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INTERACTION BETWEEN CLINICAL AND PSYCHOSOCIAL FACTORS IN THE TREATMENT OF HEROIN ADDICTED PATIENTS

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[INTERACCIÓN ENTRE FACTORES CLÍNICOS Y PSICOSOCIALES EN EL TRATAMIENTO DE PERSONAS ADICTAS A LA HEROÍNA]

[INTERACCIÓ ENTRE FACTORS CLÍNICS I PSICOSOCIALS EN EL TRACTAMENT DE PERSONES ADDICTES A L'HEROÏNA]

[INTERAKTION ZWISCHEN KLINISCHEN UND PSYCHOSOZIALEN FAKTOREN BEI DER BEHANDLUNG VON HEROINABHÄNGIGEN PATIENTEN]

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War is peace

Freedom is slavery

Ignorance is strength

George Orwell, 1984

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Abstract

The German model project for heroin assisted treatment of opiate addicts implied a change in the drug policy of this country. In this study we present five papers relating to clinical and psychosocial factors that influence the recovery of these patients and should be taken into account for their proper treatment. Specifically, the consumption of alcohol and benzodiazepines, the effects of psychiatric comorbidity, the influence of prior treatment experiences and gender differences are analysed. Finally we present four models predicting outcomes on reducing illegal drug use and improving health status in both the total sample (using baseline variables) and in patients who completed the study (using longitudinal variables).

Resumen

El proyecto modelo alemán para el tratamiento asistido con heroína en adictos a los opiáceos supuso un cambio en la política de drogas en este país. En este estudio se presentan cinco trabajos referentes a los factores clínicos y psicosociales que influyen en la recuperación de estos pacientes y que deben ser tenidos en cuenta para su correcto tratamiento. Específicamente se analiza el consumo de alcohol, de benzodiacepinas, los efectos de la comorbilidad psiquiátrica, el efecto de experiencias de tratamiento previas y las diferencias de género. Finalmente se presentan cuatro modelos de predicción de resultados sobre la reducción del consumo de drogas ilegales y la mejora del estado de salud tanto en la muestra total (utilizando variables de la línea base) como en los pacientes que terminaron el estudio (utilizando variables longitudinales).

Resum

El projecte model alemany per al tractament assistit amb heroïna en addictes als opiacis va suposar un canvi en la política de drogues en aquest país. En aquest estudi es presenten cinc treballs referents als factors clínics i psicosocials que influeixen en la recuperació d'aquests pacients i que s'han de tenir en compte per al seu correcte tractament. Específicament s'analitza el consum d'alcohol, de benzodiazepines, els efectes de la comorbiditat psiquiàtrica, l'efecte d'experiències de tractament prèvies i les diferències de gènere. Finalment es presenten quatre models de predicció de resultats sobre la reducció del consum de drogues il·legals i la millora de l'estat de salut, tant en la mostra total (utilitzant variables de la línia base), com en els pacients que van acabar l'estudi (utilitzant variables longitudinals).

Zusammenfassung

Das bundesdeutsche Modellprojekt zur heroingestützten Behandlung Opiatabhängiger stellte eine Änderung der Drogenpolitik in diesem Land dar. In dieser Studie werden fünf Artikel zu klinischen und psychosozialen Faktoren präsentiert, die den Behandlungserfolg der Patienten beeinflussen, und im Therapieansatz Berücksichtigung finden sollten. Dabei geht es im Einzelnen um den Konsum von Alkohol und Benzodiazepinen, die Auswirkungen von psychiatrischer Komorbidität, den Zusammenhang mit Behandlungsvorerfahrungen sowie Unterschieden zwischen den Geschlechtern. Schließlich werden vier multivariate Modelle vorgestellt, die den Einfluss unterschiedlicher Faktoren auf den Rückgang des illegalen Drogenkonsums und die Verbesserung des Gesundheitszustands sowohl in der gesamten Stichprobe (mit Baseline-Variablen) als auch bei Patienten, die die Studie abgeschlossen haben (mit Verlaufsvariablen), analysieren.

List of abbreviations

AD: Anno Domini

ANOVA: Analysis of Variance

ANCOVA: Analysis of Covariance

ASI: Addiction Severity Index

BC: Before Christ

BMI: Body Mass Index

BZD: Benzodiazepine

CDT: Carbohydrate Deficient Transferrin

CM: Case management and Motivational interviewing

CS: Composite Score

EuropASI: European version of the Addiction Severity Index

GSI: Global Severity Index

HAT: Heroin Assisted Treatment

HCV: Hepatitis C Virus

HIV: Human immunodeficiency virus

ITT: Intent to Treat

PP: Per Protocol

M3G: morphine-3-glucuronide

MMT: Methadone Maintenance Treatment

MTF: Methadone Treatment Failures

NIT: Not In Treatment

OTI: Opiate Treatment Index

PE: Psycho-Education and drug counselling.

POM: Primary Outcome Measure

RCT: Randomized Clinical Trial

RMANOVA: Repeated Measures Analysis of Variance

SCL-90-R: Symptom Checklist-90-Revised

μ: mu

δ: delta

κ: kappa

1. Introduction

Heroin ($C_{21}H_{23}NO_5$; 7,8-didehydro-4,5-α-epoxy-17-methylmorphinan-3,6-α-diol diacetate or 3,6-diacetyl ester of morphine) a diacetyl morphine ester, also called diacetylmorphine (International Nonproprietary Name), diamorphine (British Approved Name), morphine diacetate or acetomorphine, is a semi-synthetic opioid drug synthesized from morphine, a derivative of dried opium latex obtained from the seed capsule of the opium poppy (United Nations International Drug Control Programme, 1998).

Heroin acts on human μ-opioid receptors producing euphoric effects when injected or smoked. It also produces, even when swallowed, a sense of wellbeing, and sedation. Its addictive potential is very high, and is characterized by a very rapid development of an abstinence syndrome.

The United Nations Office on Drugs and Crime (2011) estimates that, during 2009 there were between 12 and 14 million regular heroin users worldwide, consuming 375 megatons and mainly produced in Afghanistan, Mexico, Myanmar, India and Colombia. Regarding Europe, this institution reports that heroin is the main opiate used in the area, being consumed by 0.6% of the population or between 3.1 and 3.5 million people. Although opiate substitution treatment is provided for around half million people, heroin and its metabolites are still reported as the main cause of three quarters of drug-induced deaths in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2011a).

In line with the European Union Drugs Strategy (Council of the European Union, 2004), the European Monitoring Centre for Drugs and Drug Addiction advises the use of long-term outpatient care, addressing reduction of drug-related harms to health and society as a main objective, emphasizing the reduction of infectious diseases and drug-related deaths. This is accomplished mainly by use of maintenance substances such as methadone and buprenorphine combined with psychosocial interventions and case management oriented primarily to abstinence or at least to reduction of harms associated with illicit use (European Monitoring Centre for Drugs and Drug Addiction, 2011b).

1.1. Historical context

According to Berridge and Edwards (1981) opium has been cultivated in lower Mesopotamia since the fourth millennium BC, where Sumerian ideograms referred to it as *hul gil*, the "joy plant". Opium was used as a stimulant and analgesic drug in Persia and Egypt. Egyptians spread the plant into Asia Minor and from there to Greece, where it was studied by pioneer physicians as Hippocrates (460–370 BC), Theophrastus (372—287 BC) or Dioscorides (40—90 AD) and then to Rome where Galen (131—201 AD) was enthusiastic experimenting with mixtures made of opium. During the middle and modern ages, opium was extensively used by Arab and Western doctors in such a way that, at the beginning of the nineteenth century, it was not considered to be a threatening substance. Opium has even been a matter of great geopolitical concern as

can be deduced from the existence of wars (1839–1842 and 1856–1860) caused by disagreements about its trade between China and England.

Heroin was first synthesized by Charles Romley Alder Wright in 1874, an English chemist at St. Mary's Hospital Medical School in London. It was tested in dogs and rabbits but did not, at the time, become an analgesic drug of choice (Wright, 1874). Diacetylmorphine only became popular 23 years later when Felix Hoffmann, a chemist working at the *Aktiengesellschaft Farbenfabriken* (today Bayer) under the supervision of Heinrich Dreser in Elberfeld (Germany) acetylated morphine with the aim of producing codeine, a therapeutic drug extensively used at that time. Instead, the experiment produced an acetylated form of morphine that seemed even more potent. Hoffman tested the new drug on animals, Bayer workers (who said that it made feel them heroic, "*heroisch"* in German, baptizing the new substance) and even on himself. Heroin was first presented by Dreser to the Congress of German Naturalists and Physicians as a new drug "10 times" more effective than codeine as a cough medicine and better and less addictive than morphine as a painkiller. Bayer produced and commercialized heroin internationally until 1931, when its addictive potential was recognized and the League of Nations regularized its distribution (see below).

Although opium use was unrestricted in England until 1868 (when the Pharmacy Act, which restricted the sale of opium to professional pharmacists, became law), along the 19th century, the English public health movement was not in favour of the medicinal use of opium (Berridge & Edwards, 1981).

Opiates were object of serious discussion internationally since the USA convened a special commission in Shanghai in 1909. The Hague Convention, held in 1912, was the

first global attempt to regulate opium. As a result, the Harrison Narcotics Tax Act regulated opium for the first time in the United States of America in 1914. This act allowed prescription and sale for medical purposes but started the dangerous policy of drug prohibition (Schuebeler, 2002). England took similar measures after the First World War in 1920, when the Dangerous Drugs Act was introduced aiming to exercise strict control (Berridge, 1982, 1984). Thereafter heroin was restricted to registered medical practitioners (Stimson & Metrebian, 2003), and it became a maintenance drug for compliant English middle-class addicts (Berridge, 2009).

The League of Nations organized two opium conferences, one in 1924, strengthening the Hague Convention, and the second in 1925, adding practical control measures. In 1931 a new convention proposed a more strict regulation, though not calling for the need to limit the cultivation of the opium poppy, an issue that was discussed until the end of the Second World War (United Nations, 2009). Nevertheless, in Germany, heroin could be sold in pharmacies until 1958 and it was not officially banned until 1971 (Altrock, 2009).

In the 1960s, Dole and Nyswander, two US-American physicians at the Rockefeller Institute, researched the possibility of treating heroin dependent patients with methadone, a synthetic long half-life opioid without euphoric effects (Dole & Nyswander, 1968) developed in Germany in 1937 (Bockmühl & Ehrhart, 1949). The first trial was very successful (Dole, Nyswander, & Kreek, 1966), although the authors noted that patients soon became tolerant to the effects of methadone, remaining dependent to it, but otherwise *"living socially acceptable lives"* (Dole & Nyswander, 1967). Methadone is considered today a first choice maintenance treatment

internationally (Clark et al., 2002; Farrell & Hall, 1998; Mattick, Breen, Kimber, & Davoli, 2009).

Stimson and Metebrian (2003) review the evolution of heroin prescription in the United Kingdom. Heroin remained a treatment option in England until 1967 when, caused by the increase of its hedonistic use, a Dangerous Drug Act restricted the prescribing of heroin (and also cocaine) to doctors holding licenses from the Home Office, mainly NHS psychiatrists in charge of drug dependency units. A number of reasons contributed to the change to methadone maintenance treatment (MMT) in the seventies, namely threat of heroin diversion to the black market, optimism about methadone, change in mentality about lifelong maintenance vs. abstinence, and bad clinical experiences. A clinical trial conducted in the drug-dependence unit at London's University College Hospital (Hartnoll et al., 1980), although producing mixed results, was interpreted by many as a clear proof that heroin encouraged continued drug use while methadone was a more confrontative method that could be used with an abstinence goal, legitimating a change already underway. The use of maintenance as opposed to abstinence oriented treatments appeared to again be legitimated in the 80s as it was viewed as a harm reduction approach in times of Human immunodeficiency virus (HIV) expansion, with methadone being the treatment of choice (Stimson & Metrebian, 2003).

In 1967, Sweden was the first continental European country to introduce methadone. The Netherlands followed in 1968, although a shift from abstinence orientation to maintenance only occurred with the increase in the number of heroin users in the mid-

70s and, as was the case in the UK, with the onslaught of the HIV epidemic in the mid-80s.

In 1967, Sweden was the first continental European country to introduce methadone (Robertson & Solberg, 2000). The Netherlands followed in 1968, although a shift from abstinence orientation to maintenance only occurred with the increase in the number of heroin users in the mid-70s and, as was the case in the UK, with the onslaught of the HIV/AIDS epidemic in the mid-80s (Blanken et al., 2010).

Spain, due to the hard prosecution and negation of any drug problem under the fascist dictatorship of Francisco Franco, saw the rise of the heroin problem slightly later. Until the end of the 1970s, when parenteral use of drugs was becoming a problem, there were almost no drug treatment facilities. Methadone was regulated in 1983, and the country had a unified national plan on drugs in 1985 (Torrens, 2000).

Germany was relatively late accepting MMT in the late 1980s, after almost 20 years of black market use due to a rigid adherence to the abstinence paradigm (Kalke, 1997). The first experimental methadone program was conducted in Hannover between 1973 and 1975 (Krach et al., 1978). This study was designed as a maintenance-to-abstinence program and its poor results were interpreted as a proof of the superiority of abstinence oriented therapeutic communities over MMT (Gerlach, 2002). Due to legal prosecution, general practitioners often prescribed codeine or dihydrocodeine instead of methadone, as the latter was considered illegal. Finally, starting from 1988, the special federal system in Germany made it possible to establish MMT programs in some states (being Nordrhein-Westfalen the first, followed by Hamburg) against the opposition of the Federal Government (Verthein, Kalke, & Raschke, 1998).

Since 2001 MMT is available in all members of the current European Union except Cyprus (European Monitoring Centre for Drugs and Drug Addiction, 2011c) although some countries of Eastern and Central Europe are still in a process of improving the provision of these services (European Monitoring Centre for Drugs and Drug Addiction, 2011d).

Other forms of maintenance treatment have also been developed. Buprenorphine, combined or not with the opiate antagonist naloxone is also considered an alternative medication as a first choice maintenance treatment (Gowing, Ali, & White, 2009; Kakko et al., 2007; Mattick, Kimber, Breen, & Davoli, 2008). Slow release oral morphine used as first choice in some countries would appear to be a promising opiate substitute (Kraigher et al., 2005). Levo-alpha-acetymethadol was used from the late seventies (Judson & Goldstein, 1979) in the United States showing very good results (Longshore, Annon, Anglin, & Rawson, 2005), but removed afterwards from the European market due to reports of life threatening ventricular rhythm disorders (The European Agency for the Evaluation of Medicinal Products, 2000).

In 1992, Swiss public health authorities commissioned a series of clinical trials studying heroin as a maintenance therapy to determine whether it could be an effective treatment for heroin-addicted patients who did not benefit from MMT and other opiate substitution substances such as morphine (Rehm et al., 2001). These patients were recruited and retained in Heroin Assisted Treatment (HAT) to a *"satisfactory degree"* (Uchtenhagen et al., 1999). Since this initial success, clinical trials with intravenous or intrapulmonary Diacetylmorphine have been conducted in a variety of countries in Europe and North America: Switzerland (Perneger, Giner, del Rio, & Mino,

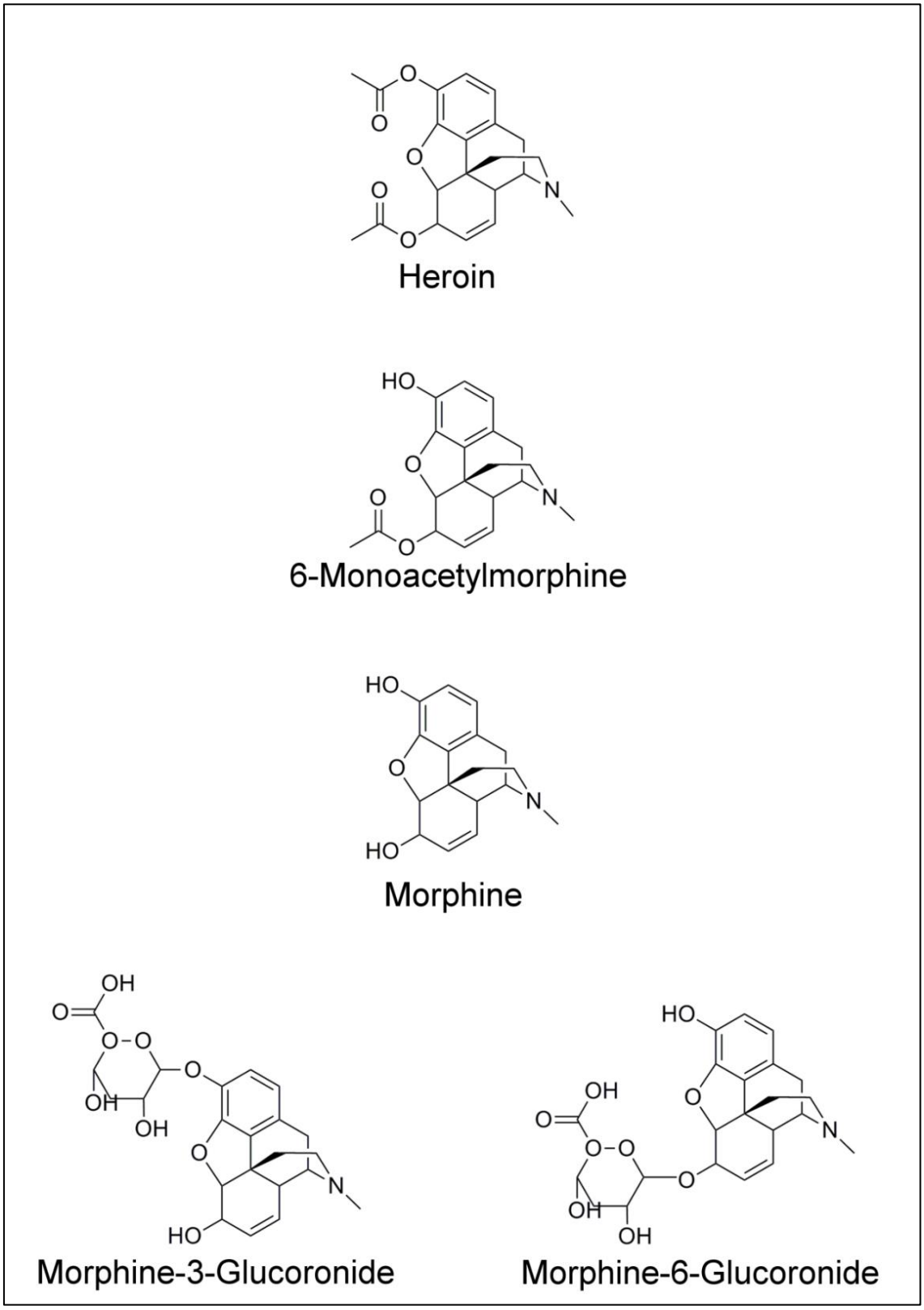
1998), Netherlands (van den Brink et al., 2003), Spain (March, Oviedo-Joekes, Perea-Milla, & Carrasco, 2006), Germany (Haasen et al., 2007), United Kingdom (Strang et al., 2010); and Canada (Oviedo-Joekes et al., 2009), showing HAT's effectiveness as an alternative to conventional forms of maintenance treatment for people who are currently having difficulties with or have in the past have failed maintenance treatment (Ferri, Davoli, & Perucci, 2011).

Although HAT has effectively demonstrated its therapeutic potential (Ferri et al., 2011), it remains polemical in the political field (B. Fischer et al., 2007). Currently, HAT is allowed for difficult to reach patients in the United Kingdom, Switzerland, the Netherlands, Germany and Denmark. However, it remains an experimental substance in some countries where successful trials were conducted such as Spain and trials have been rejected in countries like Australia (Farrell & Hall, 1998).

1.2. Pharmacodynamics and pharmacokinetics of heroin

Pert & Snyder (1973), conducted a pioneer study with naloxone (an opioid antagonist) at the Johns Hopkins University School of Medicine, where they discovered that opiates target certain molecular receptors located on the surfaces of brain cells modulating its activity. Since then three opiate receptors have been identified (Biederman & Vessel, 2006): mu(μ), delta(δ) and kappa(κ). The μ-opioid receptors appear to be involved in the euphoric effects of heroin (van Ree, Slangen, & de Wied, 1978).

Figure 1. Metabolism of heroin and its major metabolites (adapted from Rook et al., 2006)



Studies with opiate dependent patients show dose dependent effects for subjective effects such as craving and wellbeing. Slight increase in reaction time and marginal changes in heart rate, blood pressure and skin temperature have also been detected (Rook et al., 2006).

The positive effects of maintenance treatment such as reduction of craving, normalization of stress-responsive hypothalamic-pituitary-adrenal, reproductive, gastrointestinal function, improvement in immune function and normal responses to pain are modulated in part by the μ and in some cases by the κ opioid systems (Kling et al., 2000).

Differences in the blood brain barrier penetration of heroin in comparison with morphine, codeine and methadone were studied by W. H. Oldendorf, Hyman, Braun, & Oldendorf (1972) at the University of California. Using an experimental design with rats, the study group detected an uptake of heroin above two thirds, while methadone was below half and codeine below a quarter (morphine was below measurability). The higher lipid solubility of heroin seems to account for this difference (W. H. Oldendorf, 1974).

The study group led by Charles E. Inturrisi at the Cornell University in New York suggested that heroin could be viewed as a lipid soluble drug which determines the distribution of its active metabolites (Inturrisi et al., 1983). It has an enhanced potency and faster onset of action compared with morphine (although differences have been noted between opioid-dependent and opiate-naive persons; Halbsguth, Rentsch, Eich-Höchli, Diterich, & Fattinger, 2008) and is considerably more water soluble than morphine, and as such shows a practical advantage when injected intramuscularly

(Sawynok, 1986). After intravenous administration in its hydrochloride form, a large proportion converts to a lipophilic non-ionised (base) form, favouring the absorption into systemic circulation and rapid tissular distribution making heroin a very versatile drug as it can be administered via many routes (Blanken et al., 2010).

According to a classical study also carried out by the Cornell University group (Inturrisi et al., 1984) oral administration of heroin results in measurable blood levels of morphine but not of heroin or 6-acetylmorphine (parenteral heroin is rapidly converted to 6-acetylmorphine and then to morphine, see figure 1). They concluded that heroin is a morphine prodrug, i.e. precedes morphine after metabolization. The major metabolite, morphine-3-glucuronide (M3G) has low affinity for μ-opioid receptors, displaying no opiate agonistic activity. On the other hand, M3G accumulation seems to be related to the neurotoxic effect of long-term morphine administration (Smith, 2000 cited in Rook et al., 2006).

2. Objectives

As previously noted, HAT has been studied extensively (Ferri et al., 2011), its cost-effectiveness balance has been demonstrated (Dijkgraaf et al., 2005) and its impact in criminal behaviour is well known (Löbmann & Verthein, 2009). However, little is known about moderating factors that may account for the superior efficacy of HAT. Previous studies of our research group focusing on the German study on heroin treatment addressed the importance of associated clinical factors such as benzodiazepine

consumption (Eiroa-Orosa et al., 2010), alcohol abuse (Haasen, Eiroa-Orosa, Verthein, Soyka, Dilg, & Schäfer, 2009), no previous experience in maintenance treatment (Haasen, Verthein, Eiroa-Orosa, Schäfer & Reimer, 2010), comorbidities (Schäfer et al., 2010), and psychosocial factors such as gender (Eiroa-Orosa et al., 2010), quality of life (Karow et al., 2011) and psychosocial interventions during treatment (paper in preparation).

Our objective with this study is to address clinical and psychosocial factors involved in the outcome of maintenance treatment with heroin or methadone and the interaction between them. We studied in depth five characteristics of patients undergoing heroin or methadone maintenance treatments that could interact with the pharmacological and psychotherapeutic treatment, namely: 1) alcohol consumption, 2) previous maintenance treatment experiences 3) psychiatric comorbidity, 4) benzodiazepine (BZD) use and 5) gender issues. These characteristics, although covering a wide range of predictors of treatment outcome (Blanken, Hendriks, Koeter, van Ree, & van den Brink, 2005; Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998), will be completed with other characteristics in the multivariate unified results section (see below).

3. Hypotheses

The following hypotheses are going to be tested in this work. It should be noted that for the purposes of the present study, efficacy is understood to be the capability of HAT or MMT to improve health or to help reaching abstinence of illegal drugs within this clinical trial as it will be defined in the method section.

H1) Alcohol consumption has a negative influence on the efficacy of both maintenance treatments.

