Heroin-assisted treatment: from efficacy to effectiveness and long-term outcome
Blanken, P.

Citation for published version (APA):
Blanken, P. (2011). Heroin-assisted treatment: from efficacy to effectiveness and long-term outcome
Chapter 5.

Craving and illicit heroin use among patients in heroin-assisted treatment.

Abstract

AIMS: To investigate in heroin-assisted treatment (HAT) compared to methadone maintenance treatment (MMT): the course of heroin craving and illicit heroin use; their mutual association; their association with multi-domain treatment response. DESIGN: RCTs on the efficacy of 12 months co-prescribed injectable or inhalable HAT compared to 12 months continued MMT. SETTING: Outpatient treatment in MMT- or specialized HAT-centres in the Netherlands. PARTICIPANTS: Chronic, treatment-refractory heroin dependent patients (n = 73). STUDY PARAMETERS: General (OCDUS) and current (VAS) heroin craving; self-reported illicit heroin use; multi-domain treatment response in physical, mental and social health and illicit drug use. FINDINGS: The course of heroin craving and illicit heroin use differed significantly, with strong reductions in HAT but not in MMT. General heroin craving was significantly and current heroin craving was marginally related to illicit heroin use. Heroin craving was not and illicit heroin use was marginally related to overall treatment response, but only in MMT and not in HAT. CONCLUSIONS: Heroin craving and illicit heroin use were significantly associated and both strongly decreased in HAT but not in MMT. Craving was not related to multi-domain treatment response and illicit heroin use was marginally related to treatment response in MMT, but not in HAT. The latter was probably due to the strong reduction in illicit heroin use in most patients in HAT and the small sample size of the sub-study. It is hypothesized that the strong reductions of heroin craving in HAT are related to the perceived stable availability of prescribed, pharmaceutical grade heroin.

* This paper - by Blanken P, Hendriks VM, Koeter MWJ, van Ree JM, van den Brink W - has been submitted for publication and is under review.
5.1 Introduction

In 1994, the first studies on the feasibility and efficacy of supervised prescription of injectable heroin to treatment-refractory heroin addicts were initiated in Switzerland, including a large naturalistic cohort study (Rehm et al., 2001) and a small RCT (Perneger et al., 1998). Between 1998 and 2001, two parallel RCTs in the Netherlands were conducted to study the efficacy of supervised co-prescribed injectable or inhalable heroin plus oral methadone, compared with continued oral methadone maintenance treatment for chronic, treatment-refractory heroin dependent patients (Van den Brink et al., 2003). Both studies showed favourable outcomes for heroin-assisted treatment (HAT) compared to continued methadone maintenance treatment (MMT) in terms of physical and mental health, social functioning (including criminality) and drug use. More recently, comparable positive results favouring HAT were reported in Spain (March et al., 2006), Germany (Haasen et al., 2007), Canada (Oviedo-Joekes et al., 2009) and the United Kingdom (Strang et al., 2010).

One of the key features of HAT is that long-term heroin addicted patients who did not benefit from methadone maintenance treatment, are offered a treatment with a predictable and stable availability of pharmaceutical grade heroin. This stable availability of prescribed heroin might not only enable treatment-refractory heroin addicts to - at least partly - withdraw from the illicit drug scene, it may also reduce craving for heroin and lead to a better outcome in terms of physical, mental and social well-being.

Craving is a multidimensional phenomenon, consisting of cognitive, emotional and neurobiological aspects (Franken, 2003; Verheul et al., 1999). Although craving is considered to be an important aspect in the continuation of alcohol and drug use, as well as in the relapse to alcohol and drug use after abstinence, the nature of this relationship is not fully understood. One of the theories on craving, by Tiffany and colleagues, states that compulsive drug use is a form of automatized behaviour that is regulated by automatic (cognitive) processes (Carter and Tiffany, 1999; Tiffany and Carter, 1998; Tiffany and Conklin, 2000). Only when this automatized behaviour is interrupted, drug addicts will experience craving. In this view, craving is the resultant of interrupted drug use behaviour. Since patients in HAT have daily predictable and
stable access to pharmaceutical grade heroin, thereby reducing the need to consume illicit heroin, supervised intake of prescribed heroin might become automatized behaviour, unlikely to be interrupted, and may thus lead to reduced craving for heroin.

