Is heroin assisted treatment effective for patients with no previous maintenance treatment? Results from the German randomised controlled trial.

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Abstract

Until now medical prescription of diamorphine (heroin) has been suggested to be suitable for patients who have failed previous maintenance treatments. The German project of heroin assisted treatment of opiate dependent patients compared diamorphine versus methadone maintenance treatment and included 107 patients with no previous maintenance treatment experience (NPME). When comparing this subsample with the rest of the participants of the study, large baseline differences were found, showing a more severe drug use profile in those without maintenance experience. However, no differences were found in treatment outcome or treatment retention. In the subsample of NPME, outcome measures on the reduction of illicit drug use were significantly better under diamorphine treatment compared to methadone treatment, while health outcome showed no difference. The results imply that diamorphine treatment could be considered as one of several options in treating severely opioid dependent patients, regardless of previous maintenance treatment experience.

Keywords

1. Introduction

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

A rather new development is the medical prescription of diamorphine (heroin) to chronic, treatment refractory heroin dependent patients. This intervention that has been tested in a variety of countries in Europe and North America [9], and further studies are currently underway. Medical prescription of heroin (Heroin Assisted Treatment, HAT) has been found to be more effective than methadone for chronic, treatment refractory heroin-dependent patients [10-13].

Until now all trials have included only patients with previous experience in maintenance treatment. The Swiss National Cohort study included as admission criteria at least two previous maintenance treatment attempts without satisfactory results [14]. Previous experience in Methadone Maintenance Treatment (MMT) in the last six months was a necessary inclusion criteria in the Dutch randomised controlled trials, where HAT was designed to be an add-on treatment to MMT [11]. Inclusion in the Spanish controlled trial necessitated two previous MMT treatment attempts [12]. The Canadian study required at least one previous episode of maintenance treatment with an adequate dose for at least 30 days [15]. Inclusion in the ongoing British Randomised Injecting Opioid Treatment Trial requires previous effective MMT for an extended period of time [16]. The recently initiated Belgian HAT trial also requires patients to have had two failed attempts of MMT or to presently be a

non-responder in MMT [17]. Previous abstinence-based treatment was found to be a predictor of effectiveness in the Dutch study [18], 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 non-responders in MMT or to have undergone two unsuccessful previous addiction treatment attempts (mainly maintenance, but also outpatient or inpatient abstinence-based treatment [19]). Therefore, patients could be included with two previous unsuccessful treatment attempts in abstinence-based programmes without previous maintenance treatment experience. The aim of this study is to assess the efficacy of diamorphine versus methadone treatment for patients with no previous maintenance treatment experience.

2. Methods

2.1 The German heroin trial

In a randomized controlled trial, HAT and MMT was compared in a multicenter study among 1015 patients in 7 cities in Germany. This intent to treat 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. Recruitment was stratified from two target groups: 1. methadone 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 details). Patients were randomised into four subgroups depending on type of treatment (HAT or MMT) and psychosocial care received (psychoeducation plus individual counselling or case management plus motivational interviewing). Heroin or methadone was dispensed over 12 months. HAT patients received an individually adjusted maximum of three doses of intravenous diamorphine (heroin) per day with an additional

(maximum of) 60 mg oral methadone when needed, while MMT patients received one individually adjusted single dose of oral methadone daily. Long term effects have been analysed for HAT patients who continued in treatment for another 12 months [20].

2.2 Measures

Information used in this study included: (1) Self-reported information on drug use and criminal activity according to the EuropASI [21], based on the fifth edition of the Addiction Severity Index [22]; German version: [23]. (2) Psychopathology, measured with the health scale and Global Severity Index (GSI) of the Symptom Checklist-90-Revised (SCL-90-R, [24]). (3) Health status measured with the Opiate Treatment Index Health-Symptoms-Scale [25]. (4) Urine samples for heroin and cocaine use. (5) Mental and physical health improvement as well as reduction of illicit drug use (difference between baseline and 12 months) was used to determine dichotomous outcome measures (see Haasen et al. [13] for details).