H2) Previous maintenance treatment experiences do not influence the course of HAT nor MMT.

H3) Psychiatric comorbidity has a negative influence on the efficacy of both maintenance treatments.

H4) Concomitant BZD consumption has a negative influence on the efficacy of both maintenance treatments.

H5) Female gender is a predictor of both negative health and abstinence outcomes, although it is mediated by psychosocial characteristics such as: prostitution, responsibility for children, partnership and problematic drug use by partners.

H6) There are interactions between clinical and psychosocial factors within special profiles of difficult to reach patients.

4. Methods

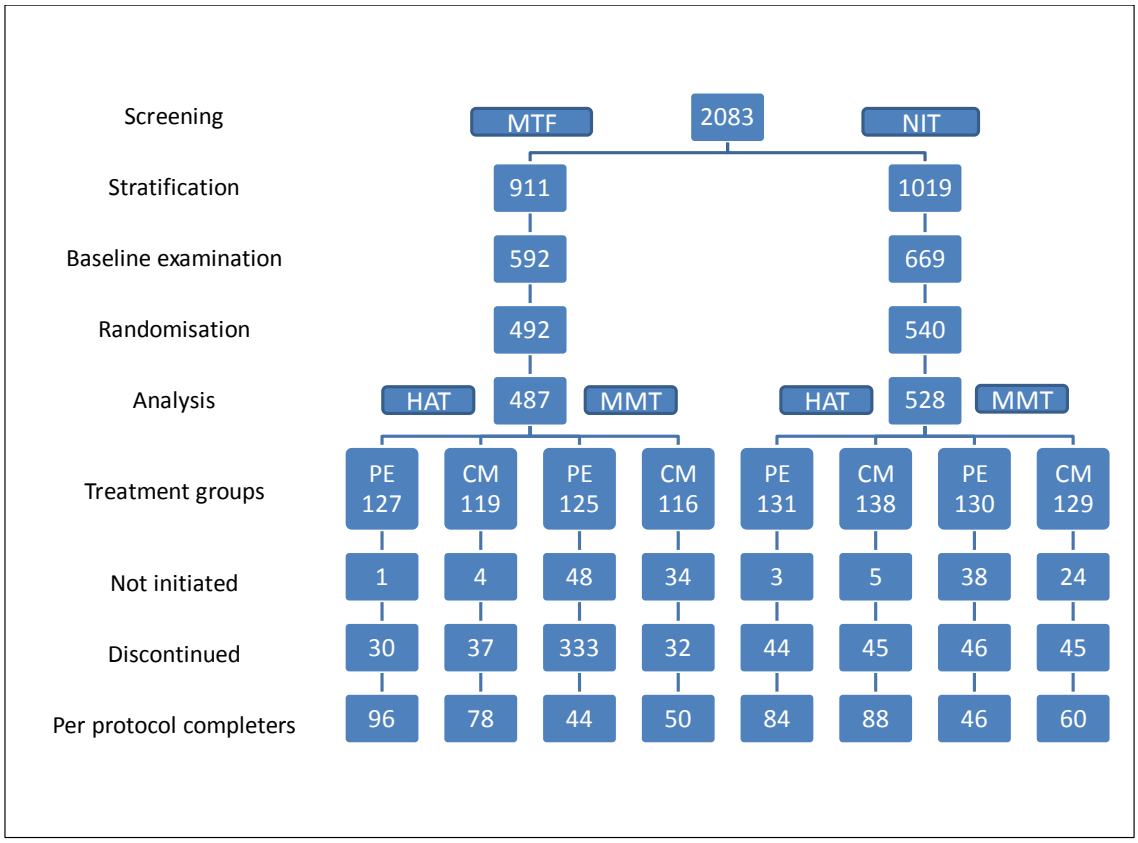
4.1. Patients and setting: The German project of heroin assisted treatment of opiate dependent patients

In 2000 German authorities designated the Centre for Interdisciplinary Addiction Research of Hamburg University as the coordinating centre of a large randomized clinical trial (RCT) with the main objective of investigating whether, in structured treatment settings, prescription of pure heroin to heroin addicts, who had not responded sufficiently to MMT or were not reached by the German addictions system, would have better outcomes than patients treated in MMT.

HAT and MMT was compared in a multicentre study among 1015 patients in 7 cities in Germany. This sample was the result of a randomisation of 1032 heroin addicted patients fulfilling inclusion criteria and attending examination from a previous screening of 2038 patients.

According to the main objective, recruitment was stratified within two target groups: 1) MMT non-responders, and 2) patients not in treatment for the last 6 months but with two previous treatment attempts, either abstinence-based or maintenance; see Haasen et al. (2007) for further details. Patients were randomised into four subgroups depending on type of medical treatment (HAT or MMT) and psychosocial care received (psychoeducation plus individual counselling, PE, or case management plus motivational interviewing, CM). The flow chart of the study can be seen in figure 2.

Figure 2. Flow Chart of the German trial of heroin assisted treatment



MTF: Methadone Treatment Failures. NIT: Not In Treatment. HAT: Heroin Assisted Treatment. MMT: Methadone Maintenance Treatment. PE: Psycho-Education and drug counselling. CM: Case management and Motivational interviewing

Heroin or methadone was dispensed over 12 months. HAT patients received an individually adjusted maximum of three doses of intravenous heroin per day with an additional maximum of 60 mg oral methadone when needed (mean daily dose 442 mg of heroin and 8 mg of methadone being necessary on 20.6% of heroin treatment days) while MMT patients received one individually adjusted single dose of oral methadone daily (mean 99 mg). From the original 1015 patients (sample included in intent to treat, ITT, analyses) 546 patients completed the trial (sample included in the per-protocol, PP, analyses).

4.2. Measures

The German project of heroin assisted treatment of opiate dependent patients used mental and physical health improvement as well as reduction of illicit drug use (difference between baseline and 12 months) as two different primary outcome measures (POM, Haasen et al., 2007). These measures included:

1) Addiction severity was assessed using composite scores (CSs) calculated on the basis of self-reported information according to the German version (Gsellhofer, Küfner, Vogt, & Weiler, 1999) of the EuropASI (Kokkevi & Hartgers, 1995), based on the fifth edition of the Addiction Severity Index (McLellan et al., 1992).

2) Psychopathology, measured with the health scale and Global Severity Index (GSI) of the Symptom Checklist-90-Revised (SCL-90-R; Derogatis, 1994).

3) Health status measured with the Opiate Treatment Index Health-Symptoms-Scale OTI (Darke, Hall, Wodak, Heather, & Ward, 1992; Darke, Ward, Zador, & Swift, 1991).

5) Urine samples for heroin and hair analysis of cocaine use at baseline, month 6 and month 12.

Response to the POM on health was defined as at least 20% improvement and at least 4 points in the OTI health scale and/or at least 20% improvement in the GSI (SCL-90-R), without a deterioration of more than 20% in the complementary area of health.

Response to the POM on illicit drug use was defined as a reduction in the use of street heroin with at least 3 of 5 negative urines in the month prior to T12 and no increase in

cocaine use (hair samples). If fewer than 3 urines or no hair were available at T12, T6 data on urines or hair were used (last observation carried forward). If these were also not available, data was replaced by data from the EuropASI. If these self-reported data were used, response was defined as a 60% decrease in the number of days with street heroin use and no increase of cocaine use of more than two days during the last month. To distinguish between prescribed and illicit heroin, urines were tested for papaverine and acetylcodeine, common impurities of street heroin (Haasen et al., 2007).

4.3. Statistical analyses

Chi square tests, Analysis of Variance (ANOVA), and t tests were used in order to address statistical association between clinical and psychosocial baseline characteristics in the different patients groups. Pearson's correlations were used between convergent measures (e.g. objective vs. subjective measures of alcohol consumption). Factorial logistic regressions were used to assess the efficacy of HAT on health and illegal drug use controlling for different confounding factors. Changes in continuous variables were assessed using Repeated Measures Analysis of Variance (RMANOVA). Analyses of Covariance (ANCOVAs) were used to test dependent variables such as illegal activities controlling for confounding variables.

4.4. Results of the main study

Haasen et al. (2007) analysed the results of the RCT confirming the results of the Swiss (Rehm et al., 2001) and (van den Brink et al., 2003) Dutch studies providing further evidence of the efficacy of HAT in difficult to reach heroin patients. The HAT group showed better retention in treatment and greater response on physical and mental health as well as the illicit drug use POMs. Nevertheless, more serious adverse events, mainly associated with intravenous use, were found in the HAT group. Long term effects of HAT have been analysed for patients who continued treatment for another 12 months (Verthein et al., 2008) and patients who switched treatment from MMT to HAT (Verthein, Haasen, & Reimer, 2011) showing continued benefits for patients joining or switching to HAT.

5. Results summary

In this section we present an outline of the results of the five publications included as fundamental and non-fundamental parts of this thesis. All of the articles are based on the German project of heroin assisted treatment of opiate dependent patients and were designed in order to improve the present knowledge of the predictors of health and abstinence outcomes in maintenance treatments, as well to test the superiority of HAT over MMT within different mediators.

5.1. Effects of Heroin-Assisted Treatment on Alcohol Consumption: Findings of the German Randomized Controlled Trial (non-fundamental; Haasen et al., 2009).

Three "concentric" samples were analysed: The original ITT sample, a subsample (n=849) with ASI alcohol measures, and a subsample (n=346) with carbohydrate-deficient transferrin (CDT, a biological marker widely used to monitor alcohol use in treatment settings; Anton, 2001) measures. Both self-reported and biological measures of alcohol consumption had statistically significant but moderate correlations both at baseline and treatment end.

Stronger reductions in alcohol consumption were detected in the HAT group, and these patients had better outcomes in health improvement and in reduction of illicit drug use both for alcohol dependent and non-dependent patients. Alcohol dependence (using a threshold of 0.17 for ASI CS on alcohol according to Rikoon, Cacciola, Carise, Alterman, & McLellan, 2006) predicted POM on health improvement but no effect was found over the illegal drug consumption POM.

5.2. Is Heroin-Assisted Treatment Effective for Patients with No Previous Maintenance Treatment? Results from a German Randomised Controlled Trial (non-fundamental; Haasen, Verthein, Eiroa-Orosa, Schäfer, & Reimer, 2010).

This study was carried out dividing the ITT sample into two subsamples: patients with previous maintenance treatment experience (PME, n=899) and patients without (NPME, n=107). NPME patients included fewer females, were younger, had less experience with detoxification and drug free treatments, had consumed cocaine and heroin for a shorter amount of time, the proportion of Hepatitis C (HCV) infected was lower, they had a lower rate of suicide attempts and higher score in the Global Assessment of Functioning Scale but had more days of heroin use and injected drugs on more days in the last month and a worse housing situation. Despite these baseline differences, these two groups did not differ in treatment retention or duration, dosage, and POMs.

The superiority of HAT in the NPME subsample was found in the POM on reduction of illicit drug use and the reduction of illegal activity, but not in the POM on health, although HAT was also found to be superior to MMT on both health and drug use POMs taken together. HAT superiority in outcome was statistically significant for patients with previous abstinence treatment experience both for health and illegal drug consumption but not in the case of the health POM or both POMs taken together for patients without this experience.

5.3. Effects of Psychiatric Comorbidity on Treatment Outcome in Patients Undergoing Diamorphine or Methadone Maintenance Treatment (non-fundamental; Schäfer et al., 2010).

Half of the sample had at least one comorbid psychiatric diagnosis, mainly neurotic, stress-related, somatoform or affective. Drug use was found to be significantly higher among patients with a comorbid diagnosis at the beginning and the end of treatment. HAT had a better outcome than MMT for the reduction of illicit drug use in both comorbid and non-comorbid patients, but weaker effects were found in the comorbid group. HAT worked better than MMT in improvement of health for non-comorbid patients; however, this difference was not present among patients with psychiatric comorbidities.

5.4. Benzodiazepine use among patients in heroin-assisted vs. methadone maintenance treatment: Findings of the German randomized controlled trial (fundamental; Eiroa-Orosa et al., 2010).

For this study BZD users were identified at baseline (at least one day of BZD use in the last month and/or a BZD positive urine at baseline) and only in the PP sample (due to availability of urine samples) during treatment (26% BZD positive urines during treatment). Also among completers, BZD prescription patterns were analysed in three

groups: no, intermittent or regular prescription. Baseline BZD users were found to be less often employed, initiated heroin use at an earlier age, had fewer days of heroin use in the past month but more days of cannabis use, were more likely to have a comorbid diagnosis, and higher SCL-90-R anxiety and phobic anxiety subscale T scores, had higher ASI CSs (indicating higher severity) of physical state of health, economic situation, drug use, legal problems, family, social relations and mental status areas. BZD users were more likely to be HIV positive although the statistical test didn't reach significance.

Statistically higher retention rates were observed in patients who did not use benzodiazepines at baseline only in the HAT treatment group. No significant differences were detected in outcome measures. BZD use during treatment was found to have a negative association with health outcome in both treatment groups but, when analysing drug use outcome, differences were only statistically significant when both treatment groups were combined. Better outcomes for those with regular prescription of BZD were found in the course of phobic anxiety symptomatology in comparison with patients with irregular or no prescription at all. Finally, the proportion of BZD positive urine tests during treatment decreased more in HAT than in MMT.

5.5. Implication of Gender Differences in Heroin-Assisted Treatment: Results from the German Randomized Controlled Trial (fundamental; Eiroa-Orosa et al., 2010).

Significant baseline gender differences were found being female participants younger, having more often children, less years of previous heroin use, earlier initiation of benzodiazepine use, higher severity of addiction in the ASI domains of physical health, drug use, and mental status, higher OTI and GSI scores, greater proportion of suicide attempts, and more had previous maintenance treatment experience. They also were more often HIV positive, and had worse ASI scores for family relationships, although in the latter only a statistical tendency was found.

Men had significant better outcomes for the POM of illegal drug use but not for health or retention. Among women statistically significant differences between treatments (HAT or MMT) were only found for retention. After multivariate analyses including various possible psychosocial characteristics, only prostitution was found to predict worse outcomes among women.

6. Discussion

Stronger effect of HAT than methadone on the reduction of alcohol use could be explained by a global positive effect on health status of the patients, as showed in the main study (Haasen et al., 2007). Hard drinkers, as measured with ASI composite

scores and CDT thresholds, have comparable results in regard to illegal substance use but not to health. We propose new studies which could test whether the reduction of alcohol use results in better overall health outcomes or whether better overall health outcomes lead to reductions in alcohol use. On the other hand, patients had to be sober at the moment of heroin or methadone dispensation, forcing MMT patients to be sober on the mornings of MMT dispensation and HAT patients to be sober up to three times a day. This schedule worked as a behavioural contingency, having a positive influence on treatment effects, similar to other studies on contingent reinforcement (Rogers et al., 2008).

Patients without previous maintenance treatment experience had a shorter addiction career, but benefited from both HAT and MMT to almost the same extent as those with maintenance treatment experience. The superiority of HAT in this subsample has to be considered taking into consideration the fact that, unlike the rest of the sample, they have had no previous (negative or not sufficiently effective) experience with MMT. Therefore, in light of these results, it may be that political interests should reconsider whether HAT may be implemented as a first line treatment option – among other opioid substitution treatments – cautiously addressing its limitations within adverse events due to injection.

HAT was also superior to MMT in patients with psychiatric comorbidity for both POMs. Comorbidity had an influence on the strength of treatment group effects, with higher odds of response rates for non-comorbid patients relative to those with psychiatric comorbidity. These milder results may be due to the sedative effect of methadone and the overall lower, although not statistically significant, treatment effect in the group

with psychiatric comorbidity. This is in line with previous studies that did not find statistically significant differences in treatment outcome between patients with or without psychiatric comorbidities in maintenance treatment (Verthein, Degkwitz, Haasen, & Krausz, 2005). Nevertheless, this milder difference may be also due to the specific psychosocial and psychiatric interventions provided to these patients as should be the case when psychiatric symptoms and substance use are interrelated.

Baseline differences between illegal and non-illegal users of BZD may arise from underlying mental health issues. No negative impact of BZD use on treatment outcomes was found for the HAT group. Baseline BZD use also led to poorer treatment retention in HAT, distinct from the absence of such an effect on MMT retention, which may be due to the early dropout rate in this group. The negative impact on HAT retention can be explained by an increased sedation among BZD users which limited the ability to identify an effective dose of heroin. The fact that BZD users treated with HAT had a greater reduction in BZD use and better outcomes for drug use, alcohol use and legal problems than those treated with MMT, suggests that HAT may be a better treatment option for difficult to reach opioid dependent patients with comorbid benzodiazepine dependence despite their reduced treatment retention. The greater reduction in phobic anxiety symptoms among patients with ongoing BZD use who were prescribed benzodiazepines suggests that prescribing BZD (if indicated) in this population may be recommended in order to avoid illicit BZD use, and to cautiously screen side effects and dosage. Neurobiological aspects can also explain the higher decrease of BZD use on the HAT group and why this is also true for heroin dependents not in maintenance treatment (Backmund, Meyer, Soyka, Reimer, & Schütz, 2006). Benzodiazepines seem to boost the subjective effects of methadone (Busto, Romach,

& Sellers, 1996) or increase the effect of methadone (Eap, Buclin, & Baumann, 2002). Less BZD use may be related by the greater dopamine release of diamorphine than methadone in the mesolimbic dopamine system (Xi, Fuller, & Stein, 1998).

Women in the study with a higher rate of prostitution, a source of income to finance illicit drug use as well as daily living, had a much more complicated clinical picture. Furthermore, more women had children, an additional responsibility further complicating the psychosocial circumstances of these patients. The female HAT subsample did not have significantly better primary outcome measures than the MMT subsample; however they did show greater treatment retention. The lack of statistically significant differences may be due to a smaller sample size as the HAT group performed slightly better. The greater extent of mental distress for women at baseline may also hamper significant better improvement in the whole sample.

The results on the specific factors affecting heroin dependent women during treatment (mainly prostitution and problems related to family and social relationships) imply that treatment considerations need to be responsive to women's specific context. Nevertheless, prostitution and other secondary measures decreased in the HAT group to a greater extent than in the MMT group, indicating that HAT constitutes a viable treatment option for women.

There are limitations of these studies that need to be considered. The study was not developed to analyse the effect of maintenance treatment on alcohol use, previous treatments, comorbidities, benzodiazepine use or gender, so no causality can be attributed and the associations found may need to be confirmed in future trials. The

patient groups were not randomized according to these characteristics, and the large baseline differences were controlled for only in a statistical manner.

All this studies taken together show the efficacy of HAT particularly within especially difficult to reach populations of heroin dependent persons. From an etiological point of view, these results confirm that addiction to opiates may be due to a combination of biological and environmental (including behavioural) factors (Kreek, 2006) that should be addressed together in a multidisciplinary way using the best pharmacological and psychosocial methods available as it was done in this trial.

7. Multivariate unified results: predictors of outcomes in illegal drug use and health

7.1. Rationale

A meta-analysis carried out by Brewer, Catalano, Haggerty, Gainey, & Fleming (1998) identified predictors of continued drug use during and after treatment. Ten variables remained statistically significant after multivariate analyses: high level of pre-treatment opiate and other drugs use, prior experiences in treatments for opiate addiction, no prior abstinence from opiates, abstinence from/light use of alcohol, depression, high stress, unemployment or employment problems, association with substance abusing peers, short length of treatment, and leaving treatment prior to completion.

Furthermore, a study based in the Dutch trial (Blanken et al., 2005) addressed different physical health, mental status and social functioning aspects in order to predict treatment response, finding previous experience in abstinence-oriented treatment as the greatest predictor of outcome (multi-domain including abstinence and health improvement). Nevertheless, to date there is no study that analyses the interactions between psychosocial and clinical predictors of abstinence accounting for HAT and MMT in a detailed way. The objective of this section will address baseline predictors of the Primary Outcome Measures in illegal drug use and improvement of health.

7.2. Method

In order to build a unified model of risky and protective features we selected the most important variables according to clinical experience and previous literature. These variables can be classified in these categories: baseline sociodemographic characteristics, information on heroin use, additional past month drug use information, physical health, mental health and emotional wellbeing, previous treatments and psychometric scales.

7.2.1. Additional measures

In addition to the instruments cited above (section 4.2) different psychometric instruments were added for this special analysis. These scales included coping resources (Brandtstädter & Renner, 1990), self-esteem (Rosenberg, 1965), attitudes

towards gratification delay (Utz, 1979) various aspects of self-control (Grasmick, Tittle, Bursik, & Arneklev, 1993), motivation for change (Heidenreich & Hoyer, 1995; according to Prochaska & DiClemente, 1982), possibilities of social support (Sommer & Fydrich, 1989), reasons for the development of drug dependence (Muthny, 1988), the goals and motivations for participating in the pilot project and emotions related to abstinence.

The motivation for change scale, based in Prochaska & DiClemente's Transtheoretical Model (1982), includes various dimensions that describe the various stages of change towards a healthy behaviour. It includes:

- Precontemplation- Still not intending to take action in the foreseeable future. This stage is compatible with being unaware that the behaviour is problematic.
- Contemplation- Beginning to recognize that the behaviour in question is problematic.
- Preparation- Intending to take action in the immediate future. A person in this stage may begin taking small steps toward behaviour change.
- Action – People in this stage of change have made specific modifications in their problematic behaviour or are acquiring new healthy behaviours.
- Maintenance – People in this stage are supposed have been able to sustain action and are already working to prevent relapse.

7.2.2. Statistical Analysis

Odds ratio and Chi square tests within crosstabs and t tests will be used in order to address the statistical association between clinical and psychosocial baseline characteristics in the treatment groups. Statistical significant clinical and psychosocial variables will be selected for a multivariate analysis. Discriminant analyses will be used in order to build predictive models of health and illegal drug use outcomes according to baseline and on treatment characteristics. Four analyses were done using the POMs on health and illegal drug use.

7.3. Results

Table 1 shows psychosocial and clinical features according to outcomes in health and illegal drug use. Statistically significant differences were found for the POM on illegal drug use regarding type of treatment, gender, days of heroin and intravenous drug use in the 30 days prior to study entry, HCV and previous experience in a drug free treatment. No statistically significant baseline differences in regard to psychometric scales were detected. However, in the PP sample, during treatment (6 months) differences regarding outcome in illegal drug use were statistically significant in the case of drug, legal and family EuropASI CSs, self-esteem, action stage of change, and temptations and craving.

Regarding health, baseline statistical significant differential variables were found to be: Type of treatment, Stable housing, days of heroin, cocaine and dangerous alcohol use

in the 30 days previous to study entry; being alcoholic according to ASI CS (0.17; Rikoon et al., 2006), the OTI health scale, a HCV positive test, and the SCL-90-R GSI T score. Differential psychometric measures were: self-centeredness (subscale from the Utz gratification delay scale), and having become drug addicted because of lack of support by cultural or religious peers, physical or mental health problems and lack of perspectives after school. Statistically differential psychosocial and clinical characteristics at 6 months according to health improvement can be seen directly in table 2.

Retention had a very high correlation with both POMs (illegal drug use: OR=1.310, 95% CI=1.016-1.690; p<.05, health improvement: OR=2.171, 95% CI=1.610-2.298; p<.0001), and was used in the models as a predictor, also in the longitudinal analyses as they were done within the completers sample.

Many interactions between independent variables were statistically significant. Especially remarkable differences were found for patients without a previous drug free treatment experience. These patients were in a situation of harder consumption, more psychological, legal and social problems (statistical significant differences in all ASI scores, self-esteem, coping resources, self-control, social support and scored higher in the precontemplation subscale of the motivation for change scale).

Table 2 shows the standardized canonical discriminant function coefficients from the discriminant analyses performed with the ITT (baseline predictors) and PP (longitudinal predictors) samples. With the exception of the ITT analysis for health outcome, HAT had high standardised canonical coefficients, and therefore can be considered the most reliable predictor of outcome.

Table 3 shows classification results for the four models. Sensitivity was moderate in the four cases (range 60.9-67.3%), although lower specificity was found (60.3-64.8%). Global correct classification ranged from 60.7 to 66.5%.

7.4. Discussion

The results of the unified multivariate analysis confirm the importance of the analysed variables and the superiority of HAT over MMT in our sample.

Regarding reduction of illicit drug use, HAT, treatment retention, female gender, days of heroin use in the past month, HCV, previous drug free treatment, and occupational stress or worries as a reason for drug dependence were found to be liable baseline predictors of reduction of illicit drug use. On the other hand, HAT, the proportion of positive BZD urine samples during the study, female gender, age of beginning of heroin use, previous drug free treatment, EuropASI Illegal drug use, legal problems, family problems, action stage, and Temptations and craving predicted reduction of illicit drug use in the PP sample.