Therefore, in this paper, the following three hypotheses are tested:

(1) The course of both heroin craving and illicit heroin use differs between patients in HAT and patients in continued MMT, with patients in HAT showing stronger reductions in both heroin craving and illicit heroin use than patients in continued MMT.

(2) Craving during treatment is related to non-prescribed, illicit heroin use in both HAT and continued MMT.

(3) Heroin craving and illicit heroin use during treatment are predictors of treatment response in HAT and continued MMT.

5.2 Methods

5.2.1 Design

Two parallel randomised controlled trials were conducted from July 1998 till December 2001 in six cities in the Netherlands. In these trials the effectiveness of 12 months prescription of either injectable or inhalable heroin plus oral methadone was compared to continued standard oral methadone alone. For a detailed description of the trials and procedures the reader is referred to the original publications (Blanken et al., 2010b; Van den Brink et al., 2003). In two of the six participating cities, The Hague and Heerlen, an additional craving sub-study was carried out, within the context of the randomised controlled trials. The craving study was approved by the medical-ethical committee METiGG, and all participating patients provided written informed consent.

5.2.2 Treatment

Patients in the control groups continued to participate in regular, oral methadone maintenance treatment (maximum dosage 150 mg per day). Patients in the experimental groups were referred to newly established heroin treatment units and were offered oral methadone (maximum dosage: 150 mg per day) plus pharmaceutical grade heroin. Prescribed heroin was offered seven days
per week and three times per day, with a maximum dosage of 400 mg per visit and 1,000 mg per day. Under medical supervision, 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 (Hendriks et al., 2001)) had to be inhaled. Patients in continued MMT were prescribed an average methadone dosage of 59.9 mg (95%-CI: 55.2-64.5). Patients in HAT received 58.3 mg methadone (95%-CI 46.5-70.1) plus an additional average heroin dosage of 444.1 mg (95%-CI: 357.4-530.7) per day. Patients in HAT visited the treatment center 1.7 times per day (95%-CI: 1.5-1.9) during the last month of treatment. Both treatment conditions offered comparable, standard psychosocial interventions.

5.2.3 Patients
All patients in the heroin trials in The Hague and Heerlen were eligible for the craving sub-study. Due to the late start of the craving sub-study, only 87 of the 104 patients were approached for the craving sub-study and 73 of them (84%) gave informed consent: 37 in MMT and 36 in HAT (see Figure 1). Patients included in the trials were chronic, treatment-refractory heroin dependent subjects. They were at least 25 years old and met diagnostic criteria for DSM-IV heroin dependence for at least five years. In spite of adequate methadone maintenance treatment, all patients used illicit heroin (nearly) daily and displayed poor physical, mental and/or social health (Van den Brink et al., 2003).

5.2.4 Assessments and instruments
Patients were interviewed bimonthly. Interviews were held in a 'neutral' environment, outside the methadone and heroin treatment centres and after intake of the daily methadone and/or heroin dose.

