Efficacy of heroin-assisted treatment in Belgium: a randomised controlled trial

Abstract

Background/Aims: Heroin-assisted treatment (HAT) can improve the condition of heroin addicts still using street heroin after a methadone treatment. In Belgium, a new trial compared the efficacy of a HAT to existing methadone maintenance treatment. **Methods**: In this randomised controlled trial, HAT was limited to 12 months. Participants were assessed every 3 months. They were responders if they showed improvement on the level of street heroin use, health or criminal involvement. **Results**: 74 participants were randomised in the trial. The experimental group (n=36) counted 30% of responders more than the control group (n=38) at each assessment point (p<0.05), except at 12 months where the difference (11%) was no longer significant (p=0.35). Still, after 12 months, participants in the experimental group reported significantly greater improvements (p<0.05) than the control group on the level of street heroin use and on the level of physical and mental health. Both groups reported significantly less criminal facts after 12 months (p<0.001), but with no significant difference between the groups. **Conclusions**: This trial confirms the short-term efficacy of HAT for severe heroin addicts, who already failed methadone treatment.

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Introduction

As other European countries, Belgium is confronted with a large number of heroin addicts. In this country, methadone maintenance treatment (MMT), the most recommended response to heroin addiction [1, 2], is generally available and is reimbursed by social insurance. General practitioners can prescribe methadone in private practice or in health institutions but the organisation of this treatment is not centralised and can differ between regions. At the national level, 15000 heroin addicts were on MMT in 2012 [3]. In Liège, heroin addiction is especially problematic: in this urban area of 500,000 inhabitants, 3,000 people were heroin addicts in 2007 [4]. As a reaction, MMT is largely available from general practitioners, addiction specialised centres, medical and mental health services. The availability of MMT is enhanced by the liberty for patients to choose their treatment centre and/or physician.

However, as in other regions [5, 6], a fraction of heroin users pursues their street heroin use. For these severe heroin addicts, heroin-assisted treatment (HAT) showed greater efficacy than MMT [7]. In HAT, patients receive medically prescribed diacetylmorphine (DAM) in an ambulatory setting. DAM is self-administered under the supervision of nurses up to 3 times a day [7-9]. This model of treatment was developed in Switzerland in the nineties [10-12]. After this experience, five randomised controlled trials [5, 6, 13-15], based on the same treatment model, concluded that HAT was more effective for severe heroin addicts than MMT.

Therefore, the Belgian government decided to start the TADAM (Treatment-Assisted by DAM) trial. Unlike in other European studies, the duration of HAT was strictly limited to 12 months for legal and political reasons. In this paper, we assessed the efficacy of HAT in a controlled and supervised setting compared to a liberal system of MMT.

Methods

Design

TADAM was an open label, randomised controlled trial, which began in January 2011 and ended in January 2013. We planned to recruit and to randomise 200 participants in two groups: an experimental group treated with DAM and a control group with MMT. The Ethics Committee of the University of Liège approved this trial (number 2009/189) on March 16, 2010. It was registered in the European database of all clinical trials with the EudraCT number 2010-019026-13. The National Federal Agency for Medicines and Health Products gave its approval on May 7, 2010.

Participants

Inclusion criteria comprised heroin dependency for at least 5 years; (almost) daily use of street heroin; at least one previous experience of MMT (with a minimum daily dose of 60 mg); heroin use through injection or inhalation; a poor (physical or mental) health or criminal involvement. Moreover, participants had to be at least 20 years old and legal residents in the judicial district of Liège for at least 12 months. Before being randomised, each participant signed the informed consent form approved by the Ethics committee.

Treatments

The experimental group received DAM for 12 months in a new setting (the HAT centre), located in the middle of the city. DAM was self-administered up to three times a day (between 7:30 AM and 18:30 PM), seven days a week. Dosages were individually titrated with a maximum of 400 mg per dose and 1000 mg per day. Changes in the dosage were individually discussed between the participant and a physician of the HAT centre. Nurses closely supervised self-administration in the centre. Our protocol did not permit take-away.