Whereas psychopathology, baseline alcoholism, lifetime psychiatric comorbidity, lack of support by cultural or religious peers as a reason for drug dependence, and stable housing were the more reliable predictors of health improvement in the ITT sample; low benzodiazepine consumption during treatment, HAT, a lack of perception of time pressure when injecting heroin or taking methadone, HCV, and maintenance stage, (motivation for change), were the more reliable predictors of health improvement in the PP sample.

Table 1. Differential baseline characteristics between patients according to their response to Primary Outcome Measure on Illegal Drug Use and Improvement of Health (ITT sample, n=1015)

	POM Illegal Drug Consumption					**POM Health improvement**				
	Positive (n=632)		Negative (n=383)			Positive (n=782)		Negative (n=233)		
	N	%	N	%	Significance	N	%	N	%	Significance
Treatment										
HAT	356	56.3	159	41.5	OR=1.871, 95% CI=1.405-2.350; p<.0001	412	52.7	103	44.2	OR=1.405, , 95% CI=1.047-1.886, p=.023
MMT	276	43.7	224	58.5		370	47.3	130	55.8	
Baseline sociodemographic characteristics										
Gender										
Males	523	82.8	288	75.2	OR=1.583, 95% CI=1.160-2.159; p=.004	629	80.4	182	78.1	OR=1.152, , 95% CI=0.806-1.647, p=0.437
Females	109	17.2	95	24.8		153	19.6	51	21.9	
Employed	81	12.9	50	13.1	OR=.981, 95% CI=.673-2.159; p=.993	108	13.9	23	9.9	OR=1.472, , 95% CI=0.914-2.379, p=0.110
Stable housing	434	69.0	267	69.3	OR=.959, 95% CI=.727-1.264; p=.764	554	71.1	147	63.4	OR=1.424, , 95% CI=1.046-1.939, p=0.25
	M	SD	M	SD		M	SD	M	SD	
Age	36.54	6.85	36.09	6.52	t= 1.040. p=0.298	36.41	6.73	36.22	6.76	t=0.375, p=0.708
Education in years	9.76	1.89	9.83	1.71	t= -0.585. p=0.559	9.80	1.81	9.76	1.86	t=0.330 p=0.741
Information on heroin use										
Age of beginning of use	19.99	5.18	20.45	5.49	t= -1.325 ,p=0.186	20.25	5.36	19.86	5.08	t=0.988, p=.323
Years of use	13.76	6.35	13.40	6.29	t=0.883, p=0.377	13.56	6.28	13.87	6.50	t= -0.655, p=.512
Days of use in the past 30 days	20.33	11.11	22.67	10.18	t= -3.419, p<0.001	21.69	10.46	20.17	11.57	t= 1.895, p=0.058
Additional past month drug use information										
Days of intravenous drug use in the past 30 days	21.96	10.66	23.49	9.95	t= -2.270, p=0.023	22.78	10.22	21.70	11.03	t= 1.382, p=0.167
Days of cocaine use in the past 30 days	9.31	11.84	9.19	12.01	t=-0.102, p=0.919	21.60	10.54	19.94	11.67	t= 1.975, p=0.049
Days of dangerous alcohol use in the past 30 days	10.15	12.33	9.31	12.16	t=1.054, p=0.292	15.83	5.70	14.78	4.91	t= 2.294, p=0.022
Days of tranquilizer use in the past 30 days	9.31	11.84	9.19	12.01	t=0.145, p=0.885	9.05	11.75	9.98	12.40	t= -1.050, p=0.294
	N	%	N	%		N	%	N	%	
Alcoholic according to ASI CS (0.17)	167	27.7	87	24.0	OR=.826, 95% CI=0.612-1.115, p=0.211	182	24.4	72	32.9	OR=1.518, 95% CI=1.094-2.106, p=0.012
Baseline BZD consumption	459	72.6	277	72.3	OR=1.015, 95% CI=0.764-1.349, p=0.917	562	71.9	174	74.7	OR=0.866, 95% CI=0.620-1.210, p=0.399

HAT: Heroin Assisted Treatment, MMT: Methadone Maintenance Treatment, ASI: Addiction Severity Index, CS: Composite Score, BZD: Benzodiazepine

Table 1. Differential baseline characteristics between patients according to their response to Primary Outcome Measure on Illegal Drug Use and Improvement of Health (ITT sample, n=1015) (Continued)

	POM Illegal Drug Consumption					**POM Health improvement**				
	Positive (n=632)		Negative (n=383)			Positive (n=632)		Negative (n=383)		
Physical health										
	M	SD	M	SD		M	SD	M	SD	
OTI health scale (0-50 pts. mean±SD)	19.13	5.24	18.63	5.37	t= 1.470, p=.142	19.15	5.25	18.25	5.38	t= 2.270, p=0.023
BMI	22.72	3.40	22.46	3.64	t= 1.148, p=.251	22.69	3.50	22.42	3.48	t= 1.019, p=0.308
	N	%	N	%		N	%	N	%	
HIV positive	53	8.5	38	10.0	OR=.832, 95% CI=.537-1.289; p=.411	66	8.5	25	10.8	OR=0.772, , 95% CI=0.475-1.254, p=0.295
HCV positive	526	83.8	291	77.0	OR=1.542, 95% CI=1.120-2.123; p=0.008	615	79.4	202	87.4	OR=0.552, , 95% CI=0.360-0.845, p=0.006
Mental health										
Attempted suicide	234	38.2	133	35.7	OR=1.114, 95% CI=.853-1.456; p=.428	286	37.7	81	35.5	OR=1.100, , 95% CI=0.808-1.497, p=0.546
Lifetime Axis I disorder	248	60.6	131	60.4	OR=1.011, 95% CI=.722-1.416; p=.948	301	58.9	78	67.8	OR=0.680, , 95% CI=0.443-1044, p=0.077
Last 12 months Axis I disorder	201	49.1	105	48.4	OR=1.031, 95% CI=0.741-1.433; p=.857	243	47.6	63	54.8	OR=1.336, , 95% CI=0.890-2.006, p=0.161
	M	SD	M	SD		M	SD	M	SD	
SCL-90-R GSI	69.37	10.52	69.17	10.23	t= -.290, p=.772	70.46	9.92	65.39	11.05	t= 6.670, p<0.0001
Previous treatments										
	N	%	N	%		N	%	N	%	
Previous detox	547	87.8	340	89.5	OR=.847, 95% CI=.564-1.271; p=.422	678	87.9	209	90.1	OR=0.802, , 95% CI=0.495-1.299, p=0.370
Previous Optiate Substitution	562	89.6	337	88.9	OR=1.078, 95% CI=.715-1.625; p=.722	690	89.0	209	90.5	OR=0.854, , 95% CI=0.522-1.400, p=0.562
Previous Psychosocial care	322	52.9	188	50.8	OR=1.086, 95% CI=.839-1.407; p=.531	386	51.2	124	55.1	OR=0.854, , 95% CI=0.634-1.152, p=0.302
Previous drug free	405	66.6	218	58.8	OR=1.400, 95% CI=1.072-1.828; p=.013	471	62.5	152	67.3	OR=0.813, , 95% CI=0.594-1.114, p=0.197

BMI: Body Mass Index, OTI: Opiate Treatment Index, HIV: Human immunodeficiency virus, HCV: Hepatitis C Virus, SCL-90-R: Symptom Checklist-90-Revised, GSI: Global Severity Index

Table 2. Standardised canonical discriminant function coefficients

Intention To Treat (all variables measured at baseline, N=1015)			
Illicit drug use		**Health improvement**	
HAT	0.628	HAT	0.178
Treatment retention	0.156	Stable housing	0.264
Gender	0.364	HCV	0.115
Days of heroin use in the past month	0.376	Alcoholic according to ASI CS	0.402
HCV	0.324	Lifetime Axis I disorder	0.339
Previous drug free treatment	0.257	Cocaine consumption in the last month	0.132
Occupational stress or worries as a reason for drug dependence.	0.305	Street heroin consumption in the last month	0.042
		OTI-Score	0.215
		SCL-90-R-GSI	0.809
		Self-centeredness	0.177
		Lack of support by cultural or religious peers as a reason for drug dependence	0.334
		Physical health problems as a reason for drug dependence	0.134
		Mental health problems as a reason for drug dependence	0.190
		Lack of direction after school as a reason for drug dependence	0.160
Per Protocol (all variables measured during the study, N=546)			
Illicit drug use		**Health improvement**	
HAT	0.478	HAT	0.338
Proportion of positive BZD urine samples during the study	0.132	HCV	0.245
Gender	0.225	Proportion of positive BZD urine samples during the study	0.369
Age of beginning of heroin use	0.287	Alcoholic according to ASI CS	0.054
Previous drug free treatment	0.445	Female gender	0.052
EuropASI Illegal drug use (6 months)	0.484	EuropASI Medical Problems(6 months)	0.072
EuropASI Legal problems (6 months)	0.003	EuropASI Illegal drug use (6 months)	0.082
EuropASI Family problems (6 months)	0.154	EuropASI Legal problems (6 months)	0.030
Action stage (6 months)	0.033	EuropASI Family problems (6 months)	0.026
Temptations and cravings (6 months)	0.041	EuropASI Social problems (6 months)	0.130
		EuropASI Psychological problems (6 months)	0.176
		Maintenance (Motivation for change subscale score at 6 months).	0.223
		Social support (score at 6 months)	0.069
		Unpleasant feelings	0.080
		Temptations and craving (6 months)	0.172
		Pleasant feelings	0.168
		Compliance with physicians' examinations and conversations	0.165
		Time pressure when injecting heroin or taking methadone	0.286
		Compliance with the study treatment-related appointments	0.052

HAT: Heroin Assisted Treatment, MMT: Methadone Maintenance Treatment, ASI: Addiction Severity Index, CS: Composite Score, BZD: Benzodiazepine, OTI: Opiate Treatment Index, HCV: Hepatitis C Virus, SCL-90-R: Symptom Checklist-90-Revised, GSI: Global Severity Index

Table 3. Classification results of the four discriminant models

Intention To Treat N=1015									
Illicit drug use					**Health improvement**				
	Predicted					**Predicted**			
	Positive		Negative			Positive		Negative	
Original	N	%	N	%	**Original**	N	%	N	%
Positive	385	60.9	247	39.1	Positive	512	65.5	270	34.5
Negative	152	39.7	231	60.3	Negative	82	35.2	151	64.8
Global 60.7% correct classified					Global 65.3% correct classified				
Per Protocol N=546									
Illicit drug use					**Health improvement**				
	Predicted					**Predicted**			
	Positive		Negative			Positive		Negative	
Original	N	%	N	%	**Original**	N	%	N	%
Positive	237	66.6	119	33.4	Positive	306	67.3	149	32.7
Negative	70	36.8	120	63.2	Negative	34	37.4	57	62.6
Global 65.4% correct classified					Global 66.5% correct classified				

All the results appear to be concordant with our previous studies, as well as the work of Brewer et al. (1998) regarding high level of pre-treatment opiate use, prior treatment for opiate addiction, prior abstinence from opiates, use of alcohol, depression, high stress, short length of treatment, and leaving treatment prior to completion. Unemployment was not statistically associated with illegal drug use or health improvement outcomes. In line with Blanken et al. (2005), a previous drug free treatment was found to predict illicit drug use reduction. The role of HCV seems controversial due to its protective role regarding illegal drug use, while it can prevent health improvement. This must be seen in the special context of the co-treatment of HCV (Reimer & Haasen, 2009; Reimer, Backmund, & Haasen, 2005) in a trial were, as usual in injection drug contexts, 80% of participants were HCV positive. These patients were more able to stop drug consumption probably influenced by health behaviours acquired during treatment but the infection could be a barrier to health improvement.

Motivation for change appears to be consistent with what can be expected. Action (i.e. hard work on the drug problem) and maintenance behaviours (i.e. relapse prevention and healthy behaviour consolidation) are covariates during the treatment period for improvement in illegal drug use and health respectively.

Social and family support appears to be also an important factor. Patients with a good social support have been proved to be more likely to maintain abstinence from opiates and general improvement due to the multiple positive effects that social reintegration has over health behaviours (Havassy, Hall, & Wasserman, 1991; Wasserman, Stewart, & Delucchi, 2001).

Furthermore, impulsive behaviours related to a low self-centeredness (i.e. self-control) are related with failed reduction of illegal drug reduction in line with neurobiological models of addiction as a disruption in self-control (Baler & Volkow, 2006).

Specific reasons for drug dependence such as occupational stress or worries predicted relapse in illicit drug use. Lack of support by cultural or religious peers, physical and mental health, and lack of direction after school as reasons of drug dependence predicted no health improvement. These (not exclusive) profiles of drug dependence initiation must be cautiously analysed. Whereas occupational stress and lack of direction may correspond to persons who had difficulties coping with a given situation, lack of support by cultural or religious peers may correspond with a person with low perceived social support within his community. Lastly, a group of people initiated heroin used in response to mental and physical health problems which are associated with a lack of health improvement in the study.

Finally, feelings related to treatment personal and settings, appear to mediate also outcome. For example, the perception of time pressure when injecting heroin or taking methadone should correspond with a negative view of the treatment facilities and relation with the health personal in the maintenance points.

In light of these unified results, we may accept our six hypotheses. These special profiles of patients lead us to conclude what will be described in the following section.

8. Conclusions

This study has shown profiles of difficult to reach heroin addicted patients that should be addressed regardless of the opiate therapy they receive. The following highlights may be considered as a way of improving maintenance treatment programs.

8.1. Highlights

1) Specific interventions are needed in alcoholic, HCV and benzodiazepine consuming patients entering maintenance treatment in order to provide them extra help regarding health improving behaviours.

2) Previous maintenance treatment should be reconsidered as a requirement for HAT entry. Patients without previous drug free experiences have a more complicated clinical picture that should be addressed carefully.

3) Dual diagnosis patients (i.e. patients diagnosed with comorbid psychiatric disorders) need to have specific psychiatric, psychotherapeutic and psychosocial interventions helping them to overcome the diseases and facilitate them the advantages of maintenance treatments.

4) Social support appears to be a key factor that may be addressed using systemic interventions within families and communities.

5) Women constitute a special risk group. Risk taking due to extreme psychosocial conditions may be addressed by multidisciplinary teams that can treat globally cases hard to reach both from the clinical and psychosocial points of view.

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ANEX I. PUBLICATIONS INCLUDED AS NON-FUNDAMENTAL PART OF THE THESIS

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Effects of heroin-assisted treatment on alcohol consumption: findings of the German randomized controlled trial

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Abstract

Alcohol has been suggested to be a risk factor for opioid-dependent patients in methadone maintenance treatment (MMT). Literature shows that MMT has limited effects on alcohol use. Nevertheless, a decrease in alcohol use was detected in the Swiss heroin-assisted treatment (HAT) study. In this article, we carry out an in-depth analysis of the German HAT trial with the aim of determining whether alcohol use was affected among patients undergoing HAT and MMT. Analysis was carried out using self-reported data on consumption units of alcohol used (CU), Addiction Severity Index composite scores (ASI CSs), and carbohydrate-deficient transferrin (CDT) measures. Results suggest significant reduction of CU and CDT in both groups, yet larger effects in the HAT group. ASI CS significantly decreased in the HAT but not in the MMT group. The greater benefit of HAT in reducing alcohol use may be due to the greater daily frequency of dispensing heroin coupled with a requirement of sobriety at each dosing occasion.

Keywords: Alcohol abuse; Alcohol dependence; Diamorphine; Heroin-assisted treatment; Methadone maintenance treatment

Introduction

Heroin-assisted treatment (HAT) has been implemented in clinical trials in Switzerland, the Netherlands, Spain, Germany, United Kingdom, and Canada (Fischer et al., 2007). HAT has shown feasibility, effectiveness, and safety in the Swiss, Dutch, and Spanish trials (van den Brink et al., 2003; March et al., 2006; Rehm et al., 2001). In the German model project, HAT users showed better results than methadone maintenance treatment (MMT) in terms of health improvement and reduced illicit drug use (Haasen et al., 2007), and these results lasted over time (Verthein et al., 2008).

Concerning alcohol abuse and dependence in HAT patients, few results have been published. The Swiss study reported decreasing rates of occasional alcohol use, whereas daily alcohol use remained approximately constant (Uchtenhagen et al., 1999). No reports of treatment effects on alcohol consumption have been published on the Dutch or Spanish HAT trials. The British and Canadian trials are currently in progress and no analyses have been published yet.

Effects of MMT on alcohol use have been analyzed in several studies. Srivastava et al. (2008) carried out a review of 14 longitudinally designed studies on the effects of MMT on alcohol use. Of the articles reviewed, nine found no change, three found an increase, and another three articles a decrease in alcohol use. According to the authors, the studies that found no change or a decrease in alcohol use were stronger methodologically, as they were randomized controlled trials and prospective cohorts, whereas the studies that found an increase were all retrospective. Thus, although conclusions are complicated to make due to the heterogeneity of the reviewed studies, an increase of alcohol use was not considered to be probable. Using a two-group design, Lollis et al. (2000) carried out a study where opioid-dependent patients not in MMT reported significantly more alcohol intake than the group in MMT, confirming the hypothesis that patients in MMT are not likely to drink more.

The extent and reasons to which patients in MMT believed to change their drinking behavior during MMT were analyzed by Hillebrand et al. (2001). These authors found subjective norms (normative influence by ‘‘important others’’) and perceived functions of alcohol use (such as relaxing or empowering the effect of methadone) to be

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the strongest positive predictors. Bickel et al. (1987) reviewed treatments for alcoholic patients in MMT and found reduction both in alcohol and drug consumption in combined behavioral-pharmacological treatment but not in abstinence oriented, controlled drinking or voluntary disulfiram treatment.

Alcoholism has been suggested to be a relevant health risk factor for patients treated with methadone. Alcohol has been found to increase the risk of fatal opiate overdose (Hickman et al., 2008; Polettini et al., 1999; Ruttenber et al., 1990). A study carried out with 100 patients attending treatment showed that those who consumed alcohol had poorer diets and smoked more (Best et al., 1998). Another study (el-Bassel et al., 1993) pointed out the relationship between alcoholism and psychiatric symptomatology. The authors found higher rates of somatization, obsessive-compulsive behavior, depression, phobic anxiety, and psychosis in alcohol dependent than in nondependent MMT patients. The higher prevalence of hepatitis C for MMT patients makes those who have an extensive history of alcohol use more vulnerable, leading to a poorer prognosis (Sylvestre, 2002) and even causing death (Zador and Sunjic, 2000). If treatment is intended, alcohol use can impair the efficacy of interferon-based treatments (Cooper and Mills, 2006). The absence of alcohol use has also been related to lower criminality in MMT clients (Patterson et al., 2000).

Nevertheless, the literature suggests that there are no important interactions between alcoholism and MMT outcome. Rowan-Szal et al. (2000) reported no influence of alcohol use in an outpatient methadone treatment in terms of session attending and retention rate, even though they had lower levels of trust and respect for the counselors than other patients with no alcohol abuse. Chatham et al. (1995) found similar results and suggested that heavy drinking clients were significantly more likely to have prior experience with self-help groups and therefore, more capable to stay in treatment.

Considering the importance of addressing alcohol use in the treatment of opioid dependence, the effect of HAT compared to MMT on the possible reduction of alcohol use was analyzed as a secondary outcome measure in the German HAT trial.

Materials and methods

The original German trial sample was composed of 1,015 heroin-dependent patients, either not in treatment in the last 6 months or who were not responding to maintenance treatment. This sample was the result of an initial screening of 2,083 heroin users, of which 1,272 came to the initial baseline examination, 1,032 fulfilled inclusion criteria and were randomized. Seventeen patients dropped out before treatment by withdrawing their consent. Finally 515 persons were randomized to the HAT group and 500 to the MMT group constituting the intention-to-treat (ITT) sample. The treatment duration was 12 months, with 67.2% of HAT patients completing study treatment

Table 1
Characteristics of the sample

	Original ITT sample (n = 1015)		ASI subsample (n = 849)		CDT subsample (n = 364)	
Variable	Heroin (n = 515)	Methadone (n = 500)	Heroin (n = 439)	Methadone (n = 410)	Heroin (n = 182)	Methadone (n = 182)
Sociodemographic characteristics						
Male gender (%)	80.0	79.8	81.3	78.3	80.2	81.3
Age (mean ± SD)	36.2 ± 6.7	36.6 ± 6.8	36.4 ± 6.7	36.7 ± 6.9	36.5 ± 6.3	35.9 ± 7.0
Education in years (mean ± SD)	9.8 ± 1.8	9.7 ± 1.9	9.9 ± 1.8	9.7 ± 1.9	10.2 ± 1.7	9.7 ± 2.0*
Employed (%)	13.6	12.3	13.7	13.2	17.0	15.5
Stable housing (%)	69.0	69.7	69.9	71.4	72.5	67.4
Duration of heroin misuse (mean ± SD)	13.6 ± 6.3	13.6 ± 6.3	13.8 ± 6.4	13.6 ± 6.3	13.4 ± 6.4	13.1 ± 6.4
Selected ASI CSs at baseline, t-1						
ASI CS for alcohol misuse (mean ± SD)	0.12 ± 0.18	0.12 ± 0.19	0.12 ± 0.19	0.12 ± 0.19	0.12 ± 0.20	0.12 ± 0.20
ASI CS for drug misuse (mean ± SD)	0.52 ± 0.14	0.53 ± 0.13	0.52 ± 0.14	0.53 ± 0.13	0.52 ± 0.15	0.52 ± 0.13
ASI CS for legal problems (mean ± SD)	0.42 ± 0.27	0.53 ± 0.13	0.41 ± 0.27	0.39 ± 0.27	0.42 ± 0.28	0.38 ± 0.27
Treatment outcome, t12						
Response in health	80.0	74.0*	84.1	73.9***	84.1	74.2*
Response in illicit drug use	85.2	65.8***	85.4	65.6***	85.2	69.8***

ITT = intention to treat; ASI = Addiction Severity Index; CDT = carbohydrate-deficient transferrin; SD = standard deviation.
Original ITT sample: Original intention-to-treat sample at t-1.
ASI subsample: Patients whose composite scores could be calculated both in t-1 and t12.
CDT subsample: Patients with available CDT data both at t-1 and t12.
*$P < .05$.
***$P < .001$.

Table 2
Correlation matrix (Pearson, two tailed) of alcohol measures at *t*-1 and *t*12

Measures	CDT	ASI CS	CU
Baseline, *t*-1			
CDT	1		
CS	$r = 0.400$***, $n = 348$	1	
CU	$r = 0.248$***, $n = 356$	$r = 0.658$***, $n = 961$	1
12 Months, *t*12			
CDT	1		
CS 12	$r = 0.479$***, $n = 339$	1	
CU	$r = 0.403$***, $n = 348$	$r = 0.701$***, $n = 895$	1

CDT = carbohydrate-deficient transferrin in % of the total transferrin; ASI CS = Addiction Severity Index (ASI) composite score; CU = consumption units of alcohol.

***Correlations significant $P < .001$, two tailed.

compared with 40.0% of MMT patients. The HAT patients received up to three times a day a maximum single intravenous dose of 400 mg of diamorphine (=heroin) with a maximum daily dose of 1,000 mg (average dose: 442 mg/day). A maximum of 60 mg oral methadone was supplied if needed for take-home night use. MMT patients received one dose of oral methadone per day, which could be individually adjusted according to clinical judgment (average dose: 99 mg/day). Methadone was dispensed on daily attendance of a MMT clinic, take-home doses were only allowed in exceptional cases. A breath alcohol test of 0 was required before receiving methadone or diamorphine. Psychosocial treatment was also randomized within two groups. Patients received psychoeducation plus individual counseling or case management and motivational interviewing (for further details on the methodology of the trial see Degkwitz et al., 2007 and Haasen et al., 2007).

Data for the calculation of Addiction Severity Index composite scores (ASI CSs) according to the EuropASI (Kokkevi and Hartgers, 1995; based on the fifth edition of the Addiction Severity Index by McLellan et al., 1992; German version: Gsellhofer et al., 1999), was available for 965 patients at baseline (*t*-1) and 895 at the end of the 12-month period (*t*12), but only for 849 (ASI subsample) both at *t*-1 and *t*12. Self-reported data on alcohol use in average consumption units per day (CU, each unit = 20 g) was collected for 955 patients at *t*-1 and 902 at *t*12, and only for 850 patients both at *t*-1 and *t*12. Sample size differences are due to missing data.