2.3 Subjects

To carry out this study the ITT sample (N=1015) was divided into two subsamples: patients with previous maintenance treatment experience (PME, n=899) and patients without (NPME, n=107). Nine patients were not included in the analysis due to missing data on previous maintenance treatment.

2.4 Statistical analysis

Baseline characteristics were compared using t-tests for continuous variables and Chi square tests for nominal variables between patients in HAT or MMT and subsamples with or without previous maintenance treatment experience (PME or NPME). As noted in the previous publication [13], this trial demonstrated the higher effect of HAT on treatment outcomes without influence of other factors such as target group (methadone treatment failures versus not in treatment), type of psychosocial intervention (psychoeducation versus case management) and study site. Therefore, a two-factorial logistic regression model was used to assess the possible effect of previous maintenance treatment only controlling for type of medication. Additionally, Chi square 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. 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 confidence interval was set up at 95%. Analyses were made using SPSS version 15 for Windows.

3. Results

3.1 Participant characteristics

Table 1 shows baseline characteristics of the participants. Between the two medication groups in the subsample without maintenance treatment experience (NPME), there was only one significant difference with HAT patients having a higher proportion of hepatitis C infections (χ^2=7.308, p=.007).

Table 1: *Baseline characteristics of the 107 participants who didn't have a previous maintenance treatment 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 (n, %)	53, 89.8	43, 89.6	96, 89.7	*n.s.*	709, 78.9	**
Age (years)	34.37±6.57	35.75±6.81	34.99±6.68	*n.s.*	36.55±6.67	*
Stable housing (n, %)	38, 64.4	24, 51.1	62, 58.5	*n.s.*	635, 70.9	**
Employed (n, %)	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	***
Cocaine	4.78±6.41	4.02±4.73	4.44±5.71	*n.s.*	5.70±6.59	*
Benzodiazepines	2.92±4.71	1.83±3.93	2.43±4.39	*n.s.*	5.56±7.19	***
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	***
Cocaine (n, %)	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.*
Benzodiazepines (n, %)	33, 55.9	19, 40.4	52, 49.1	*n.s.*	519, 57.9	*n.s.*
Benzodiazepines (days)	9.27±10.24	12.89±11.75	10.60±10.85	*n.s.*	16.85±11.51	***
Intravenous drug use (n, %)	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	***
Alcohol use (n, %)	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 (n, %)	49, 83.1	36, 75.0	85, 79.4	*n.s.*	794, 89.4	**
Previous drug free treatment (n, %)	29, 49.2	20, 41.7	49, 45.8	*n.s.*	571, 65.7	***
Physical health:						
OTI health scale (0-50 pts)	17.78±4.81	19.48±4.40	18.54±4.69	*n.s.*	18.99±5.36	*n.s.*
Body mass index (BMI)	22.59±3.54	22.08±3.15	22.36±3.36	*n.s.*	22.67±3.51	*n.s.*
HIV positive (n, %)	3, 5.3	2, 4.2	5, 4.7	*n.s.*	85, 9.5	*n.s.*
HCV positive (n, %)	45,79.0	26, 54.2	71, 67.6	**	740, 83.0	***
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 (n, %)	11, 20.0	11,22.9	22, 20.6	*n.s.*	340, 38.9	***

Social functioning:

GAFS (0-100)[b]	55.92±13.37	55.50±10.77	55.73±12.22	*n.s.*	53.36±11.45	*
Illegal activities past month (days)	16.64±13.27	17.67±12.57	17.09±12.91	*n.s.*	15,07±12,84	n.s.
Ever convicted (n, %)	55, 96.5	45, 95.7	100, 96.2	*n.s.*	847, 96.3	n.s.
Ever incarcerated (n, %)	44, 74.6	29,69.1	73, 72.3	*n.s.*	649, 74.9	n.s.

* p <.05
** p <.01
*** p <.001
n.s. nonsignificant
HAT: Heroin Assisted Treatment
MMT: Methadone Maintenance Treatment
NPME: Participants with no previous maintenance treatment experience.
PME: Rest of the sample (Participants with previous maintenance treatment experience).