To prevent craving during the night, the physicians of the HAT centre encouraged participants to take an additional dose of oral methadone (prescribed in the centre and delivered in pharmacies). After 12 months, HAT was stopped and the best available treatment was offered to each participant. The treating staff of the HAT centre reported significant adverse events in the patient record form.

Each participant could choose at baseline between injecting and inhaling DAM. This choice was offered because, in Belgium, drug users used heroin through inhalation more often than through injection [16]. Besides, the Dutch trial showed that inhalable DAM was as effective as injectable DAM [6]. In our trial, DAM originated from The Netherlands, the only European country where inhalable DAM was registered for HAT [17]. We did not use oral DAM because there was no evidence that it was more effective than MMT, even if its feasibility has been demonstrated [18-20].

Participants in the control group received MMT in the partner centres involved in the trial. Methadone was prescribed by a physician in these centres and delivered in a pharmacy. These centres also provided psychosocial services to both groups.

Recruitment process

To find partner centres, the researchers contacted 31 multidisciplinary centres in the judicial district before the start of the trial. After examination, the research team signed an agreement with 9 centres (5 addiction specialised centres, 2 mental health services and 2 primary health care centres), which had at least one physician specialised in MMT. Heroin users interested in the project first had to be registered in a partner centre and could then be referred to the research team by the centre. To enhance the recruitment process, researchers sent letters to 1600 physicians and visited 26 other institutions (social, health or addiction settings), offering folders and posters. The media also spread information on the trial.

Street heroin use was measured by the number of days of use during the previous month on the Drug/Alcohol section of the European Addiction Severity Index (EuropASI) [21]; a poor physical health was defined by a score of 8 on the Maudlsey Addiction Profile – Health Symptoms Scale (MAP-HSS) [22] and a poor mental health by a score of at least 41 (for men) or at least 60 (for women) on the total score of the Symptom Check-List (SCL–90–R) [23, 24]. Criminal involvement was characterised by at least 6 self-reported facts committed or experienced as a victim, during the previous month, according to 18 questions on criminal facts and victimisation [25].

The research team was independent from the treating staff and assessed the participants every 3 months with the Drug/Alcohol section of the EuropASI, the MAP-HSS, the SCL-90-R and the 18 questions on the criminal facts that were committed and experienced. Each participant also had to provide a urine sample for toxicological analyses. In addition, at baseline, at 6 and 12 months, a medical examination was performed by the physician of the research team. The researchers assessed participants at the policlinic of the Liège University Hospital, except, after baseline, for participants remaining in the experimental treatment who were interviewed in the HAT centre. When necessary, participants were assessed in prison or in a residential treatment centre. At each assessment, participants who were in the control group and participants who stopped HAT received between 15 and 60 euro (depending on the presence of medical examination, blood and urine sample). The 12-month assessment was planned a month before to ensure that participants were assessed during the study period.

Primary outcome

Our primary outcome criterion was a dichotomous, multidomain index, based on three domains: street heroin use (days of use during the previous month on the EuropASI

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Drug/Alcohol section), health (scores on the MAP-HSS and the SCL-90-R) or criminal involvement (number of self-reported facts that were committed or experienced as a victim during the previous month). A participant was considered as a responder if he showed improvement in at least one domain and no deterioration in any domain. For each participant, improvement or deterioration was indicated by a difference of 40% between data at baseline and at 12 months. Deterioration was also recorded if a participant used 20% more cocaine than at baseline, i.e. *if (days of use at 12 months/days of use at baseline) – 1 ≥ 20%*. With α=0.05, we calculated that 200 participants were needed for a 80% statistical power and for a difference of at least 20% between the percentage of responders in each group.

Validation of self-reported data

For each participant, we compared self-reported drug use (during the previous month) to the toxicological urinalysis. Participants gave a urine sample the day they completed the EuropASI. In this sample, the detection of meconin indicated street heroin use. Meconin is a metabolite of noscapine, an opium constituent that is not found in DAM. The presence of benzoylecgonine, a metabolite of cocaine in the sample, revealed cocaine use. We performed laboratory urinalysis with ultra-high-pressure liquid chromatography coupled with mass spectrometry. If the urinalysis detected street heroin (or cocaine) in the sample of a participant and if this participant reported no use of street heroin (or cocaine) at the same assessment, we did not use this self-reported value. Instead when analysing the primary outcome, we replaced this self-reported value by "≥1", which was considered as 40% higher than no day of use and equal to any positive value.

