requested, where it was performed, and whether the situation was pleasant or unpleasant. Each subject was asked to deliver a urine sample once or several times, depending on the treatment phase and visits. In the NM test group, information was also gathered on the given marker, whether the patient took the urine test at home, and, if so, whether the sample was delivered. For each NM group sample, the laboratory bar code label was added to the data.

2.3.1 New marker test group

Marker substances were provided by RUMA GmbH (Co-

logne, Germany). Three different molecular weight markers were used and were given to the patients in a random fashion. The patients did not know the molecular weight of the solution they received. The marker vials, which contained 30 ml of the marker solution, were individually labelled. The marker was then mixed with approximately 100 ml of a sweet soft drink. Patients were asked to drink this solution 30 min prior to delivery of urine. They were then allowed to urinate without supervision in the clinic or to take the urine test tube home and return it to the clinic within 1 week. After patients submitted the urine sample (20–50 ml), the test tube was identified with a bar code label according to the routine procedure of the Central Laboratory in Cologne. An accompanying order sheet was labelled with the patient's name, the type of drug analyses requested (amphetamine/methamphetamine, barbiturates, benzodiazepines, cannabis, EDDP/methadone, cocaine and/or opiates), and the type of marker substance that was used. Samples were then sent to the Central Laboratory in Cologne via shuttle service. Prior to shipping, the samples were stored in a refrigerator in a closed room. At the Central Laboratory, order sheets were read by an automatic chart reader. Urine samples were centrifuged and directly transported to the analytical site for determination of marker substances and drug analyses. The cost for the marker and analysis, including sample collection material and transportation to Germany, was approximately 20 Euros per sample.

2.3.2 Traditional supervised test group

Standard direct inspection of patients while urinating was conducted by trained clinical staff. The patients were asked to provide the sample using a test toilet, which had mirrors on the walls to ease supervision. Patients were asked to undress sufficiently, which was determined by the person supervising. After depositing the sample in the test tube, the patient closed the test tube and gave it to the supervisor. The urine was then quickly screen tested in a separate closed room immediately, or later the same day; in the latter case, the sample was stored in a refrigerator before testing. The testing included cannabis, amphetamine, opioids, benzodiazepines, methadone and cocaine. The qualitative immunochromatographic screening test used was from ANL Produkter AB, a Swedish-registered medical device manufacturer, and was supplied by Pragmatic Oy. The cost for one immunological rapid screening test was 7.9 Euros.

2.4 Study measures

Background information included gender, age, and time in treatment. Patient satisfaction with the method used was recorded by the personnel soon after each urine test. A questionnaire was created that included background information,

two questions measuring satisfaction on a 1-6 scale, and the patient's preferred testing system. The questionnaire was given to the subjects at the end of the study period, or earlier if the patient was unlikely to return to treatment during that period, for example, if the patient was in detox treatment.

2.5 Primary and secondary outcomes

The primary outcomes were return rate of the urine samples, detected manipulation of urine samples, and patient satisfaction. The secondary outcomes were patient and staff satisfaction, estimated time used for the sampling and controlling procedure, and economic tradeoff.

2.6 Laboratory analysis of the marker substance, drugs and manipulation

2.6.1 Marker

Polyethylene glycols were determined in urine after a protein precipitation and centrifugation with HPLC. The samples were transferred to a guard column in an automatic dispenser, where most urine components were separated from the markers, which were then transferred onto the actual separating column. After separation, the chromatograms were obtained. Each signal in the chromatogram is characteristic of a polyethylene glycol of a specific chain length. The qualitative test analysis was performed by comparing the samples with Marker C and the controls A and B. The detection limit was at 0.2 ml marker/l urine. False negative results occurred when the time between intake of the marker and delivery of the urine was too short. Delayed excretion of the marker led to a negative result in < 0.5% of the patients, in whom the waiting period was extended to 45 min.

2.6.2 Drug testing

Tests for drug analyses were performed with reagents from Microgenics (Passau, Germany) on an automatic analyzer AU400 from Olympus (Hamburg, Germany). To cleave glucuronic acids from benzodiazepines, 0.3 U-glucuronidase/arylsulfatase from *Helix pomatia* (EC 3.2.1.31 and EC 3.1.6.1; Merck, Darmstadt, Germany) and 0.5 U of a recombinant β -glucuronidase from *E. coli* (EC 3.2.1.31; Roche, Mannheim, Germany) in 20 ml of 2 mol/l sodium acetate buffer (pH 4.8) were added to 1 ml urine and incubated for 30 min at room temperature prior to investigating benzodiazepines. Urine samples that were positive were retested on a gas chromatography/mass spectrometry (GC/MS) system (Hewlett Packard, 5790 Series II, connected with a mass selective detector 5972; Hewlett Packard, Palo Alto, USA) according to a previously described procedure [12]. For sample preparation, Bond Elute-Certify (130 mg/3 ml) solid-phase extraction columns from Varian Inc. were used. The extraction procedures were carried out as described in the Certified Methods manual by Varian Germany GmbH, Darmstadt.

2.6.3 Manipulation attempts

Urine samples were further investigated for creatinine, sample check reaction, and sucrose. To measure sucrose concentration, 3 μ l of urine were first incubated with 50 μ l of 48 μ g/ml invertase (46 U/ml) (EC 3.2.1.26) (Sigma, Deisenhofen, Germany, EC 3.2.1.26, Grade VII, 960 U/mg) in citrate/phosphate buffer (pH 4.5). The mixture was incubated at 37° C for 5 min. Then, 350 μ l of the glucose reagent [13], prepared as described by Sigma, were added. The absorbance was measured at 505 nm at the beginning and end of a 5-min incubation at 37° C. Calibration was done with

