

# Matching of treatment-resistant heroin-dependent patients to medical prescription of heroin or oral methadone treatment: results from two randomized controlled trials

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## ABSTRACT

**Aims** To investigate which baseline patient characteristics of treatment-resistant heroin addicts differentially predicted treatment response to medical heroin prescription compared to standard methadone maintenance treatment.

**Design** Two open-label randomized controlled trials; pooled data.

**Setting** Methadone maintenance programmes and heroin treatment centres in six cities in the Netherlands.

**Participants** Four hundred and thirty heroin addicts.

**Intervention** Methadone plus injectable heroin or methadone plus inhalable heroin compared to methadone alone prescribed over 12 months: heroin maximum 1000 mg per day, methadone maximum 150 mg per day.

**Main outcome measure** Dichotomous, multi-domain response index, including validated indicators of physical health, mental status and social functioning.

**Findings** Data of the inhalable and injectable heroin trials were pooled. Intention-to-treat analysis showed that treatment with medically prescribed heroin plus methadone was significantly more effective (51.8% response) than standard methadone maintenance treatment (28.7%) (95% CI of response difference: 14.1–32.2%). Multivariate logistic regression analyses showed that only one of all baseline characteristics was predictive of a differential treatment effect: patients who had previously participated in abstinence-orientated treatment responded significantly better to heroin-assisted treatment than to methadone treatment (61% versus 24%), while patients without experience in abstinence-orientated treatment did equally well in heroin-assisted or methadone maintenance treatment (39% and 38%, respectively).

**Conclusions** The effect of heroin-assisted treatment is not dependent on clinical characteristics, with the exception of previous abstinence-orientated treatment: medical prescription of heroin is most effective for those patients who have previously participated in abstinence-orientated treatment.

**KEYWORDS** Heroin-assisted treatment, opiate dependence, patient-treatment-matching, pharmacotherapy, RCT.

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## INTRODUCTION

The medical co-prescription of heroin to chronic, treatment-resistant heroin-dependent patients has shown to

be effective in randomized controlled trials [1,2] and in one large-scale naturalistic study [3]. Supervised heroin-assisted treatment resulted in a sharp decline of illegal heroin use, as well as in a significant improvement in

physical and mental health and social functioning, including a substantial reduction in illegal activities. These studies also indicate that not all patients benefit from this last-resort pharmacological intervention, that is offered to treatment-resistant heroin-dependent patients after other treatments, including first-choice methadone maintenance treatment, have not succeeded in stabilizing patients at an acceptable level of functioning. In the Dutch trial, 48% of the patients treated with inhalable heroin and 57% of the patients treated with injectable heroin responded to this treatment (compared to 25% and 32% of the patients in the methadone control condition) [2].

Supervised medical prescription of heroin is a costly treatment: approximately €15 000 per patient per year [4]. The majority of the costs is due to personnel costs, including physicians, nurses and security staff (68%), while the costs of the prescribed heroin amounts to 12%. More important, however, is that recent studies have indicated that supervised heroin-assisted treatment is cost-effective. The relatively high treatment costs are counterbalanced by reductions of other costs, including reduced health-care consumption, reduced costs of the judicial system and a reduction in societal costs as a result from a sharp decrease of illegal activities. The total benefit per patient per year is estimated to be between €5000 and €10 000 [5,6]. Cost effectiveness of heroin prescription treatment can be increased by giving precedence to heroin addicts who are most likely to respond to this treatment.

In the current paper we therefore investigate which patient characteristics in the Dutch heroin prescription trials are predictive of a differential response to either methadone or methadone plus heroin treatment. In order to investigate this question, patients from both the experimental (methadone plus heroin) and control (methadone only) condition are included in the analysis, using significant treatment condition by patient characteristic interactions as the main indicator for significant patient-treatment-matching effect.