For each participant, we also compared criminal proceedings recorded by the public prosecutor's department to self-reported criminal facts. If more facts were prosecuted than self-reported during the previous month, we registered the number of prosecuted facts.

Randomisation and masking

Before the recruitment, two researchers prepared two sets of opaque and sealed envelopes. These two sets were sorted in random permuted blocks of 4 and 6 envelopes [26, 27]. Nine boxes (each with the name of a partner centre) were prepared with a certain amount of blocks (according to the number of possible participants in each centre). The research physician who randomised the participants did not assist to this preparation. The final decision to enrol a participant was taken by the research coordinator after discussion with the research team. Directly after randomisation, the research physician made two appointments by phone for the participant: one with a physician for the allocated treatment (in the HAT centre or in the partner centre) and one for psychosocial counselling (in the partner centre).

Statistical analysis

Each randomised participant was included in our intention-to-treat analysis. The efficacy outcome was based on the difference of percentage of responders between the groups. If data were missing at 12 and at 9 months for a participant, he was considered as non-responder. Significance of primary outcome and retention rates were analysed using Fisher's exact tests for 2 x 2 contingency tables. Mixed-design analyses of variance (ANOVA), with the experimental group (two levels) as a between-subject factor and time post-inclusion (five levels: baseline, 3, 6, 9 and 12 months post-inclusion) as a within-subject factor, were used for secondary analyses of continuous data. The ANOVAs were followed by Newman-Keuls post-hoc comparisons to assess between-group differences. Statistical significance was set at $p<0.05$. Statistical analyses were performed with STATISTICA 10.

Results

Inclusion process and participants' characteristics

Between January 12, 2011 and January 16, 2012, 74 participants were included and randomised (Figure 1). No significant differences were found between the groups (Table 1). The partner centres referred 116 participants willing to participate but 33 participants (28%) did not show up to meet the research team and 9 (8%) did not meet the inclusion criteria.

Follow-up

70 participants (95%; 35 in each group) were assessed at the 12-month assessment, which was realised on average 335 days after baseline. The last participant was interviewed on December 28, 2012. The 4 missing participants at 12 months were also missing at 9 months (3 in the control group refused to continue the study and 1 died in the experimental group). They were included in the intention-to-treat analysis as non-responders. At 3 months, 67 participants were assessed (33 in the experimental group and 34 in the control group); at 6 months, 70 (35 in each group) and, at 9 months, 67 (34 and 33 respectively).

Treatments

On average, participants used a daily dose of 573 (±230) mg DAM and came to the HAT centre 2.3 times a day. At the 360 day of treatment (Figure 2), the 27 completers were receiving a mean dose of 355 (±182) mg DAM. Participants in HAT received an additional daily dose of methadone of 20 (±24) mg. Most of them refused additional methadone at first: at 3 months, 11 were receiving a mean daily dose of 10 (±14) mg and, at 12 months, 18 received 24 (±24) mg. In the control group, participants in partner centres used a mean daily dose of 77 (±21) mg methadone.

Retention rate

At the 12-month assessment, 27 (75%) participants completed the experimental treatment and 13 (34%) participants in the control group were still in MMT in a partner centre (Table 2). This difference was significant (p<0.001) on Fisher's exact test. However, 2 (6%) participants in the experimental group and 16 (42%) in the control group were following an addiction treatment (methadone or abstinence-based) outside of a partner centre. In each group, 1 was abstinent.