The standard assessment battery in the trials included the European Addiction Severity Index (EuropASI) (Kokkevi and Hartgers, 1995), the Health Symptoms Scale of the Maudsley Addiction Profile (MAP-HSS) (Marsden et al., 1998), and the 90 items version of the Symptom Checklist (SCL-90) (Derogatis, 1983).
In the craving sub-study three additional assessments were used: the Obsessive Compulsive Drug Use Scale (OCDUS) (Franken et al., 2002), a Visual Analogue Scale (VAS) for subjective craving, and the Eysenck Personality Questionnaire (EPQ) with a measure of Social Desirability (Eysenck and Eysenck, 1964; Sanderman et al., 1991). The Obsessive Compulsive Drug Use Scale (OCDUS) is a 12-item version of the Obsessive-Compulsive Drinking Scale (OCDS) (Anton et al., 1996), adapted for heroin dependence and measuring self-reported heroin craving in the past week (Franken et al., 2002). All items have a 5-point Likert scale (0-4) and the total score ranges from 0 to 48. Recently, de Wildt et al. showed that a selection of only five items of the OCDS ((1) duration and (2) frequency of obsession with heroin (i.e., ideas, thoughts, impulses, or images); (3) the distress caused by those obsessions; (4) the effort to resist the obsessions; and (5) the strength of the drive to use heroin - all assessed over the past seven days) were able to tap the core concept of
Heroin-assisted treatment craving and showed good internal consistency in alcohol dependent patients (α = 0.81) (de Wildt et al., 2005). In the current sub-study, this core set of five craving items of the OCDUS, pertaining to thoughts and feelings and behavioural intentions (score ranging from 0 to 20; internal consistency in this sample of heroin dependent patients: α = 0.77) was used for analysis, together with the score on a Visual Analogue Scale (range: 0 to 100) for self-reported 'current' craving (i.e., craving at the time the VAS was scored).

5.2.5 Outcome parameters
The 5-item OCDUS-craving score and the VAS-craving score (both measured at bimonthly intervals from baseline to month 10, the last assessment prior to the endpoint of the study at month 12) were used to assess the course of craving. Illicit (non-prescribed) heroin use was measured in terms of self-reported number of days over the previous month and any use in the preceding 48 hours. Overall treatment response, for each bimonthly assessment, was defined in terms of a pre-specified dichotomous, multi-domain response index (Central Committee on the Treatment of Heroin Addicts, 2002): improvement (compared to baseline) of at least 40% in at least one of the domains of inclusion at baseline assessment (i.e. physical, mental or social health). In addition, the improvement should, compared to baseline, not be at the expense of a serious deterioration (≥ 40%) in any of the other outcome domains, nor be at the expense of a substantial increase (> 6 days/month) of cocaine or amphetamine use.

5.2.6 Statistical analysis
The first hypothesis, regarding the temporal course of craving for heroin and illicit heroin use, was tested by means of Generalized Estimation Equation (GEE) modelling, using an exchangeable correlation matrix. Since almost all patients had used illicit heroin in the 48 hours preceding baseline assessment (MMT: 100%; HAT 94%), the course of illicit heroin use in the preceding 48 hours could only be analyzed from month 2 onwards.

The second hypothesis (association between craving for heroin and illicit heroin use) and the third hypothesis (associations between heroin craving and
illicit heroin use, on the one hand, and treatment response on the other hand), were also tested by means of GEE, using an exchangeable and unstructured correlation matrix, respectively. It was tested whether treatment group (MMT versus HAT) modified the association between heroin craving and illicit heroin use (second hypothesis), and between heroin craving and treatment response, as well as between illicit heroin use and treatment response (third hypothesis). If this was not the case, data were pooled over MMT and HAT and treatment group was retained in the analyses as an independent variable. Finally, the effect of three potential confounders was tested: (1) treatment status at the time of assessment (discontinued versus retained), (2) time of craving assessment since last substitution (methadone or heroin) prescription (in hours), and (3) tendency to provide social desirable answers (EPQ at baseline). When addition of a potential confounder to the model changed the size of the effect parameter by more than 10%, the potential confounder was added to the final regression model as a covariate.

In the analyses for the second and third hypothesis, VAS-scores (originally ranging from 0 to 100) were divided by 5, for reasons of comparability with the OCDUS (range: 0 to 20), resulting in similar ranges for VAS and OCDUS (0 to 20); thus, $\beta$'s and OR's for the VAS refer to 5-point changes in VAS-scores.