[a]	The mean days of consume were calculated only in patients who had at least one day of consume.
[b]	Global Assessment of Functioning Scale.

Table 2. *Effectiveness of heroin versus methadone treatment on primary outcome measures (POM).*

	NPME					PME				
	HAT		MMT		Significance HAT vs. MMT	HAT		MMT		Significance HAT vs. MMT
	N	%	N	%		N	%	N	%	
Response POM Health	46	78.0	39	81.3	OR=.817, 95%-CI: .315-2.113; χ^2=0.175, p=.676	363	80.1	327	73.3	OR=1.468, 95%-CI: 1.074-2.005; χ^2=5.848, p=.016
Response POM Illegal drug use	46	78.0	19	39.6	OR=5.401, 95%-CI: 2.320-12.570, χ^2=16.353, p<0.0001	309	68.2	253	45.0	OR=1.673, 95%-CI: 1.247-2.149, χ^2=12.651, p<0.0001
Response both POM	38	64.4	15	31.6	OR=3.981, 95%-CI: 1.770-8.951, χ^2=9.187, p<0.005	256	56.5	207	46.4	OR=1.500, 95%-CI: 1.153-1.952, χ^2=9.178, p<0.005

Compared to patients with previous maintenance treatment experience (PME) at baseline, NPME patients included less females (χ^2=7,046, p=.008), were younger (t=2.292, p=.022), had a poorer housing situation (χ^2=6.861, p=.009), had less experience with detoxification (χ^2=9.266, p=.002) and drug free treatment (χ^2=16.304, p<.0001), had fewer years of heroin use (t=5.306, p<.0001), cocaine use (t=1.888, p=.059) and benzodiazepine use (t=6.402, p<.0001), and more days of heroin use in the last month (t=-12.497, p<.0001). They also had injected drugs (t=-6.224, p<.0001) and consumed benzodiazepines (t=3.939, p<.0001) on more days in the last month, but the proportion of HCV infected was lower (χ^2=14.586, p<.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=.001) and a higher score in the Global Assessment of Functioning Scale (t=-2.008, p=.045).

3.2 Treatment retention

Treatment retention for NPME (53.84%) did not differ from PME patients (53.27%). In contrast with the results of the main study, no significant differences were found in treatment retention between HAT and MMT in the NPME subsample (HAT: 55.93%, MMT: 50.00% (χ^2=.374, n.s.). No significant differences were found in 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, SD= 9.94) of methadone over all heroin treatment days. In the methadone group the mean daily dose was 87.35 (range: 36.03-165.62, SD=37.61). Compared to PME patients, no significant differences in dosage were found.

3.3 Treatment effectiveness

The two-factorial logistic regression model analysis showed no influence of previous maintenance treatment experience on primary outcome measures (POM) health, illegal drug use or both when analyzing for treatment group. When analyzing subsamples separately, no influence of treatment was found in NPME patients on health in contrast with PME patients, but a significantly greater response for HAT patients was found in the POM illicit drug use and for response in both outcome measures (see table 2). With respect to the outcome measure of reduction of illegal activity, the subsample of patients without previous maintenance treatment experience showed no difference at baseline between the HAT and MMT groups (see table 1), but after 12 months illegal activity 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: $F=10.120$, $p=.002$).

Figure 1 shows the course of health indicators. Physical health (as measured with the OTI Health-Symptoms-Scale) showed an overall high improvement in the first phase of the study. A slight deterioration for MMT patients can be perceived in the last 6 months of the study, while HAT patients continued to show a stable amelioration. Mental health (as measured with the GSI of the SCL-90-R) 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. Towards the end of the study, MMT patients slightly worsened while stable effects were found in the HAT group.