Efficacy

In the intention-to-treat analysis, 24 (67%) participants in the experimental group and 21 (55%) in the control group were responders at the 12-month assessment (Table 2). The difference (11%) was not significant (p=0.35). At every other assessment, the percentage of responders in the experimental group was significantly higher (>=30%; p<0.05) than in the control group. In fact, the number of responders decreased at the 12-month assessment in the experimental group while it continued to rise in the control group. In the per protocol analysis, there were 19 (70%) responders in the experimental group and 8 (62%) in the control group. The difference was not significant (p=0.72). In a second per protocol analysis including participants following a treatment for heroin addiction or abstinent, the difference was also not significant (p=0.79).

Evolution of the efficacy indicators

Street heroin use during the previous month decreased significantly more in the experimental group than in the control group. The mixed-design ANOVA indicated a significant main effect of group (experimental vs. control group) [$F(1.62)=36.87$; $p<0.001$], a significant main effect of time post-inclusion [$F(4.248)=49.93$; $p<0.001$], as well as a significant interaction between these factors [$F(4.248)=4.74$; $p=0.0011$]. Newman-Keuls Post-hoc tests showed

significant differences between the two groups at each assessment (Figure 3), except at baseline. Street heroin use was higher at 12 months than at 9 months in the experimental group but the rise was not significant (Newman-Keuls post-hoc test; p=0.40). For cocaine use, there was no significant main effect of either the group [F(1.62)=1.17; p=0.28] or time post-inclusion [F(4.248)=1.85; p=0.12] and no significant interaction [F(4.248)=0.46; p=0.77]. On the MAP-HSS score, there was a significant main effect of time post-inclusion [F(4.248)=9.10; p<0.001] and a significant interaction [F(4.248)=2.51; p=0.043], whereas the main effect of the group was not statistically significant [F(1.62)=1.82; p=0.18]. On the SCL-90-R score, there was also a significant main effect of time post-inclusion [F(4.248)=18.38; p<0.001] and a significant interaction [F(4.248)=2.63; p=0.035], whereas the main effect of the group was not statistically significant [F(1.62)=2.33; p=0.13]. The two groups significantly reduced their criminal involvement as indicated by a significant main effect of time post-inclusion [F(4.248)=8.96; p<0.001], but no significant main effect of the group was noticed [F(1.62)=1.46; p=0.23] and no significant interaction [F(4.248)=1.56; p=0.19].

Other significant results from exploratory analyses

Participants in the experimental group showed greater improvement with respect to depression and psychoticism dimensions on the SCL-90-R, as indicated by significant interactions group x time post-inclusion [F(4.248)=4.33; p=0.0021] and [F(4.248)=4.48; p=0.0016], respectively. Self-reported use of benzodiazepines in the EuropASI decreased significantly more in the experimental group, as indicated by a significant interaction group x time post-inclusion [F(4.248)=2.92; p=0.022]. However, the medical staff in the experimental centre had a policy of diminishing benzodiazepine use because of the potential interaction with DAM. No other significant difference in drug use was noticed between the groups.

Serious adverse events

5 serious adverse events occurred involving 5 participants in HAT. In 3 cases, a participant arrived at the centre in a severe state of intoxication because of drug use (alcohol, benzodiazepines or unspecified drugs). In another case, a participant had an accident outside the centre, could not walk and was transported to the hospital by ambulance. In the last case, the serious adverse event was followed by death: the participant was hospitalised because of a flu-like condition and respiratory problems; he died 25 days later at the hospital; AIDS was presumed to be the cause of death. No event was related to DAM administration: in each case, the clinical staff called an ambulance before DAM administration.

Discussion

Efficacy primary outcome

HAT was significantly more effective than MMT at each assessment, except at 12 months where its efficacy was still superior but not statistically significant. Still, the experimental group improved significantly more than the control group on the level of street heroin use as in five other trials [5, 12-15] and on the level of physical and mental health as in the Dutch and German trials [6, 14]. The experimental group also reported less criminal facts and less contact with drug users after 12 months than the control group (data not shown). However, the difference between treatment groups was not significant, unlike in other trials [7, 28]. This could be explained by the smaller sample size in the present study and by the fact that at baseline only half (47%) of our participants reported criminal facts during the previous month. Nevertheless, these reductions are in line with the observation that, in opioid maintenance treatment, a decrease in heroin use is associated with a decline in criminal involvement [28, 29] and with a reduction in social contacts with other drug users [30, 31].

