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RESEARCH REPORT

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Outcome of long-term heroin-assisted treatment offered to chronic, treatment-resistant heroin addicts in the Netherlands

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ABSTRACT

Aims To describe 4-year treatment retention and treatment response among chronic, treatment-resistant heroin-dependent patients offered long-term heroin-assisted treatment (HAT) in the Netherlands. **Design** Observational cohort study. **Setting and intervention** Out-patient treatment in specialized heroin treatment centres in six cities in the Netherlands, with methadone plus injectable or inhalable heroin offered 7 days per week, three times per day. Prescription of methadone plus heroin was supplemented with individually tailored psychosocial and medical support. **Participants** Heroin-dependent patients who had responded positively to HAT in two randomized controlled trials and were eligible for long-term heroin-assisted treatment ($n = 149$). **Measurements** Primary outcome measures were treatment retention after 4 years and treatment response on a dichotomous, multi-domain response index, comprising physical, mental and social health and illicit substance use. **Findings** Four-year retention was 55.7% [95% confidence interval (CI): 47.6–63.8%]. **Treatment** Response was significantly better for patients continuing 4 years of HAT compared to patients who discontinued treatment: 90.4% versus 21.2% [difference 69.2%; odds ratio (OR) = 48.4, 95% CI: 17.6–159.1]. Continued HAT treatment was also associated with an increasing proportion of patients without health problems and who had stopped illicit drug and excessive alcohol use: from 12% after the first year to 25% after 4 years of HAT. **Conclusions** Long-term HAT is an effective treatment for chronic heroin addicts who have failed to benefit from methadone maintenance treatment. Four years of HAT is associated with stable physical, mental and social health and with absence of illicit heroin use and substantial reductions in cocaine use. HAT should be continued as long as there is no compelling reason to stop treatment.

Keywords Diamorphine, heroin, heroin-assisted treatment, long-term outcome, opioid dependence.

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INTRODUCTION

Methadone maintenance treatment is accepted broadly as the first-choice, most effective treatment for heroin dependence [1,2]. However, not all opiate-dependent patients benefit from this treatment and, in spite of their poor health status, not all heroin addicts take part in this treatment. A number of randomized controlled trials (RCTs) [3–6] and one large cohort study [7] have shown that medical prescription of heroin to chronic heroin addicts who have not responded favourably to methadone maintenance treatment is more effective than ongoing methadone maintenance treatment, in terms of physical and mental health, illicit heroin use, criminality and—to a lesser extent—cocaine use. The efficacy of heroin-assisted treatment (HAT) was demonstrated for treatment periods ranging from 6 to 18 months. Treatment completion rates for these periods centred around 70% in Switzerland, the Netherlands, Spain and Germany. However, much less is known about the outcome of long-term HAT.

Güttinger presented 6-year follow-up results for the first cohort of 366 patients treated with medically prescribed heroin in Switzerland [8]. After 6 years, 40.4% of the patients were (mainly without interruption) in HAT.

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Compared to their baseline situation, patients in long-term HAT showed marked reductions in illegal drug consumption and involvement in illegal activities, whereas modest improvements in living condition and social situation were reported. Patients in HAT, however, differed significantly from patients who were discharged from HAT only in terms of a stronger reduction of illicit heroin use. The mortality rate among patients in HAT was estimated at 1% per year over a 7-year treatment period, compared to an estimated 2.5–3% mortality rate among Swiss opioid users in the 1990s [9]. In Germany, after 2 years of HAT, treatment retention was 54.8% and the improvements in health and illicit heroin and cocaine use that were achieved after 1 year stabilized, while the social situation continued to improve during the second year of HAT [10].

In the Dutch heroin trials, patients were offered 6 or 12 months' treatment with methadone plus inhalable or injectable heroin, either from the start or after an initial period of 6 or 12 months' standard oral methadone treatment [11]. After completion of HAT, 51% of the patients receiving 6 or 12 months' co-prescribed inhalable heroin and 58% of the patients receiving injectable heroin had responded positively according to a predefined dichotomous multi-domain outcome index [4]. Following this experimental treatment with co-prescribed heroin, HAT was discontinued for a period of at least 2 months. In most cases, heroin dosages were tapered-off and methadone dosage was increased gradually, and patients received psychosocial and medical support. After 2 months' discontinuation of HAT, 82% of the original HAT responders had deteriorated seriously [4]. These deteriorated responders were then eligible for reinstatement of HAT for reasons of compassionate use. Thus, long-term HAT was offered only to patients who had responded positively to co-prescribed heroin treatment and who had deteriorated seriously after planned termination of HAT.