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

Figure 1: Assessment of health according to OTI health scale (left) and Global Severity Index (GSI) of the SCL-90-R[a] (right) during the study period in the subsample of patients without maintenance treatment experience [b]
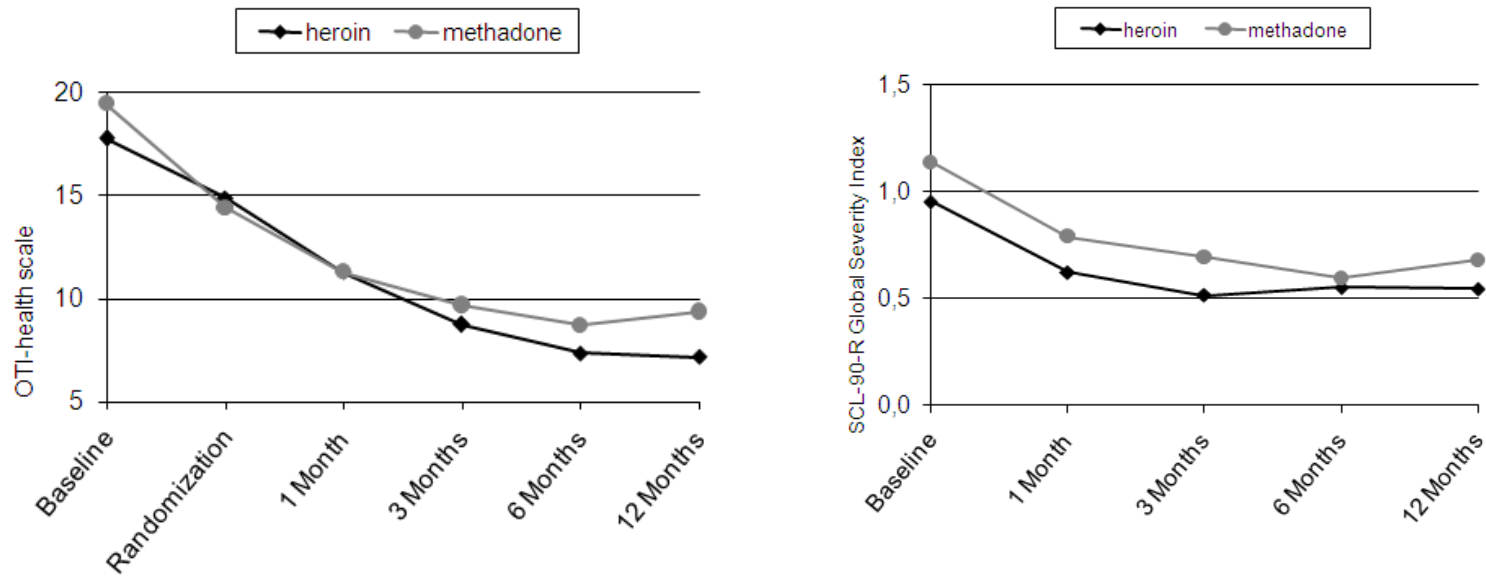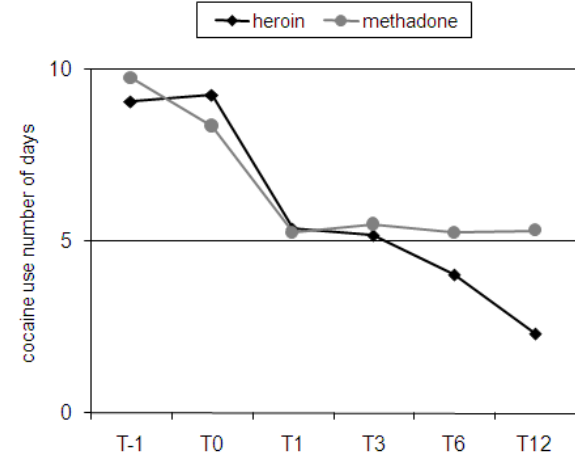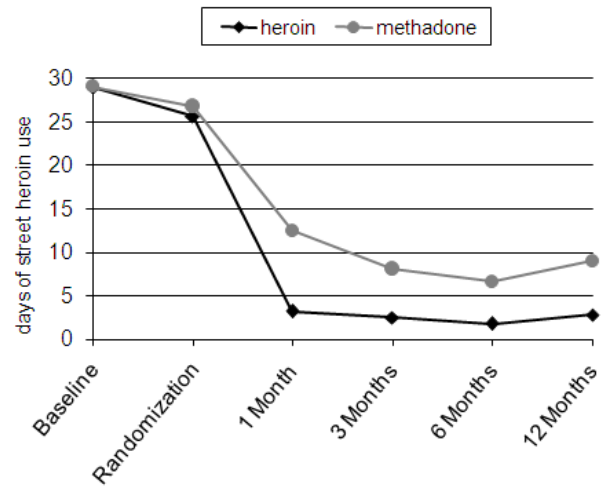