Treatments

In the experimental group, the DAM doses quickly rose <u>but</u> decreased after a few weeks (Figure 2). The same phenomenon <u>was observed</u> in <u>Switzerland, but without</u> a clear explanation [32]. In the control group, among the 17 (45%) participants who were on MMT outside a partner centre at baseline, 12 (32%) were still on MMT outside the partner centres at 12 months. This explained the high rate of drop out after the randomisation. However, as in other trials [5, 6, 12-15], the control group also showed improvement after 12 months (Table 2). This confirmed that a prolonged MMT is still associated with improvements, even if the participants are discharged before 12 months [33].

Strengths and weaknesses of the study

In line with the other trials [5-7, 12-15], HAT was more effective than MMT. The modalities of our trial were comparable to other trials and we included the same target group of severe heroin addicts. The main difference with other trials was the 12-month duration of HAT, which was introduced for legal and political reasons. The only other trial with a predetermined end of HAT was the Canadian <u>study</u>, <u>in which</u> street heroin use rose in the experimental group between the 9 and 12-month assessments [5, 34]. In the Dutch trial, after 12 months, an interruption of HAT for 2 months also had a negative impact: 82% of the participants who were completers and responders deteriorated substantially [6].

The limited duration of HAT could <u>have</u> influence<u>d</u> our outcomes in two ways. First, <u>this</u> could explain <u>why</u> the number of participants was lower (n=74) than expected (n=200). In fact, during the recruitment process, the research team learned from the partner centres that many heroin users were not interested in the trial. To understand why, the research team interviewed 52 heroin users who had never met the researchers <u>before</u>. According to the interviewees, the main reason <u>for</u> not participat<u>ing</u> in the trial was that the length of HAT was

limited: they were afraid to be still addicted after 12 months [35]. The reduced number of participants influenced the statistical power which was lower than planned. Secondly, the rise of street heroin use in our experimental group between the 9-month and the 12-month assessments can be a consequence of the anticipation of the end of HAT. However, this increase was not statistically significant.

Meaning of the study

HAT is more effective than MMT for severe heroin addicts, resistant to other treatments, but our results compared with other trials suggest that a predetermined duration of treatment reduces the efficacy of HAT. Moreover, setting an arbitrary time limit to HAT is in contradiction with the long-term character of this chronic relapsing disease [7, 36]. Scientific evidence speaks in favour of a prolonged treatment: in other countries, HAT prolonged for more than 12 months was associated with sustained improvement [31, 37-39]. We hope that this conclusion will help policy makers and clinicians not to limit arbitrarily the duration of an effective treatment for severe heroin addicts, even within the frame of a trial.

Unanswered question and future research

Despite the predetermined duration of HAT, the retention rate (75%) in our experimental group was higher than in other trials (68% in The Netherlands, 67% in Germany and Canada) [5, 6, 14]. This difference and the proportion of exclusion for violation of house rules (14% in TADAM, 15% in the Canadian trial and 6% in the Dutch study) indicate that HAT could still be improved. Additional international research is needed to identify the best practices and to enhance compliance with this effective treatment.

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Table 1: Baseline characteristics

Sociodemographic characteristics[a]	Experimental group (n=36)	Control group (n=38)	n=74
No (%) of men [b]	30 (83%)	35 (92%)	65 (88%)
Age – years [c]	43 [6]	42 [7]	43 [7]
No (%) employed in past month [b]	1 (3%)	1 (3%)	2 (3%)
No (%) with social welfare as main source of income[b]	28 (78%)	30 (79%)	58 (78%)
No (%) with no stable housing in past month [b]	10 (28%)	11 (29%)	21 (28%)
Criminal involvement			
No (%) with illegal activities in past month [b, d]	19 (53%)	18 (47%)	37 (50%)
No (%) with victimisation in past month [b, d]	11 (31%)	11 (29%)	22 (30%)
No (%) ever convicted [b, d]	35 (97%)	37 (97%)	72 (97%)
No (%) ever condemned [b]	28 (78%)	28 (74%)	56 (76%)
No (%) ever incarcerated [b]	26 (72%)	21 (55%)	47 (64%)
Physical and mental health			
MAP-HSS - total score [c]	18 [8]	18 [8]	18 [8]
SCL-90-R - total score [c]	105 [55]	107 [51]	106 [53]
Drug use			
Regular street heroin use – years [c]	21 [7]	20 [7]	20 [7]
Street heroin in past month – days [e, d]	27 [5]	28 [5]	27 [5]
No (%) with alcohol use in past month (+ 5 gl. per day) [b]	9 (25%)	12 (32%)	21 (28%)
No (%) with cocaine use in past month [b, d]	14 (39%)	20 (53%)	34 (46%)
No (%) with benzodiazepines use in past month [b]	18 (50%)	13 (34%)	31 (42%)