The primary goal of this paper is to describe the 4-year outcome among patients who were offered long-term HAT in terms of treatment retention and treatment response. Secondary goals are to identify reasons and predictors for HAT discontinuation. A final goal is to describe the course of 4 years of HAT in terms of physical and mental health, social functioning and the use of non-prescribed drugs and alcohol.

METHODS

Subjects

All chronic, treatment-resistant heroin-dependent patients showing a positive response to 6 or 12 months' HAT on a multi-domain dichotomous outcome measure in the Dutch randomized heroin trials, who deteriorated seriously when HAT was discontinued, were eligible for reinstatement of long-term HAT and were included in this observational cohort study [11].

Long-term HAT

Eligible patients were offered reinstatement of long-term HAT for as long as continuation of treatment was medically justified based on clinical observation and yearly, standardized follow-up assessments (see below). Ultimately, the decision to (dis)continue HAT was the responsibility of the medical treatment staff. Patients were treated in out-patient treatment centres in six cities in the Netherlands and were offered pharmaceutical grade heroin 7 days per week, three times per day. The maximum co-prescribed heroin dosage was 400 mg per visit and 1.000 mg per day. Methadone (≥35 mg) was prescribed daily. Patients were offered an individually tailored package of psychosocial and medical support. The study was approved by the Central Committee on Research involving Human Subjects (CCMO). All participants provided written informed consent.

Assessments and instruments

In the Dutch heroin trials patients were screened at baseline and at bi-monthly intervals during 18 months. Assessments at baseline (t0) and at the end of HAT during the trials (t1) will be reported in this paper. Patients reinstated on long-term HAT were assessed each year during treatment by specially trained research nurses at the end of the second, third and fourth years of HAT (t2, t3 and t4, respectively). Patients who discontinued long-term HAT were interviewed by an independent research assistant at t4.

All assessments contained a core set of instruments:

1. European Addiction Severity Index (EuropASI) measuring—among others—substance use, social contacts outside the drug scene and illegal activities [12];
2. Health Symptoms Scale of the Maudsley Addiction Profile (MAP-HSS) measuring last month physical health status [13]; and
3. Symptom Checklist (SCL-90) measuring mental health status [14].

Self-reported data on substance use and criminal charges were validated against urinalysis and police registers, respectively. Overall agreement for self-reported cocaine use and urinalysis was 86% [K = 0.66; 95% confidence interval (CI): 0.58–0.75] and for self-reported criminal charges and police registers overall agreement was 90% (K = 0.62; 95% CI: 0.43–0.82) [4].

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Outcome measures

In this study, the same pre-specified dichotomous, multi-domain response index as in the original RCTs was used as primary outcome at the 4-year follow-up assessment. Response was thus defined as:

1. improvement (compared to baseline) of at least 40% at the 4-year follow-up in at least one of the domains of inclusion at baseline assessment, i.e. physical, mental or social health;
2. no serious deterioration (≥40%) in any of the other outcome domains, compared to baseline; and
3. no substantial increase (>6 days/month) of cocaine or amphetamine use compared to baseline.

A secondary outcome measure was defined in terms of the criteria used originally as an indication of poor health status and patient inclusion in HAT. At each yearly evaluation it was determined whether patients no longer met criteria of 'poor functioning': MAP-HSS total score < 8; SCL-90 total score < 41 for men and <60 for women; days without personal contact with non-drug-users in past month < 25; and days involved in illegal activities in past month < 6. In addition, it was determined whether patients had terminated the use of illegal heroin, cocaine and amphetamine and had stopped excessive alcohol (≥5 glasses/day) use. Finally, two overall dichotomous indicators of success were defined: 'health recovery' as the absence of health problems on all four domains and 'complete recovery' as absence of any health problems plus absence of non-prescribed drug and excessive alcohol use.

Statistical analysis

Earlier reports on the 12-month outcome of the Dutch RCTs showed that the co-prescription of injectable and inhalable heroin was equally effective [4,15]. Therefore, data for the two patient groups were pooled.