a) At T_0 the SCL-90-R was not assessed, in order to avoid overlap artefacts, since the SCL-90-R measures symptoms occurring in the last 7 days.
b) OTI-HSS: $N_{-1}=107$, $N_0=94$, $N_1=89$, $N_3=82$, $N_6=81$, $N_{12}=101$, SCL-90-R: $N_{-1}=107$, $N_1=89$, $N_3=81$, $N_6=81$, $N_{12}=101$.
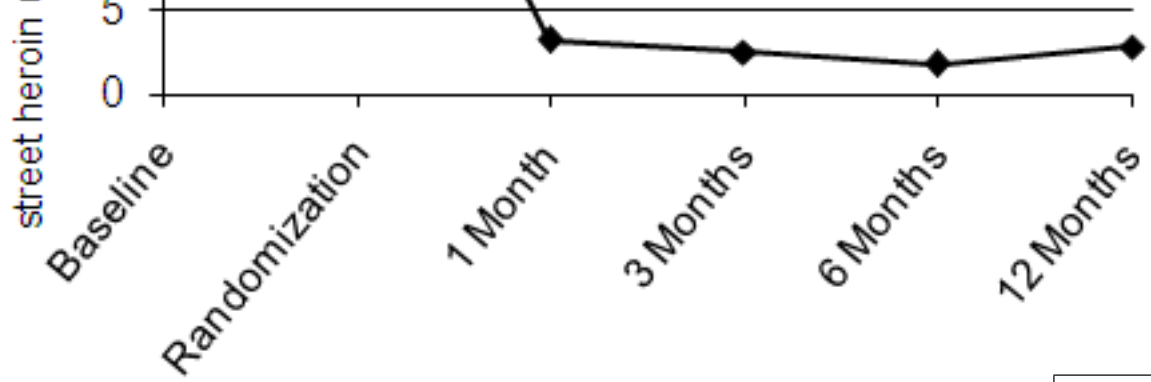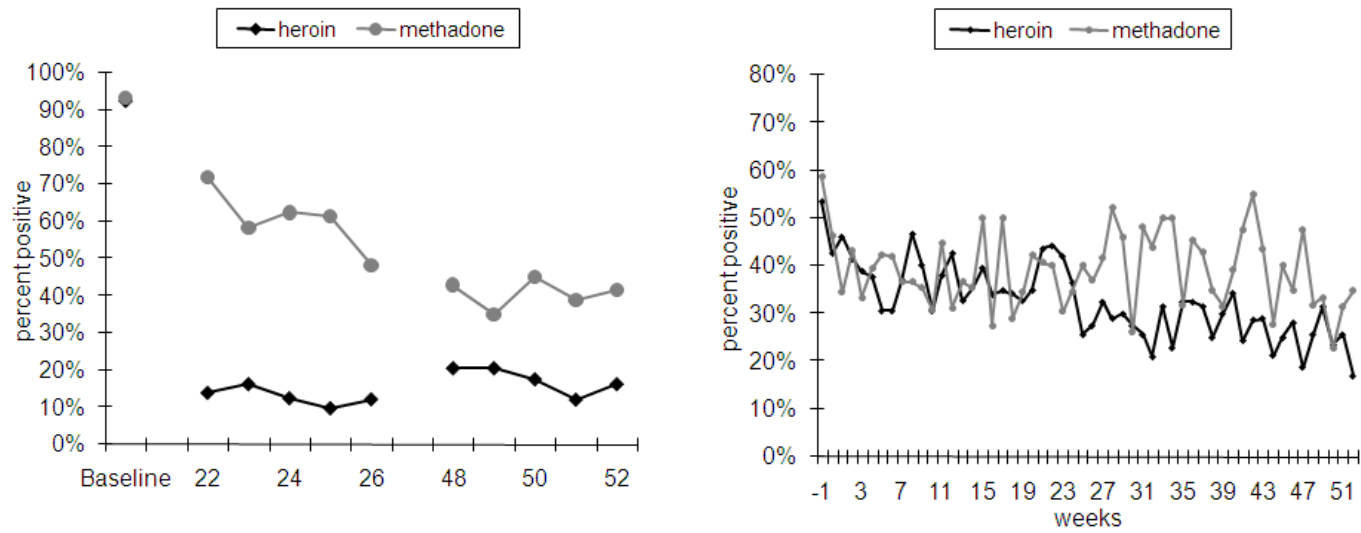
without maintenance treatment experience [a]