As a biological marker of heavy alcohol use, carbohydrate-deficient transferrin (CDT) is widely used to monitor alcohol use in treatment (Anton, 2001). In this study, it was used as an additional measure to assess changes in alcohol use. CDT blood measures were available only for part of the sample at *t*-1 ($n = 484$) and *t*12 ($n = 696$) and only for 364 (CDT subsample) both at *t*-1 and *t*12. CDT sample size was considerably smaller due to protocol violations (wrong laboratory units at baseline or not having completed CDT analyses to save costs). Furthermore, an ASI CS threshold of 0.17 for predicting alcohol dependence diagnosis has been recommended (Rikoon et al., 2006), whereas a cut-off of 3% is recommended for clinical relevance of CDT (Hock et al., 2005), both of which were used in this study.

Outcome was evaluated according to two primary outcome measures (see also Haasen et al., 2007): improvement of health and reduction of illicit drug use. Physical and mental health was based on the Opiate Treatment Index (Darke et al., 1991, 1992) health scale and Global Severity Index of the Symptom Checklist-90-Revised (Derogatis, 1994).

Results

The main characteristics of the ITT sample and two subsamples can be seen in Table 1. Regarding sociodemographic characteristics and ASI CS at baseline, the two

Table 3
Change in alcohol measures: means, standard deviations, *t*-tests, and repeated-measure ANOVAs

Measures	HAT (mean ± SD)	MMT (mean ± SD)	Significance *t*-test between treatment groups	Significance RM ANOVA between treatment groups
CDT	$n = 182$	$N = 182$		
t-1	3.06 ± 2.19	2.80 ± 1.52	$t = 1.379$, $df = 321.8$, $P = .169$	Time effect: Pillai's Trace = 0.081, $df = 1$, $P = .000$
*t*12	2.24 ± 1.2	2.48 ± 1.45	$t = -1.769$, $df = 350.5$, $P = .078$	Between-group interaction: Pillai's Trace = 0.019, $df = 1$, $P = .009$
ASI CS	$n = 439$	$N = 410$		
t-1	0.12 ± 0.18	0.12 ± 0.19	$t = 0.183$, $df = 963$, $P = .855$	Time effect: Pillai's Trace = 0.001, $df = 1$, $P = .487$
*t*12	0.09 ± 0.18	0.13 ± 0.20	$t = -2.7$, $df = 852.3$, $P = .007$	Between-group interaction: Pillai's Trace = 0.013, $df = 1$, $P = .001$
CU	$n = 468$	$N = 438$		
t-1	6.67 ± 12.11	7.12 ± 13.67	$t = -0.897$, $df = 994$, $P = .370$	Time effect: Pillai's Trace = 0.026, $df = 1$, $P = .000$
*t*12	4.00 ± 9.27	5.69 ± 11.51	$t = -2.182$, $df = 874.5$, $P = .03$	Between-group interaction: Pillai's Trace = 0.002, $df = 1$, $P = .136$

HAT = heroin-assisted treatment group; MMT = methadone maintenance treatment group; RM ANOVA = repeated-measure analysis of variance; CU = consumption units of alcohol; ASI CS = Addiction Severity Index (ASI) composite score; CDT = carbohydrate-deficient transferrin; SD = standard deviation;. *t*-1 = Baseline; *t*12 = Treatment after 12 months.

Table 4
Treatment outcome according to alcohol dependence (according to ASI CS and CDT thresholds) and treatment groups

Outcome criteria	Alcohol dependence groups	HAT		MMT		Total		Significance between treatment groups		Total significance[a]	
		N	%	*N*	%	*N*	%	OR	95% CI	OR	95% CI
Response in health improvement (*n*, %)	No alcohol dependence (ASI CS, *n* = 661)	307	85.8	233	76.9	540	81.7	1.808	1.213–2.695	1.794	1.291–2.493
	Alcohol dependence (ASI CS, *n* = 234)	80	76.9	85	65.4	165	70.5	1.765	0.986–3.158		
	No alcohol dependence (CDT, *n* = 578)	266	85.3	197	74.1	463	80.1	2.025	1.336–3.070	2.110	1.442–3.086
	Alcohol dependence (CDT, *n* = 118)	40	85.1	49	69.0	89	75.4	2.566	0.995–6.618		
Response in reduction of illicit drug use (*n*, %)	No alcohol dependence (ASI CS, *n* = 661)	255	71.2	161	53.1	416	62.9	2.184	1.583–3.011	2.114	1.602–2.789
	Alcohol dependence (ASI CS, *n* = 234)	74	71.2	73	56.2	147	62.8	1.926	1.114–3.331		
	No alcohol dependence (CDT, *n* = 578)	219	70.2	152	57.1	371	64.2	1.766	1.253–2.489	1.910	1.395–2.614
	Alcohol dependence (CDT, *n* = 118)	34	72.3	34	47.9	68	57.6	2.846	1.291–6.276		

HAT = heroin-assisted treatment group; MMT = methadone maintenance treatment group; OR = odds ratio; CI = confidence interval; ASI CS = Addiction Severity Index (ASI) composite score; CDT = carbohydrate-deficient transferrin.
Alcohol dependence (ASI CS): ASI composite score above 0.17 (26.1% of *n* = 895).
Alcohol dependence (CDT): carbohydrate-deficient transferrin % value above 3 (17% of *n* = 696).
[a]Mantel–Haenszel test between no alcohol dependence and alcohol dependence groups.

subsamples are fairly comparable to the ITT sample, with only one significant difference between treatment groups (HAT or MMT) in years of education in the CDT sample ($t = 2.33$, $df = 361$, $P = .02$), where there is no difference in the ITT sample or ASI subsample. Main outcome information is also provided, with better outcome results for the HAT group in the ITT sample as well as in the two subsamples. CDT measures, ASI CS, and CU showed significant correlations (Pearson, two tailed) both in *t*-1 and *t*12 as shown in Table 2.

Changes and differences in alcohol use

Table 3 shows the three measures for alcohol use and the results of independent *t*-tests at *t*-1 and *t*12 and repeated-measure analyses of variance carried out within treatment groups upon the three measures to explore time effects and between-group interactions. CDT measures showed both time and between-group significant interactions, with a stronger reduction in the HAT group. ASI CS had no overall time effect due to the missing reduction in the MMT group, but analysis was significant between groups. CU reduction can be seen in both groups, represented by the overall time effect, but without between-group interaction despite a greater reduction in the HAT group and significantly lower CU at *t*12.

Interaction with treatment outcome

The overall reduction in ASI CS for alcohol correlated slightly with reduction of ASI CS for drug use ($r = 0.145$, $P < .001$) and ASI CS for legal problems ($r = 0.152$, $P < .001$); 17.0% of the 696 patients with CDT measures at *t*12 and 26.1% of the 895 patients with ASI CS at *t*12 fulfilled criteria for alcohol dependence according to the recommended thresholds. Table 4 shows the different treatment outcomes after splitting the sample according to alcohol dependence using the two different thresholds. HAT patients had better outcomes in health improvement and in reduction of illicit drug use both for alcohol dependent and nondependent patients, with higher odds ratios (ORs) in the alcohol-dependent sample when using the CDT threshold and higher ORs for the nondependent sample when using the ASI CS threshold.

To assess the effects of alcohol dependence on health and illegal drug use outcomes at the end of the treatment in both HAT and MMT groups, binary logistic regressions were carried out (results in Table 5). Regarding health outcome, when a threshold of CDT over 3 was used, only treatment group ($\beta = 0.745$, $P < .0001$) was a reliable predictor of health outcome. When a threshold of ASI CS over 0.17 was used, improvement of health was predicted by both factors (alcohol dependence by ASI CS: $\beta = 0.576$, $P < .001$; treatment group: $\beta = 0.585$, $P < .0001$). No effect of alcohol dependence was detected

Table 5
Binary logistic regression models for health improvement and illegal drug use outcomes

Outcome criteria	Predictor	β	Wald χ^2	*df*	OR	95% CI	*P*
Response in health improvement	Model 1 (ASI CS over 0.17)						
	Treatment group	0.585	12.122	1	1.794	1.291–2.494	<.0001
	Alcohol dependence	0.576	10.627	1	1.780	1.258–2.517	.001
	Model 2 (CDT over 3)						
	Treatment group	0.745	14.774	1	2.107	1.441–3.080	<.0001
	Alcohol dependence	0.173	.515	1	1.189	0.741–1.910	.473
Response in reduction of illicit drug use	Model 1 (ASI CS over 0.17)						
	Treatment group	0.749	28.020	1	2.115	1.603–2.791	<.0001
	Alcohol dependence	−0.069	0.184	1	0.933	0.681–1.279	.668
	Model 2 (CDT over 3)						
	Treatment group	0.647	16.311	1	1.910	1.395–2.614	<.0001
	Alcohol dependence	0.190	0.829	1	1.210	0.803–1.822	.362

OR = odds ratio; CI = confidence interval; ASI CS = Addiction Severity Index (ASI) composite score; CDT = carbohydrate-deficient transferrin.
Alcohol dependence (ASI CS): ASI composite score above 0.17 (26.1% of $n = 895$).
Alcohol dependence (CDT): carbohydrate-deficient transferrin % value above 3 (17.0% of $n = 696$).

in illegal drug use outcome both using CDT ($\beta = 0.190$, $P = .362$) or ASI CS ($\beta = -0.069$, $P = .668$) as predictors.

Discussion

This is the first controlled study examining the effect of HAT on alcohol use among opioid-dependent patients, as well as being a further study on the effect of MMT on alcohol use. Previous findings in methodologically stronger studies indicating a potentially positive effect of MMT on alcohol use were confirmed in part by our study, whereas HAT seems to have a significantly more positive effect of reducing alcohol use.

The reduction of alcohol use in the HAT group is confirmed by a reduction of CDT values, a reduction of ASI CSs, and also a reduction in number of alcohol units. In the MMT group, there is a reduction of CDT values and number of alcohol units, but ASI CSs were slightly higher at the end of the 12-month treatment period. Considering that ASI CSs include other alcohol-related problems, such as days intoxicated, the improvement with respect to the secondary measure alcohol use in the MMT group is not as clear as in the HAT group. This confirms the findings of the recent review on the effects of MMT on alcohol use (Srivastava et al., 2008), with an increase of alcohol use being improbable but also insufficient clear evidence of a reduction.

The stronger effect of HAT on a reduction of alcohol use could be explained on the one hand by a global positive effect on health status of the patients, as the primary outcome analysis of both mental and physical health showed significant improvement (Haasen et al., 2007), thereby decreasing the necessity of drinking if a perceived positive function of alcohol is expected to be a strong predictor (Hillebrand et al., 2001). When looking at the more severe cases of alcohol use, those considered to be alcohol dependent according to ASI CSs and CDT thresholds, it becomes apparent that there is no interaction between alcoholism and treatment outcome regarding street heroin use, but there is an interaction with health outcomes. Whether it is the reduction of alcohol use that results in better overall health outcomes or it is the better health outcomes that lead to a reduction of alcohol use, needs to be analyzed in future studies.

On the other hand, another main reason that could explain the reduction of alcohol use under HAT is the fact that diamorphine and methadone were only dispensed if patients were sober at that moment, forcing MMT patients to be sober in the mornings (once daily dispensing) and HAT patients to be sober up to three times a day. The fact that diamorphine needs to be dispensed three times a day (morning, midday, and evening), due to the shorter half-life, increases the motivation to be sober not just in the morning. In general, HAT starts with three times daily dispensing, but most patients reduce their clinic visits to twice a day (morning and evening) for convenience reasons, nonetheless demanding soberness in the evening. The dispensing schedule therefore is a de facto behavioral contingency, and this structuring element seems to have a positive influence on treatment effects, similar to the effect in studies on contingency reinforcement in other substance use treatments (Rogers et al., 2008; Stitzer and Vandrey, 2008).

A limitation of the study is the lack of full data for all patients of the ITT sample, necessitating analyses of subsamples to determine the effects on alcohol use. However, data were missing to the same extent for both HAT and MMT groups. Furthermore, both the comparison of demographics of subsamples with ITT sample, showing no major differences, and the strong correlations shown between CDT values, ASI CSs and number of drinking units, confirm the validity of the study measures.

Considering the multimorbidity of severely opioid-dependent patients, a stronger focus on secondary measures when evaluating maintenance treatment is of great importance. The negative health effect of alcohol use, especially

the higher risk of fatal opiate overdose under the influence of alcohol (Hickman et al., 2008), therefore stands out as one of the most important factors to be addressed. The limited effect of MMT in this special group of patients warrants the introduction of alternatives, and HAT deserves to be considered as such an alternative due to the better results shown in this and previous studies.

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Is Heroin-Assisted Treatment Effective for Patients with No Previous Maintenance Treatment? Results from a German Randomised Controlled Trial

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Key Words
Diamorphine · Heroin-assisted treatment · Methadone maintenance · Opioid dependence

Abstract
Background/Aims: Until now, the medical prescription of diamorphine (heroin) has been suggested as suitable for patients who have failed previous maintenance treatments. The aim of this paper is to assess the effects of diamorphine on opioid-dependent patients with no previous maintenance treatment experience (NPME). ***Methods:*** The German heroin trial compared diamorphine versus methadone maintenance treatment and included 107 patients with NPME. This paper is a sub-analysis of these patients. ***Results:*** When comparing this subsample with the rest of the participants in the study, large baseline differences were found, showing a more severe drug use profile in patients with NPME. However, no differences were found in terms of treatment outcome and treatment retention. In the subsample with NPME, outcome measures on the reduction of illicit drug use were significantly better under diamorphine compared to methadone treatment, while there was no difference in health outcomes. ***Conclusion:*** Controlled studies are now necessary to examine whether diamorphine treatment could be considered as one of several options in treating severely opioid-dependent patients, regardless of previous maintenance treatment experience.

Introduction

As opioid dependency is a chronic relapsing disorder, agonist maintenance is considered to be the first line of treatment [1]. Methadone is the most extensively studied and widely used substance in maintenance treatment and is, therefore, considered first choice in most countries [2–4]. Though less effective, buprenorphine is an alternative medication which is also considered a first-choice maintenance treatment [5–7]. Finally, slow-release oral morphine seems to be promising and is the first choice treatment in some countries [8].

A rather new development is the medical prescription of diamorphine (heroin) to patients with chronic treatment-refractory heroin dependency. This intervention has been tested in a variety of countries in Europe and North America [9], and further studies are currently underway. The medical prescription of heroin, known as heroin-assisted treatment (HAT), has been found to be more effective than methadone for patients with chronic treatment-refractory heroin dependency [10–14].

Until now, all trials have included only patients with previous maintenance treatment experience (PME). As criteria for inclusion, the Swiss National Cohort study required patients to have had at least 2 previous maintenance treatment attempts without satisfactory results [15]. Previous experience with methadone maintenance treatment (MMT) in the last 6 months was an inclusion

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criterion for the Dutch randomised controlled trials, in which HAT was designed to be an add-on treatment to MMT [11]. Inclusion into the Spanish controlled trial required 2 previous MMT attempts [12]. Inclusion into the Canadian study required at least 1 previous episode of maintenance treatment with an adequate dose for at least 30 days [16]. Inclusion into the ongoing British Randomised Injecting-Opioid Treatment Trial requires continuous methadone treatment for at least 6 months while continuing the injection of heroin on a regular basis [17]. The recently initiated Belgian HAT trial also requires patients to have had 2 failed attempts at MMT or to presently be a non-responder to MMT [18]. Previous abstinence-based treatment was found to be a predictor of effectiveness in the Dutch study [19], but no other influence of previous treatment experience on outcome measures has been reported in other trials.

In contrast to these studies, the German heroin trial required patients to be nonresponders to MMT or to have undergone 2 unsuccessful previous addiction treatment attempts (mainly maintenance, but also outpatient or inpatient abstinence-based treatment [20]). Therefore, patients could be included with 2 previous unsuccessful treatment attempts in abstinence-based programmes with no previous maintenance treatment experience (NPME). The aim of this study is to assess the efficacy of diamorphine versus methadone treatment for patients with NPME, in order to clarify whether previous maintenance treatment should remain an inclusion criterion for HAT.

Methods

The German Heroin Trial

In a randomised controlled trial, HAT and MMT were compared in a multicentre study among 1,015 patients in 7 cities in Germany. This intent-to-treat sample was the result of the randomisation of 1,032 heroin-addicted patients fulfilling the inclusion criteria and attending examination from a previous screening of 2,038 patients. Recruitment was stratified into 2 target groups: (1) methadone non-responders and (2) patients not in treatment for the last 6 months but with 2 previous treatment attempts (either abstinence-based or maintenance; for details, see Haasen et al. [13]). Patients were randomised into 4 subgroups, depending on the type of medical treatment (HAT or MMT) and psychosocial care (psychoeducation plus individual counselling or case management plus motivational interviewing) received. Heroin or methadone was dispensed over a 12-month period. HAT patients received an individually adjusted maximum of 3 doses of intravenous diamorphine per day with an additional 60 mg (maximum) of oral methadone when needed, while MMT patients received 1 individually adjusted single dose of oral methadone daily. Long-term effects have been analysed for HAT patients who continued treatment for another 12 months [21].

Measures

Information used in this study included: (1) Self-reported information on drug use and criminal activity, according to the German version [22] of the EuropASI [23], based on the fifth edition of the Addiction Severity Index [24]. (2) Psychopathology, measured with the health scale and Global Severity Index of the Symptom Checklist-90-Revised [25]. (3) Health status measured with the Opiate Treatment Index Health Symptoms Scale [26]. (4) Urine samples for determining heroin and cocaine use. (5) Mental and physical health improvement as well as a reduction of illicit drug use (difference between baseline and 12 months). This information was used to determine dichotomous outcome measures (see Haasen et al. [13] for details).

Subjects

In order to carry out this study, the intent-to-treat sample (n = 1,015) was divided into two subsamples: patients with PME (n = 899) and patients with NPME (n = 107). Nine patients were not included in the analysis due to missing data on their previous maintenance treatment.

Statistical Analysis

Baseline characteristics were compared using t tests for continuous variables and χ^2 tests for nominal variables between patients in HAT or MMT and subsamples with PME or NPME. As noted in our previous publication [13], this trial demonstrated the stronger effect of HAT on treatment outcomes without the influence of other factors, such as target group (cases of methadone treatment failures vs. cases not in treatment), type of psychosocial intervention (psychoeducation vs. case management) and study site. As demonstrated by Blanken et al. [19] in the Dutch study, differences between MMT and HAT were only significant in patients who had previously undergone abstinence-orientated treatment. Therefore, a three-factorial logistic regression model was used to assess the possible effect of previous maintenance treatment, controlling for type of medication and previous abstinence-orientated treatment. Additionally, χ^2 and odds ratio were calculated separately in the PME and NPME subsamples in order to assess the differential effect of the type of medication on outcome measures. The same analyses were carried out within groups of patients with and without previous experience with abstinence-orientated treatment. A one-factor ANCOVA was carried out in the NPME subsample between treatment groups for illegal activities in the last 30 days at end of treatment controlling for baseline data. The Cl was set at 95%. Analyses were made using SPSS version 15 for Windows.

Results

Participant Characteristics

Table 1 shows the baseline characteristics of the participants. Between the 2 medication groups in the subsample with NPME, there was only 1 significant difference: HAT patients had a higher proportion of hepatitis C infections ($\chi^2 = 7.308$, $p = 0.007$).

Table 1. Baseline characteristics of the 107 participants with NPME and the rest of the sample

	NPME subsample				Rest of the sample (PME)	
	HAT (n = 59)	MMT (n = 48)	total (n = 107)	significance HAT vs. MMT	(n = 899)	significance NPME vs. PME
Male	53 (89.8)	43 (89.6)	96 (89.7)	n.s.	709 (78.9)	<0.01
Age, years	34.37 ± 6.57	35.75 ± 6.81	34.99 ± 6.68	n.s.	36.55 ± 6.67	<0.05
Stable housing	38 (64.4)	24 (51.1)	62 (58.5)	n.s.	635 (70.9)	<0.01
Employed	4 (6.8)	7 (14.9)	11 (10.4)	n.s.	120 (13.4)	n.s.
Regular drug use, years						
Heroin	10.19 ± 5.16	11.88 ± 5.68	10.94 ± 5.44	n.s.	13.95 ± 6.33	<0.001
Cocaine	4.78 ± 6.41	4.02 ± 4.73	4.44 ± 5.71	n.s.	5.70 ± 6.59	<0.05
Drug use in past month[a]						
Heroin, days	27.95 ± 4.89	28.74 ± 3.91	28.30 ± 4.48	n.s.	21.29 ± 10.37	<0.001
Cocaine	44 (74.6)	31 (66.0)	75 (70.8)	n.s.	657 (73.2)	n.s.
Cocaine, days	8.05 ± 10.36	10.58 ± 12.76	9.09 ± 11.40	n.s.	7.49 ± 9.93	n.s.
Intravenous drug use	58 (98.3)	47 (100.0)	105 (99.1)	n.s.	855 (95.6)	n.s.
Intravenous drug use, days	27.16 ± 6.6	27.43 ± 5.8	27.28 ± 6.23	n.s.	22.95 ± 9.80	<0.001
Alcohol use	33 (56.9)	23 (48.9)	56 (53.3)	n.s.	532 (59.4)	n.s.
Alcohol use in past month, days	14.64 ± 11.19	14.83 ± 12.73	14.71 ± 11.74	n.s.	17.02 ± 11.85	n.s
Previous detox treatment	49 (83.1)	36 (75.0)	85 (79.4)	n.s.	794 (89.4)	<0.01
Previous drug-free treatment	29 (49.2)	20 (41.7)	49 (45.8)	n.s.	571 (65.7)	<0.001
Physical health						
OTI health scale (0–50 patients)	17.78 ± 4.81	19.48 ± 4.40	18.54 ± 4.69	n.s.	18.99 ± 5.36	n.s.
HIV-positive	3 (5.3)	2 (4.2)	5 (4.7)	n.s.	85 (9.5)	n.s.
HCV-positive	45 (79.0)	26 (54.2)	71 (67.6)	<0.01	740 (83.0)	<0.001
Mental health						
GSI (standardised T-score)	66.92 ± 10.89	69.10 ± 10.47	67.90 ± 10.71	n.s.	69.52 ± 10.30	n.s.
Previous suicide attempts	11 (20.0)	11 (22.9)	22 (20.6)	n.s.	340 (38.9)	<0.001
Social functioning						
GAFS (0–100)	55.92 ± 13.37	55.50 ± 10.77	55.73 ± 12.22	n.s.	53.36 ± 11.45	<0.05
Illegal activities in past month, days	16.64 ± 13.27	17.67 ± 12.57	17.09 ± 12.91	n.s.	15.07 ± 12.84	n.s.

OTI = Opiate treatment index; GSI = Global Severity Index; GAFS = Global Assessment of Functioning Scale.
[a] The mean days of consumption were calculated only in patients who had at least 1 day of consumption.
Numbers in parentheses denote percent values.

Compared to patients with PME at baseline, NPME patients included fewer females (χ^2 = 7.046, p = 0.008), were younger (t = 2.292, p = 0.022), had a poorer housing situation (χ^2 = 6.861, p = 0.009), had less experience with detoxification (χ^2 = 9.266, p = 0.002) and drug-free treatment (χ^2 = 16.304, p < 0.0001), had fewer years of heroin (t = 5.306, p < 0.0001) and cocaine use (t = 1.888, p = 0.059) and had more days of heroin use in the last month (t = –12.497, p < 0.0001). They had also injected drugs (t = –6.224, p < 0.0001) on more days in the last month, but the proportion of patients infected with hepatitis C virus was lower (χ^2 = 14.586, p < 0.0001), which corresponds to fewer years of heroin use. Finally, those in the NPME subsample had a lower rate of suicide attempts (χ^2 = 12.102, p = 0.001) and a higher score on the Global Assessment of Functioning Scale (t = –2.008, p = 0.045).