In the primary analysis, patients with missing assessment at the 4-year follow-up end-point (t4) were treated as non-responders. In secondary analyses, missing end-point assessments were imputed by means of (1) a last observation carried forward (LOCF) procedure and (2) a worst-case scenario, in which patients with missing end-point assessment who discontinued HAT were considered to be responders, while patients who continued long-term HAT with missing end-point data were considered to be non-responders.

Figure 1 shows that only two of the 83 patients who completed 4 years of HAT had missing t4 assessments, leaving 81 patients in this group with valid end-point data (98%). For the two patients with missing end-point data, the last available—third-year evaluation (t3)—was carried forward to the end-point assessment, while in the worst-case scenario they were treated as non-responders. Of the patients who did not restart ($n = 2$) or discontinued long-term HAT ($n = 64$), 36 patients were interviewed at the end of the 4-year follow-up and one patient had died (7.5 months after discontinuation of HAT). Twenty-nine patients (44%) were not reached for follow-up assessment. For 16 patients the last available yearly evaluation assessment could be carried forward to the end-point assessment. For the remaining 13 patients no assessment was available after reinstatement of co-prescribed heroin treatment. In the worst-case scenario all patients with missing end-point assessment were treated as responders. The patient who had died was a non-responder in all analyses.

The retention rate for long-term HAT is presented as the percentage of patients still in treatment at the 4-year follow-up end-point (t4) and the reasons for

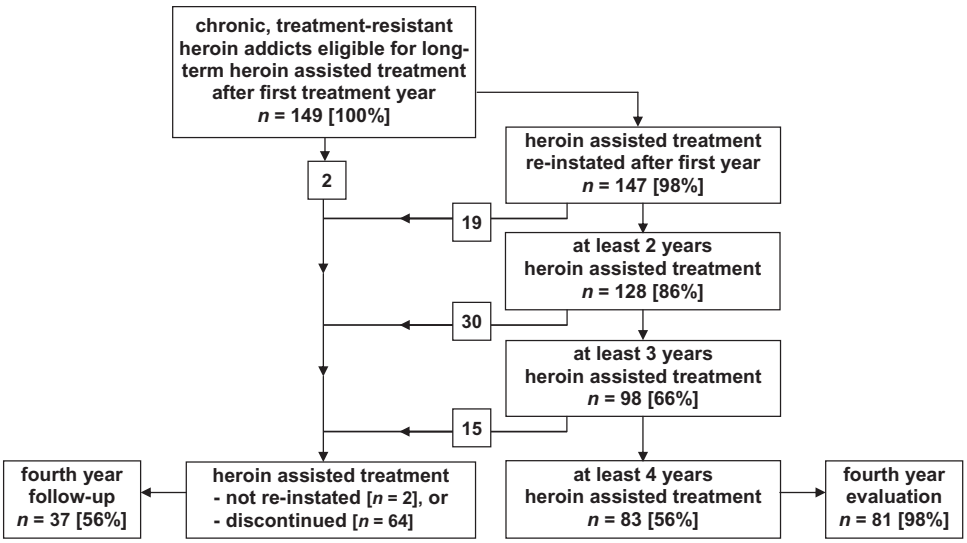

Figure 1 Disposition of patients

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discontinuation of long-term HAT, provided by the treatment staff, are summarized.

In order to test for predictors of treatment discontinuation, patients still in long-term HAT after 4 years were compared, in terms of baseline characteristics, with patients who discontinued HAT, by means of Fisher's exact tests and non-parametric Kruskal–Wallis tests. Bonferroni correction was applied to correct for multiple testing.

The outcome of 4 years of HAT is presented as percentage of responders. Logistic regression analyses were used to test the difference in response rates between patients still in HAT at t4 versus patients who discontinued HAT, controlling for treatment site and route of heroin administration (inhaling versus injecting).

Finally, longitudinal logistic regression analysis was used to test the course of long-term HAT in terms of physical, mental and social health status and non-prescribed substance use for patients still in HAT at t4. In this longitudinal logistic regression analysis time was modelled linearly, from the end of treatment in the trials (t1) throughout the next 3 years of reinstated HAT, until t4.

All statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

The second column of Table 1 shows that, at the time of inclusion in the heroin trials (between 1998 and 2000), patients had a mean age of 39.2 years and were predominantly male (83.2%) and of Dutch or western European origin (89.9%). Most patients had poor physical (70.5%) and/or mental (59.7%) health and/or poor social functioning (75.8%). The majority of patients functioned poorly on at least two inclusion domains (70.5%). Patients had a long history of regular heroin use (16.9 years) and they were all polydrug users. In the month before baseline assessment (data not shown in Table 1), they used heroin [mean: 26.2 days, standard deviation (SD) 6.0] and methadone (mean: 29.3 days, SD 3.4) almost daily. In addition, they frequently drank five or more glasses of alcohol (mean: 6.9 days, SD 11.4) and used benzodiazepines (mean: 12.1 days, SD 13.3) and cocaine (mean: 13.3 days, SD 11.3).

Treatment, retention and reasons for discontinuation

Figure 1 shows that two of the 149 patients (1.3%) eligible for long-term HAT did not restart treatment, that 64 patients (43.0%) discontinued long-term HAT within the follow-up period and that 83 patients were in HAT at t4, resulting in a 4-year treatment retention rate of 55.7% (95% CI: 47.6–63.8%).

Table 2 shows that the majority of patients were prescribed inhalable heroin (71.5%). During long-term HAT six of 37 patients, who were originally prescribed injectable heroin, changed to inhalable heroin, most probably because of vein damage, as a result of long-term heroin dependence and injecting illicit street heroin. On average, patients visited the treatment unit 1.9 times per day for 24.7 days per month. The average dose of heroin prescribed was 268 mg per visit and 502 mg per day.

Compared with patients who had terminated long-term HAT, patients who were still in treatment at t4 visited the treatment unit more often (27.7 versus 20.8 days per month, $P < 0.001$; 2.0 versus 1.7 visits per day, $P < 0.01$) and were prescribed a higher heroin dosage (280 mg versus 253 mg per visit, $P = 0.02$; 546 mg versus 445 mg per day, $P < 0.01$) (see Table 2). These differences, however, are due at least partly to the process of treatment discontinuation and tapering-off of heroin dosage.

During HAT, 11 serious adverse events (SAEs) were registered, two of which were probably related to the prescribed heroin (inpatient drug detoxification and pneumonia). All SAEs were non-fatal. Eight of the SAEs were among patients still in treatment at t4. The SAEs among patients who discontinued HAT were not related to the discontinuation of treatment.

Table 3 shows that the major reasons for discontinuing long-term HAT were insufficient treatment response according to the treatment staff (21.2%) and (repeated) violation of house-rules (22.7%), i.e. mainly attempts to smuggle heroin out of the treatment centre. Fifteen patients discontinued long-term HAT on their own initiative of whom seven patients had opted for abstinence-orientated treatment (10.6%). Of the 66 patients who discontinued long-term HAT, 56 patients were in (primarily substitution) treatment at t4 (84.8%), nine patients were no longer in addiction treatment (13.6%) and one patient had died 7 months after HAT discontinuation (1.5%).

Predictors of discontinuation of HAT

In the third and fourth columns of Table 1, patient characteristics are broken down by the treatment status at t4 ('not in HAT' versus 'still in HAT'). In general, baseline data of the two groups were very similar, with only one significant difference: education level at the start of HAT. In addition, there were no significant differences at t1 (at the end of the first treatment year, when response status was determined) between the two groups in the proportion of patients who were free of problems in the physical, mental and social health domains, nor were there any differences in the proportion of patients who had stopped using non-prescribed drugs or drinking large quantities of alcohol at t1.

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Table 1 Patient characteristics at baseline (t0) and patient status after the experimental period of heroin-assisted treatment (HAT) (t1) ($n = 149$).