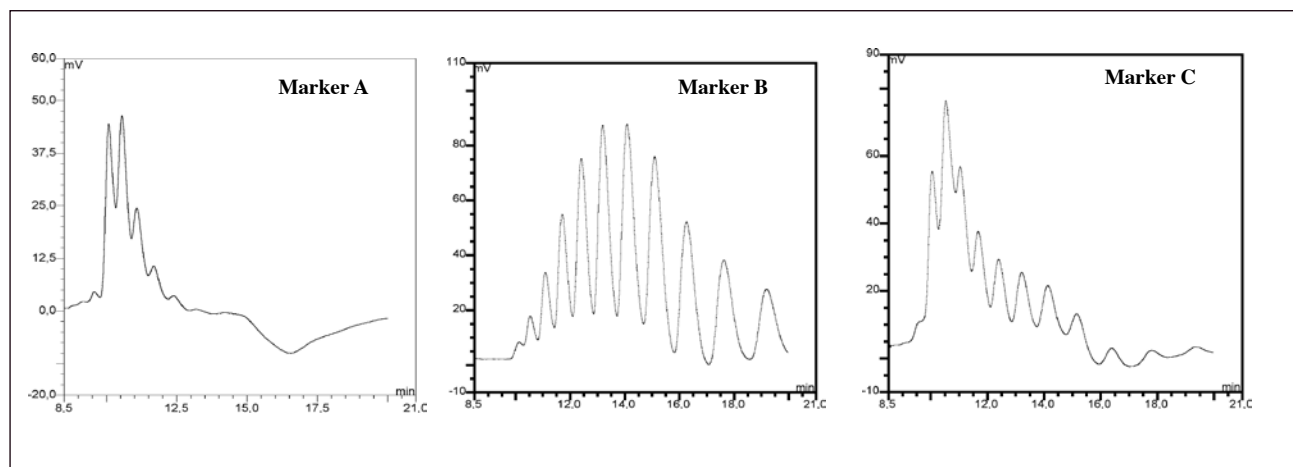


Figure 1. HPLC chromatograms of the three different markers

2–500 mmol/l sucrose solutions. This protocol was applied to an AU400 analyzer. Urine samples that were positive for sucrose were retested for glucose without pre-incubation with invertase by automatic reflex testing. Only samples that were positive for sucrose and negative for glucose were reported as “positive” for sucrose.

2.7 Statistical analyses

Subject and staff background information and questionnaire responses were manually entered into a Microsoft Excel spreadsheet and then analyzed using Excel.

2.8 Ethical conduct of study

The study was coordinated by the Department of Mental Health and Alcohol Research of the National Public Health Institute in Finland. The study was approved by the independent Hospital District of Helsinki and Uusimaa, Ethical Committee (permission 347/13/03/00/08). The study was conducted in accordance with the ICH Guidelines for Good Clinical Practice and the 1964 Declaration of Helsinki. All patients were required to have the ability to read and understand the patient information sheet and sign the informed consent. The patients were not paid or reimbursed for participation. Patient data were collected by the treating physician at each treatment site. Data protection was ensured throughout in accordance with the regulations of the National Public Health Institute.

3 Results

3.1 Subject disposition

The subject population comprised 65% males ($n = 37$) and 35% females ($n = 20$). There was no gender difference between the two study groups. The mean age was 36 years in the NM test group and 40 years in the TS test group. The average time in treatment was 32.4 months in the NM group compared to 16.5 months in the TS group. In the NM group, one study subject discontinued the study after three samples, and another discontinued the study after three samples but returned to the study 2 days later. Both completed the study questionnaire.

3.2 Unfulfilled urine samples and urine sample return rate

In total, 168 samples were requested; 116 for the NM test group, and 52 in the TS test group. In the NM group, the total return rate was 98.3% ($n = 114$). When the samples were taken home, which was done in 87% ($n = 101$) of the NM cases, the return rate was 97% ($n = 98$) (Fig. 2). In the

TS group, all urine samples were returned.

3.3 Urine manipulation

In the NM test group, the marker was missing in only two cases, demonstrating that manipulation attempts occurred in less than 2% of the returned samples. In the TS test group, no manipulation attempts were reported by the supervising employees.

3.4 Patient satisfaction

Of the 57 patients, 53 returned the questionnaire (93%). Subjects were also asked if they had experience with the method to which they had not been assigned during randomization. In the NM test group, 88.8% ($n = 32$) answered this question, and 87.5% ($n = 28$) stated that they had also given TS urine samples. In the TS test group, 84% ($n = 21$) answered the question, and 52% ($n = 11$) said they had experienced the NM test system.

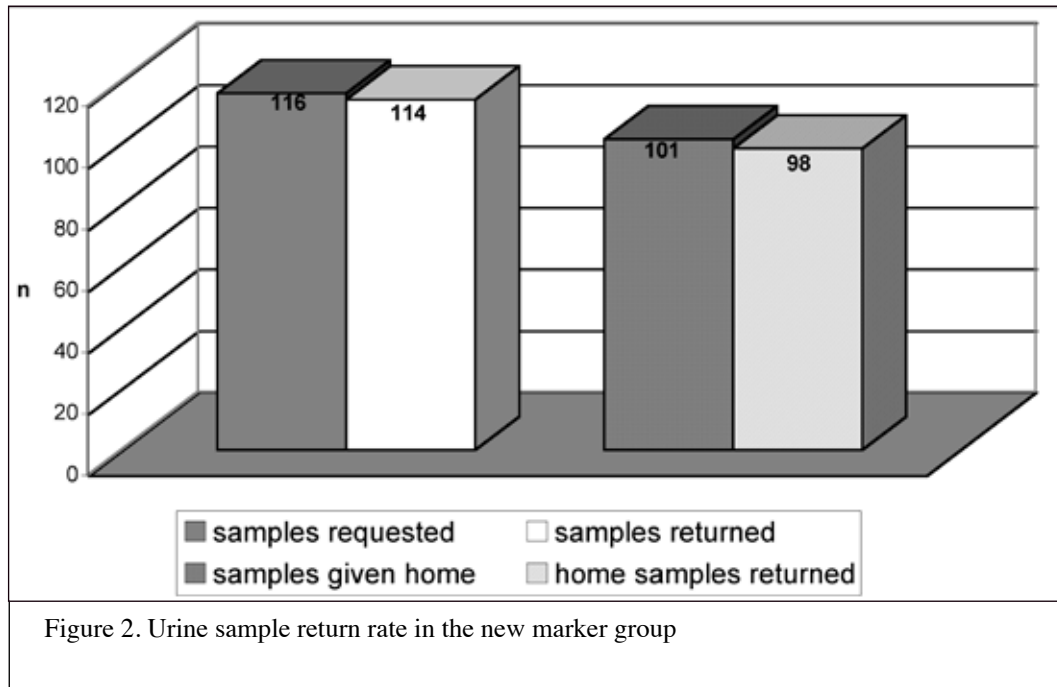
In the NM group, 94% ($n = 31$) answered the question of whether “taking the marker was an unpleasant experience”, and 83.9% ($n = 26$) stated that it was not unpleasant. Four study subjects indicated that the marker solution tasted bitter and, therefore claimed it was an unpleasant experience. On a 1–6 point scale (1 being not unpleasant and 6 being very unpleasant), the question “How unpleasant is the waiting time after taking the marker before giving in the urine sample?” was answered by 96.7% ($n = 32$) of the NM group. The mean score of their answers was 1.9. In the TS group, 84% answered the question “How unpleasant is it to provide a urine sample under supervision?”, which was rated on a 1–6 point scale (1 being not unpleasant and 6 being very unpleasant). The mean score of their answers was 2.9.