The majority of patients complied with all five bimonthly follow-up assessments (51/73 = 69.9%), and only one patient (1.4%) had no post-baseline assessment. Bimonthly compliance rates varied from 79.5% at month 2 to 97.3% at month 10. Although compliance was somewhat higher in HAT compared to MMT at all bimonthly assessments, differences were not significant (p-values ranging from 0.06 to 0.49). Bimonthly assessment compliance was also not related to treatment status at the time of assessment, except for month 2 (p = 0.03), nor to baseline craving, again except for month 2 (OCDUS: p = 0.08; VAS: p = 0.03). Since bimonthly assessment compliance rates were not related to treatment group, treatment retention status, or baseline craving for heroin, we have no indication that the GEE assumption of missing data to be missing completely at random has been violated. Statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, NC).
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>patients in heroin craving sub-study (n = 73)</th>
<th>patients not in heroin craving sub-study (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% or mean (sd)</td>
<td>% or mean (sd)</td>
</tr>
<tr>
<td>- injectable heroin versus inhalable heroin</td>
<td>34.3 % - 65.8 %</td>
<td>29.0 % - 71.0 %</td>
</tr>
</tbody>
</table>

**Background**
- gender (% male) | 80.8 % | 80.7 % |
- age (years) | 39.2 (5.3) | 39.6 (5.3) |
- ethnicity (% Dutch/Western-European ethnicity) | 87.7 % | 90.3 % |

**Inclusion scores and profiles**
- included with physical health problems (%) | 72.6 % | 74.2 % |
- included with psychiatric health problems (%) | 61.6 % | 74.2 % |
- included with problematic social functioning (%) | 68.5 % | 61.3 % |

**Substance use**
- lifetime regular substance use (years)
  - heroin | 16.1 (6.5) | 15.0 (5.1) |
  - methadone | 12.9 (6.2) | 11.5 (5.0) |
  - alcohol (≥ 5 glasses) | 5.5 (7.3) | 7.4 (7.7) |
  - benzodiazepines | 7.0 (8.0) | 7.3 (7.9) |
  - cocaine | 6.5 (6.0) | 6.9 (6.9) |
  - amphetamines | 1.6 (3.7) | 2.0 (3.8) |
  - polydrug use | 17.2 (6.7) | 16.8 (5.8) |

- substance use past month (days)
  - heroin | 26.9 (5.4) | 26.0 (6.6) |
  - methadone | 28.8 (3.6) | 27.6 (6.6) |
  - alcohol (≥ 5 glasses) | 7.5 (11.9) | 11.7 (12.2) |
  - benzodiazepines | 14.4 (12.9) | 15.0 (13.8) |
  - cocaine | 11.3 (11.3) | 12.2 (11.3) |
  - amphetamines | 0.1 (0.6) | 0.1 (0.4) |
  - polydrug use | 29.1 (2.3) | 28.5 (3.2) |

- methadone dose at start (in mg) * | 60.9 (12.3) | 53.9 (15.8) |
- number of lifetime drug overdoses | 1.4 (2.8) | 1.0 (2.2) |
- any abstinence oriented treatment | 61.6 % | 51.6 % |

* p < .05

All interval variables were tested non-parametrically, except: age and lifetime years of regular heroin and methadone use (Student's T-test). Dichotomous variables were tested with Fisher's Exact Test.
5.3 Results

Table 1 displays the sample characteristics, broken down for patients that did (second column) or did not (third column) participate in the craving sub-study. The majority of the patients in the craving sub-study were male (81%) and of Dutch-western origin (88%) with an average age of almost 40 years. Patients had a long career of poly drug use (17 years), using heroin and methadone, and quite often also alcohol, benzodiazepines and cocaine. At baseline, patients used illicit heroin and prescribed methadone on an almost daily basis.

Patients were included in the heroin co-prescription trial for reasons of poor physical health (73%), poor mental status (62%) and/or poor social functioning (69%), including involvement in illegal activities (59%; not shown). Almost two-thirds (48/73 = 65.8%) of the patients in the HAT condition of this sub-study were prescribed inhalable heroin and the others received injectable heroin (25/73 = 34.2%). Except for methadone dosage at the start of the HAT trial, there were no significant differences between the patients that did or did not participate in the craving sub-study.