No (%) who ever injected [b]	27 (75%)	33 (87%)	60 (81%)
No (%) with habitual use of street heroin through injection [b]	3 (8%)	9 (24%)	12 (16%)
No (%) who choose to inject DAM in the trial [b]	1 (3%)	4 (11%)	5 (7%)
Previous addiction treatment			
Regular methadone use – years [c]	15 [6]	13 [7]	14 [7]
Number of previous drug treatments [e]	11 [17]	8 [8]	9 [13]

[a] *Data are number of participants (%) or mean [s.d.]*

[b] *Fischer exact test*

[c] *Student t test*

[d] *Self-reported data complemented with toxicological analysis or registered criminal proceedings*

[e] *Mann-Whitney U test*

Table 2: Response rate at each assessment time

Assessment time after baseline	Experimental group		Control group		P [a]
Intention-to-treat analysis (n=74)	n	Responders	n	Responders	
3 months	36	24 (67%)	38	13 (34%)	**p=0.010**
6 months	36	26 (72%)	38	16 (42%)	**p=0.011**
9 months	36	27 (75%)	38	17 (45%)	**p=0.0099**
12 months	36	24 (67%)	38	21 (55%)	p=0.35
Per protocol analysis 1 [b]	27	19 (70%)	13	8 (62%)	p=0.72
Per protocol analysis 2 [c]	30	20 (67%)	30	18 (60%)	p=0.79

[a] *p for Fisher's exact test*

[b] *Participants in the allocated treatment and <u>in the</u> allocated treatment centre after 12 months.*

[c] *Participants in a treatment for heroin addiction or abstinent after 12 months.*