		4-year heroin-assisted treatment status		
	All patients n = 149	*Not in HAT n = 66*	*Still in HAT n = 83*	
	% or mean (SD)	*% or mean (SD)*	*% or mean (SD)*	*P*[a]
Background at baseline (t0)				
Gender (% male)	83.2%	86.4%	80.7%	0.39
Age (years)	39.2 (5.2)	39.7 (5.5)	38.8 (4.9)	0.19
Ethnicity (% Dutch/western European ethnicity)	89.9%	84.9%	94.0%	0.10
Education level (% middle/high education level)	32.9%	22.7%	41.0%	0.02
Inclusion profile and scores at baseline (t0)				
Included with physical health problems (%)	70.5%	71.2%	69.9%	1.00
MAP-HSS sum score (range: 0–40)	11.9 (7.4)	12.0 (8.1)	11.8 (6.9)	0.98
Included with psychiatric health problems (%)	59.7%	62.1%	57.8%	0.62
SCL-90 sum score (range: 0–360)	73.9 (64.0)	81.9 (68.3)	67.5 (60.0)	0.17
Included on basis of illegal activities (%)	61.1%	59.1%	62.7%	0.74
Days illegal activities past month	12.2 (11.3)	11.1 (10.7)	13.1 (11.8)	0.38
Included on basis of social contacts (%)	40.9%	45.5%	37.4%	0.40
Days without social contact with non-drug users	15.7 (12.5)	17.2 (12.5)	14.5 (12.4)	0.13
Included with problematic social functioning (%)	75.8%	77.3%	74.7%	0.85
Included on two or more health domains (%)	70.5%	75.8%	66.3%	0.28
Substance use history at baseline (t0)				
Life-time years regular substance use				
Heroin	16.9 (5.4)	17.5 (5.6)	16.4 (5.3)	0.26
Methadone	12.5 (6.0)	12.6 (6.0)	12.4 (6.0)	0.71
Alcohol (≥5 glasses)	8.0 (9.0)	8.2 (9.0)	7.8 (9.0)	0.95
Benzodiazepines	5.7 (7.3)	6.3 (7.2)	5.3 (7.3)	0.13
Cocaine	9.1 (7.1)	8.8 (6.9)	9.4 (7.2)	0.53
Amphetamines	2.3 (5.0)	2.2 (5.0)	2.3 (5.0)	0.77
Polydrug use	18.7 (6.3)	19.4 (6.2)	18.1 (6.3)	0.24
Any previous abstinence-orientated treatment (%)	68.7%	75.0%	63.9%	0.16
Patient status after experimental period of HAT (t1)				
Absence of physical health problems (%) (MAP-HSS < 8)	73.8%	69.7%	77.1%	0.35
Absence of psychiatric health problems (%) (SCL-90 < 41 for males or <60 for females)	72.5%	66.7%	77.1%	0.20
Illegal activities < 6 days/month (%)	96.0%	95.5%	96.4%	1.00
Days without personal contact non-drug using individuals < 25 days/month (%)	83.2%	77.3%	88.0%	0.12
No illicit heroin use	60.4%	63.6%	57.8%	0.50
No alcohol (≥5 glasses) use	71.1%	71.2%	71.1%	1.00
No cocaine use	22.8%	16.7%	27.7%	0.12
No amphetamine use	98.0%	100%	96.4%	0.25

[a]Reported *P*-values are before Bonferroni correction, and are based on Fisher's exact test (dichotomous variables) and non-parametric Kruskal–Wallis test (interval variables). MAP-HSS: Health Symptoms Scale of the Maudsley Addiction Profile; SCL-90: Symptom Checklist 90; SD: standard deviation.

After Bonferroni correction for multiple testing, none of the patient characteristics at baseline or t1 predicted treatment status significantly at t4.

Four-year outcome

Table 4 shows the 4-year outcome according to different methods of handling missing data. If all patients with missing end-point were regarded as non-responders, 59.7% of all patients responded favourably to this treatment offer. Patients who continued HAT for 4 years did considerably better than those who discontinued HAT: 90.4% versus 21.2% response. Treatment site, heroin administration route and their interaction with treatment retention at t4 were not related significantly to the 4-year outcome. Controlling for treatment site and

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Table 2 Treatment consumption, broken down by 4-year heroin-assisted treatment (HAT) status ($n = 131$).[a]

		4-year heroin-assisted treatment status		
	All patients n = 131	*Not in HAT n = 57*	*Still in HAT n = 74*	
	% or mean (SD)	*% or mean (SD)*	*% or mean (SD)*	*P*[b]
Treatment consumption				
Inhalable heroin	71.5%	78.6%	66.2%	0.17
Days per month visiting treatment unit	24.7 (5.9)	20.8 (6.6)	27.7 (2.8)	<0.001
Visits per day	1.9 (0.4)	1.7 (0.5)	2.0 (0.4)	<0.01
Heroin dose (mg) per visit	268 (68)	253 (78)	280 (59)	0.02
Heroin dose (mg) per day	502 (191)	445 (206)	546 (168)	<0.01

[a]Of the total sample of 149 patients, two patients never reinstated heroin-assisted treatment and for 16 patients accurate medication data are lacking.
[b]Reported *P*-values based on Fisher's exact test (dichotomous variables) and non-parametric Kruskal–Wallis test (interval variables). SD: standard deviation.