5.3.1 Course of heroin craving and illicit heroin use

The course of both general and current heroin craving differed significantly between patients in HAT and continued MMT (see Figure 2a); general craving OCDUS: $\chi^2$-time*group = 54.6; df = 5; $p < .001$; current craving VAS: $\chi^2$-time*group = 18.6; df = 5; $p = .002$. Patients in HAT reported lower craving levels at all bimonthly follow-up assessments, compared to baseline. However, from month 2 onward, heroin craving did not decline consistently for the OCDUS and remained stable for the VAS. Patients in MMT, on the other hand, showed only marginal reductions in craving and craving at month 10 did not differ significantly from baseline craving (OCDUS baseline-month 10: $z = 0.33$; $p = 0.74$; VAS baseline-month 10: $z = -.22$; $p = 0.83$).

In a similar way, the course of illicit heroin use was significantly different for patients in HAT compared to patients in MMT (see Figure 2b); days illicit heroin use (previous month): $\chi^2$-time*group = 232.2; df = 5; $p < .001$; any heroin use (past 48 hours; from month 2 onward): $\chi^2$-time*group = 9.6; df = 4; $p < .047$. 

Craving and illicit heroin use
Figure 2a. Effect of co-prescribed heroin treatment compared to standard, oral methadone treatment on heroin craving

While days illicit heroin use in the previous month as well as any illicit heroin use in the preceding 48 hours sharply declined after baseline in HAT, both indicators of illicit heroin use remained rather high and stable in MMT.
5.3.2 Craving and illicit heroin use

General heroin craving (OCDUS) and - to a lesser extent - current heroin craving (VAS) were both associated with self-reported illicit heroin use (days past month, and any use past 48 hours). Treatment group did not modify the association between general craving and days illicit heroin use ($p = 0.43$). However, adding treatment group as a dependent variable to the GEE model did change the relationship between general craving (OCDUS) and days illicit
heroin use by more than 10%. The associations between general heroin craving and illicit heroin use were not confounded (i.e., < 10% change in effect parameter) by treatment status, time of craving assessment since last substitution prescription (either methadone or heroin) or social desirability. Adjusted for treatment group, general craving was significantly related to days illicit heroin use ($\beta$-OCDUS = 0.62 [95%-CI: 0.31-0.94; $p < .001$], indicating that a one-point difference in OCDUS heroin craving (either between patients, or within patients over time) is associated with 0.62 days difference in illicit heroin use over the past month).

Similarly, treatment group did not modify the association between general craving and any illicit heroin use in the previous 48 hours ($p = 0.13$). After adjustment for treatment group, and in absence of other relevant confounders (treatment status, time of craving assessment, and social desirability), general craving for heroin was also significantly related to any illicit heroin use in the previous 48 hours (OR-OCDUS = 1.14 [95%-CI: 1.05-1.23; $p = .001$], indicating that a one-point difference in OCDUS heroin craving is associated with 14% difference in the odds of any heroin use in the past 48 hours).

The association between current craving (VAS) and days illicit heroin use and any illicit heroin use were also not modified by treatment group ($p = 0.91$ and $p = 0.18$, respectively). After adjustment for treatment group (and in absence of changes in effect parameters > 10% caused by the three other confounders) the effect parameters for current craving and illicit heroin use, compared to general craving, were smaller; for days illicit heroin use in the past month, $\beta$-VAS = 0.19 (95%-CI: 0.01-0.37; $p = 0.04$) and for any heroin use in the past 48 hours OR-VAS = 1.05 (95%-CI: 1.00-1.11; $p = 0.06$).

### 5.3.3 Craving and overall treatment response
Treatment response was higher among patients in the 12-months HAT group (44.4%) compared to patients in the 12-months MMT group (27.0%), but the 17.4% response difference (in this relatively small sub-sample) was not significant (OR = 2.16; 95%-CI: 0.95-4.91; $p = 0.12$). The bimonthly, cross-sectional associations between general heroin craving (OCDUS) and treatment response were not significantly modified by treatment group ($p = 0.61$) and the
association between craving and treatment response was non-significant after controlling for the effect of treatment group (OR = 0.99; 95%-CI: 0.92-1.05; p = 0.66). Similarly, current craving for heroin (VAS) was not associated with treatment response in the two different models tested (p-interaction = 0.73, and p-VAS = 0.24; OR = 0.98; 95%-CI: 0.95-1.01).