Figure 1: Progress of participants through stages of trials

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┌─────────────────────────────────────────────────────────────────────────────┐
│              116 registered in the partner centres for the trial             │
└─────────────────────────────────────────────────────────────────────────────┘
                                        │
                                        │    ┌──────────────────────────────────┐
                                        ├────┤ 33 not motivated                 │
                                        │    └──────────────────────────────────┘
┌─────────────────────────────────────────────────────────────────────────────┐
│              83 assessed for eligibility by the research team                 │
└─────────────────────────────────────────────────────────────────────────────┘
                                        │    ┌──────────────────────────────────┐
                                        │    │ 9 excluded                       │
                                        │    │ - 4 no street heroin use almost  │
                                        ├────┤   every day                      │
                                        │    │ - 2 no health problem or criminal│
                                        │    │   behaviour                      │
                                        │    │ - 1 heroin addiction for less    │
                                        │    │   than 5 years                   │
                                        │    │ - 1 no previous methadone        │
                                        │    │   treatment                      │
                                        │    │ - 1 no residence in the judicial │
                                        │    │   district for 12 months         │
                                        │    └──────────────────────────────────┘
┌─────────────────────────────────────────────────────────────────────────────┐
│                        74 included and randomised                            │
└─────────────────────────────────────────────────────────────────────────────┘
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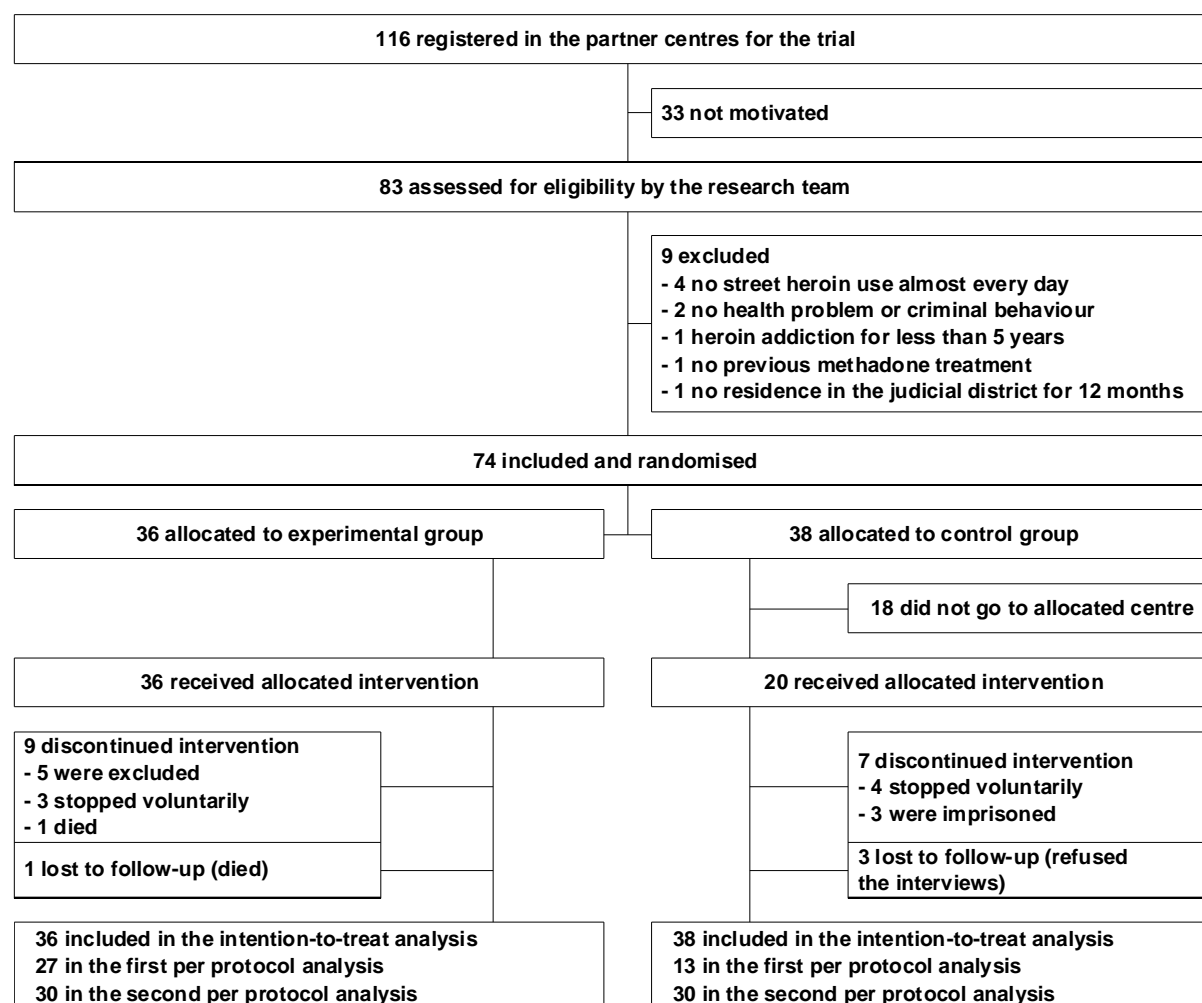| 36 allocated to experimental group	38 allocated to control group
	18 did not go to allocated centre
36 received allocated intervention	20 received allocated intervention
9 discontinued intervention - 5 were excluded - 3 stopped voluntarily - 1 died 1 lost to follow-up (died)	7 discontinued intervention - 4 stopped voluntarily - 3 were imprisoned 3 lost to follow-up (refused the interviews)
36 included in the intention-to-treat analysis 27 in the first per protocol analysis 30 in the second per protocol analysis	38 included in the intention-to-treat analysis 13 in the first per protocol analysis 30 in the second per protocol analysis

