Heroin-assisted treatment: from efficacy to effectiveness and long-term outcome
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Chapter 8.

General discussion and conclusion.

In this final chapter, the results that were presented in the preceding chapters, will be summarized and discussed in a broader context, addressing the following questions: (1) Does heroin-assisted treatment work?, (2) For which patients does heroin-assisted treatment work?, (3) How does heroin-assisted treatment work?, and (4) How to improve the way heroin-assisted treatment works? The chapter will end with the major conclusion of this thesis and suggestions for future research to further improve the quality and effectiveness of heroin-assisted treatment (HAT).

8.1 Does HAT work?

8.1.1 Efficacy

In 1994 Switzerland started with a naturalistic cohort study of supervised heroin-assisted treatment (HAT), in which pharmaceutical grade injectable heroin for the first time was prescribed, under supervision, to long-term, treatment-refractory heroin addicts. Following a small-scale RCT conducted in Geneva, the heroin trials conducted in the Netherlands, and described in chapter 2, were the first two full scale RCTs comparing the efficacy of supervised, co-prescribed injectable or inhalable heroin with standard oral methadone maintenance treatment (MMT). Since then, a series of RCTs comparing the efficacy of injectable heroin and various forms of methadone maintenance treatment have been conducted in Spain, Germany, Canada and the United Kingdom (Blanken et al., 2010b; Fischer et al., 2007; Fischer et al., 2002). In six RCTs over two thousand patients participated in HAT (n = 1,043), oral MMT (n = 945), and injectable MMT (n = 42) or injectable hydromorphone (n = 25).*

* Including 119 patients in the Dutch trial who were prescribed inhalable heroin for six months and who are not listed in table 1. The total number of patients in HAT and oral MMT differ slightly from the number reported in Blanken et al. 2010, due to a computational error in that paper.
Table 1. Overview of randomized controlled trials on the efficacy of supervised heroin-assisted treatment

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Duration in months</th>
<th>Treatment Interventions</th>
<th>Dispensing Frequency Times * Days</th>
<th>N</th>
<th>Dosage</th>
<th>Primary Outcome Measure(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland socially marginalised heroin addicts, with failed drug treatments</td>
<td>6</td>
<td>- injectable heroin</td>
<td>3 * 7</td>
<td>27</td>
<td>509 mg</td>
<td>- consumption of street heroin and other drugs (among many other outcome variables)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- waiting list (mostly M)</td>
<td>3</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands chronic, methadone-resistant heroin addicts, with poor physical,</td>
<td>12</td>
<td>- injectable H + oral M</td>
<td>3 * 7</td>
<td>76</td>
<td>549 mg H + 57 mg oM 71 mg</td>
<td>- dichotomous, multi-domain response index (improvement in physical, mental social health; no increased illicit drug use)</td>
</tr>
<tr>
<td>mental or social health in MMT</td>
<td></td>
<td>- ongoing standard oral M</td>
<td>1 * 3-5</td>
<td>98</td>
<td>547 mg H + 60 mg oM 67 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- inhalable H + oral M</td>
<td>3 * 7</td>
<td>117</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ongoing standard oral M</td>
<td>1 * 3-5</td>
<td>139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany methadone-resistant heroin addicts in MMT, or: herion addicts not in</td>
<td>12</td>
<td>- injectable H</td>
<td>3 * 7</td>
<td>515</td>
<td>442 mg H + 8 mg oM 99 mg</td>
<td>- improvement in physical health and/or mental health</td>
</tr>
<tr>
<td>MMT for &gt; 6 months</td>
<td></td>
<td>- oral M</td>
<td>1 * 7</td>
<td>500</td>
<td>99 mg oM</td>
<td>- reduction in the use of street heroin and no increase in cocaine</td>
</tr>
<tr>
<td>Spain injecting, methadone-resistant heroin addicts (in or out of MMT) with poor</td>
<td>9</td>
<td>- intravenous H + oral M</td>
<td>2 * 7</td>
<td>31</td>
<td></td>
<td>- dichotomous multidimensional outcome index (improvement in general health or psychological or family adjustment)</td>
</tr>
<tr>
<td>physical, mental or social health</td>
<td></td>
<td>- oral M</td>
<td>1 * 7</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada treatment-refractory heroin addicts not in MMT for &gt; 6 months</td>
<td>12</td>
<td>- injectable H</td>
<td>3 * 7</td>
<td>115</td>
<td>392 mg H + 0 mg oM / 366 mg H + 34 mg oM / 96 mg oM</td>
<td>- treatment retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- best practice oral M</td>
<td>1 * 7</td>
<td>111</td>
<td>366 mg H + 34 mg oM 96 mg oM</td>
<td>- reduction in (severity of) illicit drug use or other illegal activities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- injectable HM</td>
<td>3 * 7</td>
<td>25</td>
<td>198 mg HM</td>
<td></td>
</tr>
<tr>
<td>United Kingdom chronic heroin addicts in oral MMT with ongoing regular injection</td>
<td>6</td>
<td>- injectable H + oral M</td>
<td>2 * 7</td>
<td>43</td>
<td>399 mg H + 42 mg oM 128 mg iM + 31 mg oM 107 mg oM</td>
<td>- reduction of regular use of street heroin (urinalysis)</td>
</tr>
<tr>
<td>of street heroin</td>
<td></td>
<td>- injectable M + oral M</td>
<td>1 * 7</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- optimised oral M</td>
<td>1 * 5-7</td>
<td>42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