When asked which method the subjects would prefer, 96.7% ($n = 32$) of the NM test group answered the question; in this group, 71.9% ($n = 23$) preferred marker testing, 18.7% ($n = 6$) supervised testing, and 9.4% ($n = 3$) had no preference. In the TS test group, 80% ($n = 20$) answered the question; 60% ($n = 12$) preferred the marker system and 40% ($n = 8$) preferred supervised testing (Fig. 3).

In answering the questionnaire, staff members stated that urine sample collection was unpleasant only with the traditional, supervised method due to the low level of patient cooperation or the long urination time.

3.5 Use of work time and employee satisfaction

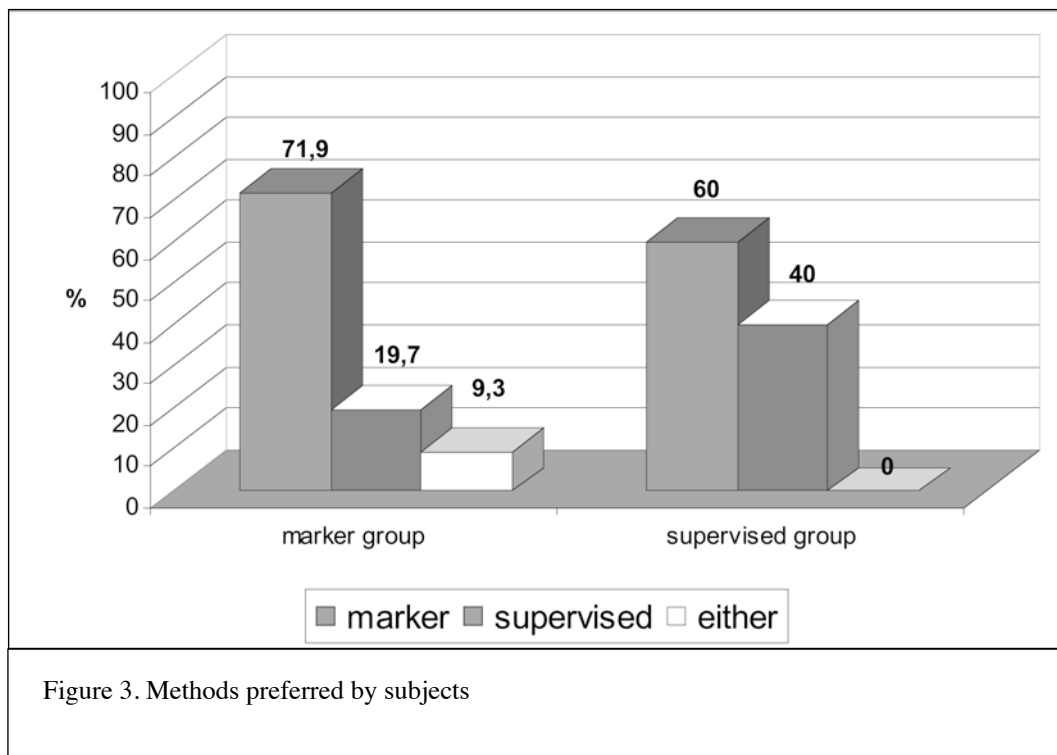
All personnel members ($n = 10$) completed the questionnaire, which included 12 multiple-choice questions and two open-ended questions. All employees were experienced in the addiction field and were, on average, 40 years old. All of them had had experience in collecting TS urine tests. In