## METHODS

### Design

Two randomized controlled trials were conducted from July 1998 to December 2001 in six cities in the Netherlands. In one trial the effectiveness of 12 months prescription of injectable heroin plus oral methadone was compared to standard oral methadone alone. In the other, parallel trial, inhalable heroin was prescribed in combination with methadone and compared to standard oral methadone treatment for 12 months. [In the inhalable heroin trial a second comparison group was treated

with oral methadone for 6 months, followed by 6 months treatment with methadone plus heroin. This group was excluded from the analyses in this paper]. After 12 months, the primary end-point of the trial, co-prescription of heroin, was discontinued and replaced by an increased methadone dose. Randomization was carried out separately for the two trials and for each city by an independent clinical research organization, stratified by gender and ethnicity. An extensive description of the procedures can be found in the original publications [2,4].

### Assessments

Every 2 months, patients were screened medically and interviewed by independent research assistants using the European Addiction Severity Index (EuropASI) [7], the Health Symptoms Scale of the Maudsley Addiction Profile (MAP-HSS) [8] and the Symptom Checklist-90 items (SCL-90) [9]. At baseline and after 12 months, psychiatric diagnoses were assessed by means of the Composite International Diagnostic Interview (CIDI) [10]. Self-reported substance use data and criminal charges were validated against urinalysis and police registers, respectively, and showed good agreement [2,4].

### Participants

Included participants were at least 25 years old, met diagnostic criteria for heroin dependence during the past 5 years (DSM-IV) [11] and had regularly attended methadone maintenance programmes during the previous 6 months. All patients had been prescribed a methadone dosage of at least 50 mg (inhalable heroin trial) or 60 mg (injecting trial) for a consecutive period of at least 4 weeks in the past 5 years; used illicit heroin (nearly) daily; and functioned poorly on at least one of the following domains: physical health (MAP-HSS score  $\geq 8$ ), mental health (SCL-90 score  $\geq 41$  for men and  $\geq 60$  for women) and social functioning (involvement in criminal activities for at least 6 days during the past month and/or at least 6 days without personal contact of at least 30 min with a non-drug-using person).

### Treatments

Patients in the control groups continued to participate in their methadone maintenance programme of origin to receive standard methadone maintenance treatment. Patients in the experimental groups were referred to newly established heroin treatment units and were offered the prescription of heroin for 7 days per week and three times per day. A maximum methadone dosage of 150 mg was prescribed daily and the maximum

prescribed heroin dosage, either injectable or inhalable, was 400 mg per visit and 1.000 mg per day. Either an aqueous solution of heroin-hydrochloride had to be injected or a 3 : 1 mixture of heroin-base and caffeine (added to increase bioavailability [12]) had to be inhaled under supervision. Both treatment conditions offered comparable, standard psychosocial interventions.

### Outcome measure

A pre-specified dichotomous, multi-domain outcome index was used as primary outcome parameter. Treatment response was defined as:

- a health improvement of at least 40% at the end of the 12 months treatment compared to baseline in at least one of the domains of inclusion (i.e. physical, mental or social health);
- no serious deterioration ( $\geq 40\%$ ) in any of the other outcome domains; and
- no substantial increase ( $>6$  days) in cocaine or amphetamine use.

### Statistical analysis

Because both trials indicated very similar effectiveness for injectable and inhalable heroin [2], data were pooled in order to achieve optimal power. All analyses were conducted on the intention-to-treat sample, i.e. incorporating all patients who were notified about the result of randomization. The total number of patients in the 12-month heroin condition was 193 (injecting: 76; inhaling: 117) and 237 in the 12-month methadone condition (injecting: 98; inhaling: 139).

Missing end-point assessments (3.6% in the heroin condition; 8.9% in the methadone condition) were estimated with a multiple imputation procedure (Solias, version 3.2), based on baseline, month 6 and month 10 data, using the predictive model option with five imputed data sets. A patient with a missing end-point assessment was considered to be a responder when the multiple imputation program considered him/her a responder in at least three of the five imputed data sets.