Table 3 Reasons for discontinuation of long-term heroin-assisted treatment (HAT) and 4-year follow-up status ($n = 66$).

		Treatment status for patients not in HAT at t4	
	Patients not in HAT at t4	*In treatment*	*Not in treatment*
Reasons for treatment discontinuation	*n (%)*	*n (%)*	*n (%)*
Insufficient response	14 (21.2)	14/14 (100)	0/14 (0)
Deterioration	6 (9.1)	3/6 (50.0)	3/6 (50.0)
Violating house-rules	15 (22.7)	14/15 (93.3)	1/15 (6.7)
Incarceration	3 (4.6)	3/3 (100)	0/3 (0)
Other reasons initiated by treatment centre	13 (19.7)	10/13 (76.9)	3/13 (23.1)
Abstinence	7 (10.6)	5/7 (71.4)	2/7 (28.6)
Other reasons initiated by patient	8 (12.1)	7/8 (85.5)	1/8 (12.5)
Total	66 (100)	56/66 (84.8)	10/66 (15.2)

Table 4 Four-year response among patients eligible for long-term heroin-assisted treatment (HAT) ($n = 149$).

		4-year heroin-assisted treatment status		
Missing data handling	*All patients n = 149*	*Not in HAT at t4 n = 66*	*Still in HAT at t4 n = 83*	*OR (95% CI)*[a]*; P-level*
Missing = non-response	59.7%	21.2%	90.4%	48.4 (17.6–159.1); $P < 0.0001$
First LOCF, then missing = non-response	67.8%	37.9%	91.6%	25.0 (9.6–75.4); $P < 0.0001$
Missing = worst-case	79.2%	65.2%	90.4%	6.0 (2.4–16.3.); $P = 0.0002$

[a]Odds ratios (ORs) are adjusted for treatment centre and heroin administration protocol (inhalable versus injectable heroin). LOCF: last observation carried forward; CI: confidence interval.

administration route, the 69.2% difference in response between patients who continued and patients who discontinued long-term HAT corresponded with an odds ratio (OR) of 48.4 (95% CI: 17.6–159.1).

In secondary analyses, missing end-point assessments were imputed by means of an LOCF procedure and a worst-case scenario. In the LOCF procedure the response among patients who continued and who terminated long-term HAT was 91.6% and 37.9%, respectively. Controlling for treatment site and administration route, the response difference of 53.7% corresponded with an OR of 25.0 (95% CI: 9.6–75.4). Even in the unrealistic worst-case

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Table 5 Course of treatment outcome on primary outcome parameters, indicating 'absence of problems', among patients in long-term heroin-assisted treatment (HAT) for 4 years ($n = 83$).

	Baseline	*HAT year 1*	*HAT year 2*	*HAT year 3*	*HAT year 4*	*Linear-modelled time effect*[a]
	t0	*t1*	*t2*	*t3*	*t4*	*t1–t4*
Absence physical health problems (MAP-HSS < 8)	30.1%	77.1%	86.8%	78.3%	81.5%	1.06 (0.87; 1.30) p|z| = 0.56
Absence psychiatric health problems [SCL-90 < 41 (males) or <60 (females)]	42.2%	77.1%	85.5%	81.9%	87.7%	1.18 (0.95; 1.46) p|z| = 0.13
Illegal activities < 6 days/month	37.4%	96.4%	97.6%	97.6%	100%	1.75 (0.95; 3.21) p|z| = 0.07
Days without personal contact non-drug using individuals < 25 (month) (%)	62.7%	88.0%	94.0%	92.8%	92.6%	1.24 (0.87; 1.77) p|z| = 0.24
No illicit heroin use	0%	57.8%	79.5%	86.8%	86.4%	1.67 (1.31; 2.14) p|z| < 0.0001
No alcohol (≥5 glasses) use	63.9%	71.1%	83.1%	79.5%	77.8%	1.09 (0.92; 1.30) p|z| = 0.32
No cocaine use	21.7%	27.7%	37.4%	43.4%	53.1%	1.40 (1.23; 1.60) p|z| < 0.0001
No amphetamine use	92.8%	96.4%	97.6%	97.6%	97.5%	1.20 (0.67; 2.08) p|z| = 0.53
Health 'recovery'	0%	59.0%	75.9%	65.1%	70.4%	1.09 (0.91; 1.32) p|z| = 0.35
Complete 'recovery'	0%	12.1%	22.9%	24.1%	24.7%	1.24 (1.04; 1.48) p|z| = 0.02