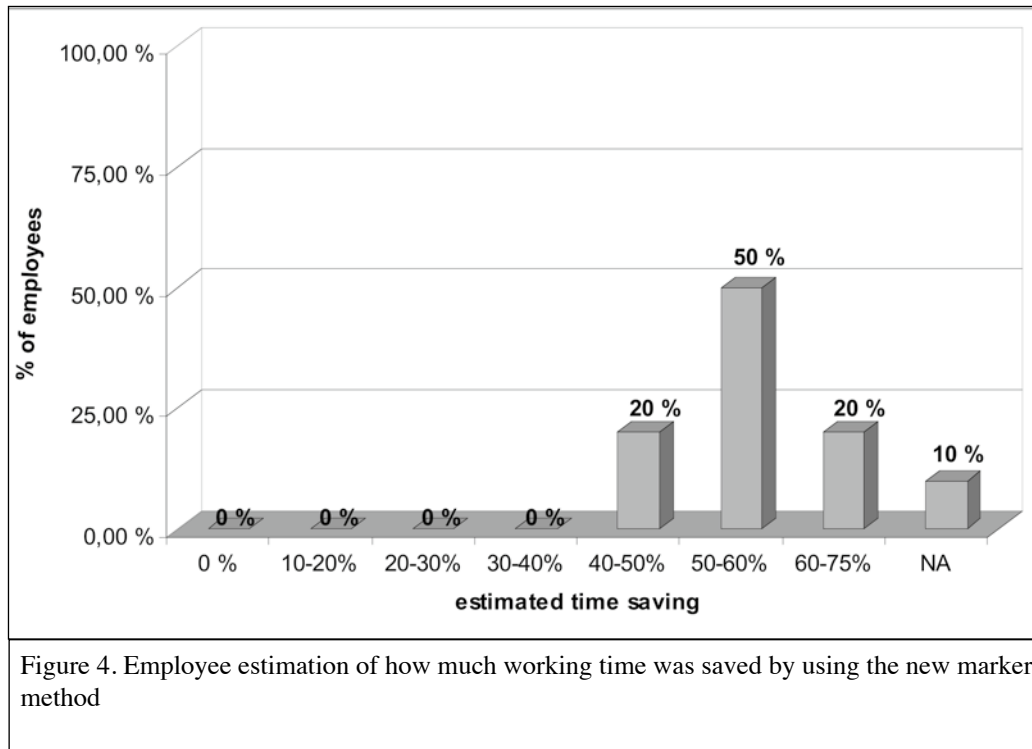


addition, 60% (n = 6) had performed over 20 NM tests, 10% had performed between 10 and 20 tests, 20% had performed less than 5 tests. On a 1-6 point scale (1 being not unpleasant and 6 being very unpleasant), the personnel rated the unpleasantness of preparing and giving the NM test as 1.2 (mean). The unpleasantness of supervising patients (TS group) was rated

at 3.4. All employees preferred to administer the NM test.

The employees were also asked to estimate the total average working time (in minutes) that they needed for one urine sample. For TS urine samples, 40% took 5-10 minutes, 50% took 10-20 minutes, and 10% required over 20 minutes. When using the NM test, 30% needed less than 5 minutes and 70% took between 5 and 10 minutes. When asked to





estimate how much working time the NM test saves, two employees specified a 40-50% time saving, five estimated a 50-60% time saving, and two a 60-75% time saving (Fig 4.). One staff member was unable to estimate the time saved due to limited experience with the method.

Eight employees also commented on the effects of urine testing on the staff-patient relationship. Most ($n = 7$) stated that TS urine sample testing has a negative impact on openness in therapeutic treatment, especially if the supervisor is also the patient's therapist. Many employees expressed the opinion that supervising may lead to manipulation attempts, due to the mistrust felt by patients. Interestingly, there were several comments that using the NM test also includes a therapeutic element, as the patient is given responsibility for his/her own treatment. A majority of comments referred to the work time saved and ease of applying the NM test.

4 Discussion

The current study has some limitations. The study sample was collected from two different patient groups (maintenance treatment and detox), and may thus have some selection bias. The number of reported attempts at manipulation could be biased, as patients in different phases or treatments have a different motivation to manipulate their urine depending on the advantages they might obtain. The focus of this study, however, was on analysing the risk of manipulation when using the new marker method. As a result, this factor may

have had little impact on the outcomes.

Few patients refused to participate in the study. Those who refused expressed the view that the NM test method was complicated, and others were not asked by the treating personnel to participate in the study due to their low cognitive capacity.

In most cases, arranging for the delivery of a urine sample under supervision is an unpleasant experience both for patients and employees; this finding was again confirmed in this study. It is therefore not surprising that most of the patients and all of the employees preferred the NM test. What was surprising was that a certain proportion of patients preferred the traditional supervised urine testing because they felt incapable of adequately providing unsupervised urine samples. One explanation could be that patients are concerned that mistakes could occur (e.g., sample mixing) when the process is not under their control. Another reason why patients may feel concern is that they might make mistakes that would lead to sample testing failure and, therefore, unwelcome consequences during treatment. On the other hand, only two sample collections failed in this study, demonstrating that the real risk of testing failure is very low; this finding may reassure patients.

A large number of patients in the NM test group were allowed to collect the sample outside the treatment unit (87%), and, surprisingly, a high percentage returned the sample without any attempt at manipulation. One major benefit was the working time saved as estimated by the personnel. Because urine testing is quite common, the total

working time saved is clinically significant. For example, when collecting 20 supervised samples (15 min each) every day, the total time taken would be 6 hours (on average), excluding situations when the patients cannot urinate for hours and must be supervised throughout that entire time. With an average time saving as high as 50%, the mean time required would fall to 3 hours. This 3-hour savings can be dedicated to therapeutic work, which is the most significant part of treatment. The time saved should therefore have a positive impact on treatment outcomes.

In calculating the total costs of the different methods, the new marker system clearly involved a greater expense than fast immunological drug-screening methods. Even so, considering the ethical problems arising from supervised urine sampling and the opportunity created for employees to concentrate on therapeutic work, however, it is hard to attribute a value and calculate the costs. This should be taken into account when considering the higher costs of marker drug testing.

In conclusion, the new marker urine test appears to be favoured compared to the traditional supervised urine testing. The patients preferred the NM method, and, because of this, there was also greater compliance. Because most samples can be collected by the patient outside the clinic, the personnel can focus on treatment rather than supervising non-therapeutic urine sampling. This shift in duties could have positive effects on treatment outcomes and save resources. When considering the NM test, the patient must have sufficient cognitive ability to handle the tasks of taking, storing, and returning the sample. For patients affected by certain psychiatric comorbidities that result in, for example, instability, high insecurity, or suspicions, TS urine sampling may be the better choice. In addition, when instant results are needed, saliva tests could be used; however, they have their own limitations. Nonetheless, the new marker testing technique could become the first choice in most cases.