Treatment Retention

Treatment retention among NPME patients (53.84%) did not differ from that found among PME patients (53.27%). In contrast with the results of the main study, no significant differences were found with regard to treatment retention between HAT (55.93%) and MMT (50.00%) in the NPME subsample (χ^2 = 0.374, n.s.). No significant differences were found in terms of treatment duration between HAT (276 days) and MMT (244 days) groups in the NPME subsample (t = 1.12, n.s.). The mean daily dose of diamorphine was 401.90 mg (range 15.00–710.30, SD = 177.84) with an additional 8.50 mg (range 0.26–41.18,

Table 2. Effectiveness of heroin versus methadone treatment on POM with respect to previous maintenance and previous abstinence-oriented treatment

	NPME								PME							
	HAT		MMT		significance HAT vs. MMT				HAT		MMT		significance HAT vs. MMT			
	n	%	n	%	OR	95% CI	χ^2	p	n	%	n	%	OR	95% CI	χ^2	p
Response POM																
Health	46	78.0	39	81.3	0.817	0.315–2.113	0.175	0.676	363	80.1	327	73.3	1.468	1.074–2.005	5.848	<0.05
Illegal drug use	46	78.0	19	39.6	5.401	2.320–12.570	16.353	<0.0001	309	68.2	253	45.0	1.673	1.247–2.149	12.651	<0.0001
Response both POM	38	64.4	15	31.6	3.981	1.770–8.951	9.187	<0.01	256	56.5	207	46.4	1.500	1.153–1.952	9.178	<0.01
	NPATE								PATE							
	HAT (n = 187)		MMT (n = 169)		significance HAT vs. MMT				HAT (n = 309)		MMT (n = 314)		significance HAT vs. MMT			
	n	%	n	%	OR	95% CI	χ^2	p	n	%	n	%	OR	95% CI	χ^2	p
Response POM																
Health	149	79.7	133	78.7	1.061	0.636–1.772	0.052	0.820	247	79.9	224	71.3	1.601	1.105–2.319	6.241	<0.05
Illegal drug use	118	63.1	85	50.3	1.690	1.107–2.851	5.940	<0.05	226	73.1	179	57.0	2.054	1.476–2.875	17.819	<0.0001
Response both POM	98	52.4	75	44.4	1.380	0.909–1.096	2.290	0.130	187	60.5	140	44.6	15.851	1.385–2.620	9.178	<0.0001

SD = 9.94) of methadone over all heroin treatment days. In the methadone group, the mean daily dose was 87.35 mg (range 36.03–165.62, SD = 37.61). Compared to PME patients no significant differences in dosage were found.

Treatment Effectiveness

The three-factorial logistic regression model analysis showed no influence of PME on primary outcome measures (POM) of health, illegal drug use or both when analysing for treatment group. Previous abstinence treatment experience (PATE) was found to be significant with regard to response in the outcome measure of drug use reduction (OR = 1.434, 95% CI = 1.091–1.884) but not for health improvement (OR = 0.829, 95% CI = 0.603–1.140).

When analyzing subsamples separately, no influence of treatment on health was found in NPME patients in contrast with PME patients, but a significantly greater response from HAT patients was found in the POM of illicit drug use (table 2). The more rigorous criteria of response in both outcome measures also shows a greater response from HAT patients. Table 2 shows the relationship between treatment effectiveness and PATE. Among patients with PATE, a significant influence of treatment in reduction of drug use, health improvement and both outcome measures together was found. Nevertheless, patients without PATE profited significantly more from HAT than from MMT only in reduction of drug use. With respect to the outcome measure of reduction of illegal activity, the subsample of patients with PME showed no difference, at baseline, between the HAT and MMT groups (table 1), but after 12 months illegal activity was reduced to 0.81 days (of the last 30 days) in the HAT group as compared to 5.56 days in the MMT group (ANCOVA: F = 10.120, p =0.002).

Figure 1 shows the course of health indicators. Physical health (as measured with the Opiate Treatment Index Health Symptoms Scale) showed an overall high improvement in the first phase of the study. A slight deterioration can be perceived among MMT patients in the last 6 months of the study, while HAT patients continued to show a stable amelioration of their symptoms. Mental health (as measured with the Global Symptom Index of the Symptom Checklist-90R) showed a parallel course in both subgroups. While HAT patients had a better outcome in the first 3 months, at 6 months, both groups showed similar results. Toward the end of the study, symptoms among MMT patients worsened slightly, while the effects of the therapy remained stable among patients in the HAT group.

Figure 2 shows the course of street use of heroin and cocaine according to self-reported data. Although both groups reduced the use of illicit heroin, a greater reduction can be seen in the HAT group. Cocaine use reduction was steady among HAT patients, while MMT patients showed a reduction of cocaine use only during the first few months. These results were confirmed by urinalysis throughout the course of the study (fig. 3). The percentage of cocaine-positive urine samples found during treatment was 32.2% among HAT and 38.9% among MMT patients.

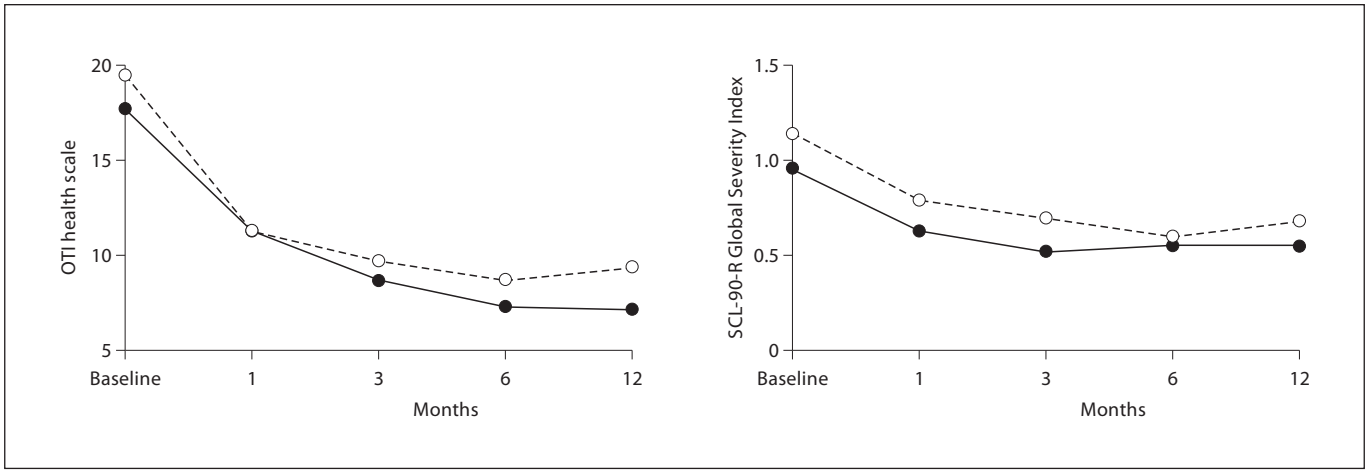

Fig. 1. Assessment of health according to OTI health scale (left) and Global Severity Index (GSI) of the SCL-90-R (right) during the study period in the subsample of patients without maintenance treatment experience: —●— = heroin; ---○--- = methadone. At T_0 the SCL-90-R was not assessed, in order to avoid overlapping artefacts, since the SCL-90-R measures symptoms occurring in the last 7 days. OTI: $n_{baseline} = 107$, $n_1 = 89$, $n_3 = 82$, $n_6 = 81$, $n_{12} = 101$; SCL-90-R: $n_{baseline} = 107$, $n_1 = 89$, $n_3 = 81$, $n_6 = 81$, $n_{12} = 101$.

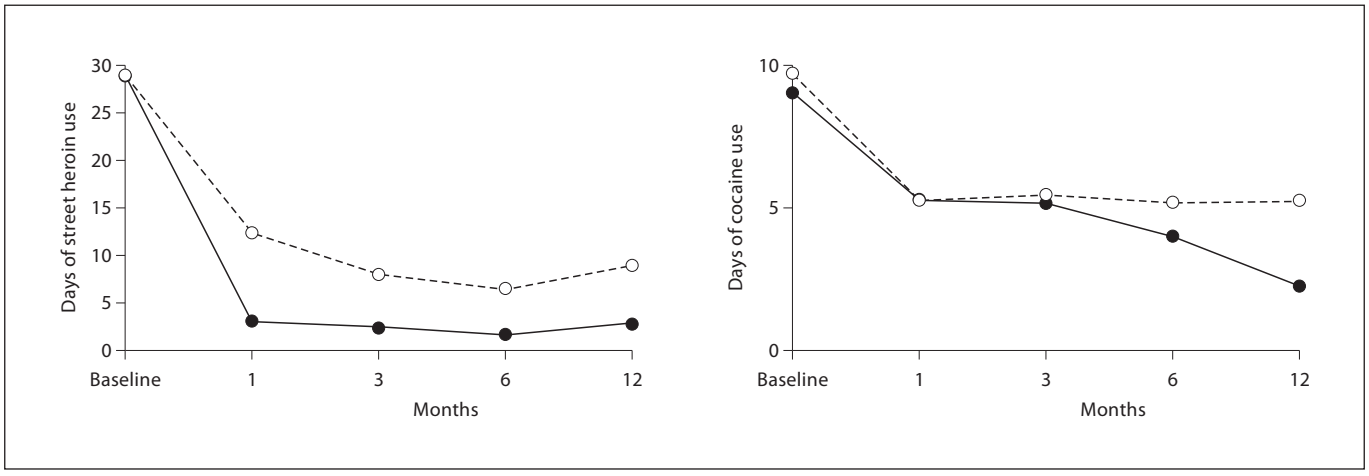

Fig. 2. Change in street heroin use (left) and cocaine use (right) in the subsample of patients without maintenance treatment experience: —●— = heroin; ---○--- = methadone. Self-reported data of use in the last 30 days: street heroin: $n_{baseline} = 107$, $n_1 = 88$, $n_3 = 82$, $n_6 = 85$, $n_{12} = 103$; cocaine: $n_{baseline} = 107$, $n_1 = 88$, $n_3 = 82$, $n_6 = 85$, $n_{12} = 103$.

Discussion

HAT has been considered a second- or last-choice intervention. This consideration largely rests on 4 facts: First, injecting bears higher health risks than does oral treatment, so that maintenance treatment is suggested to be initiated with an oral substance. Second, injecting a substance is thought to maintain the craving-related aspects of addiction, which could be avoided with the use of an oral substance. Third, the psychoactive central-nervous effect of diamorphine also upholds craving, which is considered problematic in the long-term treatment of an addictive disorder. Finally, HAT is more expensive than MMT and requires more resources. On the other

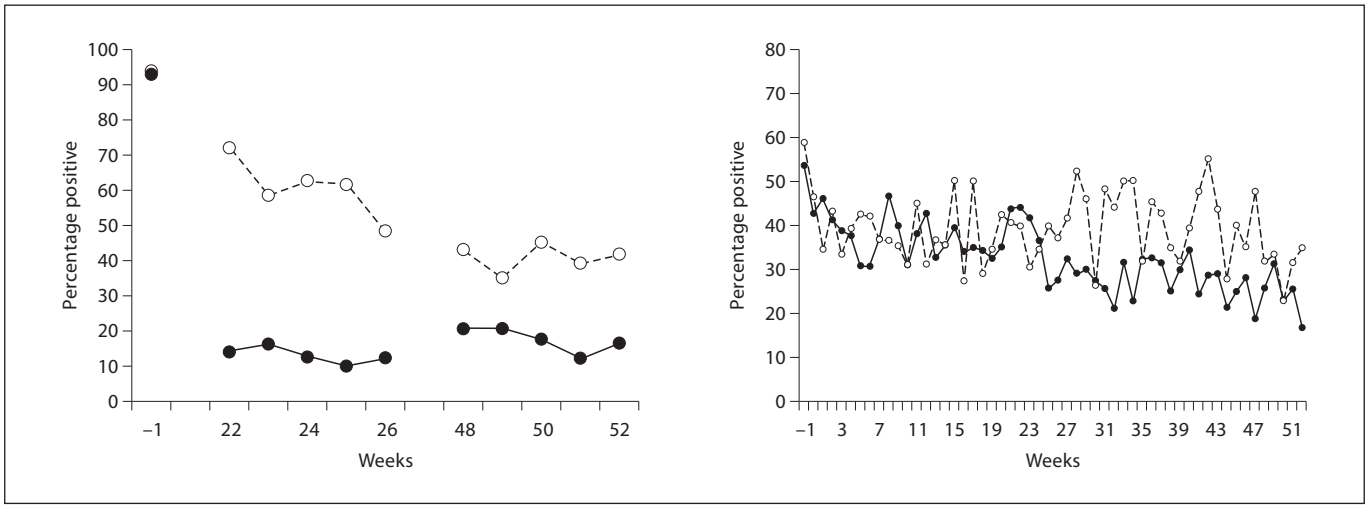

Fig. 3. Urine samples testing for street heroin (left) and cocaine (right) in the subsample of patients without maintenance treatment experience: —●— = heroin; ---○--- = methadone. Urine samples for street heroin (n = 51–101) in the 5 weeks prior to T_6 (W22–W26) and T_{12} (W48–W52) and weekly urine samples for cocaine (n = 51–104).

hand, HAT might have an advantage over MMT in that it includes patients who would, otherwise, choose not to enter maintenance treatment at all. If this were the case, it would be necessary to evaluate whether HAT is more effective than MMT only for chronic opioid-dependent patients who have been in maintenance treatment before, or also for those without this type of treatment experience.

The present study is the first to analyse the effect of HAT in patients with NPME. The results show that patients with NPME, who have a shorter addiction career, benefit from both HAT and MMT to almost the same extent as those with PME. The most important finding is the superior effectiveness of HAT in this subsample, considering the fact that, unlike the rest of the sample, they have had no previous (negative) experience with MMT. This was not found in all outcome measures. While no difference was found in the POM on health, a significant difference became apparent in the reduction of illicit drug use and illegal activity, which are generally considered two main goals of maintenance treatment. In the more rigorous outcome definition of having to respond to both POMs, HAT was also found to be superior to MMT in this subsample.

These findings cannot be explained by a higher dropout rate in the MMT group, as the retention rates did not differ in the 2 treatment groups of patients with NPME. Nonetheless, all 107 patients entered the study with the intention of possibly being randomised into the diamorphine group. Even those patients randomised into the methadone group had the possibility of switching into the diamorphine group after completing 1 year of methadone maintenance. In this way, the attractiveness of HAT may have still played an important role in drawing these patients into maintenance treatment, a path which they previously had not chosen to follow despite the low threshold for entry into maintenance treatment in Germany.

These results, therefore, should lead us to reconsider whether HAT should only be implemented as a second-line treatment, or whether it should be made available to all chronic severely opioid-dependent patients irrespective of PME. Other factors such as PATE seem to be of greater importance for the effectiveness of HAT. However, this study was self-selective and did not control for the factor of PME in an experimental design. In the future, it would be necessary to confirm our results in a controlled trial, as this would have important implications for the scope of this innovative treatment option.

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Effects of Psychiatric Comorbidity on Treatment Outcome in Patients Undergoing Diamorphine or Methadone Maintenance Treatment

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Comorbidity · Methadone maintenance treatment · Diamorphine · Heroin-assisted treatment

Abstract
Background: Comorbid psychiatric disorders among opioid-dependent patients are associated with several negative outcome factors. However, outcomes of maintenance treatment have not been sufficiently established, and no evidence is available with respect to heroin-assisted treatment (HAT). ***Methods:*** For patients in the German heroin trial outcome measures were analyzed for HAT versus methadone maintenance treatment (MMT) both for patients with and without a comorbid diagnosis according to CIDI. ***Results:*** 47.2% of the sample had at least one comorbid psychiatric diagnosis, mainly neurotic, stress-related or somatoform (F4) or affective (F3) disorders. HAT had a better outcome than MMT concerning improvement of health and reduction of illicit drug use in both comorbid and non-comorbid patients, but weaker effects were found in the comorbid group. ***Conclusions:*** The better outcome of HAT also in comorbid patients suggests that psychiatric comorbidity should be an inclusion criterion for HAT. The weaker advantage of HAT may be due to pharmacological or methodological reasons.

Introduction

Comorbid psychiatric disorders are common among opioid-dependent patients undergoing maintenance treatment. Although comorbidity is difficult to diagnose and figures vary between the different studies, about 80% of patients with a diagnosis of drug dependence also have a comorbid psychiatric disorder, if personality disorders are included [1]. Comorbid opiate-dependent patients have been found to have a higher use of nonopiate drugs (benzodiazepines, alcohol, cannabis, and cocaine) [2], as well as a higher level of HIV risk taking behavior [3]. Personality disorders have also been found to be related to poorer social functioning among comorbid patients [4].

Few studies have analyzed the effects of psychiatric comorbid disorders on the outcome of maintenance treatment. Severity of psychological distress has been found to be negatively associated with treatment outcome for methadone maintenance treatment (MMT) patients with respect to benzodiazepine abuse, risk taking behaviors and prevalence of hepatitis C infection, but not with respect to opiate abuse [5]. Other studies showed a stronger correlation of comorbidity or severe mental illness with negative psychosocial outcomes, but not with higher illicit substance use [6–9]. Furthermore a comorbid mental disorder had no influence on the long-term course of drug dependence [10].

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Heroin-assisted treatment (HAT), a relatively new form of maintenance treatment based on the philosophy of harm reduction, has been proposed for difficult-to-treat populations, with psychiatric comorbidity as one of the inclusion criteria. It has been implemented in clinical trials worldwide showing feasibility, effectiveness and safety [11]. However, the response of patients with psychiatric comorbidity has not been evaluated separately in these studies, despite the high number of comorbid patients. In the Dutch study, for instance, 30% of patients were diagnosed as having a comorbid nonsubstance disorder [12, 13]. The Swiss study reported 41% of patients to have poor or very poor mental health and a high need for psychological treatment [14]. In this study we used the data of the German heroin trial in order to assess the effects of comorbidity on the outcome of treatment.

Methods

The German Project on HAT of Opiate-Dependent Patients

HAT and MMT were compared in a multicenter trial among 1,015 patients in seven German cities. This intent-to-treat sample resulted after screening 2,038 heroin-addicted patients, of which 1,032 were randomized into four subgroups depending on type of medication (heroin or methadone) and psychosocial care received (psychoeducation plus individual counseling or case management plus motivational interviewing). Patients were recruited from two target groups: patients insufficiently responding to other maintenance treatments and patients not in treatment in the previous 6 months. Treatment duration was 12 months. The retention rate was 67.2% for HAT patients compared with 40.0% for MMT patients. HAT patients received a maximum of three doses of intravenous diamorphine (heroin) per day (maximum daily dose of 1,000 mg, average dose: 442 mg/day) with an additional (maximum of) 60 mg oral methadone when needed. MMT patients received one single dose of oral methadone daily, which was individually adjusted according to clinical judgment (average dose: 99 mg/day). Take-home methadone doses were only allowed in exceptional cases. Further details on randomization, treatment and outcome were published previously [15]. In a second 12-month phase of the study long-term effects of HAT were analyzed [16].

Measures

Besides sociodemographic data, assessment included self-reported information on drug use and composite scores (ASI CS) according to the EuropASI [17], based on the fifth edition of the Addiction Severity Index by McLellan et al. [18], German version [19]; psychopathology based on the health scale and Global Severity Index (GSI) of the Symptom Checklist-90-Revised (SCL-90-R [20]), and the Composite International Diagnostic Interview (CIDI-10 [21]). Only the CIDI sections for ICD-10 group categories F2, F3, F4 and F5 were completed – personality disorders were not assessed due to the unreasonable interview length [22, 23]. Response was determined according to primary outcome measures for health improvement (at least 20% improvement in the OTI health scale and/or at least 20% improvement in the GSI without a deterioration of more than 20% in the other area of health) and reduction of illicit drug use (reduction in the use of street heroin with at least 3 of 5 negative urines in the month prior to the end of the trial and no increase in cocaine use). Double-blind studies are not feasible when comparing oral methadone with intravenous diamorphine [24], among other things because the effect of intravenous diamorphine cannot be blinded and it is considered unethical for patients in the control group to inject a placebo agent, as injecting per se is considered to be a health risk. Therefore, a 'worst case analysis' was used instead, where dropouts in the control group (MMT) were considered responders and in the experimental group (HAT) were considered nonresponders. Further details are described elsewhere [15].

Study Population

Figure 1 shows the distribution of the sample according to treatment completion and availability of CIDI diagnostics. The CIDI was administered 1 month after study treatment initiation, as the CIDI was not necessary for assessing inclusion and exclusion criteria. Furthermore, because of the length of the CIDI, a more stabilized treatment situation was considered to be more appropriate for this interview. A consequence of this procedure was missing data both due to dropouts (144 MMT patients and 12 HAT patients abandoned treatment before initiation mainly due to disagreement with the randomization process) and nonattendance at the CIDI interview. A total of 626 patients were successfully interviewed. Of these, 485 completed the 12 months of treatment according to the study protocol (329 in HAT, 156 in MMT). The analyses were carried out using this subsample of CIDI-interviewed completers.

Statistical Analysis

t tests and χ^2 tests where used to compare characteristics of the sample between treatment groups in the total sample with CIDI interviews, the subsample of completers and between completers and noncompleters. Risk estimates and Mantel-Haenszel tests were used to estimate the odds ratios of meeting outcome criteria. Analyses of variance (ANOVA) and repeated measures analyses of variance (RM ANOVA) were used to compare treatment groups with and without comorbid diagnoses at the beginning and end of treatment with respect to ASI CS for drug use and psychiatric problems as well as GSI t-value scores.

Results

Participant Characteristics

Table 1 shows the participants' characteristics at initiation of treatment. No major differences were found between treatment groups in the whole CIDI sample or the subsample of completers. Nevertheless completers were older, had a stable housing situation more frequently and a slightly lower ASI CS for drug misuse than noncompleters.

Table 1. Description of the CIDI sample (total sample, completers, and dropouts)

	Total CIDI interviews			Completers with CIDI		
	HAT (n = 421)	MMT (n = 205)	total (n = 626)	HAT (n = 329)	MMT (n = 156)	total (n = 485)
Female gender, %	21.14	22.44	21.57	19.76	24.36	21.24
Age, years	36.31 ± 6.59	36.57 ± 6.76	36.40 ± 6.64	36.61 ± 6.68	36.85 ± 7.03	36.69 ± 6.79
Education, years	9.79 ± 1.78	9.79 ± 1.77	9.79 ± 1.78	9.94 ± 1.70	9.70 ± 1.62	9.86 ± 1.68
Employed, %	15.00	12.75	14.26	15.85	13.55	15.11
Stable housing, %	70.24	71.22	70.56	73.17	73.72	73.35
Years of heroin use	13.69 ± 6.34	13.56 ± 6.29	13.65 ± 6.32	13.74 ± 6.31	13.83 ± 6.48	13.77 ± 6.36
Age of heroin use onset	19.99 ± 5.37	20.36 ± 5.19	20.11 ± 5.31	20.29 ± 5.41	20.34 ± 5.32	20.30 ± 5.37
ASI CS for drug misuse	0.38 ± 0.10	0.39 ± 0.10	0.39 ± 0.10	0.38 ± 0.10	0.38 ± 0.10	0.38 ± 0.10
ASI CS for alcohol misuse	0.12 ± 0.18	0.12 ± 0.18	0.12 ± 0.18	0.12 ± 0.18	0.13 ± 0.19	0.12 ± 0.18
ASI CS for psychiatric problems	0.23 ± 0.21	0.23 ± 0.21	0.23 ± 0.21	0.23 ± 0.21	0.23 ± 0.21	0.23 ± 0.21
GSI-SCL (t value)	68.89 ± 10.63	69.57 ± 9.99	69.11 ± 10.43	68.59 ± 10.91	69.40 ± 9.73	68.85 ± 10.54

Data shown as mean ± SD except for gender, employment and stable housing. Statistically significant differences are marked in bold.

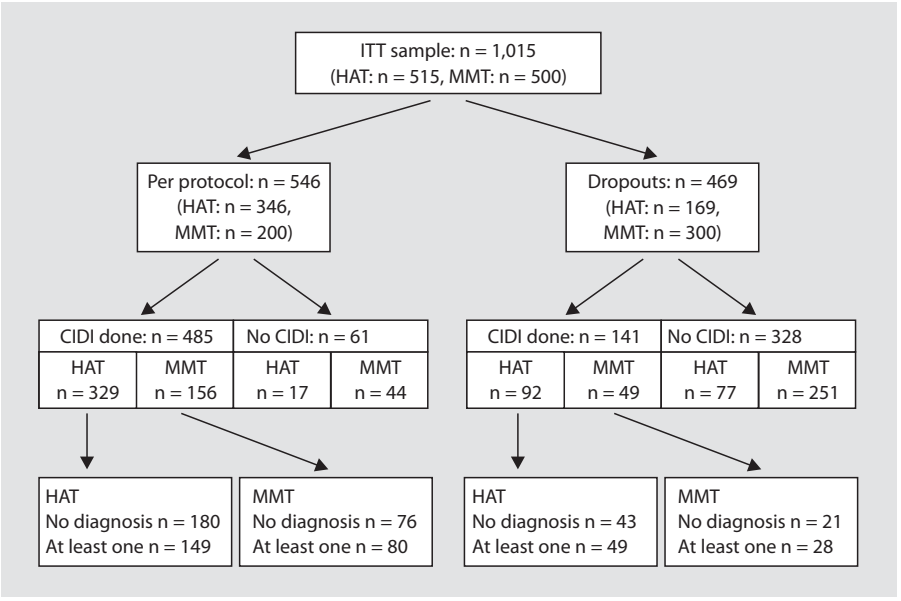

Fig. 1. Sample distribution by treatment completion and CIDI diagnosis for the last 12 months. ITT = Intent to treat.