[a] Self-reported data of use in the last 30 days, street heroin: $N_{-1}=107$, $N_0=95$, $N_1=88$, $N_3=82$, $N_6=85$, $N_{12}=103$, cocaine: $N_{-1}=107$, $N_0=95$, $N_1=88$, $N_3=82$, $N_6=85$, $N_{12}=103$.

Figure 3: Urine samples[a)] testing for street heroin (left) and cocaine (right) in the subsample of patients without maintenance treatment experience

[a)] 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=51-10)

Discussion

Heroin assisted treatment (HAT) has been considered a second- or last-choice intervention. This consideration largely rests on four facts: First, injecting bears higher health risks than 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 aspects of addiction, which could be avoided by 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 necessitates more resources. On the other hand HAT might have an advantage in including patients in treatment that would otherwise choose not to enter maintenance treatment at all. If this was the case, it would be necessary to evaluate whether HAT is just as effective as MMT for chronic opioid dependent patients.

The present study is the first to analyse the effect of HAT in patients without previous maintenance treatment experience. The results show that patients without previous maintenance treatment experience, who have a shorter addiction career, benefit from both HAT and MMT to almost the same extent than those with maintenance treatment experience. The most important and surprising finding is the superiority 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 superiority was not found in all outcome measures. While no difference was found in the primary outcome measure on health, a significant difference became apparent in the reduction of illicit drug use and the reduction of illegal activity, which are generally considered two main goals of maintenance treatment.

These findings cannot be explained with a higher drop-out rate in the MMT group, as the retention rates did not differ in the two treatment groups of patients without previous maintenance treatment experience. Nonetheless, the 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 one year of methadone maintenance, so that the attractiveness of HAT may still have 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 to 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 for all chronic severely opioid dependent patients. However, this study was self-selective and did not control for the factor of previous maintenance treatment experience in an experimental design. Therefore 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.

References

1   Haasen C, van den Brink W: Innovations in agonist maintenance treatment of opioid-dependent patients. Curr Opin Psychiatry 2006;19:631-636.

2   Sorensen JL: Methadone treatment for opiate addicts. BMJ 1996;313:245-246.

3   Clark NC, Lintzeris N, Gijsbers A, Whelan G, Dunlop A, Ritter A, Ling WW: Laam maintenance vs methadone maintenance for heroin dependence. Cochrane Database Syst Rev 2002

4   Mattick RP, Breen C, Kimber J, Davoli M, Breen R: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev 2003

5   Gowing L, Ali R, White JM: Buprenorphine for the management of opioid withdrawal. Cochrane Database Syst Rev 2006

6   Kakko J, Gronbladh L, Svanborg KD, von Wachenfeldt J, Ruck C, Rawlings B, Nilsson L-H, Heilig M: A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: A randomized controlled trial. Am J Psychiatry 2007;164:797-803.