References

- HONOUR, J. W. (1996): Testing for drug abuse, *Lancet*, 348(9019):41-3.
- CHUTUAPE, M. A., SILVERMAN, K. & STITZER, M. L. (2001): Effects of urine testing frequency on outcome in a methadone take-home contingency program, *Drug and alcohol dependence*, 62(1):69-76.
- LEIBFARTH, M. (2003): Use and Interpretation of Drug Screenings During Inpatient Treatment, *Krankenhauspsychiatrie*, 14(24-30).
- SHARON LEVY, L. S., BRIGID L. VAUGHAN, MATTHEW GERMAK, AND JOHN R. KNIGHT. (2007): Results of Random Drug Testing in an Adolescent Substance Abuse Program, *Pediatrics*, 119(4):e843 - e8.
- BOTTCHER, M. & BECK, O. (2005): Evaluation of buprenorphine CEDIA assay versus GC-MS and ELISA using urine samples from patients in substitution treatment, *Journal of analytical toxicology*, 29(8):769-76.
- REISFIELD GM, S. E. A. B. R. (2007): Rational Use and Interpretation of Urine Drug Testing in Chronic Opioid Therapy, *Ann Clin Lab Sci*, 37(301-14).
- CONNOCK, M., JUAREZ-GARCIA, A., JOWETT, S., FREW, E., LIU, Z., TAYLOR, R. J., FRY-SMITH, A., DAY, E., LINTZERIS, N., ROBERTS, T., BURLS, A. & TAYLOR, R. S. (2007): Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation, *Health technology assessment (Winchester, England)*, 11(9):1-171, iii-iv.
- JONES, E. S., MOORE, B. A., SINDELAR, J. L., O'CONNOR, P. G., SCHOTTENFELD, R. S. & FIELLIN, D. A. (2009): Cost analysis of clinic and office-based treatment of opioid dependence: results with methadone and buprenorphine in clinically stable patients, *Drug and alcohol dependence*, 99(1-3):132-40.
- HUPPERTZ, B., GAUCHEL, G., FEIERTAG, H., SCHWEIZER, H., KRIEGER, H., RICHTER, F., HEINZ, H., BLANKE, J., GASTPAR, M. & KELLER, R. (2004): Urine labeling with orally applied marker substances in drug substitution therapy, *Clin Chem Lab Med*, 42(6):621-6.
- GAUCHEL, G., HUPPERTZ, B., FEIERTAG, H. & KELLER, R. (2003): Clinical use of polyethylene glycols as marker substances and determination in urine by liquid chromatography, *Journal of chromatography*, 787(2):271-9.
- SCHNEIDER, H. J., RUHL, B., MEYER, K., KELLER, R. & BACKMUND, M. (2008): Efficacy of a polyethylene glycol marker system in urine drug screening in an opiate substitution program, *European addiction research*, 14(4):186-9.
- MAUER, H. (1992): Role of Gas Chromatography-Mass Spectrometry With Negative Ion Chemical Ionization in Clinical and Forensic Toxicology, Doping Control, and Biomonitoring, *Therapeutic Drug Monitoring*, 24(Special Toxicology Issue):247-54.
- TRINDER, P. (1969): Determination of blood glucose using an oxidase-peroxidase system with a non-carcinogenic chromogen, *Journal of clinical pathology*, 22(2):158-61.

Competing interests, funding

None of the authors have a conflict of interest. The study was funded by the National Institute for Health and Welfare, Finland.

Authors' contributions

KS planned the study design, collected the patient data, and analyzed the data; KS drafted and revised the manuscript; KS and HA finalized the manuscript; and both authors read

and approved the final version.

Acknowledgements

We thank the personnel of the Espoo Treatment and Rehabilitation Centre, A-clinic Foundation, for their help in recruiting patients and collecting urine samples.

Received October 11, 2009 - Accepted January 22, 2010



Pacini Editore & AU CNS

Letter to the editor

Heroin Addict Relat Clin Probl 2008; 12(1): 33-36

HEROIN ADDICTION &
RELATED CLINICAL
PROBLEMS

www.europad.org

Quality of Life As a Means of Assessing Outcome in Opioid Dependence Treatment

Marta Torrens

Drug Addiction Unit, Hospital del Mar, University of Barcelona

TO THE EDITOR: The World Health Organization (WHO) (21) has defined quality of life as the “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment”. This presupposes six dimensions: 1) physical, 2) psychological, 3) degree of independence; 4) social relationships, 5) environment and, 6) spirituality. The concept of ‘Quality of Life’ continues to be so wide in scope that it needs to be considered in the entire health context, whereas in clinical assessments it is the more specifically health-related Quality of Life (HRQoL) that seems to be most useful. HRQoL refers to the patient’s subjective evaluation oriented outside himself/herself; it focuses on the impact of perceived health status on the patient’s potential to carry out a subjectively satisfactory life. HRQoL reflects a subject’s self-perception of his/her health, and offers a different viewpoint for the study of health status

The assessment of the HRQoL of chronically ill patients has become a focus of increasing interest. The development of health-related quality-of-life means of assessment has allowed comparisons between the impact of disease and the outcomes of treatment in various different conditions (e.g. chronic obstructive pulmonary disease, coronary artery disease) (12). The changes discovered in HRQoL constitute a way of measuring treatment effectiveness and are an important tool in evaluating treatment programmes. HRQoL

has been investigated in many populations, including the general population, and populations with specific diseases, especially chronic ones (1,2).

HRQoL may be measured through different rating scales. There are already over 200 of these (11). These instruments can be subdivided into two classes – according to whether they are *generic* or *specific*. The *generic* instruments for assessing HRQoL consider overall health status, without being focused on any concrete problem. The most widely used generic instruments are: Nottingham Health Profile (10); SF-36 (18); SF-12 (19); EUROQoL (7) and WHO (Five) Well-Being Index (4). The *specific* instruments assess problems related to a particular disease. In the case of opioid dependence, only one instrument designed to measure HRQoL in opioid-dependent subjects is currently available, the Injection Drug User Quality of Life (IDUQoL) (5)

Opioid dependence is recognized as a chronic disease for which patients need to stay in treatment for many years. Adding to the adversities usually associated with opioid dependence, health-related problems may lead to a significant deterioration in the quality of life of these patients. Recently, a number of studies on opioid-dependent subjects seeking treatment have documented that these subjects show a very poor HRQoL (6, 13-16). Thus, in addition to the classical means of assessing the effectiveness of opioid dependence treatments: reduction in illicit opioid use, mortality, criminal activities and risk behaviours (3), over the last few years evaluation of the improvement in the health-related quality of life has come to constitute an interesting means of assess-

ing treatment effectiveness, and, therefore, an important tool in choosing between various opioid dependence treatment programmes (9,16,17,20).