The patient-treatment-matching question was answered using a two-step procedure suggested by Hosmer & Lemeshow [13]. In the first step, bivariate logistic regression analyses were performed for each patient characteristic separately to determine which patient characteristics modified the effect of treatment condition on outcome or response. Depending on their prevalence and distribution, interval patient characteristics were dichotomized as either absent/present (e.g. number of drug overdoses) or below/above median (e.g. years regular heroin use). In addition, recent drug use patterns were dichotomized into (nearly) daily use versus no or

irregular use. Dichotomizing of the interval variables did not effect the direction or strengths of the relationship between patient-treatment interaction terms and response. In the second step, all patient characteristics that interacted with treatment condition (using a lenient  $P$ -value threshold;  $P < 0.25$ ) as well as all variables of clinical importance were entered in a multivariable backward logistic regression model to identify a profile of patients likely to benefit more from medical prescription of heroin than from standard methadone maintenance treatment.

## RESULTS

### Patient characteristics

Table 1 shows the background variables, health indicators and drug use characteristics of the patients at baseline. Patients in the experimental (heroin plus methadone) and control group (methadone alone) did not differ significantly on any of the variables. Patient recruitment had been successful in terms of reaching chronic, treatment-resistant heroin addicts. On average, patients were almost 40 years of age and had a long-term history of heroin, methadone and cocaine use (average 16, 12 and 9 years, respectively). In addition to heroin and methadone, 62% of the patients used cocaine and 43% used benzodiazepines (nearly) daily. Patients were included in the trial because of poor functioning in the physical (66%), mental (60%) or social (73%) domain and two-thirds of the patients functioned poorly in two or more domains. The average methadone dosage patients were prescribed at the time they entered the trial equalled 66 mg.

### Treatment effectiveness

Treatment response was significantly higher in the 12 months methadone plus heroin condition (51.8%; 95% CI: 44.7–58.9%) compared to the 12 months methadone alone condition (28.7%; 95% CI: 22.9–34.5%;  $P = 0.0001$ ).

### Patient-treatment-matching

In Table 2 the results of the bivariate logistic regression analyses are presented for only those patient baseline characteristics that met the criteria for entering into the backward multiple logistic regression analysis ( $P < 0.25$ ). The percentage response is displayed for each predictor variable, broken down by the heroin and methadone treatment group. There is a significant interaction effect of treatment condition, with only one of the 44 baseline patient characteristics displayed in Table 1. Heroin-addicted patients with a history of abstinence-orientated

**Table 1** Patient characteristics at baseline (*n* = 430).

	<i>% or mean</i>	<i>SD/median</i>
<b>Background</b>		
Gender (% male)	80.2%	–
Age (years)	39.3	5.7/39
Ethnicity (% Dutch/Western-European ethnicity)	87.2%	–
Education level (% middle/high education level)	26.3%	–
<b>Inclusion profiles</b>		
Physical health problems (%)	65.8%	–
Psychiatric health problems (%)	60.0%	–
Social functioning (%)	73.3%	–
<b>Physical health</b>		
MAP-HSS sumscore (range: 0–40)	11.3	7.3/11
Life-time number of hospitalizations	3.8	7.5/2
Prescribed somatic medication (%)	23.7%	–
Additional need for somatic treatment (range: 0–4)	1.1	1.6/0
<b>Psychiatric health</b>		
SCL-90 sumscore (range: 0–360)	71.5	59.9/56
Life-time number residential treatments	0.4	2.2/0
Ever attempted suicide (%)	28.0%	–
Prescribed psychiatric medication (%)	33.8%	–
Any current DSM-IV (non-substance) Axis I diagnosis (%)	30.0%	–
Additional need for psychiatric treatment (range: 0–4)	1.0	1.5/0
<b>Social functioning</b>		
Living arrangement (% living alone)	60.4%	–
Housing arrangement (% stable housing situation)	90.2%	–
Employment major income source (%)	6.8%	–
Amount of debts (in thousand €)	4.3	7.9/1.4
Number of property crime charges	24.4	31.4/10
Months ever incarcerated	26.1	30.1/14
Days illegal activities past month	11.6	11.4/10
Days contacts with non-drug-using people	14.8	12.9/14
<b>Substance use</b>		
Life-time years regular substance use		
Heroin	16.4	5.8/16
Methadone	12.4	6.3/13
Alcohol (>5 glasses)	6.4	8.2/3
Benzodiazepines	6.1	7.5/2
Cocaine	9.1	6.6/9
Amphetamines	2.1	5.2/0
Polydrug use	17.4	6.6/17
Days substance use past month		
Heroin	25.8	6.5/30
Methadone	28.9	3.9/30
Alcohol (>5 glasses)	7.2	11.5/0
Benzodiazepines	12.5	13.0/6
Cocaine	15.9	11.4/15
Amphetamines	0.5	3.2/0
Polydrug use	28.8	3.8/30
Number of drug overdoses	1.7	5.3/0
Money spent on drugs (in €)	929	784/681
Any abstinence-orientated treatment (%)	61.0%	–
Additional need for substance use treatment (range: 0–4)	2.2	1.7/3
Methadone dose at start (in mg)	65.8	21.8/65

