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Effects of psychiatric comorbidity on treatment outcome in patients undergoing diamorphine or methadone maintenance treatment.

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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 analysed 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.

Keywords

Comorbidity, methadone maintenance treatment, diamorphine, heroin-assisted treatment

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 non opiate 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].

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 to have a comorbid non-substance 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.

2. Methods

2.1 The German project on heroin assisted treatment of opiate dependent patients

HAT and MMT were compared in a multicenter trial among 1015 patients in 7 German cities. This intent to treat (ITT) sample resulted after screening 2038 heroin addicted patients, of which 1032 were randomised 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). 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 1000 mg, average dose: 442 mg/d) 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 judgement (average dose: 99mg/d). 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 analysed [16].

2.2 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 [18]; German version: [19], psychopathology based on the health scale and Global Severity Index (GSI) of the Symptom Checklist-90-Revised (SCL-90-

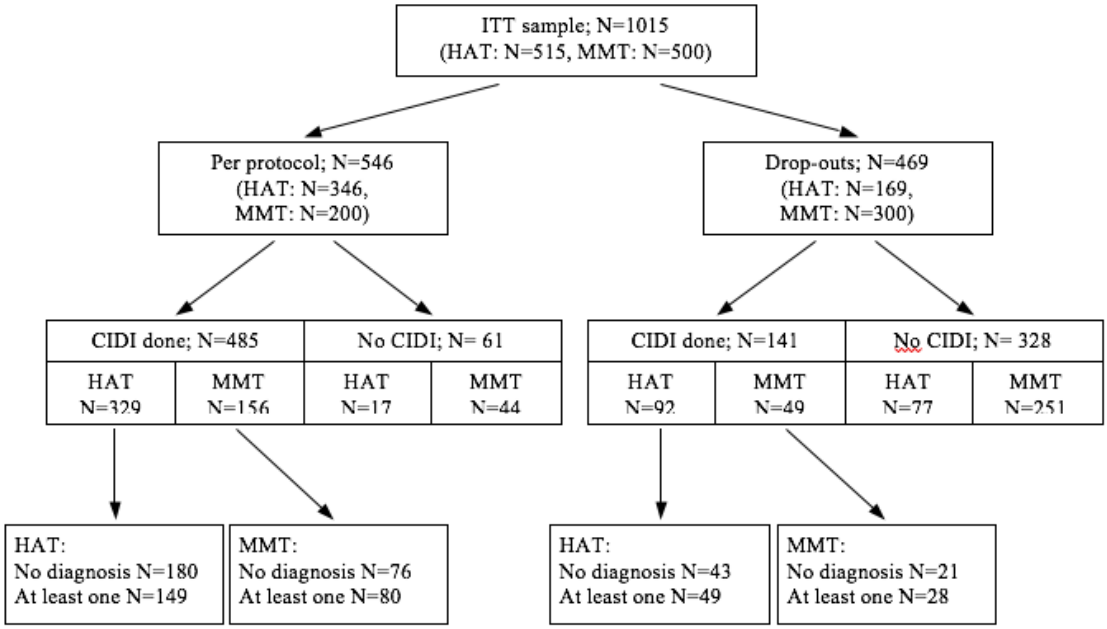
R, [20]), and the Composite International Diagnostic Interview (CIDI-10, [21]). Only the CIDI sections for ICD-10 group categories F2, F3, F4 and F5 were completed – personality disorders were not assessed due to the unreasonable interview length [22, 23]. Response was determined according to primary outcome measures (POM) 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 reasons 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 drop-outs in the control group (MMT) were considered responders and in the experimental group (HAT) were considered non-responders. Further details are described elsewhere [15].

2.3 Study population

Figure 1 shows the distribution of the sample according to treatment completion and availability of CIDI diagnostics. The CIDI was administered one 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 drop-outs (144 MMT patients and 12 HAT patients abandoned treatment before initiation mainly due to disagreement with the randomization process) and non-attendance 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.

Figure 1. Sample distribution by treatment completion and CIDI diagnosis for the last 12 months.



2.4 Statistical analysis

T-tests and Chi square 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 non completers. 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 (RMANOVA) were used to compare treatment groups with and without comorbid diagnoses at the beginning and the end of treatment with respect to ASI composite scores for drug use and psychiatric problems as well as GSI T-value scores.

3. Results

3.1 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 ASICS for drug misuse than non completers.