Comorbid Mental Disorders

In the total sample (n = 626) 306 patients (48.9%) were diagnosed with at least one additional mental disorder in the last 12 months. In the subsample of completers (n = 485) 229 patients received an additional psychiatric diagnosis (47.2%). The proportion of comorbid patients did not differ significantly between HAT or MMT patients as well as completers or dropouts.

The distribution of comorbid diagnoses by CIDI categories in the subsample of completers is displayed in table 2. Neurotic, stress-related and somatoform disorder (F4) was the most frequent diagnosis and was more often diagnosed in MMT patients. Mood (affective) disorders (F3) were also common. Only a few patients were diagnosed with behavioral syndromes associated with physiological disturbances and physical factors (F5), and only

Drop outs with CIDI			Significance of differences between completers and dropouts
HAT (n = 92)	MMT (n = 49)	Total (n = 141)	
26.09	16.33	22.70	$\chi^2 = 0.137$, p = 0.711
35.25 ± 6.15	35.67 ± 5.76	35.40 ± 6.00	**t = 2.035, p = 0.042**
9.25 ± 1.98	10.06 ± 2.16	9.53 ± 2.07	t = 1.957, p = 0.051
11.96	10.20	11.35	$\chi^2 = 1.266$, p = 0.261
59.78	63.27	60.99	**$\chi^2 = 8.023$, p = 0.005**
13.48 ± 6.48	12.71 ± 5.63	13.21 ± 6.19	t = 0.926, p = 0.335
18.92 ± 5.14	20.43 ± 4.83	19.45 ± 5.07	t = 1.687, p = 0.092
0.40 ± 0.11	0.41 ± 0.10	0.40 ± 0.11	**t = –2.238, p = 0.026**
0.12 ± 0.19	0.09 ± 0.13	0.11 ± 0.17	t = 0.547, p = 0.566
0.23 ± 0.18	0.24 ± 0.22	0.24 ± 0.20	t = –0.289, p = 0.773
69.93 ± 9.55	70.10 ± 10.87	69.99 ± 9.99	t = –1.142, p =0.254

Table 2. CIDI diagnosis in the last 12 months by treatment group among completers

Diagnostic category	HAT (n = 329)		MMT (n = 156)		Total patients (n = 485)		Significance
	n	%	n	%	n	%	
F20–F29 Schizophrenia, schizotypal and delusional disorders	1	0.3	1	0.6	2	0.4	$\chi^2 = 0.293$, p = 0.588
F30–F39 Mood (affective) disorders	92	28.0	40	25.6	132	27.2	$\chi^2 = 0.288$, p = 0.591
F40–F48 Neurotic, stress-related and somatoform disorders	88	26.7	64	41.0	152	31.3	**$\chi^2 = 10.025$, p = 0.002**
F50–F59 Behavioral syndromes associated with physiological disturbances and physical factors	5	1.5	6	3.8	11	2.3	$\chi^2 = 2.584$, p = 0.108
No additional diagnosis (F20–F59)	180	54.7	76	48.7	256	52.8	$\chi^2 = 1.525$, p = 0.217

Statistically significant differences are marked in bold.

2 patients with schizophrenia, schizotypal and delusional disorders (F2), with no significant differences between treatment groups regarding these categories.

Treatment Retention

Table 3 shows the rates of treatment retention according to treatment group and comorbidity. The slightly higher retention rate for HAT and noncomorbid patients was not significant.

Severity of Symptomatology

GSI scores and ASI CS 'psychiatric problems' are shown in table 4 according to treatment groups and comorbid versus noncomorbid patients in the subsample of CIDI-interviewed completers. Comorbid patients had significantly higher GSI t values at the beginning and end of treatment. No GSI differences were found between treatment groups at the beginning of treatment, but MMT patients had significantly higher scores at the end. RM ANOVA showed a large time and treatment group effect, but no effect of comorbidity or interaction between co-

Table 3. Treatment retention by comorbidity group and treatment group

	Completers		Dropouts		Significance treatment	Significance comorbidity
	n	%	n	%		
No comorbid disorder					no comorbid disorder:	HAT:
HAT	180	80.72	43	19.28	OR = 1.16; 95% CI = 0.64–2.08	OR = 1.38; 95% CI = 0.87–2.19
MMT	76	78.35	21	21.65		
Total	256	80.00	64	20.00	comorbid disorders:	MMT:
At least one comorbid disorder					OR = 1.06; 95% CI = 0.62–1.82	OR = 1.27; 95% CI = 0.66–2.42
HAT	149	75.25	49	24.75		
MMT	80	74.07	28	25.93	total[1]:	total[1]:
Total	229	74.84	77	25.16	OR = 1.11; 95% CI = 0.74–1.64	OR = 1.34; 95% CI = 0.92–1.95

[1] Mantel-Haenszel tests.

morbidity and treatment groups. A similar tendency could be observed concerning ASI CS for psychiatric problems. Comorbid patients also had higher scores at the beginning and end of treatment, but no differences were found between treatment groups. Again, RM ANOVA showed significant time and between-treatment-group effects, but no comorbidity or interaction effects.

Treatment Outcome/Drug Use

Table 5 describes the course of ASI CS 'drug use' in the subsample of CIDI-interviewed completers. Drug use was found to be significantly higher among patients with a comorbid diagnosis at the beginning and the end of treatment. The differences between treatment groups were not significant at the beginning, but highly significant at the end of treatment. The RM ANOVA showed time and treatment group effects, no effect of comorbidity, but an interaction between type of treatment and comorbidity indicating a slightly stronger improvement for comorbid patients in MMT compared to MMT patients without comorbidity. Table 6 shows the distribution of responders according to the different outcome measures by treatment group and comorbidity, showing a significantly higher response for HAT compared to MMT, but with higher odds ratios for the noncomorbid group.

Discussion

As HAT is considered a second-line maintenance treatment for difficult-to-treat opioid-dependent patients, more evidence is needed to help clinicians identify suitable patients. All data from HAT trials published so far have not provided any evidence on the indication and outcome of heroin maintenance in patients with psychiatric comorbidity.

The presented study revealed treatment group effects between HAT and MMT in both patients with and without psychiatric comorbidity. The findings suggest that HAT is superior to MMT with regard to improvement of health and reduction of illicit drug use also in patients with psychiatric comorbidity. However, psychiatric comorbidity had an influence on the strength of treatment group effects: while comorbidity status had no effect on the decrease of both mental health scores or the ASI CS for drug use over time, the odds ratios of response rates were higher for noncomorbid patients compared to those with psychiatric comorbidity.

The less distinct benefit of HAT in patients with psychiatric comorbidity may be due to several reasons. First, patients with anxiety or depressive disorders may benefit from the sedative effect of methadone, which is not a property of diamorphine. Second, the overall lower treatment effect in the group with psychiatric comorbidity, regardless of the type of treatment, makes differences between treatment groups less apparent. This is in line with the well-known result of a lower effectiveness of addiction treatment in the presence of psychiatric comorbidity.

A limitation of the study is the fact that, due to the requirements of a controlled clinical trial, patients with very severe mental disorders had to be excluded. This explains the surprisingly low number of patients with a schizophrenia spectrum disorder. This subsample should be analyzed in the future, when more patients have been

Table 4. Mental health (GSI t value and ASI CS composite scores for psychiatric problems) at baseline (t-1) and after 12 months of treatment (t12) in the per-protocol sample (n = 485) by treatment and comorbidity group (CIDI-interviewed completers)

	GSI t value	Treatment significance (two-factor RM ANOVA)	CS psychiatric problems	Treatment significance (two-factor RM ANOVA)
Baseline (t-1)				
No comorbidity		time effect:	0.19 ± 0.21	time effect:
HAT	66.35 ± 11.35	**Pillai's trace = 0.376,**	0.15 ± 0.16	**Pillai's trace = 0.019,**
MMT	66.46 ± 10.18	**F = 288.339, d.f. = 1, p < 0.0001**		**F = 8.672, d.f. = 1, p = 0.003**
At least one comorbid diagnosis				
HAT	71.22 ± 9.78		0.28 ± 0.21	
MMT	72.20 ± 8.49	treatment group effect: **Pillai's trace = 0.008, F = 3.994, d.f. = 1, p = 0.046**	0.30 ± 0.21	treatment group effect: **Pillai's trace = 0.010, F = 4.316, d.f. = 1, p = 0.038**
Significance (two-factor ANOVA)	treatment group effect: F = 0.301, p = 0.584	comorbidity effect: Pillai's trace = 0.003, F = 1.243, d.f. = 1, p = 0.256	treatment group effect: F = 0.332, p = 0.565	comorbidity effect: Pillai's trace < 0.001, F = 0.195, d.f. = 1, p = 0.659
	comorbidity effect: **F = 27.990, p < 0.001*** **	interaction treatment-comorbidity: Pillai's trace < 0.001, F = 0.163, d.f. = 1, p = 0.686	comorbidity effect: **F = 34.382, p < 0.001*** **	interaction treatment-comorbidity: Pillai's trace = 0.002, F = 0.752, d.f. = 1, p = 0.386
End of treatment (t12)				
No comorbidity				
HAT	54.66 ± 13.68		0.13 ± 0.18	
MMT	56.67 ± 13.16		0.15 ± 0.20	
At least one comorbid diagnosis				
HAT	60.38 ± 12.72		0.23 ± 0.23	
MMT	64.22 ± 13.24		0.28 ± 0.24	
Significance (two-factor ANOVA)	treatment group effect: **F = 5.104, p = 0.024***		treatment group effect: F = 2.482, p = 0.116	
	comorbidity effect: **F = 26.278, p < 0.001*** **		comorbidity effect: **F = 27.777, p < 0.001*** **	

Statistically significant differences are marked in bold.

included in HAT. The same refers to patients with personality disorders, which were not assessed in the German HAT trial. Previous studies indicated that personality disorders might be related to specific problems among comorbid patients [4], and it cannot be excluded that this type of comorbidity has additional effects on the outcome of both MMT and HAT. Another limitation is related to the fact that subjects were not blind to the type of treatment after randomization. It remains unclear whether the higher rate of patients that dropped out after being randomized to MMT had any effects on the results of the study. It could also be argued that the fact that patients were aware of the type of treatment might have had an impact on outcome in favor of heroin treatment. However, to control for such effects, a 'worst case analysis' was used where dropouts in the control group (MMT) were considered responders and in the experimental group (HAT) were considered nonresponders. Finally, patients in the MMT group had a significantly higher number of anxiety disorders according to the CIDI as compared to

Table 5. ASI CS 'drug use' at baseline (t-1) and after 12 months of treatment (t12) in the per-protocol sample (n = 485) by treatment and comorbidity group (CIDI-interviewed completers)

	ASI CS 'drug use'	Significance treatment (two-factor RM ANOVA)
Baseline (t-1)		time effect: **Pillai's trace = 0.594, F = 624.373, d.f. = 1, p < 0.0001**
No comorbidity		
HAT	0.38 ± 0.10	
MMT	0.35 ± 0.09	
At least one comorbid diagnosis		treatment group effect: **Pillai's trace = 0.186, F = 97.367, d.f. =1, p < 0.0001**
HAT	0.38 ± 0.10	
MMT	0.41 ± 0.09	
Significance (two-factor ANOVA)	treatment group effect: F = 0.018, p = 0.892 **comorbidity effect: F = 8.991, p = 0.003**	comorbidity effect: Pillai's trace = 0.043, F = 0.043, d.f. =1, p = 0.836
End of treatment (t12)		interaction treatment-comorbidity: **Pillai's trace = 0.013, F = 5.642, d.f. = 1, p = 0.018**
No comorbidity		
HAT	0.12 ± 0.10	
MMT	0.27 ± 0.12	
At least one comorbid diagnosis		
HAT	0.16 ± 0.12	
MMT	0.29 ± 0.11	
Significance (two-factor ANOVA)	**treatment group effect: F = 137.038, p < 0.0001 comorbidity effect: F = 5.164, p = 0.018**	

Statistically significant differences are marked in bold.

Table 6. Responders according to outcome measures by treatment group and comorbidity subsample (CIDI-interviewed completers)

Outcome measure	No comorbidity						At least one comorbid diagnosis						Total significance[1]	
	HAT		MMT		significance		HAT		MMT		significance		OR	95% CI
	n	%	n	%	OR	95% CI	n	%	n	%	OR	95% CI		
Reduction of illegal drug use	133	73.9	37	48.7	**2.983**	**1.705–5.219**	106	71.1	45	56.3	**1.917**	**1.088–3.378**	**2.392**	**1.608–3.558**
Improvement of health	160	88.9	59	77.6	**2.305**	**1.131–4.699**	126	84.6	62	77.5	1.590	0.800–3.164	**1.894**	**1.156–3.106**

Statistically significant differences are marked in bold.
[1] Mantel-Haenszel test between treatment groups by comorbidity.

the HAT group. However, both GSI and EuropASI scores revealed no differences in the severity of psychiatric impairment between both groups.

In conclusion, the results of our study indicate that psychiatric comorbidity can be considered an additional inclusion criterion for HAT. In clinical routine, comorbid patients may benefit from the more structuring nature of HAT, requiring three clinical contacts per day. However, as the amount of additional psychosocial care was controlled for in this study [15], it can be assumed that the

differences in outcome are to a certain extent related to the type of pharmacological treatment. Nevertheless, the primary aim of both MMT and HAT is to decrease drug use by making another substance available. In comorbid patients, where psychiatric symptoms and substance use are often interrelated, they need to be accompanied by more specific psychiatric interventions to bring about more far-reaching treatment effects.

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ANEX II. PUBLICATIONS INCLUDED AS FUNDAMENTAL PART OF THE THESIS

Eiroa-Orosa, F. J., Haasen, C., Verthein, U., Dilg, C., Schäfer, I., & Reimer, J. (2010). Benzodiazepine use among patients in heroin-assisted vs. methadone maintenance treatment: findings of the German randomized controlled trial. Drug and alcohol dependence, 112(3), 226-33.

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Benzodiazepine use among patients in heroin-assisted vs. methadone maintenance treatment: Findings of the German randomized controlled trial

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ABSTRACT

Benzodiazepine (BZD) use has been found to be associated with poorer psychosocial adjustment, higher levels of polydrug use and more risk-taking behaviors among opioid dependent patients. The aim of this paper is to analyze the correlation between BZD use, BZD prescription and treatment outcome among participants in the German trial on heroin-assisted treatment. 1015 patients who participated in the study comparing heroin-assisted and methadone maintenance treatment (HAT & MMT) for 12 months were included in the analysis. Analyses were carried out to assess the association of treatment outcome with baseline BZD use, with ongoing BZD use and with different patterns of BZD prescription. Baseline BZD use correlated with lower retention rates but not with poorer outcome. Ongoing BZD use correlated with poorer outcomes. Significantly better outcomes were found in the course of phobic anxiety symptomatology for those with regular prescription of BZD. The percentage of BZD positive urine tests decreased more in HAT than in MMT. Poorer outcome for benzodiazepine users may be mediated by a higher severity of addiction. Cautious prescribing of benzodiazepines may be beneficial due to the reduction of overall illicit use.

1. Introduction

The association between benzodiazepine use and abuse and a more complicated, negative clinical course of heroin dependence has been well established. Previous research shows that injecting drug users (IDUs) using benzodiazepines (BZDs) are more likely to show risk behaviors such as sharing injecting equipment, therefore having a higher rate of hepatitis C and polydrug use, and to have more psychosocial problems and higher levels of psychopathology (Darke, 1994). When entering methadone maintenance treatment (MMT), clients using benzodiazepines are more likely to have a higher severity of addiction, more polydrug use and risk behavior, greater number of previous non-fatal overdoses, and more mental health and social problems (Bleich et al., 1999; Brands et al., 2008; Darke et al., 1993; Meiler et al., 2005).

Regarding possible interventions for BZD abuse during treatment, Stitzer et al. (1982) reported successful use of contingent reinforcement of drug-free urines to minimize the use of benzodiazepines among MMT users. An Australian study (Weizman et al., 2003) compared two therapeutic modalities for BZD dependent patients in MMT: either BZD detoxification or BZD maintenance showing that those maintained on BZD are more successful than those detoxified from BZD. In this study, psychiatric comorbidity was positively related to success of BZD maintenance treatment. Meiler et al. (2005) analyzed the prescription and use of benzodiazepines in a sample of MMT clients and found a high proportion of patients who reported medically prescribed BZD use (92.3%). These authors pointed out that physicians find themselves in a dilemma: not prescribing means a high risk of dropout while prescribing can risk maintaining BZD dependency. Bramness and Kornør (2007) analyzed BZD prescription in methadone and buprenorphine programs in Norway and found a 40% overall prescription rate and a mean dose of 36 ± 69 mg Diazepam equivalents. Although it corresponded with the estimated prevalence of anxiety disorders for clients in maintenance treatment, the authors outlined the possible negative effects of such a high dose practice.

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An official document of the U.S. Department of Health and Human Services states that "the use of benzodiazepines in medication-assisted treatments for opioid addiction, when used in prescribed doses, are not dangerous for patients, except when they cause patients to seek other drugs with sedative effects" (Batki et al., 2005). Previously, benzodiazepine prescription to addicted patients was discouraged despite evidence suggesting it is "helpful to a certain population of patients with addictions" (Johnson and Longo, 1998). Seivewright and Iqbal (2002) suggest that there is a fine line between misuse and therapeutic use of BZDs among drug dependent patients and that prescribing may be helpful but should be done with extreme caution. Nevertheless there are no controlled studies offering evidence of benefits or disadvantages of BZD prescription in maintenance treatment.

One study analyzed the impact of benzodiazepine prescription and abuse among patients with dual disorders (drug dependence and another mental disorder) in a community health system (Brunette et al., 2003). The authors found that the use of prescribed benzodiazepines was not related to negative substance abuse outcomes, but these patients were more likely to develop benzodiazepine abuse. Furthermore, they reported no improvement of depressive or anxious symptoms in patients treated with BZD and recommend the use of other treatments.

The evidence therefore implies that BZD users in MMT can be among the most difficult-to-treat patients. Recently, it has been suggested that more difficult-to-treat patients may do better in maintenance treatment using diamorphine (heroin). Clinical studies in Switzerland (Perneger et al., 1998; Rehm et al., 2001), the Netherlands (Blanken et al., 2005; van den Brink et al., 2003), Spain (March et al., 2006), Germany (Haasen et al., 2007; Verthein et al., 2008) and Canada (Oviedo-Joekes et al., 2009) have found heroin-assisted treatment (HAT) to be more effective than MMT in the treatment of methadone non-responders. However, these studies have not analyzed the effect of HAT compared to MMT on BZD use. Furthermore, no studies have been published comparing the outcome of maintenance treatment in patients with or without additional prescribed BZD. The objective of the present study is to evaluate the prevalence and correlates of BZD use at baseline and during treatment as well as patterns of BZD prescription for patients in the German heroin trial comparing HAT and MMT in opioid dependent patients.

2. Materials and methods

2.1. The German trial on heroin-assisted treatment of opioid dependent patients

HAT and MMT were compared in a multicenter trial among 1015 patients in seven cities in Germany. This sample resulted from screening 2038 heroin dependent patients. Patients meeting inclusion and exclusion criteria were randomized into four subgroups depending on type of medication (heroin or methadone) and psychosocial care received (psychoeducation plus individual counselling or case management plus motivational interviewing). Participants were recruited from two target groups: those insufficiently responding to other maintenance treatments and those dependent on heroin but not in treatment in the previous 6 months. Treatment duration was 12 months. HAT patients received a maximum of three doses of intravenous diamorphine (heroin) per day (average dose: 442 mg/d, maximum dose: 1000 mg/d) with an additional (maximum of) 60 mg oral methadone take-home when needed, while MMT patients received one single daily dose of oral methadone individually adjusted according to clinical judgement (average dose: 99 mg/d). Additional prescription of psychopharmacological drugs, including benzodiazepines, was decided for each patient individually based upon the respective psychopathology, and there was no restriction on the prescription of benzodiazepines. Primary health care was covered by the trial team, referrals to other specialists and hospitals occurred for specific treatments. However, as medical coverage in Germany allows patients to consult any doctor, benzodiazepine prescription could occur outside the trial coverage, but this was unlikely since there were no restrictions on prescriptions of these medications in the frame of the study. Therefore, the use of BZD not prescribed in the trial was considered illicit BZD use. Further details on randomization, treatment and outcome were published previously (Haasen et al., 2007).

2.2. Measures

For this study, BZD use was assessed according to weekly scheduled urine tests as well as self-reports (EuropASI). BZD prescription was extracted from medical prescription records. Addiction severity was assessed at baseline, 6 and 12 months using self-reported information according to the German version (Gsellhofer et al., 1999) of the EuropASI (Kokkevi and Stefanis, 1995) based on the fifth edition of the Addiction Severity Index, ASI (McLellan et al., 1992). Psychopathology was assessed with the Global Severity Index (GSI) of the Symptom Checklist-90-Revised (SCL-90-R, Derogatis, 1994), with a special focus in this study on the anxiety and phobic anxiety subscales assessed at baseline, 1, 3, 6 and 12 months of treatment. The same two primary outcome measures (POM) as in the overall study (Haasen et al., 2007) were used, namely improvement of health and reduction of illicit drug use. For the POM on health, study participants were considered responders if they showed at least 20% improvement in the Opiate Treatment Index health scale (physical health) and/or at least 20% improvement in the GSI (mental health), without a deterioration of more than 20% in the other area of health. For the second POM of illicit drug use, participants were considered responders if they showed a reduction in the use of street heroin with at least 3 of 5 negative urines in the month prior to T12 and no increase in cocaine use (hair analysis). Double-blind studies have been judged not to be feasible when comparing oral methadone with intravenous diamorphine due to methodological and ethical reasons (Bammer et al., 1999). To avoid treatment bias favoring the experimental treatment, a "worst case analysis" was performed: drop-outs in the MMT group were considered responders, while those in the HAT group were considered non-responders.

2.3. Study population

For the purposes of this study, patients were assigned to groups defined by their BZD use prior to admission and during treatment and by the pattern of BZD prescribing during care:

(1) The full sample was divided into BZD users and non-users at baseline (baseline BZD use groups: BZD and NBZD). A patient was considered a BZD user at baseline if he/she reported at least 1 day of BZD use in the last month and/or had a BZD positive urine at baseline. According to these criteria, a total of 736 patients were considered BZD users (72.5%) and 279 were considered non-users (27.5%).
(2) As longitudinal data on weekly urines were only available over 12 months from patients who completed treatment, the analysis of benzodiazepine use during treatment focused on treatment completers. From the 1015 subjects in the full sample, 546 completed the treatment according to the study protocol [retention rate of 67.2% ($n = 346$) for HAT patients and 40.0% ($n = 200$) for MMT patients]. Early termination of study treatment (non-completers) was either due to somatic compli-

Table 1
Baseline characteristics of the full sample ($n = 1015$) according to treatment groups and baseline benzodiazepine use.