**Table 2** Patient characteristic predicting treatment response in the experimental heroin group and in the control methadone group and the statistical significance of patient-by-treatment interaction effects on response.\*

Patient characteristics	n	% response		Interaction effect in total group P-value
		heroin group (n = 193)	methadone group (n = 237)	
Education				
Low	148	45.3	25.6	0.16
Medium/high	45	73.3	36.8	
Ever hospitalized for physical problems				
No	29	55.2	18.8	0.21
Yes	164	51.2	30.2	
Prescribed medication for psychiatric problems				
No	128	55.5	28.2	0.21
Yes	64	43.8	29.6	
Living arrangement				
Alone	118	55.1	26.4	0.12
With others or otherwise	63	44.4	31.3	
Major source of income				
Employment	12	66.7	17.7	0.15
Other	178	51.1	29.6	
Current cocaine use				
None/irregular	72	50.0	23.3	0.21
(Near) daily	121	52.9	32.0	
Any abstinence-orientated treatment				
No	79	39.2	37.5	0.0003
Yes	114	60.5	23.8	
Inclusion physical health				
No	64	51.6	19.3	0.10
Yes	129	51.9	33.8	
Inclusion psychiatric status				
No	82	50.0	31.1	0.45
Yes	111	53.2	27.2	
Inclusion social aspect				
No	47	44.7	23.5	0.98
Yes	146	54.1	30.5	

\*Patient-by-treatment interaction effects on treatment response were tested for all patient characteristics displayed in Table 1. In this table, only patient-by-treatment interactions eligible for entering in the backward multiple logistic regression analysis ( $P < 0.25$ ) are shown.

treatment have a much higher response in heroin treatment compared to methadone treatment (60.5% versus 23.8%, respectively), while patients without a history of abstinence-orientated treatment do equally well in heroin-assisted treatment and methadone maintenance treatment (treatment response: 39.2% and 37.5%, respectively) ( $P = 0.0003$ ). (Abstinence-orientated treatment refers to in-patient or out-patient detoxification and/or residential or out-patient drug-free treatment, based on items from the European Addiction Severity Index [7].)

In a multiple logistic regression analysis, all patient characteristics that interacted with treatment condition at  $P < 0.25$  plus three clinically relevant treatment-by-

inclusion domain interactions (i.e. physical health, psychiatric status and social functioning; see Table 2) were entered into a backward model. The only patient characteristic-by-treatment interaction that remained in the model was whether or not patients had ever been in abstinence-orientated treatment; all other patient characteristic-by-treatment interactions were removed from the model (at  $P < 0.05$ ).