References

- Alonso J., Ferrer M., Gandek B., Ware J. E., Jr., Aaronson N. K., Mosconi P., Rasmussen N. K., Bullinger M., Fukuhara S., Kaasa S., Leplege A. (2004): Health-related quality of life associated with chronic conditions in eight countries: results from the International Quality of Life Assessment (IQOLA) Project. *Qual Life Res* 13:283-98.
- Alonso J., Angermeyer M.C., Bernert S., Bruffaerts R., Brugha T. S., Bryson H., de Girolamo G., Graaf R., Demyttenaere K., Gasquet I., Haro J. M., Katz S. J., Kessler R. C., Kovess V., Lepine J. P., Ormel J., Polidori G., Russo L. J., Vilagut G., Almansa J., Arbabzadeh-Bouchez S., Autonell J., Bernal M., Buist-Bouwman M. A., Codony M., Domingo-Salvany A., Ferrer M., Joo S. S., Martinez-Alonso M., Matschinger H., Mazzi F., Morgan Z., Morosini P., Palacin C., Romera B., Taub N., Vollebergh W. A. (2004): Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl.* (420):38-46.
- Amato L., Davoli M., Perucci C., Ferri M., Faggiano F., P Mattick R. (2005): An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat.* 28:321-9.
- Bech P, Olsen LR, Kjoller M, Rasmussen NK. (2003): Measuring well-being rather than the absence of distress symptoms: a comparison of the SF-36 Mental Health subscale and the WHO-Five Well-Being Scale. *Int J Methods Psychiatr Res* 12:85-91.
- Brogly S., Mercier C., Bruneau J., Palepu A., Franco E. (2003): Towards more effective public health programming for injection drug users: development and evaluation of the injection drug user quality of life scale. *Subst Use Misuse* 38:965-92.
- Calsyn D.A., Saxon A.J., Bush K.R., Howell D.N., Baer J. S., Sloan K. L., Malte C. A., Kivlahan D. R. (2004): The Addiction Severity Index medical and psychiatric composite scores measure similar domains as the SF-36 in substance-dependent veterans: concurrent and discriminant validity. *Drug Alcohol Depend.* 76:165-71.
- EUROQOL GROUP (1990): EuroQoL, a new facility for the measurement of health related quality of life. *Health Policy* 16: 199-208.
- Giacomuzzi S.M., Riemer Y., Ertl M., Kemmler G., Rossler H., Hinterhuber H., Kurz M. (2003): Buprenorphine versus methadone maintenance treatment in an ambulant setting: a health-related quality of life assessment. *Addiction* 98:693-702
- Giacomuzzi S.M., Ertl M., Kemmler G., Riemer Y., Vigl A. (2005): Sublingual buprenorphine and methadone maintenance treatment: a three-year follow-up of quality of life assessment. *Scientific World Journal.* 5:452-68
- Hunt S.M., McKenna S.P., McEwen J., Williams J., Papp E. (1981) The Nottingham Health Profile: subjective health status and medical consultations, *Social Science Medicine*, 15A, 221-229.
- Iraurgi I. (2002): Instrumentos de evaluación de la calidad de vida relacionada con la salud en toxicomanías. In I. Iraurgi and F. Gonzalez-Saiz Eds: *Instrumentos de evaluación en drogodependencias*. Aula Médica, Barcelona. pp: 481-511
- McDowell I., Newell C. (1996): *Measuring health*. 2nd edn. University Press, New York, Oxford 1996.
- Millson P.E., Challacombe L., Villeneuve P.J., Fischer B., Strike C. J., Myers T., Shore R., Hopkins S., Raftis S., Pearson M. (2004): Self-perceived health among Canadian opiate users: a comparison to the general population and to other chronic disease populations. *Can J Public Health.* 95:99-103.
- Puigdollers E., Domingo-Salvany A., Brugal M.T., Torrens M., Alvaros J., Castillo C., Magri N., Martin S., Vazquez J. M. (2004): Characteristics of heroin addicts entering methadone maintenance treatment: quality of life and gender. *Subst Use Misuse.* 2004 39:1353-68.
- Ryan C. F., White J. (1996): Health status at entry to methadone maintenance treatment using the SF-36 health survey questionnaire, *Addiction*, 91, 39-45.
- Torrens M., San L., Martinez A., Castillo C., Domingo-Salvany A., Alonso J. (1997): Use of the Nottingham Health Profile for measuring health status of patients in methadone maintenance treatment. *Addiction.* 92:707-16.
- Torrens M., Domingo-Salvany A., Alonso J., Castillo C., San L. (1999): Methadone and quality of life. *Lancet* 353 (9158):1101.
- Ware J.E., Gandek B. (1994): The SF-36 Health Survey: development and use in mental health research and the IQOLA Project. *International Journal of Mental Health* 23:49-73.
- Ware J.E., Kosinski M., Turner-Bowker D. M., Gandek B. (2002): How to score version 2 of the SF-12 Health Survey. *Quality Metrics*: Lincoln, RI.
- Winklbaaur B., Jagsch R., Ebner N., Thau K., Fischer G. (2008): Quality of life in patients receiving opioid maintenance therapy. A comparative study of slow-release morphine versus methadone treatment. *Eur Addict Res.* 14:99-105.
- WHO. (1996): Grupo de la OMS sobre la calidad de vida. ¿Qué calidad de vida? *Foro Mundial de la Salud*,

17: 385-387.

Role of funding source

This letter was supported in part by grants from Instituto de Salud Carlos III (FIS - Red de Trastornos Adictivos, RD 06/0001/1009).

Conflict of Interest

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

Received and Accepted May 23, 2009



Pacini Editore & AU CNS

Letter to the editor

Heroin Addict Relat Clin Probl 2010; 12(1): 37-40

HEROIN ADDICTION &
RELATED CLINICAL
PROBLEMS

www.europad.org

Why There Has Been an Excess of Overdoses in Norway Since 1990?

Martin Haraldsen

Former family doctor, now nursing home doctor

TO THE EDITOR: The present study of trend curves and absolute numbers of “drug-related deaths” (DRD) in European countries in the period 1985-2006 shows that the simplest and cheapest treatment modality, the “French method”, also seems to be the best, in four ways – the complicated Norwegian system seems to be the worst, besides being by far the most expensive!