[a]Odds ratios (ORs) [95% confidence interval (CI)] and *P*-values are based on a linear-interval time model, in a longitudinal logistic regression analysis (GEE). MAP-HSS: Health Symptoms Scale of the Maudsley Addiction Profile; SCL-90: Symptom Checklist 90.

scenario, the 25.2% response difference between patients who continued and patients who discontinued long-term HAT was still significant (OR = 6.0; 95% CI: 2.4–16.3).

Course of long-term HAT in terms of health and substance use

Table 5 displays the percentage of patients who met criteria for 'absence of problems' over the 4-year period. For instance, 30.1% of the patients were enrolled in the heroin trials without physical health problems (indicated by a MAP-HSS total-score < 8 at t0). At the end of the RCT (t1), the percentage of patients without physical health problems had increased to 77.1%. During long-term HAT this percentage remained stable, with 81.5% after 4 years of HAT. Although some ongoing improvements can be seen from the first to the fourth years of HAT for the physical, mental and social health outcome criteria, due to the large effect at t1 and the fluctuations over the following years of HAT none of the linear-modelled time effect estimates was significant (MAP-HSS: OR = 1.06; $P = 0.56$; SCL-90: OR = 1.18; $P = 0.13$; illegal activities: OR = 1.75; $P = 0.07$; personal contacts: OR = 1.24; $P = 0.24$). However, there were significant linear-modelled time effects, indicating further reductions with prolonged HAT, for non-prescribed heroin use (OR = 1.67; $P < 0.001$) and cocaine use (OR = 1.40, $P < 0.001$).

Finally, the proportion of patients no longer meeting any of the physical, mental and social health problem inclusion criteria and also abstaining from illicit drug and excessive alcohol use ('complete recovery') increased significantly over the years, from 12.1% at t1 to 24.7% at t4 (linear-modelled time effect estimate: OR = 1.24, $P = 0.02$).

DISCUSSION

The present observational cohort study showed that 56% of treatment-resistant heroin addicts, who were eligible for long-term HAT, continued treatment for at least 4 years. This retention rate is comparable with long-term retention in HAT reported in Switzerland [16] and with 2-year retention in Germany [10]. It should be noted, however, that this Dutch cohort of heroin addicts consisted of patients who had responded favourably to HAT during the first year of treatment and who were thus eligible for long-term HAT.

Treatment consumption during long-term HAT, in terms of clinic attendance and prescribed heroin dose

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(1.9 visits per day, 268 mg per visit and 502 mg per day), is comparable with treatment consumption during the first treatment year of the Dutch heroin trials (2.1 visits per day, 260 mg per visit and 548 mg per day) [4]. The prescribed daily heroin dose is somewhat higher than the dose prescribed at the end of the second year of long-term HAT in Germany (420 mg) [10]. This might be explained by the fact that patients who are prescribed inhalable heroin receive a somewhat higher dose than patients who are prescribed injectable heroin, due partly to the difference in bioavailability between injectable and inhalable heroin [17].

In total, 11 non-fatal SAEs were registered. Among patients who continued long-term HAT the SAE rate equals one per 31.1 patient treatment years. Unlike the German data, no respiratory depression or epileptic seizures were reported. This might be due partly to the fact that the majority of patients did not inject the prescribed heroin and that all patients were also prescribed a stable methadone dose.

Reasons to discontinue HAT were diverse, and the majority of discontinuations were related to a lack of continued treatment response or (repeated) violation of the house-rules of the treatment facility (mainly attempts to smuggle prescribed heroin). All patients who discontinued HAT were referred to methadone maintenance treatment, except for 10.6% who opted for abstinence (orientated treatment). None of the baseline patient characteristics and none of the response indicators after the first year of HAT were predictive of 4-year treatment retention.