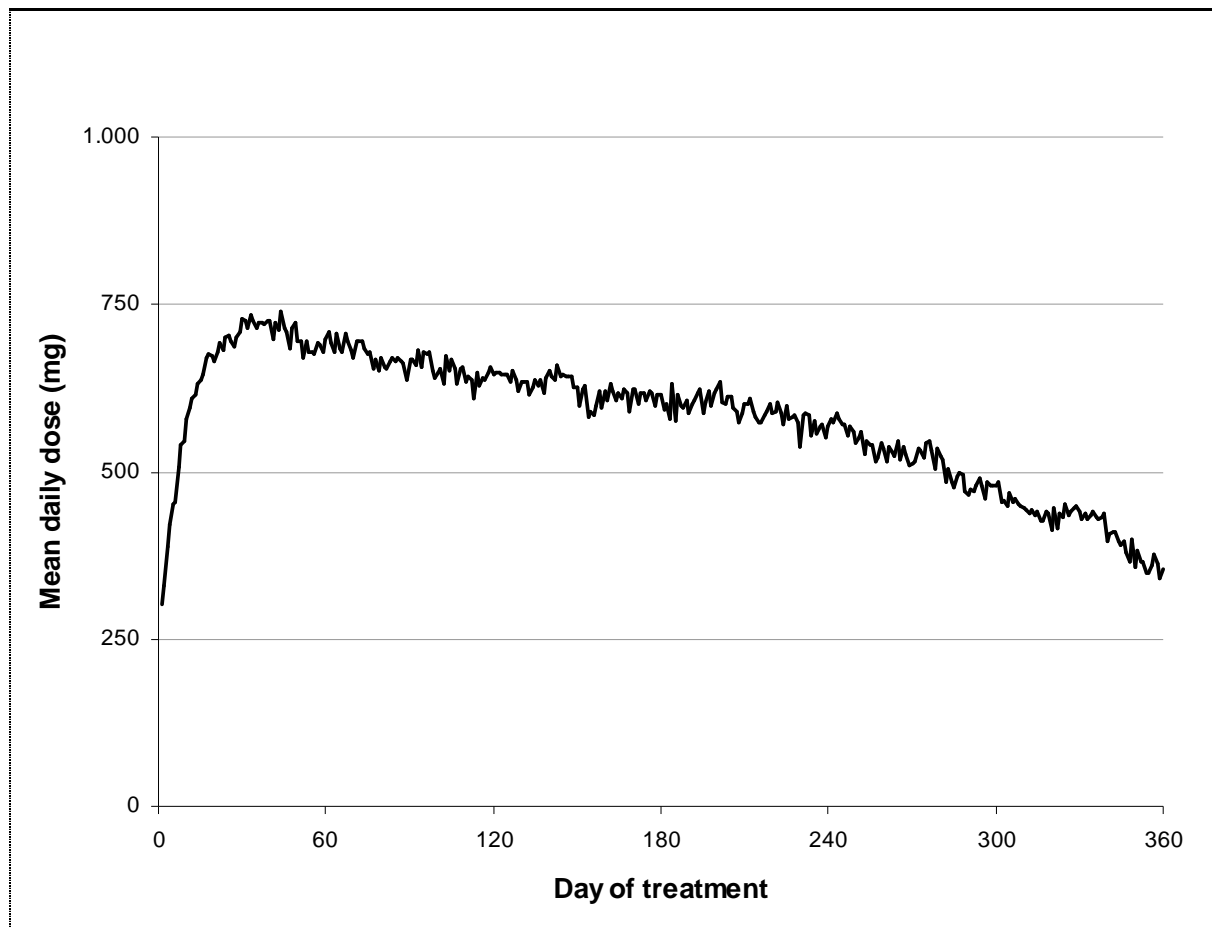**Figure 2: Dose of diacetylmorphine for <u>completers</u> (n=27)**

Figure 3: Improvement in street heroin use at each assessment point (self-reported data corrected by toxicological analyses; ** = p<0.01)