- 1) Immediate lowering of DRD after its introduction in 1995 (methadone); from 1996 mainly buprenorphine (Subutex), after a few years covering more than 2/3 of the population of heroin addicts [4].
- 2) Lasting effect – in spite of very little control over buprenorphine administration (in contrast to methadone).
- 3) French DRD/million inhabitants is about 1/3 of the EU DRD since 1998 and about 1/13 of the Norwegian DRD (besides being many times cheaper). The French DRD data were consistently understated until 2004, but have been upgraded and are now comparable with the other EU countries, and Norway.
- 4) Logically, this lowering is proportionally related to reduced heroin usage, as opioid-related deaths constitute about 75% of DRD in EU countries [2]. This is also of immense socioeconomic and international importance.

1. Comparison of EU reports (including Norway) on DRD

I have made charts of the trends of “drug-related deaths” (DRD) in EU countries and Norway in the period 1985-2006 based on single DRD numbers from EMCDDA (European Monitoring Centre for Drugs and Drug Addiction, Lisbon) [3].

Among the EU countries I have omitted DRD from France, for reasons I will explain later, and Romania too, as the DRD does not cover the whole country. I have related DRD to the actual populations of the reporting countries each year. I got my population statistics from Eurostat, EU: (<http://epp.eurostat.ec.europa.eu/portal/page/eurostat/home/>).

EMCDDA has a diagram in the last annual report showing differences between countries that emerge from the most recent DRD [2], where DRD is related to each ‘million inhabitants between 15 and 64 yrs’. For simplicity I use the numerator ‘million inhabitants’, as this too is a stable parameter. Marking off treatment changes on the trend charts helps to explain the abrupt deviations that sometimes appear on them. This procedure gives a unique opportunity to analyze two opposite systems, the rigid Norwegian one, and the very simple “French method”, with all the other EU countries in between.

I am aware that the DRD numbers are not exact, but I have used the given DRD as a basis for constructive thinking. These results turned out to be highly significant and persuasive, which leads one to trust the tendencies, rather than the exact numbers I present. I also mean that countries other than Norway can optimize their treatment by looking to France. There has been an obstacle to direct comparisons between French DRD and DRD for other EU countries, as the figures for French DRD were too low over a long period, up till 2004.. Until the change that began in 2004, the figures were reported by the police in the same way each year (personal information from EMCDDA), so they have had to be revised to show the trends. For 2005 and 2006 the updated method of DRD reporting shows 4.8/mill.inhab, about 1/3

more than in previous years.

Summing up: In France there is a markedly positive trend after the introduction of substitution treatment in 1995, the first year with methadone, thereafter mainly with buprenorphine, leading to a 2/3 fall in DRD.

Figure 1 compares DRD/mill.inhabitants in Norway to EU (minus France and Romania) and France within in the period 1985-2006. The vertical line in 1994 shows the last year before France started its substitution offensive. The line in 1997 shows the last year before Norway started its specific treatment system, LAR.

It is known that France registered too few DRD until 2004 (EU), but the calculations were always done in the same way, so the trend should be right. For 2005 and 2006 the mode of registration changed. The vertical line in 1997 is the last year before the start of “LAR”. Before 1998 the average yearly extra deaths amounted to 54/yr, whereas in 1998-2006 this figure rose to 197/yr.

plenty of enthusiasm and good intentions, made us build institutions that would allow heroin addicts to become drug-free. But after discharge many die from overdoses, and only a few others become drug-free. A turnaround is possible: many could be helped to become drug-free, as long as they show real motivation, and after having been stabilized on buprenorphine/methadone.

The next step in the official form of treatment is through the administration of substitution drugs – methadone (prescribed to 60%) and buprenorphine (40%) – in a geographically decentralized system, with 14 different quite independent treatment regions, organized by three partners working in cooperation (called LAR - “Drug assisted Rehabilitation”):

- 1) A specialist body that governs the treatment
- 2) A social welfare office
- 3) A family doctor

It may take months or even years to proceed from an application to admittance for treatment. The age limit has been

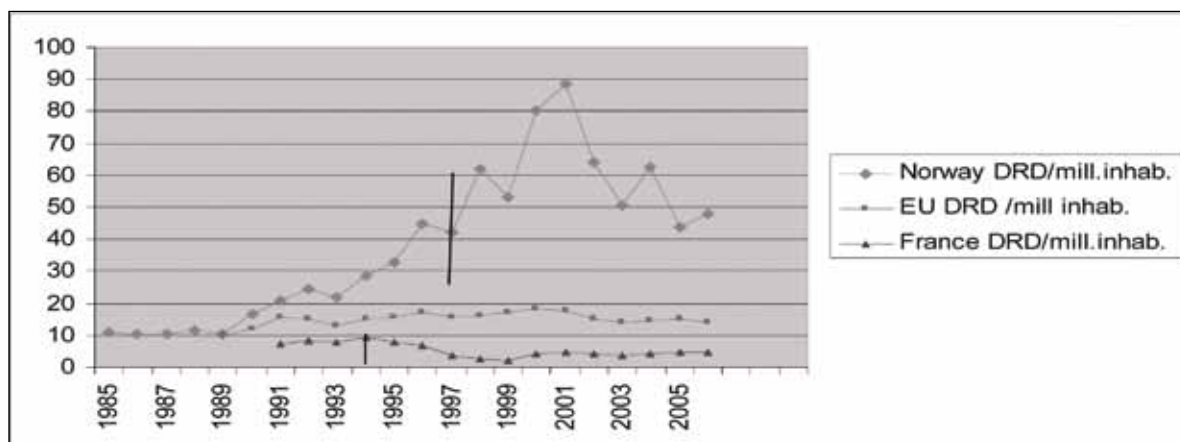


Figure 1. Drug-related deaths in Norway and European Union (minus France and Romania)

I have deduced that in the period 1990-2006 Norway had a DRD excess of 2,200 compared to “EU mortality” and 2,800 compared to France. The average age of death is about 35 yrs [2].