5.3.4 Illicit heroin use and treatment response

The bimonthly associations between days illicit heroin use in the preceding month and treatment response was modified by treatment group (p = 0.02); OR\textsubscript{MMT} = 0.95 (95%-CI: 0.92-0.98), OR\textsubscript{HAT} = 1.00 (95%-CI: 0.97-1.02). Any illicit heroin use in the preceding 48 hours and its association with treatment response was not modified by treatment group (p = 0.60), nor was any illicit heroin use in the preceding 48 hours associated with treatment response, after controlling for treatment group (p = 0.25; OR = 0.73; 95%-CI: 0.42-1.25).

5.4 Discussion

5.4.1 Summary of results

The first hypothesis was confirmed: Over the course of 10 months treatment, patients in HAT reported significant reductions in craving for heroin and illicit heroin use, while patients in MMT did not. The second hypothesis was also confirmed: craving for heroin was positively associated with illicit heroin use, in both treatment groups. The third hypothesis was only partially confirmed: craving was not related to overall treatment response, but illicit heroin use was significantly associated with overall treatment response in MMT, but not in HAT.

5.4.2 Limitations

First, due to the late start of recruitment for this craving sub-study only 73 patients were included. Comparison between included and non-included patients, however, showed that the study population was representative for the target population. Although the sample was representative for the larger trial, the current sub-study failed to show a significant effect of HAT compared to MMT on overall treatment response as it was found in the larger trial (Van den
Brink et al., 2003). This non-significant effect difference is probably due to the combination of a slightly smaller effect size in the current sub-study compared to the original, larger trial conducted in six cities (17% versus 24%) and the relatively small sample size ($n = 73$ versus $n = 430$) resulting in low power for this specific outcome. This power limitation most likely also explains the absence of a significant relationship between illicit heroin use and overall treatment outcome in the HAT condition, as will be elaborated upon further on in this discussion.

Second, our study outcome was exclusively based on self-reports measuring physical status, mental health, social function (including criminal activities), and illicit drug use. However, we previously showed that self-reported drug use and police-charges were generally consistent with random urinalysis (overall agreement 86%) and data from police registers (overall agreement 90%) respectively (Van den Brink et al., 2003).

Third, although Marissen et al. (2005) found that self-reported craving in heroin dependent patients was associated with social desirability, controlling for social desirability, in this sub-study, did not affect the reported course of craving for heroin over time, nor the associations between craving and illicit heroin use and treatment response. Therefore, we are quite confident that the results are not invalidated by the self-report nature of the data.

Finally, it should be noted that although we only presented data for the 5-item OCDUS general craving, the results for the 12-item OCDUS craving subscales were very similar.