7   Mattick RP, Kimber J, Breen C, Davoli M: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2008

8   Kraigher D, Jagsch R, Gombas W, Ortner R, Eder H, Primorac A, Fischer G: Use of slow-release oral morphine for the treatment of opioid dependence. Eur Addict Res 2005;11:145-151.

9   Fischer B, Oviedo-Joekes E, Blanken P, Haasen C, Rehm J, Schechter M, Strang J, van den Brink W: Heroin-assisted treatment (hat) a decade later: A brief update on science and politics. J Urban Health 2007;84:552-562.

10   Rehm J, Gschwend P, Steffen T, Gutzwiller F, Dobler-Mikola A, Uchtenhagen A: Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: A follow-up study. The Lancet 2001;358:1417-1420.

11   van den Brink W, Hendriks VM, Blanken P, Koeter MWJ, van Zwieten BJ, van Ree JM: Medical prescription of heroin to treatment resistant heroin addicts: Two randomised controlled trials. BMJ 2003;327:310-.

12   March JC, Oviedo-Joekes E, Perea-Milla E, Carrasco F: Controlled trial of prescribed heroin in the treatment of opioid addiction. J Subst Abuse Treat 2006;31:203-211.

13   Haasen C, Verthein U, Degkwitz P, Berger J, Krausz M, Naber D: Heroin-assisted treatment for opioid dependence: Randomised controlled trial. Br J Psychiatry 2007;191:55-62.

14   Uchtenhagen A, Dobler-Mikola A, Steffen T, Gutzwiller F, Blättler R, Pfeifer S: Prescription of narcotics for heroin addicts. Main results of the swiss national cohort study. Med prescr of narcotics. Zurich, Karger, 1999.

15   Oviedo-Joekes E, Nosyk B, Brissette S, Chettiar J, Schneeberger P, Marsh D, Krausz M, Anis A, Schechter M: The north american opiate medication initiative (naomi): Profile of participants in north america's first trial of heroin-assisted treatment. J Urban Health 2008;85:812-825.

16   Metrebian N, Carnwath Z, Mott J, Carnwath T, Stimson G, Sell L: Patients receiving a prescription for diamorphine (heroin) in the united kingdom. Drug Alcohol Rev 2006;25:115 - 121.

17   Université de Liege: Protocole. Projet pilote de traitement assisté par diacétylmorphine comparaison entre un traitement par diacétylmorphine et un traitement par méthadone. Liège, Services de psychiatrie et de criminologie, 2008,

18   Blanken P, Hendriks VM, Koeter MW, van Ree JM, van den Brink W: Matching of treatment-resistant heroin-dependent patients to medical prescription of heroin or oral methadone treatment: Results from two randomized controlled trials. Addiction 2005;100:89-95.

19   Verthein U, Degkwitz P, Haasen C: Das bundesdeutsche modellprojekt zur heroingestützten behandlung opiatabhängiger. Baden-Baden, Nomos, 2008.

20   Verthein U, Bonorden-Kleij K, Degkwitz P, Dilg C, hler WK, Passie T, Soyka M, Tanger S, Vogel M, Haasen C: Long-term effects of heroin-assisted treatment in Germany. Addiction 2008;103:960-966.

21   Kokkevi A, Stefanis C: Drug abuse and psychiatric comorbidity. Compr Psychiatry 1995;36:329 - 337.

22   McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M: The fifth edition of the addiction severity index. J Subst Abuse Treat 1992;9:199-213.

23   Gsellhofer B, Küfner H, Vogt M, Weiler D (eds): Nach der 5. Auflage der amerikanischen version von mclellan und der europäischen version des asi ed. Baltmannsweiler, 1999.

24   Derogatis LR: Scl-90-r: Administration, scoring and procedures manual (3rd edition). Baltimore, 1994.

25   Darke S, Ward J, Zador D, Swift G: A scale for estimating the health status of opioid users. Addiction 1991;86:1317-1322.