2. From beliefs to science

For various different reasons Norway in 1998 tried out, and later held on to its own way of treating heroin addicts, “which is somewhat out of tune with the general European trend towards harm reduction and diversity”, according to Professor Helge Waal in an article summing the situation up [5]. For too long we have let beliefs rather than science guide us. We have the prerequisites for a very good level of treatment, but only after a few adjustments have been made. Currently, buprenorphine/methadone is being used more as a reward than an instrument. Our traditions, together with

25 yrs, though there is now a plan to lower that limit. There is a rigid control of medication (for both drugs) and urine tests.

There are about 10,000 heroin addicts (nearly all injectors) including 5,000 get treatment in LAR. The EU countries as a whole also have about 50% coverage [2].

3. The “French Method”

Since 1996, family doctors in France, without any special training, have been the backbone in the treatment of heroin addicts. Buprenorphine (Subutex) is the drug of choice, given to 80%, and methadone to 20%, with more than 2/3 coverage [4].

The consultations and drugs are free.

There is little control of intake of urine and Subutex, in contrast to methadone. Subutex is usually prescribed for one month, to be taken home for one week at a time [2].

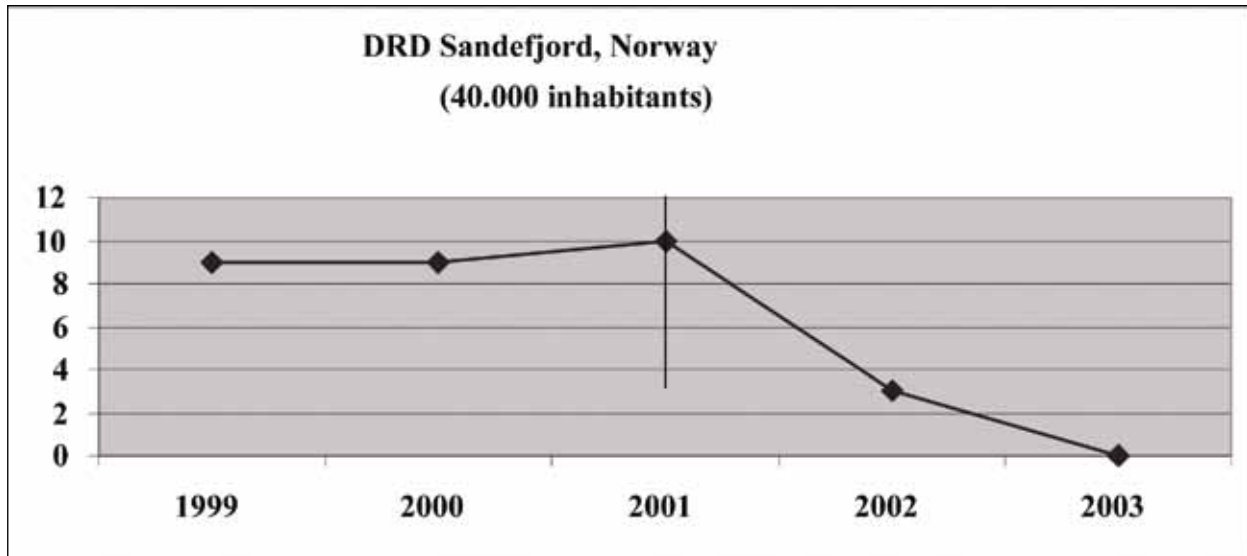


Figure 2. Decline in drug-related deaths in Sandefjord. The vertical line shows the year when many heroin addicts got buprenorphine substitution treatment from family doctor(s). Source: Sandefjords Blad (local newspaper).

4. My own experience

For 16 years I was a family doctor, often dealing with heroin addicts in our town. Sandefjord has 40,000 inhabitants and has a big narcotics problem. Like some other Norwegian doctors I searched for the “treatment of choice”. I saw that the complicated Norwegian system did not function and still fails to function. During the last years I came to test out “the French method”, which was too simple and good to be true, as buprenorphine is a quite safe drug, even when not being controlled, even when injected. Buprenorphine only not helped our patients, but also replaced heroin on the streets. This was the experience in Finland, too [1].

To explain the effectiveness of the treatment: I was nearly alone as a doctor prescribing substitution treatment independently of the LAR in Sandefjord, where LAR at that time covered less than 20% of the need.

I prescribed buprenorphine to about 2/3 of the heroin addicts (to about 60 patients).

The saying in the town was that only one of the remaining 1/3 heavily addicts preferred illegal buprenorphine to heroin.

The DRD declined dramatically (Figure 2).

Exhausted heroin addicts who otherwise would have ended their lives by taking overdoses grasped the new hope when they were offered drugs unconditionally. I saw how these patients went through a ‘metamorphosis’, behaving more normally as soon as their brain receptors were stabilized. This also opened the way to help by volunteers. Encouraging results are ‘contagious’. A family doctor colleague, Dagfinn Haarr, made an interesting comparison between those treated

according to the “LAR” system and those treated according to the “French method”. With the second, he found a decrease of 60% (with DRD falling from 1.3% to 0.5%). Those dropping out of treatment had 5.1%) (article in the Norwegian doctors’ magazine, June 2007).

References

1. Alho H., Sinclair D., Vuori E., Holopainen A. (2007): Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. *Drug Alcohol Depend.* 88:(1) 75-78.
2. Emcdda (2009): Annual Report 2009 - The state of drugs problem in Europe. http://www.emcdda.europa.eu/attachements.cfm/att_93236_EN_EMCCDDA_AR2009_EN.pdf,
3. Emcdda (2009): Number of drug-induced deaths recorded in EU Member States according to national definitions. European Monitoring Centre for Drugs and Drug Addiction. Statistical bulletin 2009. <http://www.emcdda.europa.eu/stats09/drdtab107a>
4. Fatseas M.,Auriacombe M. (2007): Why buprenorphine is so successful in treating opiate addiction in France. *Curr Psychiatry Rep.* 9:(5) 358-364.
5. Waal H. (2007): Merits and problems in high-threshold methadone maintenance treatment. Evaluation of medication-assisted rehabilitation in Norway 1998-2004. *Eur Addict Res.* 13:(2) 66-73.

Role of funding source

No funds for this letter.

Conflict of Interest

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

Received and Accepted May 23, 2009

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' full 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 squared 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 Maremmani



Fishing at the Mouth of the Danube - Tulcea, Romania, July 2001