## DISCUSSION

In this paper we investigated whether certain patients do better in heroin-assisted treatment than in standard

methadone maintenance treatment (patient-treatment-matching) using data from the Dutch heroin trials [2]. It was shown that treatment-resistant heroin addicts who had participated previously in abstinence-orientated treatment responded more favourably to co-prescribed heroin treatment (61% response) than to methadone maintenance treatment (24% response), while at the same time patients without previous experience in abstinence-orientated treatment responded in a similar way to heroin or methadone treatment (39% and 38%, respectively).

In order to better understand the meaning of this finding, we explored the differences between patients with and without a history of abstinence-orientated treatments. However, no clear-cut differences between these groups were observed. A possible (*post-hoc*) explanation for this modifying effect of previous participation in abstinence-orientated treatment could be that patients with a history of (repeated) abstinence-orientated treatments have learnt to comply better with a rather strict treatment regimen or that they are better motivated to take part in demanding interventions.

Prior to the start of the Dutch heroin trials it was debated whether prescribing heroin might result in an increased use of (crack-)cocaine, as patients no longer have to spend money on illicit heroin. Given these worries, it should be noted that current and past (crack-)cocaine use was not associated with treatment response. Moreover, response in heroin-assisted treatment was associated with moderate reductions in cocaine use [2]. Therefore, it seems that cocaine-using heroin-dependent patients should not be excluded from participation in heroin-assisted treatments.

It is striking that of the many patient characteristics that were studied only one variable moderated the response to heroin-assisted treatment compared with standard methadone treatment. Neither severity of dependence nor psychiatric severity had a moderating treatment effect, as had been reported in other studies [14,15]. Recently, however, two large randomized trials designed especially to study patient-treatment-matching prospectively reported similar results. Contrary to what was expected, no patient-treatment-matching characteristics could be identified that were strong moderators of response to different interventions among alcohol [16,17] and cocaine-dependent patients [18].

As long as medical prescription of heroin is considered to be a last-resort pharmaceutical treatment intervention, restricted to heroin addicts who have not benefited sufficiently from available addiction treatment, the criteria for defining treatment-resistant heroin addiction should be explored and elaborated continuously. Given the high response to heroin treatment

(61%) among treatment-resistant heroin addicts who had participated previously in abstinence-orientated treatment without stable, lasting effects, previous participation in abstinence-orientated treatment should be considered as an important additional element in defining treatment-resistance. On the other hand, our *post-hoc* explanation stated that previous participation in abstinence-orientated treatment might indicate a higher motivation to comply with and benefit from heroin-assisted treatment. If this is valid, then heroin treatment programmes should pay specific attention to this subgroup of heroin-dependent patients and offer additional interventions, such as motivational interviewing [19], addressing patient's ambivalence with regard to their treatment and substance use. Although this kind of differential, patient-tailored treatment approach was not possible during our randomized controlled trials (RCTs), in the present situation it is a challenge to improve heroin-assisted treatment in such a way that all eligible patients may have equal chances to benefit from and respond to this last-resort pharmacological intervention.

### Limitations

Some of the limitations of the Dutch heroin trials (open-label design, self-reported outcome data, different treatment centres for heroin and methadone dispensing) have already been discussed [2,4]. The trials were designed in order to study the difference in effects of heroin versus methadone treatment and as such the statistical power to detect patient characteristics that are associated with treatment outcome is limited. However, given the very similar effects in the inhalable and the injectable trials, we were able to pool the data of both trials resulting in adequate statistical power for the test of both main and interaction effects of baseline characteristics on treatment response. In addition, it should be noted that the effect of previous abstinence-orientated treatment was found separately in both the inhalable trial and the injectable trial.

### CONCLUSION

The current study indicates that among chronic treatment-resistant heroin addicts, those who have previously participated in abstinence-orientated treatment are most likely to benefit from medical co-prescription of heroin. Given this finding, it becomes all the more interesting to learn more about the efficacy of heroin-assisted treatment for heroin addicts who are not in contact with the treatment system, as is currently studied in a large RCT in Germany [20,21].

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