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Implication of gender differences in heroin-assisted treatment – Results from the German randomised controlled trial

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Abstract

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 carried 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 men, 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.

Keywords: Gender differences, opiate addiction, Heroin Assisted Treatment, Methadone Maintenance Treatment.

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 tranquillisers, 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 drugs users have been found to show higher drug related problems in many domains. Those entering treatment have higher rates of physical and mental health problems (6-8). Well established is the higher HIV infection rate, related to risk taking behaviour 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, 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 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 randomised controlled trial in 7 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 six months or insufficiently responding to *MMT*.

A total of 2038 patients were screened. After baseline examinations, inclusion and exclusion criteria left an intention-to-treat (*ITT*) sample of 1015 patients (811 males and 204 females). This sample was randomised 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 1000 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 judgement. The 12-month treatment retention was 67.2% for *HAT* patients compared with 40.0% 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). Primary

outcome measures (*POM*) 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 versus not in treatment), type of psychosocial intervention (psychoeducation versus 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, the alpha level for all analyses was $p < .05$.

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.

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

	Male (n=811) HAT (n=412)	MMT (n=399)	Female (n=204) 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 (%) ^{b)}	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 (standardised 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) ^{c)}	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

a) ICD-10 diagnosis of schizophrenic (F2), affective (F3), neurotic (F4) or behavioural (F5) disorder.

b) 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.

c) Global Assessment of Functioning Scale.

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 urines 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 heroin positives was equivalent (men: 34.0%, women: 35.4%, $t=-.290$, n.s.) and men had more cocaine positive urines (men: 44.5%, women: 44.5%, $t=.13$, n.s.).

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

	Female								Male											
	HAT (n=103)		MMT (n=101)		Total (n=204)		Significance		HAT (n=412)		MMT (n=399)		Total (n=811)		Significance		Total between genders		significance	
	N	%	N	%	N	%	OR	95% C.I.	N	%	N	%	N	%	OR	95% C.I.	OR	95% C.I.		
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		

POM: Primary Outcome Measure

*Significant differences are marked in bold.

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 significant 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 figure 1). A similar pattern can be observed in physical health (OTI health scale; see figure 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 figure 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.

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.

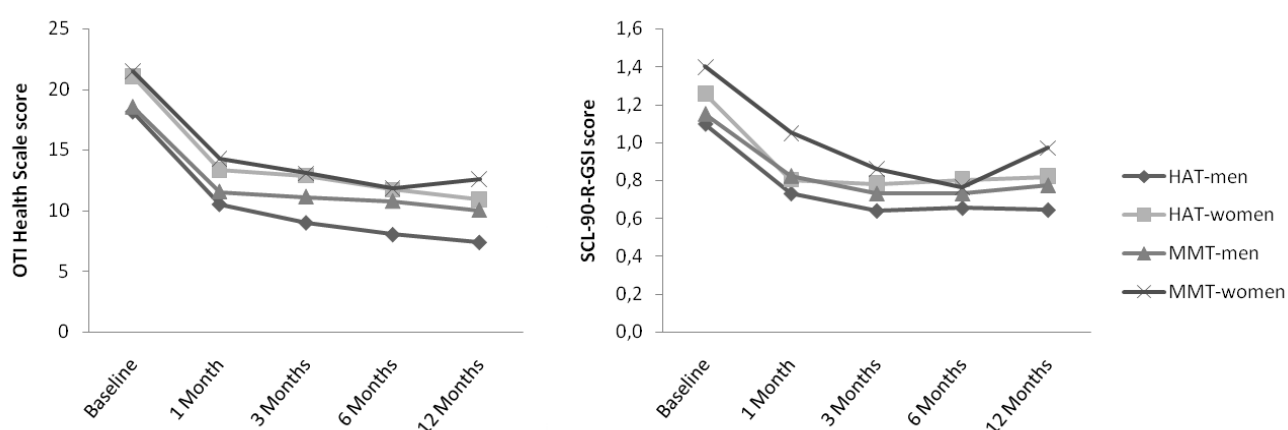
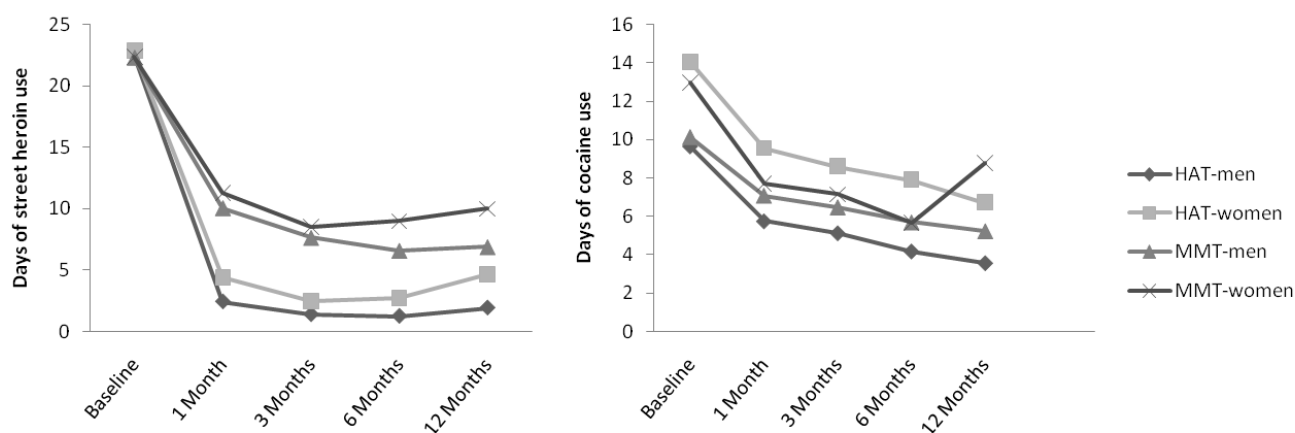


Figure 2: Change in self-reported street heroin use (left) and cocaine use (right) during the study period by treatment group and gender



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 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.

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		OR	95% CI	Prostitution t12		No prostitution t12		OR	95% CI	OR	95% CI	OR	95% CI
	N	%	N	%			N	%	N	%						
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.

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 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 4 out of the 9 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 shows that treatment outcome is mediated by a factor such as the risk-associated behaviour 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. 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 behaviour 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.

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