	HAT			MMT			Total significance between BZD and NBZD
	BZD	NBZD	Significance	BZD	NBZD	Significance	
Sociodemographic characteristics							
Female gender (n, %)[1]	73, 19.6	30, 21.0	$\chi^2 = .119$, $p = .731$	66, 18.1	35, 25.7	$\chi^2 = 3.551$, $p = .060$	$\chi^2 = 2.452$, $p = .117$
Age (mean ± SD)[1]	36.06 ± 6.57	36.52 ± 6.94	$t = -.702$, $p = .483$	36.27 ± 6.59	37.33 ± 7.28	$t = -2.293$, $p = .022$	$t = -1.591$, $p = .112$
Education in years (mean ± SD)[2]	9.75 ± 1.83	10.01 ± 1.65	$t = -1.453$, $p = .147$	9.71 ± 1.86	9.89 ± 1.88	$t = -.985$, $p = .325$	$t = -1.724$, $p = .085$
Employed (n, %)[4]	44, 11.9	23, 13.29	$\chi^2 = 1.781$, $p = .182$	41, 11.3	23, 16.9	$\chi^2 = 2.792$, $p < .095$	$\chi^2 = 4.504$, $p = .034$
Stable housing (n, %)[3]	247, 66.6	107, 75.4	$\chi^2 = 3.697$, $p = .054$	253, 69.5	96, 70.6	$\chi^2 = .055$, $p = .814$	$\chi^2 = 2.369$, $p = .124$
Information on heroin use (mean ± SD)							
Age of beginning of use[2]	19.78 ± 5.34	20.59 ± 5.38	$t = -1.524$, $p = .128$	20.00 ± 5.18	21.20 ± 5.31	$t = -2.293$, $p = .022$	$t = -2.681$, $p = .002$
Years of use[2]	13.65 ± 6.18	13.61 ± 6.72	$t = .072$, $p = .943$	13.90 ± 6.39	12.83 ± 6.14	$t = 1.677$, $p = .094$	$t = 1.220$, $p = .223$
Days of use in the past 30 days[4]	20.79 ± 10.89	22.85 ± 10.42	$t = -1.949$, $p = .052$	20.59 ± 10.82	22.34 ± 10.94	$t = -1.599$, $p = .110$	$t = -2.516$, $p = .012$
Physical health							
OTI health scale (0–50 pts, mean ± SD)[1]	18.70±5.23	18.89±5.16	$t = -.364$, $p = .716$	19.38±5.43	18.49 ± 5.22	$t = 1.661$, $p = .097$	$t = .930$, $p = .352$
HIV positive (n, %)[5]	35, 9.4	9, 6.5	$\chi^2 = 1.123$, $p = .289$	39, 10.8	8, 5.9	$\chi^2 = 2.725$, $p = .099$	$\chi^2 = 3.695$, $p = .055$
HCV positive (n, %)[5]	300, 81.1	110, 79.1	$\chi^2 = .244$, $p = .621$	302, 83.4	105, 77.8	$\chi^2 = 2.115$, $p = .146$	$\chi^2 = 1.860$, $p = .173$
Mental health							
At least one comorbid diagnostic; F2–F5 (n, %)[12]	190, 63.1	63, 52.5	$\chi^2 = 4.037$, $p = .045$	93, 64.6	33, 54.1	$\chi^2 = 1.989$, $p = .158$	$\chi^2 = 6.003$, $p = .014$
SCL-90-R GSI (T value) (mean ± SD)[1]	69.86 ± 10.42	66.41 ± 11.86	$t = 3.051$, $p = .003$	70.42 ± 9.64	67.78 ± 10.13	$t = 2.691$, $p = .007$	$t = 4.034$, $p < .0001$
SCL-90-R anxiety value (mean ± SD)[1]	1.08 ± 0.74	.93 ± .76	$t = 2.061$, $p = .040$	1.13 ± .79	.95 ± .77	$t = 2.178$, $p = .030$	$t = 3.005$, $p = .003$
SCL-90-R phobic anxiety value (mean ± SD)[1]	.68 ± .68	.62 ± .68	$t = .954$, $p = .340$	.73 ± .70	.58 ± .65	$t = 2.166$, $p = .031$	$t = 2.207$, $p = .028$
Addiction Severity Index Composite Scores at baseline (mean ± SD)							
Physical state of health[5]	.44 ± .34	0.37 ± 0.31	$t = 1.999$, $p = .046$	0.43 ± 0.35	0.38 ± 0.35	$t = 1.690$, $p = .092$	$t = 2.606$, $p = .009$
Economic situation[6]	.92 ± .22	.90 ± .27	$t = 1.058$, $p = .291$	.95 ± .17	.87 ± .29	$t = 3.855$, $p = .003$	$t = 3.325$, $p < .001$
Satisfaction from work[13]	.39 ± .33	.39 ± .36	$t = -.030$, $p = .976$	.35 ± .34	.35 ± .33	$t = .037$, $p = .970$	$t = .010$, $p = .992$
Drug use[8]	.39 ± .10	.35 ± .09	$t = 4.666$, $p < .0001$	.40 ± .10	.35 ± .09	$t = 4.863$, $p < .0001$	$t = 7.113$, $p < .0001$
Alcohol use[9]	.12 ± .18	.12 ± .20	$t = -.128$, $p = .898$	.13 ± .20	.09 ± .17	$t = 2.028$, $p = .044$	$t = 1.258$, $p = .209$
Legal status and problems[11]	.43 ± .27	.37 ± .27	$t = 2.160$, $p = .031$	.42 ± .27	.34 ± .26	$t = 2.917$, $p = .004$	$t = 3.573$. $p < .0001$
Family relationships[7]	.29 ± .21	.24 ± .20	$t = 2.385$, $p = .017$	.28 ± .20	.24 ± .20	$t = 1.720$, $p = .086$	$t = 2.918$. $p = .004$
Social environment relationships[10]	.24 ± .20	.24 ± .21	$t = 1.441$, $p = .150$	.29 ± .22	.26 ± .22	$t = 1.432$, $p = .153$	$t = 2.027$. $p = .043$
Mental status[8]	0.26 ± 0.21	0.18 ± 0.19	$t = 3.868$, $p < .0001$	0.26 ± 0.23	0.20 ± 0.20	$t = 2.842$, $p < .005$	$t = 4.735$. $p < .0001$

Sample size: 1 $n = 1015$, 2 $n = 1014$, 3 $n = 1013$, 4 $n = 1011$, 5 $n = 1006$, 6 $n = 988$, 7 $n = 985$, 8 $n = 968$, 9 $n = 965$, 10 $n = 953$, 11 $n = 951$, 12 $n = 626$, 13 $n = 436$.
HAT: heroin-assisted treatment group (total $n = 515$); MMT: methadone maintenance treatment group (total $n = 500$).
BZD: BZD use at baseline; NBZD: no BZD use at baseline (criteria: positive urine or at least 1 day of use in the last 30 days at baseline examination).

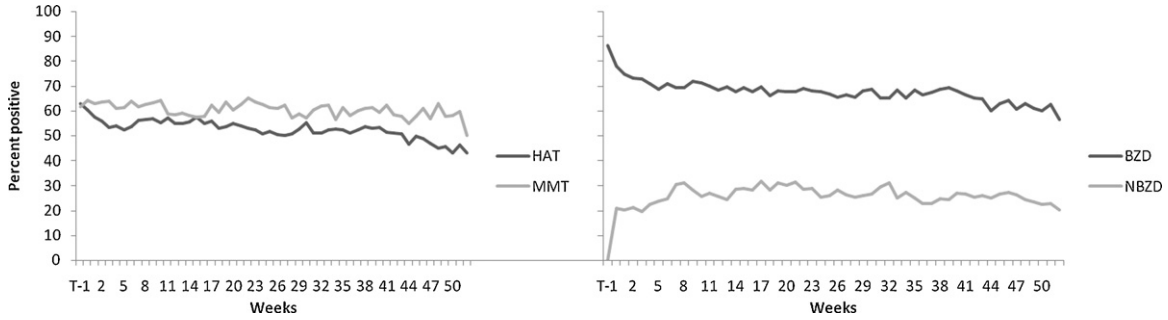

Fig. 1. Percentage of positive benzodiazepine urines by treatment group (left) and by baseline BZD use (right) for the full sample*. *Urine tests were scheduled weekly for all the patients in treatment ($n = 1015$). At baseline 984 urines were tested. During treatment, missing urine samples ranged from 209 to 519.

cations, jail terms, violent behavior, unexcused absence from treatment for more than 2 weeks or excused absence for more than 3 months.

Due to the long half-life of benzodiazepines and the resulting long time that they are detected in urine samples, a cut-off had to be chosen to differentiate between occasional and ongoing BZD use (ongoing BZD use groups). As the mean for BZD positive urines during treatment was 26.1% in the group of baseline BZD non-users (see Fig. 1 below), patients were considered ongoing users during treatment (OngBZD group) if they had at least 26.1% BZD positive urines during treatment. From the 546 completers, 366 (67%) were considered ongoing users and 180 (33%) had lower rates of positive urines and therefore were considered occasional users (OccBZD group).

(3) Completers were split into three groups according to the pattern of benzodiazepine prescription (prescription groups). In the OngBZD group, a total of 265 (72.4%, HAT: $n = 156$, MMT; $n = 109$) patients did not receive any prescription of benzodiazepines within the study treatment during the 12 months of treatment (no prescription group), 46 (12.6%, HAT: $n = 31$, MMT; $n = 15$) were prescribed benzodiazepines for no more than 90 days (25.4 ± 24.6, range = 1–90 days; intermittent prescription group) and 55 (15.0%, HAT: $n = 31$, MMT; $n = 24$) for more than 90 days (285.5 ± 90.0, range = 108–365 days; regular prescription group). Only six patients from the OccBZD users in the subsample of completers received a BZD prescription during treatment (HAT: 2 intermittently, MMT: 3 intermittently and one regularly).

2.4. Data analysis

Baseline characteristics were compared between treatment and baseline BZD use groups using *t*-tests for continuous variables and χ^2 tests for nominal variables. Odds ratios were calculated to assess differences in treatment outcome and retention between baseline and ongoing BZD use. In order to analyze urine samples Friedman tests for non-parametric repeated measures comparisons were carried out. Pearson correlations were used to examine the association between positive urine tests and self-reported information on BZD use.

Regarding ongoing use of BZDs, odds ratios were also calculated to assess differences in treatment outcome between ongoing and occasional BZD users in the subsample of completers. Two factor RM ANOVAs were used to analyze changes over time in ASI Composite Scores (ASI CS) at three time points within treatment groups and ongoing BZD use groups.

Concerning prescription of BZDs, also in the subsample of completers, binary logistic regressions were carried out in order to build an adjusted model to assess the effect of treatment, ongoing BZD use and type of prescription on the POMs health and drug use. As the type of BZD prescription has three levels, dummy variables were used in the analysis (Jaccard, 2001) taking the no prescription group as reference category. Changes in BZD positive urine tests and anxiety symptomatology (SCL-90-R anxiety and phobic anxiety subscales over 5 time points) were calculated using two factor RM ANOVAs within treatment and prescription groups.

The alpha level for all analyses was $p < .05$. All the statistical analyses were conducted using SPSS 18.0 for Windows.

3. Results

3.1. Baseline BZD use analysis

3.1.1. Sociodemographic characteristics. Table 1 shows sociodemographic data according to baseline BZD use groups and treatment groups. BZD users had 12.77 ± 12.26 days of use in the past 30 days prior to baseline (HAT group: 12.69 ± 12.22, MMT group: 12.86 ± 12.33, $t = -.187$, n.s.). The proportion of BZD users was not found to be significantly different between treatment groups. Data on drug use, physical and mental health and ASI CS are provided in Table 1.

BZD users at baseline were found to be less often employed, initiated heroin use at an earlier age, had less days of heroin use in the past month but more days of cannabis use, were more likely to have a comorbid diagnosis, and have higher SCL-90-R T anxiety and phobic anxiety subscale scores. Regarding ASI CS, they had higher scores (indicating higher severity) for physical state of health, economic situation, drug use, legal problems, family, social relations and mental status areas. Although not statistically significant, BZD users were more likely to be HIV positive.

3.1.2. Relation of baseline BZD use with treatment retention and outcome. Table 2 shows treatment retention and POMs by treatment group and BZD use at baseline. A statistically significant higher retention rate can be observed in those patients who did not use benzodiazepines at baseline. This difference is significant only in the HAT treatment group, not in the MMT group. No significant differences were detected in outcome measures.

3.1.3. BZD use during treatment. Fig. 1 shows weekly percentage of all treated patients with BZD positive tests in urine samples during the 12-month treatment period according to treatment and baseline BZD use groups, with a greater decrease in BZD positive tests in the HAT treatment group. The mean for BZD positive tests in urine samples was 52.3% for HAT patients and 60.3% for MMT patients. A Friedman test carried out with the full sample showed a significantly greater reduction in BZD positive urines for HAT patients compared to MMT patients (Friedman's $\chi^2 = 50.074$, $p < .0001$). Baseline BZD users had an average of 67.2% positive tests and baseline non-users of 26.1% in the 12-month treatment period. Among baseline BZD users, HAT patients showed a greater but not significant reduction in BZD positive tests in urine samples (mean

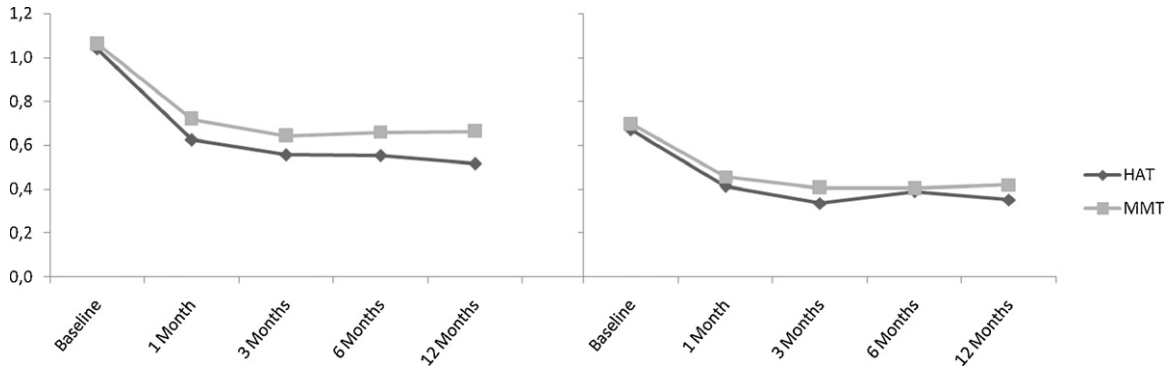

Fig. 2. Anxiety (left) and phobic anxiety (right) GSL SCL-90-R scores by treatment group in the subsample of completers*. *Scores calculated in the subsample of completers ($n = 546$) in those patients whose anxiety levels were registered in all the 5 time points ($N = 516$, HAT $n = 330$, MMT $n = 186$).

of positives; HAT: 64.3%, MMT: 65.9%), while among baseline non-users the percentage BZD positive urines was less in HAT than MMT patients (mean of positives; HAT: 21.8%, MMT: 28.1%). The proportion of BZD positive tests in urine samples showed positive correlations with ASI information on BZD use in the last 30 days at both baseline (full sample $r = .464$, $p < .0001$, completers $r = .499$, $p < .0001$) and at 12 months (full sample $r = .499$, $p < .0001$, completers $r = .492$, $p < .0001$).

3.2. Ongoing BZD use analysis

Using the cut-off of 26.1% of BZD positive urines to differentiate between occasional and ongoing users, correspondence of BZD baseline and ongoing use was significantly high ($\chi^2 = 107.033$, $p < .0001$), showing that 80.8% of the baseline users remained ongoing users while only 35.5% of the baseline non-users became ongoing users.

3.2.1. Ongoing BZD use relation with treatment outcomes. Table 3 shows POMs by treatment and ongoing benzodiazepine use in the subsample of completers ($n = 546$). Ongoing BZD use was found to have a negative association with health outcome in both treatment groups but, when analyzing drug use outcome, differences were only statistically significant when both treatment groups were combined.

Results of the repeated measures analysis of variance of ASI composite scores (CS) showed that ongoing BZD use was statistically associated with significantly poorer results in CS for satisfaction from work (Pillai's Trace = .072, $F = 3.320$, $p < .05$), alcohol use (Pillai's Trace = .025, $F = 6.004$, $p < .005$) and social relationships (Pillai's Trace = .013, $F = 2.975$, $p < .05$), while HAT patients with ongoing BZD use performed better on CS for alcohol use (Pillai's Trace = .044, $F = 11.008$, $p < .0001$), drug use (Pillai's Trace = .186, $F = 51.524$, $p < .0001$), and legal status and problems (Pillai's Trace = .026, $F = 6.275$, $p = .002$) compared to MMT patients with ongoing BZD use.

3.3. BZD prescription analysis

3.3.1. Type of benzodiazepine prescribed. Among completers, patients were prescribed diazepam ($n = 75$, 69.5%), clonazepam ($n = 15$, 13.9%), flunitrazepam ($n = 7$, 6.5%), oxazepam ($n = 3$, 2.8%), lorazepam ($n = 3$, 2.8%), clorazepate ($n = 2$, 1.9%), temazepam, nitrazepam and lormetazepam ($n = 1$ each, 0.9%). During treatment, 21 (19.4%) of these patients had a prescription change to another type of benzodiazepine.

3.3.2. BZD prescription and outcome measures. The results of the adjusted model for the sample of treatment completers receiving prescribed benzodiazepines, with ongoing BZD use and treatment groups as independent variables, showed that only treatment group was a reliable predictor of the POM on drug use with better results for the HAT group (OR = 2.513, 95% CI = 1.738–3.634). Belonging to the HAT treatment group and having an occasional BZD use predicted better results for the POM on health (treatment: OR = 1.802, 95% CI = 1.113–2.866; ongoing BZD use: OR = .331, 95% CI = .178–.615). Regarding prescription patterns, no significant differences were found when comparing regular or irregular prescription with no prescription at all. For the POM on health, the intermittent prescription group (OR = .438, 95% CI = .166–1.157) as well as the regular prescription group (OR = 1.326, 95% CI = .683–2.575) did not differ significantly from the no prescription group. For the POM on drug use, the intermittent prescription group (OR = 1.357, 95% CI = .745–2.538) as well as the regular prescription group (OR = .812, 95% CI = .438–1.507) did not differ significantly from the no prescription group.

3.3.3. Course of anxiety symptomatology according to pattern of BZD prescription. SCL-90-R scores for anxiety and phobic anxiety by treatment group in the completers sample can be seen in Fig. 2. Both scores showed a significant time effect (anxiety: Pillais trace = .170, $F = 25.949$, $p > .0001$; phobic anxiety: Pillais Trace = .129, $F = 18.791$, $p > .0001$). Despite a greater decrease in anxiety and phobic anxiety scores in the HAT group, the effects were not statistically significant for treatment groups (anxiety: Pillais Trace = .010, $F = 1.317$, $p = .262$; phobic anxiety: Pillais Trace = .033, $F = .164$, $p = .686$). Nevertheless a significant effect of BZD prescription was detected in phobic anxiety (Pillais Trace = .045, $F = 2.928$, $p < .005$), reflecting a higher decrease of phobic anxiety in the regular prescription group.

4. Discussion

Benzodiazepine use at treatment entry and during opioid maintenance treatment is a marker for greater complexity of patient need and poorer treatment outcomes in previous studies. This study confirms several findings of previous studies including: BZD use at treatment entry is associated with more severe problems related to drug use, physical health and psychosocial function, and an earlier age of initiation of heroin use; BZD use at baseline is highly correlated with ongoing BZD use during treatment; ongoing BZD use during methadone maintenance treatment is associated with poorer treatment outcome but does not lead to decreased treatment retention in MMT (Brands et al., 2008).

This study extends the findings from previous studies by also evaluating the impact of BZD use on outcomes from Heroin-Assisted Treatment (HAT). Using an intent-to-treat analysis and predefined primary outcome measures, the present study showed no negative impact of BZD use on treatment outcomes from HAT.

Table 2
Treatment retention and primary outcome measure (POM) response according to treatment groups and baseline benzodiazepine use (*n*, %) in the full sample.[a].

	HAT			MMT			Total		
	BZD	NBZD	Significance	BZD	NBZD	Significance	BZD	NBZD	Total significance between BZD and NBZD
12 months retention	240, 64.5	106, 74.1	OR = .635, 95% CI = . .413–976; p = .038	140, 38.5	60, 44.1	OR = .792, 95% CI = .531–1.180; p = .251	380, 51.63	166, 59.50	OR = .727, 95% CI = .550–.961; p = .025
POM reduction of illicit drug use	250, 67,2	106, 74.1	OR = .715, 95% CI = .464–1.102; p = .128	209, 57.4	67, 49.3	OR = 1.389, 95% CI = .935–2.062; p = .103	459, 62.36	173, 62.01	OR = 1.015, 95% CI = .764–1.349; p = .917
POM health improvement	293, 78.8	119, 83.2	OR = .748, 95% CI = .452–1.238; p = .258	269, 73.9	101, 74.3	OR = .981, 95% CI = .626–1.539; p = .934	562, 76.36	220, 78.85	OR = .866, 95% CI = .620–1.210; p = .399

BZD: BZD use at baseline (report of at least 1 day of BZD use in the last month and/or positive urine analysis at baseline), NBZD: no BZD use at baseline, POM: primary outcome measure.
[a] These variables were measured for all the participants and therefore there are no missing values (n = 1015, HAT n = 515, MMT n = 500).

Table 3
Primary outcome measure (POM) response according to treatment groups and ongoing benzodiazepine use (*n*, %) in the sample of completers.[a].

	HAT			MMT			Total		
	OngBZD	OccBZD	Significance	OngBZD	OccBZD	Significance	OngBZD	OccBZD	Total significance between OngBZD and OccBZD
POM reduction of illicit drug use	153, 70.2	100, 78.1	OR = .659, 95% CI = .396–.097; p = .108	74, 50.1	29, 55.8	OR = .793, 95% CI = .420–.497; p = .474	227, 62.0	129, 71.7	OR = .646, 95% CI = .439–516; p = .026
POM health improvement	183, 83.9	118, 92.2	OR = .443, 95% CI = .211–929; p = .028	106, 71.6	48, 92.3	OR = .210, 95% CI = .071–620; p = .002	289, 79.0	166, 92.2	OR = .317, 95% CI = .174–577; p < .0001

OngBZD: ongoing BZD use; OccBZD: occasional BZD use (<6.1% positive urines during treatment).
[a] This table was calculated using data from the participants who completed the treatment (n = 546, HAT n = 346, MMT n = 200).

This may be related to the generally negative outcomes for those who leave treatment regardless of BZD use. Baseline BZD use also led to poorer treatment retention in HAT, distinct from the absence of such an effect on MMT retention. BZD use has been linked to increased rates of non-fatal overdose in heroin users (Kerr et al., 2005) and it is possible that the negative impact on HAT retention arises from increased sedation among BZD users limiting the ability to prescribe an effective dose of diamorphine.

Focussing only on treatment completers, ongoing BZD use during care is associated with poorer outcomes in both MMT and HAT for health and poorer outcomes for drug use when both opioid treatment groups are combined. BZD users however had a greater reduction in BZD use and better outcomes for drug use, alcohol use and legal problems when treated with HAT than with MMT. This suggests that HAT may be a preferred treatment option for long-term opioid dependent patients with benzodiazepine dependence despite the reduced treatment retention discussed above.

In this study, benzodiazepine users at baseline had a higher level of mental distress and greater levels of anxiety and phobic anxiety. This suggests that the illicit use of benzodiazepines in this patient population may arise from underlying mental health issues. Indeed, those patients with ongoing BZD use who were prescribed benzodiazepines during the study reported a greater reduction in phobic anxiety symptoms. In general, prescription of benzodiazepines during maintenance treatment has been cautiously suggested for some patients. Only one in four patients with ongoing BZD use received a benzodiazepine prescription during the trial, about half of them received a prescription not just intermittently, but on a regular basis, demonstrating how cautiously benzodiazepines were prescribed despite the high level of mental health problems. This suggests that illicit benzodiazepine use remains an important factor to consider. However, the results do not show significant outcome differences between the two prescription groups and the group with ongoing illicit BZD use. Considering the fact that illicit BZD use is also associated with illicit polydrug use as well as criminal behavior, loosening the restrictive criteria for prescribing BZD (if indicated) in this population may be recommended in order to (a) avoid illicit BZD use, (b) have some input in the type of medication (short or long-term, side effects) and (c) have better dosage control. Future randomized studies evaluating the impact of prescribing benzodiazepines to opioid maintenance treatment patients with ongoing BZD use may be warranted to clarify the clinical situations in which this is in the best interests of patients.