Patients who continued long-term HAT were much more likely to be responders at 4-year follow-up (90.4–91.6%) than patients who had discontinued HAT (21.2–65.2%) and all ORs were significant, even in the worst-case scenario of handling missing data.

Among patients continuing long-term HAT, the positive changes that were achieved in the first year of HAT stabilized or slightly improved further with the duration of HAT. This is shown most clearly in terms of the increase of the proportion of patients who refrained from non-prescribed heroin use (from 0% at baseline, via 58% after 1 year, to 86% after 4 years of HAT) or cocaine (from 22% at baseline, to 28% after the first year, increasing further to 53% after 4 years of HAT) and in the increase of the proportion of patients who 'completely recovered', i.e. they no longer met any of the original criteria of 'poor functioning' in terms of physical, mental and social health, and they no longer used illegal substances or excessive alcohol (0% at baseline, 12% after 1 year of HAT to 25% after 4 years of HAT).

Similar results were reported for patients in 2-year HAT in Germany: improvement in physical and mental health, as well as reductions in illicit drug use, were already achieved during the first months of treatment [10].

Limitations

Due to the design and protocols of the original Dutch RCTs, long-term HAT was offered only to patients who had responded to this treatment during the first experimental treatment phase and who deteriorated during the 2 months protocolized discontinuation of HAT. Patients who had not responded or did not deteriorate were not eligible for reinstatement of long-term HAT. As a consequence, only 34% of all patients who had started HAT in the two trials were eligible for long-term HAT and the results presented can only be generalized to chronic treatment-resistant heroin addicts who responded favourably in the first year of HAT.

Another possible confounding aspect in comparing response status between patients still in HAT after 4 years and those who discontinued HAT is due to the requirement that treatment staff had to evaluate the medical indication to continue long-term HAT on a year-by-year basis. As a result, the majority of patients who discontinued long-term HAT were 'forced' to do so, primarily because they did not show sufficient response during long-term HAT or because of violating the house-rules. Thus, for some patients who discontinued long-term HAT the non-response status at t4 reflects a lack of sufficient response during HAT, while for other patients their non-response status might be due to their involuntary, forced discontinuation of HAT.

Finally, nearly half the patients who discontinued long-term HAT were not reached or refused to cooperate in the 4-year follow-up assessment. The outcome status of these patients could not be determined. However, even in the unlikely 'worst-case' scenario, where all non-reached patients who discontinued HAT were considered to be responders, 4-year outcome status of patients who continued long-term HAT was still significantly better.

Therefore, we are fairly confident that the current study has shown that among chronic, treatment-resistant heroin addicts continued long-term HAT has a much better outcome than discontinuation of long-term HAT.

CONCLUSION

Chronic, treatment-resistant heroin addicts who respond to HAT after 1 year and who continue long-term HAT for a period of at least 4 years (56%) have a much higher chance to be in good health than patients who discontinue long-term HAT (90.4–91.6% versus 21.2–65.2% response). In addition, the proportion of patients who continue long-term HAT and become free of health problems and abstain from illicit drug and excessive alcohol use increases significantly from 12% after 1 year to 25% after 4 years of HAT.

The implication of this is that heroin co-prescription should be continued as long as possible for treatment-

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resistant, heroin-addicted patients, unless there is a compelling medical or social contraindication.

It should also be noted that there remains a group of chronic, treatment-resistant heroin addicts who neither respond to methadone maintenance treatment nor to HAT or who discontinue long-term HAT. For these patients, other potentially effective pharmacotherapeutic treatments [2,18], innovative psychosocial interventions such as contingency management [19,20] and experimental treatments such as deep brain stimulation [21] or supervised user rooms [22] should be investigated in order to assess whether these interventions are potentially effective to stabilize or reduce illicit drug use and to prevent further harm and health deterioration. In a current RCT in the Netherlands, the efficacy of contingency management as an 'add-on' intervention to heroin-assisted treatment to reduce concomitant cocaine use is evaluated in terms of changes in cocaine use, as well as in terms of retention in HAT and treatment response.

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Declarations of interest

None.

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