Table 1. *Description of the CIDI sample (total sample, completers, and drop-outs)*

	Total CIDI interviews			*Completers with CIDI*			*Drop-outs with CIDI*			*Significance of differences between completers and drop-outs**
	HAT (N=421)	*MMT (N=205)*	*Total (N=626)*	*HAT (N=329)*	*MMT (N=156)*	*Total (N=485)*	*HAT (N=92)*	*MMT (N=49)*	*Total (N=141)*	
Female gender (%)	21.14	22.44	21.57	19.76	24.36	21.24	26.09	16.33	22.70	χ^2=.137, p=.711
Age (mean±SD)	36.31±6.59	36.57±6.76	36.40±6.64	36.61±6.68	36.85±7.03	36.69±6.79	35.25±6.15	35.67±5.76	35.40±6.00	**t=2.035. p=.042**
Education in years (mean±SD)	9.79±1.78	9.79±1.77	9.79±1.78	9.94±1.70	9.70±1.62	9.86±1.68	9.25±1.98	10.06±2.16	9.53±2.07	t=1.957, p=.051
Employed (%)	15.00	12.75	14.26	15.85	13.55	15.11	11.96	10.20	11.35	χ^2=1.266, p=.261
Stable housing (%)	70.24	71.22	70.56	73.17	73.72	73.35	59.78	63.27	60.99	**χ^2=8.023, p=.005**
Years of heroin use (mean±SD)	13.69±6.34	13.56±6.29	13.65±6.32	13.74±6.31	13.83±6.48	13.77±6.36	13.48±6.48	12.71±5.63	13.21±6.19	t=.926, p=.335
Age of onset of heroin use (mean±SD)	19.99±5.37	20.36±5.19	20.11±5.31	20.29±5.41	20.34±5.32	20.30±5.37	18.92±5.14	20.43±4.83	19.45±5.07	t=1.687, p=.092
ASI CS for drug misuse (mean±SD)	.38±.10	.39±.10	.39±.10	.38±.10	.38±.10	.38±0.10	.40±.11	.41±.10	.40±.11	**t=-2.238, p=.026**
ASI CS for alcohol misuse (mean±SD)	.12±.18	.12±.18	.12±.18	.12±.18	.13±.19	.12±0.18	.12±.19	.09±.13	.11±.17	t=.547, p=.566
ASI CS for psychiatric problems (mean±SD)	.23±.21	.23±.21	.23±.21	.23±.21	.23±.21	.23±0.21	.23±.18	.24±.22	.24±.20	t=-.289, p=.773
GSI-SCL (T value) (mean ± SD)	68.89±10.63	69.57±9.99	69.11±10.43	68.59±10.91	69.40±9.73	68.85±10.54	69.93±9.55	70.10±10.87	69.99±9.99	t=-1.142, p=.254

*Statistically significant differences are marked in bold.
HAT: Heroin Assisted Treatment MMT: Methadone Maintenance Treatment

3.2 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 drop-outs.

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 behavioural syndromes associated with physiological disturbances and physical factors (F5), and only 2 patients with schizophrenia, schizotypal and delusional disorders (F2), with no significant differences between treatment groups regarding these categories.

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	χ^2=.293, p=.588
F30-F39 Mood [affective] disorders	92	28.0	40	25.6	132	27.2	χ^2=.288, p=.591
F40-F48 Neurotic, stress-related and somatoform disorders	88	26.7	64	41.0	152	31.3	**χ^2=10.025, p=.002**
F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors	5	1.5	6	3.8	11	2.3	χ^2=2.584, p=.108
No additional diagnosis (F20-F59)	180	54.7	76	48.7	256	52.8	χ^2=1.525, p=.217

* Statistically significant differences are marked in bold.

3.3 Treatment retention

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

Table 3. Treatment retention by comorbidity group and treatment group.

		Completers		**Drop-outs**		**Significance treatment**	**Significance comorbidity**
		N	%	N	%	No comorbid disorder: OR=1.16; 95% CI= .64-2.08	HAT: OR=1.38; 95% CI= .87-2.19
No comorbid disorder	HAT	180	80.72	43	19.28	Comorbid disorders: OR=1.06; 95% CI= .62-1.82	MMT: OR=1.27; 95% CI= .66-2.42
	MMT	76	78.35	21	21.65	Total (a): OR=1.11; 95% CI= .74-1.64	Total (a): OR=1.34; 95% CI= .92-1.95
	Total	256	80.00	64	20.00		
At least one comorbid disorder	HAT	149	75.25	49	24.75		
	MMT	80	74.07	28	25.93		
	Total	229	74.84	77	25.16		

(a) Mantel-Haenszel tests

3.4 Severity of symptomatology

GSI-scores and ASI CS "psychiatric problems" are shown in table 4 according to treatment groups and comorbid versus non-comorbid patients in the subsample of CIDI-interviewed completers. Comorbid patients had significantly higher GSI T-values at beginning and end of treatment. No GSI differences were found between treatment groups at the beginning of treatment, but MMT patients had significant higher scores at the end. RM ANOVA showed a large time and treatment group effect, but no effect of comorbidity or interaction between comorbidity and treatment groups. A similar tendency could be observed concerning ASI CS for psychiatric problems. Comorbid patients also had higher scores at 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.