With respect to the choice of opioid maintenance treatment in the face of BZD use, HAT seems to be associated with a lower percentage of positive BZD urine tests during the 12 months, and ongoing BZD users in HAT showed better outcome measures than those in MMT in some of the composite scores for addiction severity. Illicit benzodiazepine use should be seen in a broader context of polydrug use, where additional sedation of benzodiazepines may be wanted to balance out other effects of illicit drugs such as cocaine and street heroin. Therefore, the overall better effect of HAT in reducing illicit drug use (Haasen et al., 2007; March et al., 2006; van den Brink et al., 2003) may be associated with the reduction of benzodiazepine use. The stronger association of HAT and BZD decrease may also be explained in part by neurobiological aspects, which could also explain why BZD use is lower among heroin dependents not in maintenance treatment (Backmund et al., 2005). Benzodiazepines, especially flunitrazepam, have been found to boost the subjective effects of methadone (Busto et al., 1996), and diazepam has been found to increase the effect of methadone by some undetermined mechanism (Eap et al., 2002). BZD effects have yet to be shown in an interaction with diamorphine (heroin) and may well differ considering the different pharmacokinetic profiles of diamorphine and methadone. The greater dopamine release of diamorphine in the mesolimbic dopamine system (Devine et al., 1993) may also lead to less concomitant BZD use. It has been shown that chronic treatment with opiates alters BZD receptor binding and $GABA_A$ receptor function (Lopez et al., 1990; Sivam and Ho, 1982), and it is possible that various opiate ligands exert differential effects on the $GABA_A$ receptor. These neurobiological aspects will have to be examined in future experimental studies.

There are limitations of this study that need to be considered. The study was not set out to analyze the effect of maintenance treatment on benzodiazepine use, so no causality can be attributed and the associations found need to be confirmed in future trials. The patient groups are not randomized according to BZD use, and baseline differences – such as more mental distress among BZD users – are not controlled for. Furthermore, there is no data on prescription of BZD by other doctors, as well as no possibility to distinguish between prescribed and non-prescribed BZD at baseline. Finally, the differentiation between occasional and ongoing BZD use needs to be validated in future studies, as the cut-off used in this study may not be sufficiently reliable.

The results confirm the cautious attitude towards prescribing benzodiazepines of physicians in maintenance treatment, but also suggest that benzodiazepine prescription may not have to be considered so restrictively in difficult-to-treat opioid dependent patients. These findings may need to be reflected in treatment guidelines. Future research will have to determine whether the correlation with negative treatment outcome is due to BZD use, or whether improvement during treatment leads to lower BZD demand.

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Contributors

The third author was involved in the development of the study design. All the authors excluding the first participated in its implementation. The first author managed the literature searches and summaries of previous related work and undertook the statistical analysis supervised by the second and third authors. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have no conflict of interest and nothing to disclose.

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Implication of Gender Differences in Heroin-Assisted Treatment: Results from the German Randomized Controlled Trial

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Despite a lower prevalence of opioid dependence among females, drug-related problems and risk factors such as prostitution have a negative effect for women in treatment. This study was conducted with the purpose of analyzing gender differences in the German trial on heroin-assisted treatment (HAT), which compared HAT with methadone maintenance treatment (MMT). Significant baseline gender differences were found, with females showing a greater extent of mental distress. Differences in retention and outcome were significant for male patients, but no differences between treatment options were found for female patients. Ongoing prostitution was found to influence drug use outcomes. Other outcome criteria may need to be stressed when assessing the effect of HAT for women. (Am J Addict 2010;19:312–318)

INTRODUCTION

Opioid dependence is a chronic relapsing disease. Gender differences in prevalence have been reported, with substance use being more common among men than in women. This is especially the case when considering problematic drug use.[1,2] Nevertheless, the use of licit drugs such as tranquillizers, pain relievers, or opiate analgesics has been found to be more pronounced in women rather than in men,[3,4] even when differential sex role expectations are taken into account.[5]

Despite this lower rate of illicit substance abuse, female injection drug users have been found to show higher drug-related problems in many domains. Those entering treatments have higher rates of physical and mental health problems.[6–8] Well established is the higher HIV infection rate, related to risk-taking behavior such as unsafe sexual activity or prostitution, and a higher rate of needle sharing, especially with sexual partners.[9–14] A higher rate of hepatitis C (HCV) has also been found for female compared to male drug users,[15,16] although another study found no differences.[17] Furthermore, drug using women have a higher mortality rate compared to men.[1,18]

After having been long neglected, gender-specific research on treatment outcome has emerged in the last two decades. A large review carried out by Greenfield et al.[19] found gender not to be a significant predictor of treatment retention, completion, or outcome, but individual characteristics and treatment approaches can differentially affect outcomes by gender. Several studies have shown that female drug users may not be sufficiently treated in mixed-gender treatment services.[20] It has been shown that females entering methadone maintenance treatment (MMT) have higher rates of psychological, vocational, and family problems, and were more often exposed to abuse and risky sexual situations and therefore more likely to be HIV-positive.[7,8,21–23] Nonetheless, women tend to enter treatment at an earlier age and at an earlier stage of their addiction career, which is generally considered to be a positive outcome factor,[8,24] but evidence, however, also indicates that the proportion of women entering substance abuse treatment facilities is lower than for substance abusing men.[25]

Regarding treatment outcome of MMT, different results have been reported. Studies found no gender influences on treatment outcome in retention and drug use,[21,26–29] but revealed positive advantages for men with respect to their economic situation.[27,30] Risk factors such as prostitution or childhood abuse and economic or childcare responsibilities

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have been found to have a negative impact on treatment outcome.[31] Another study showed women to be highly motivated to stay in MMT when they can maintain custody of their children.[32] Substance using partners have been identified as a negative outcome factor for female patients in MMT.[21]

Despite MMT being the treatment of choice for opioid-dependent patients,[33] heroin-assisted treatment (HAT) has been introduced in several countries as an alternative treatment option for refractory opioid-dependent persons. Trials have been conducted showing higher effectiveness of HAT compared to MMT for chronic, treatment refractory heroin-dependent patients.[34–38] However, gender differences in treatment outcomes in HAT have been insufficiently analyzed. Only Ribeaud[39] reported a better legal outcome for men than for women in the Swiss HAT trial. The purpose of this study is to analyze gender differences in the German trial on heroin-assisted treatment with respect to outcome.

MATERIALS AND METHODS

The German Trial on Heroin-Assisted Treatment of Opioid-Dependent Patients

The German trial was designed as a multicenter randomized controlled trial in seven cities in order to examine whether medical prescription of pharmacologically clean heroin (diamorphine) in a structured and controlled treatment setting for specific groups of opioid-dependent patients leads to an improvement of health and reduction of illicit drug use. Two target groups were defined: methadone treatment failures, consisting of opioid-dependent patients who are currently enrolled in MMT, but do not profit sufficiently from this treatment form (continued intravenous illicit drug use) and opioid-dependent patients not currently in treatment (patients who have dropped out of addiction services but are in need of treatment). The inclusion criteria were: a minimum age of 23 years, opiate dependency for at least 5 years, present intravenous heroin use, poor physical or mental health untreated for the last 6 months or insufficiently responding to MMT.

A total of 2,038 patients were screened. After baseline examinations, inclusion and exclusion criteria left an intention-to-treat (ITT) sample of 1,015 patients (811 males and 204 females). This sample was randomized according to type of medication (heroin or methadone) and type of psychosocial care received (psychoeducation plus individual counseling, PSE; or case management plus motivational interviewing, CM). The first phase of the study lasted 12 months. HAT patients received a maximum of three doses of intravenous diamorphine (heroin) per day (daily maximum of 1,000 mg) with an additional (maximum of) 60 mg oral methadone when needed, while MMT patients received one single dose of oral methadone daily adjusted by clinical judgment. The 12-month treatment retention was 67.2% for HAT patients compared with 40% for MMT patients. Primary outcome measures (POMs) on improvement of health and reduction of illicit drug use were significantly higher for HAT patients. Further information on treatment characteristics and study results have been published elsewhere.[37,40]

Measures

Psychopathology was assessed based on the Global Severity Index (GSI) of the Symptom Checklist-90-Revised *SCL-90-R*.[41] Physical health was measured using the OTI health scale designed specifically for the evaluation of health status of opioid users.[42] Addiction severity and psychosocial status was assessed using composite scores (CSs) calculated on the basis of self-reported information according to the EuropASI[43] based on the German version[44] of the fifth edition of the addiction severity index.[45] POMs from the overall study[37] were used, namely, *improvement of health* (at least 20% improvement in the OTI health scale and/or at least 20% improvement in the GSI, without a deterioration of more than 20% in the other area of health) and *reduction of illicit drug use* (reduction in the use of street heroin with at least 3 of 5 negative urines in the month prior to end of the study and no increase in cocaine use controlled by hair samples).

Analyses

Two factors analysis of variance (ANOVA) and chi-square tests were used to compare the characteristics of the sample between gender and treatment (MMT or HAT) groups. Odds ratios and chi-squares were calculated specifically for each gender in order to detect influence of treatment and psychosocial interventions in retention as well as in health and drug use POMs.

The main publication[37] from this trial demonstrated the higher effect of HAT on POMs without influence of other factors such as target group (methadone treatment failures vs. not in treatment), type of psychosocial intervention (psychoeducation vs. case management) and study site. In this study, multiple logistic regression models were used among women in order to assess the possible effect of factors, such as ongoing prostitution at the end of the study, responsibility for children, partnership and problematic addiction of partner, which might explain differences on treatment outcome while controlling for treatment group. As the regression analysis yielded prostitution as the only significant predictor at the end of the study, odds ratio and chi-squares were used to assess its impact. Analyses were made using SPSS version 15 for Windows (SPSS Inc., Chicago, IL), the alpha level for all analyses was $p < .05$.

TABLE 1. Baseline characteristics of the intention to treat sample by gender and treatment groups

	Male ($n = 811$)		Female ($n = 204$)			
	HAT ($n = 412$)	MMT ($n = 399$)	HAT ($n = 103$)	MMT ($n = 101$)	Significance treatment	Significance gender
Age (years)	36.46 ± 6.41	36.96 ± 6.66	35.08 ± 7.54	34.96 ± 7.10	n.s.	**
Stable housing (n, %)	288, 70.07	274, 69.02	66, 64.71	73, 72.28	n.s.	n.s.
Employed (n, %)	60, 14.6	46, 11.6	10, 9.8	15, 15.2	n.s.	n.s.
Children (n, %)	157, 38.2	132, 33.2	44, 43.1	48, 47.5	n.s.	*
Prostitution (last 30 days)	6, 1.5	7, 1.8	34, 33.7	27, 27.8	n.s.	***
Regular drug use (years)						
Heroin	13.87 ± 6.45	13.79 ± 6.29	12.71 ± 5.73	12.92 ± 6.50	n.s.	*
Benzodiazepines	5.07 ± 7.04	5.72 ± 7.33	4.97 ± 6.88	4.50 ± 6.38	n.s.	n.s.
Drug use in past month						
Heroin (n, %)	393, 95.39	381, 95.73	101, 98.06	95, 95.00	n.s.	n.s.
Benzodiazepines (n, %)	235, 57.2	229, 57.5	56, 54.4	54, 54.0	n.s.	n.s.
Addiction severity index composite scores at baseline (mean ± SD)						
Physical state of health	0.41 ± 0.33	0.40 ± 0.34	0.47 ± 0.33	0.50 ± 0.36	n.s.	*
Economic situation	0.91 ± 0.25	0.93 ± 0.21	0.95 ± 0.19	0.93 ± 0.21	n.s.	n.s.
Satisfaction from work	0.40 ± 0.34	0.36 ± 0.34	0.33 ± 0.35	0.29 ± 0.32	n.s.	n.s.
Drug use	0.37 ± 0.10	0.39 ± 0.10	0.41 ± 0.10	0.40 ± 0.10	n.s.	*
Alcohol use	0.12 ± 0.18	0.13 ± 0.19	0.12 ± 0.21	0.10 ± 0.20	n.s.	n.s.
Legal status and problems	0.41 ± 0.27	0.40 ± 0.27	0.43 ± 0.29	0.39 ± 0.27	n.s.	n.s.
Family relationships	0.27 ± 0.20	0.26 ± 0.19	0.30 ± 0.22	0.29 ± 0.22	n.s.	n.s.
Social environment relationships	0.26 ± 0.21	0.28 ± 0.22	0.26 ± 0.24	0.27 ± 0.23	n.s.	n.s.
Mental status	0.23 ± 0.21	0.23 ± 0.22	0.26 ± 0.22	0.29 ± 0.24	n.s.	*
Physical health						
OTI health scale (%)[†]	0.38 ± 0.10	0.39 ± 0.11	0.42 ± 0.12	0.43 ± 0.12	n.s.	***
HIV positive (n, %)	31, 7.6	35, 8.8	13, 12.6	12, 12.0	n.s.	n.s.
HCV positive (n, %)	324, 79.80	322, 81.31	86, 83.50	85, 84.16	n.s.	n.s.
Psychosocial and mental health						
GSI (standardized T-score)	68.67 ± 10.97	69.27 ± 9.99	69.83 ± 10.80	71.42 ± 9.04	n.s.	*
Previous suicide attempts (n, %)	134, 33.5	131, 33.9	53, 53.0	49, 49.5	n.s.	***
GAFS (0–100)[‡]	53.92 ± 11.58	53.43 ± 11.69	53.18 ± 10.60	53.32 ± 12.05	n.s.	n.s.

*$p < .05$, **$p < .001$, ***$p < .0001$.

HAT = heroin-assisted treatment; MMT = methadone maintenance treatment.

[†]GSI was calculation in proportion to 50 in female patients and proportion to 48 in male patients due to the gender differences in structure of the scale.

[‡]Global assessment of functioning scale.

RESULTS

Baseline Characteristics

As seen in Table 1, significant baseline gender differences were found. Female participants were younger and more often had children than males. Women had less years of heroin use, but had initiated benzodiazepine use earlier. Females had a higher severity of addiction in the ASI domains of physical health, drug use, and mental status. Although not significant, a tendency of higher severity was found in the domain of family relationships ($F = 3.655$, $p = 056$). Data on physical and mental health confirm ASI data: Women had higher OTI and GSI scores and a greater proportion had suicide attempts. They were more often HIV positive; however, the difference did not reach significance. A greater proportion of women had maintenance treatment experience. Due to randomization, no significant differences were found between treatment groups.

Treatment Retention and Effectiveness by Gender

Comparisons of HAT and MMT groups by gender can be seen in Table 2. Retention and better outcomes remained significant for men but no statistically significant differences between treatment options were found for female patients in POMs. When looking at the percent of positive

TABLE 2. Treatment retention and primary outcome measures (POM) by gender and treatment group

	Female								Male						Total significance between genders	
	HAT ($n = 103$)		MMT ($n = 101$)		Total ($n = 204$)				HAT ($n = 412$)		MMT ($n = 399$)		Total ($n = 811$)			
	N	%	*N*	%	*N*	%	OR	95% CI	*N*	%	*N*	%	*N*	%	OR	95% CI
Treatment retention	66	64.1	41	40.6	107	52.5	**2.610**	**1.483–4.595**	280	68.0	159	39.9	439	54.1	**3.202**	**2.400–4.271**	1.070	.787–1.455
POM Health	78	75.7	75	74.3	153	75.0	1.082	.574–2.039	334	81.07	295	73.93	629	77.6	**1.510**	**1.082–2.106**	1.152	.806–1.647
POM Illegal drug use	56	54.4	53	52.5	109	53.4	1.709	.622–1.871	300	72.8	223	55.9	523	64.5	**2.114**	**1.576–2.835**	**1.583**	**1.160–2.159**

*Significant differences are marked in bold.
POM = primary outcome measure.

urines during treatment according to treatment and gender, among HAT patients women had a greater proportion of both heroin (men: 13.1%, women: 34.1%, $t = -5.175$, $p < .0001$) and cocaine positives (men: 39.8%, women: 51.6%, $t = -2.93$, $p < .005$), while in MMT the proportion of positive urines was equivalent both for heroin (men: 34.0%, women: 35.4%, $t = -.290$, n.s.) and cocaine (men: 44.5%, women: 44.5%, $t = .13$, n.s.).

Psychosocial interventions were compared within gender in order to assess differences in outcome. No differences were detected in the POM health or in the POM illegal drug use. When analyzing the effect of gender within psychosocial care groups, men undergoing PSE had a significantly better outcome in the POM illegal drug use than women in the same psychosocial setting (OR = 1.666, 95% CI = 1.084–2.560, $p = .019$) but no differences were found for CM or the POM health.

The assessment of mental health (GSI) showed a significant improvement in both treatment groups and genders, although worse outcomes can be observed in women in MMT. The greatest improvement can be observed between baseline assessment and the first month of treatment (T-1–T1; see Fig. 1). A similar pattern can be observed in physical health (OTI health scale; see Fig. 1). The assessment of illicit drug use (according to self-reported data) showed a more pronounced reduction of street heroin use in the heroin group and higher for men, while reduction of cocaine was also greater in HAT for both men and women (see Fig. 2). There was also a reduction in prostitution, with men stopping the low activity completely and women greatly reducing their activity, but to a greater extent in HAT than in MMT.

Specific Factors Affecting Female Patient Outcomes

Treatment group, prostitution, responsibility for children, partnership, and problematic addiction by partner were used as factors to predict outcome in female patients. Only ongoing prostitution was found to influence drug use outcome (OR = 2.330, 95% CI = 1.036–5.241, $p = .041$), also showing a tendency in health outcome (OR = 2.342, 95% CI = 991–5.533, $p = .052$).

Table 3 shows differences in treatment outcome for women according to treatment groups and ongoing prostitution at the end of the study. For the POM health measures, there are no significant differences in HAT or MMT groups by prostitution, but a near significance is reached when comparing prostitution in both groups together. POM for drug use is significantly influenced by prostitution only in HAT female patients and when comparing both groups together.

DISCUSSION

As treatment outcome in the treatment of drug dependence has been shown to be influenced by gender issues, it is necessary to analyze the data on diamorphine treatment

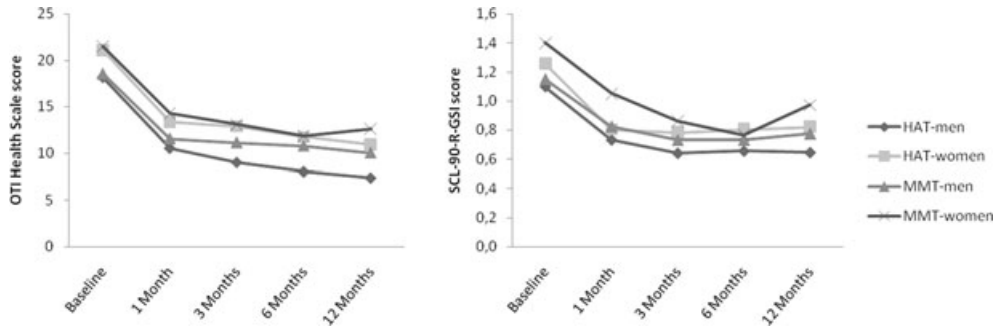

FIGURE 1. Assessment of health according to global severity index (GSI) of the SCL-90-R (left) and OTI health scale (right) during the study period by treatment group and gender.

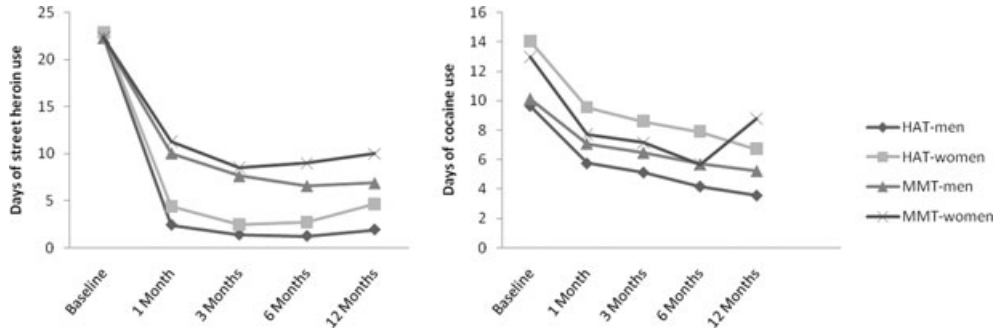

FIGURE 2. Change in self-reported street heroin use (left) and cocaine use (right) during the study period by treatment group and gender.

from the gender perspective. In previous controlled studies on diamorphine maintenance, this has not really been possible, as the low percentage of women entering this treatment option has not allowed a sufficient sample size. Therefore, the German study is the first one with a sufficiently large sample to allow analyses of gender aspects.

This study confirms previous findings that women entering maintenance treatment have a much more complicated clinical picture. In our sample, women had a higher severity of addiction on four out of the nine ASI composite scores. This is associated with a higher rate of prostitution, this being one of their important sources of income to finance daily living expenses and illicit drug use. Furthermore, a higher percentage of women compared to men have children, which for some is an additional responsibility, which may further complicate the clinical picture.

The most important finding is that the sample of women does not show better primary outcome measures for improvement of health and reduction of illicit drug use in the heroin compared to the methadone group. In other words, the better overall treatment outcome of HAT is achieved mainly by the differences among men. This may in part be the case due to the much larger sample size for men, the study therefore not being powered to detect gender differences. However, the difference in sample size between men and women reflects the overall gender difference with respect to prevalence rates for opioid dependence, so that it can be considered a representative sample. Furthermore, the greater extent of mental distress for women at baseline, represented by higher GSI scores and a higher rate of previous suicide attempts, may also hamper improvement, as both HAT and MMT are not treatment options that will have a primary effect on mental health disorders. Therefore, the results do not confirm previous findings summarized by Greenfield et al.,[19] whereby gender was not a significant predictor of treatment outcome.

However, analyses of specific factors affecting female patients show that treatment outcome is mediated by a factor such as the risk-associated behavior of prostitution, implying that outcome for women needs to be focused on other aspects than for men. In this regard, prostitution decreased in the HAT group to a greater extent than in the MMT group and had a significant influence on the reduction of illicit drug use. Another important factor to consider is that women in treatment are unable to reduce their problems related to family and social relationships, as seen in the respective ASI composite scores, which may be tied to their greater responsibilities related to children.

TABLE 3. Differences in treatment outcome for women according to treatment groups and ongoing prostitution at the end of the study

	HAT						MMT						Total significance treatment		Total significance prostitution	
	Prostitution t12		No prostitution t12				Prostitution t12		No prostitution t12							
	N	%	*N*	%	OR	95% CI	*N*	%	*N*	%	OR	95% CI	OR	95% CI	OR	95% CI
POM Health	10	71.4	64	84.2	2.133	.574–7.932	10	58.8	58	76.3	2.256	.750–6.784	1.082	.547–2.039	2.237	.968–5.166
POM Illegal drug use	4	28.6	45	59.2	**3.629**	**1.403–12.622**	7	41.2	41	53.95	1.673	.576–4.859	1.079	.622–1.871	**2.369**	**1.062–5.286**

*Significant differences are marked in bold.

These aspects are insufficiently mirrored in the primary outcome measures.

The positive results of controlled studies comparing HAT and MMT for severely opioid-dependent patients has lead to this treatment option having been added to the general health policy in Switzerland, the Netherlands, Great Britain, and Germany, while other countries, such as Denmark, are now following. In the evaluation of HAT, a focus should be placed on assessing the special needs of women in treatment, mainly the reduction of high-risk behavior such as prostitution and additional support in coping with family responsibilities, in order to make sure that their benefit from switching from MMT to HAT can become more obvious. However, addressing these special needs of women in maintenance treatment will also lead to better treatment outcome in MMT, so that the indication for switching a woman from MMT to HAT may need to be screened more carefully. HAT shows better outcome also in women, even if not in the primary outcome measures, but certainly in several secondary measures, so that it should not be questioned as an alternative treatment option even among women.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Erratum

In the following article, the affiliation of the first author was listed incorrectly.

Implication of gender differences in heroin-assisted treatment: results from the German randomized controlled trial. Eiroá-Orosa FJ, Verthein U, Kuhn S, Lindemann C, Karow A, Haasen C, Reimer J. Am J Addict. 2010 Jul-Aug;19(4):312–8.

The affiliation was listed as: Psychiatry Department, University Medical Center Vall d'Hebron, Barcelona, Spain

The correct affiliation is Psychiatry Department, University Medical Center Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

FRANCISCO JOSÉ EIROÁ OROSA

INTERACTION BETWEEN CLINICAL AND PSYCHOSOCIAL FACTORS IN THE TREATMENT OF HEROIN ADDICTED PATIENTS

The German model project for heroin assisted treatment of opiate addicts implied a change in the drug policy of this country. In this study we present five papers relating to clinical and psychosocial factors that influence the recovery of these patients and should be taken into account for their proper treatment. Specifically, the consumption of alcohol and benzodiazepines, the effects of psychiatric comorbidity, the influence of prior treatment experiences and gender differences are analysed. Finally we present four models predicting outcomes on reducing illegal drug use and improving health status in both the total sample (using baseline variables) and in patients who completed the study (using longitudinal variables).

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