5.4.3 Drug availability and heroin craving

Patients in HAT participated in a treatment-regimen in which pharmaceutical grade heroin was offered three times per day for seven days per week. As a result, patients in HAT strongly reduced illicit heroin use, as had already been documented in HAT-trials in other countries (Haasen et al., 2007; Oviedo-Joekes et al., 2009; Perneger et al., 1998; Strang et al., 2010). The guaranteed treatment offer resulted in a high and stable availability of (prescribed) heroin, and as a result a reduction of the uncertainty where to get the next dose of heroin, which is associated with the nature of the illicit drug market (Blanken et
al., 2010b; Faupel, 1987). This reduced uncertainty and increased perceived stable availability might very well have resulted in a reduced heroin craving during HAT. Zinberg (1984), for instance, pointed out that the social context in which drug use takes place, influences the rules, rituals and patterns of drug use. Tiffany and Carter (1998) have argued that craving is mainly the result of disrupted automatized drug use behaviour. In situations of illicit, non-prescribed heroin use, the heroin addict is confronted almost daily with insecurities relating to acquiring financial resources and finding a reliable supplier to buy good quality heroin. As soon as one of the activities in this chain of processes is disrupted, the heroin user will experience craving. In contrast, patients in HAT have predictable, stable access to prescribed, high quality - i.e., pharmaceutical grade - heroin. As long as patients are able to adjust their lifestyle to the requirements of the HAT-program, their daily heroin dosage(s) will be assured and co-prescribed heroin intake might become automatized, and thus no longer invoke craving for heroin. However, some experimental studies, have questioned the validity of Tiffany’s model (e.g. Field and Cox, 2008), showing increased craving just prior to drug intake (e.g. Rook et al., 2006). It should be noted, however, that participation in these experiments probably raised the awareness of drug users of their drug consumption, thereby disrupting automatized drug use behaviour and thus eliciting drug craving. In the current study, patients in HAT reported strong reductions in general craving and this was probably due to the experience of a stable availability of heroin over time and the absence of disruptions in their automatized heroin use behaviours. As a result, heroin may have lost at least some of its salience among patients in HAT, and the observed reductions in heroin craving may reflect this reduced salience attribution (e.g. Goldstein and Volkow, 2002).

5.4.4 Heroin craving, illicit heroin use and treatment response

In some studies craving predicts future drug use or relapse, whereas in other studies craving and drug use or relapse are only weakly related (de Wildt et al., 2010; Epstein et al., 2009; Lubman et al., 2009; Marissen et al., 2007). In our study there was a strong association between craving and illicit heroin use. We did not, however, find a significant relation between craving for heroin and our
multi-domain treatment response index, and the relation between illicit heroin use and treatment response was weak and only in MMT. The absence of clear associations between craving and illicit heroin use with treatment response might be due to our definition of overall treatment response. Whereas in most RCTs on HAT, illicit heroin use was (part of) the primary response parameter, treatment response in the Dutch trials was defined in terms of improvements in physical and mental health, as well as social functioning. This would imply that reductions in heroin craving and illicit heroin use during HAT are not always accompanied by improvements in health and/or social functioning.

It should be noted, however, that the absence of an association between illicit heroin use and treatment response in HAT is also due to the overall strong reductions in illicit heroin use in HAT: almost all patients in HAT substantially reduced their illicit heroin use, although this was not always accompanied by an overall treatment response, resulting in similarly low levels of illicit heroin use in both responders and non-responders at 12 months (3.4 versus 4.8 days; p = 0.59).

Finally, as already mentioned under the limitations, it might also be possible that the sub-study on craving was under-powered to detect significant associations between heroin craving and illicit heroin use on the one hand, and overall, multi-domain treatment response on the other hand. A post-hoc analysis of the total intent-to-treat sample of the full-scale RCT incorporating patients in all six cities (n = 430), showed a significant relationship between illicit heroin use and overall treatment response in HAT patients both for days of illicit heroin use in the preceding month (OR = 0.96; 95%-CI: 0.95-0.97) and for any illicit heroin use in the preceding 48 hours (OR = 0.73; 95%-CI: 0.56-0.96). Thus, this post hoc analysis showed that each additional day of illicit heroin use reduced the odds at overall treatment response by 3%, while any illicit heroin use in the preceding 48 hours reduced the odds by 27%, both in the HAT- and MMT-patient group.

### 5.5 Conclusion

Efficacy of HAT has been demonstrated in a number of randomised trials in different countries (Blanken et al., 2010b; Ferri et al., 2010; Fischer et al.,
In our current sub-study, patients in HAT, compared to those in MMT, showed a significant and substantial decrease in heroin craving and illicit heroin use during treatment. Moreover, lower craving levels during HAT (as well as during MMT) were related with lower levels of illicit heroin use. In this sub-study, craving for heroin was not and illicit heroin use was only marginally related to overall treatment response, and the latter was only true for the MMT condition. However, in the full scale RCT in six cities, reductions in illicit heroin use were clearly associated with overall, multi-domain treatment outcome both in MMT and HAT.