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		CS psychiatric problems	
Baseline (t-1)			Treatment significance (two factor RM ANOVA)*		Treatment significance (two factor RM ANOVA)*
No comorbidity	HAT	66.35±11.35	Time effect:	.19±.21	Time effect:
	MMT	66.46±10.18	**Pillai's Trace=.376, F=288.339, df=1, p<.0001**	.15±.16	**Pillai's Trace=.019, F=8.672, df=1. p=.003**
At least one comorbid diagnosis	HAT	71.22±9.78		.28±.21	
	MMT	72.20±8.49	Treatment group effect:	.30±.21	Treatment group effect:
Significance (two factor ANOVA)		Treatment group effect: F=.301, p=.584	**Pillai's Trace=.008,F=3.994, df=1, p=.046**	Treatment group effect: F=.332, p=.565	**Pillai's Trace=0.010, F=4.316, df=1. p=.038**
		Comorbidity effect: F=27.990, p<.001***	Comorbidity effect: Pillai's Trace=.003, F=1.243, df=1, p=.256	Comorbidity effect: F=34.382, p<.001***	Comorbidity effect: Pillai's Trace<.001, F=.195, df=1. p=.659
End of treatment (t12)					
No comorbidity	HAT	54.66±13.68	Interaction treatment-comorbidity : Pillai's Trace<.001, F=.163, df=1, p=.686	.13±.18	
	MMT	56.67±13.16		.15±.20	
At least one comorbid diagnosis	HAT	60.38±12.72		.23±.23	Interaction treatment-comorbidity : Pillai's Trace=.002, F=.752, df=1, p=.386
	MMT	64.22±13.24		.28±.24	
Significance (two factor ANOVA)		Treatment group effect: F=5.104, p=.024*		Treatment group effect: F=2.482, p=.116	
		Comorbidity effect: F=26.278. p<.001***		Comorbidity effect: F=27.777, p<.001***	

*Statistically significant differences are marked in bold.

3.3 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 non-comorbid group.

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:
No comorbidity	HAT	.38±.10	**Pillai's Trace=.594, F=624.373, df=1, p<.0001**
	MMT	.35±.09	
At least one comorbid diagnosis	HAT	.38±.10	Treatment group effect:
	MMT	.41±.09	**Pillai's Trace=.186, F=97.367, df=1, p<.0001**
Significance (two factor ANOVA)		Treatment group effect: F=.018, p=.892	
		Comorbidity effect: F=8.991, p=.003	Comorbidity effect:
End of treatment (t12)			Pillai's Trace=.043, F=.043, df=1, p=.836
No comorbidity	HAT	.12±.10	Interaction treatment-comorbidity :
	MMT	.27±.12	**Pillai's Trace=.013, F=5.642, df=1, p=.018**
At least one comorbid diagnosis	HAT	0.16±.12	

	MMT	0.29±.11
Significance (two factor ANOVA)		**Treatment group effect: F=137.038, p<.0001** **Comorbidity effect: F=5.164, p=.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							
	HAT		MMT		Significance*		HAT		MMT		Significance*		Total significance* (a)	
	N	%	N	%	OR	95% CI	N	%	N	%	OR	95% CI	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	.800-3.164	**1.894**	**1.156 - 3.106**

*Statistically significant differences are marked in bold.

(a) Mantel-Haenszel Test between treatment groups by comorbidity.

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 non-comorbid patients compared to those with psychiatry 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, make 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 a very severe mental disorder had to be excluded. This explains the surprisingly low number of patients with a schizophrenia spectrum disorder. This subsample should be analysed in the future, when more patients have been 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 favour of heroin treatment. However, to control for such effects, a “worst case analysis” was used where drop-outs in the control group (MMT) were considered responders and in the experimental group

(HAT) were considered non-responders. Finally, patients in the MMT group had a significantly higher number of anxiety disorders according to the CIDI as compared to 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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