H = injectable heroin (except for the Netherlands' trial on inhalable heroin)

oM = oral methadone

iM = intravenous methadone

HM = Hydromorphone
Although these trials somewhat differed in terms of target population, intervention, design, and primary outcome measure (see Table 1), the efficacy of supervised heroin-assisted treatment compared to methadone maintenance treatment according to their primary outcomes was demonstrated in all studies. Figure 1 displays the effectiveness (Relative Risks) of HAT compared to MMT in terms of the pre-defined primary outcome measures of the trials.
Patients in HAT strongly reduced their illicit heroin use (Relative Risks ranging from 1.25 in Germany to 2.75 in the United Kingdom), and showed significant improvements in their health status (Relative Risks ranging from 1.08 in Germany to 1.90 in the Netherlands in the inhalable RCT). In addition, it was shown in all trials that, compared to MMT, HAT resulted in marked reductions in criminality, even among patients who did not meet formal, pre-defined response criteria (data not shown).

8.1.2 Safety

Although HAT is more effective than MMT in treatment-refractory patients, the occurrence of Serious Adverse Events (SAEs) in HAT seems to outnumber those in MMT (see Table 2). It should be noted, however, that patients in HAT had more frequent contact with treatment staff and were monitored more closely than patients in MMT and this may have caused information bias with a relative under-estimation of SAEs in MMT compared to HAT. Table 2 summarizes the number of overdoses and seizures that were registered in HAT and that were (probably or definitively) related to the prescribed heroin, and the number of deaths, irrespective of the relation to the prescribed medication. With respect to the overdoses and seizures, two things need to be mentioned. First, the number of overdoses and seizures should be evaluated in the context of the number of prescribed heroin dosages. In the Dutch trials the total number of heroin dispensations was approximately 140,000 (Central Committee on the Treatment of Heroin Addicts, 2002), for the German heroin trial the number of treatment days (with multiple heroin administrations) was estimated at 149,350 (Haasen et al., 2007), and in the U.K. trial the rate of serious adverse events was estimated at 1 per 6,613 injections (Strang et al., 2010). Second, since all heroin administrations in HAT are under medical supervision and patients are required to stay in the treatment unit for a minimal observation period after taking the prescribed heroin, none of the overdoses or seizures was fatal or caused irreversible damage. An important question - that was coined by Haasen et al. (2010; page 60) and remains to be answered - is whether the relative high number of SAEs, including overdoses and epileptic seizures, in the German and Canadian trial might be related to the fact that most patients in HAT in those two countries did
Table 2. SAEs, overdoses, seizures and deaths in HAT and MMT

<table>
<thead>
<tr>
<th>RCT</th>
<th># SAEs in HAT all related</th>
<th># SAEs in MMT all</th>
<th>overdoses in HAT ▼ ▼ #</th>
<th>seizures in HAT ▼ ▼ #</th>
<th>deaths in HAT * n %</th>
<th>deaths in MMT * n %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL inject. heroin</td>
<td>11</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>1 1.3</td>
<td>1 1.0</td>
</tr>
<tr>
<td>NL inhal. heroin</td>
<td>26</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>1 0.9</td>
<td>0</td>
</tr>
<tr>
<td>Spain</td>
<td>7</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>1 3.2</td>
</tr>
<tr>
<td>Germany</td>
<td>177</td>
<td>138</td>
<td>31</td>
<td>10</td>
<td>5 1.0</td>
<td>7 1.4</td>
</tr>
<tr>
<td>Canada</td>
<td>51</td>
<td>24</td>
<td>11</td>
<td>7</td>
<td>0</td>
<td>1 0.9</td>
</tr>
<tr>
<td>UK</td>
<td>7</td>
<td>5</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

▼ Overdoses and seizures: related to study medication
* Deaths: irrespective of their relation to the study medication

not receive co-prescribed oral methadone on a regular basis, as did patients in The Netherlands, Spain and the United Kingdom.

Mortality seems somewhat lower in HAT compared to MMT (Table 2) and, equally important, none of the deaths was related to the prescribed heroin. Altogether, it seems that prescription of heroin is not free of medical risks, even though the probability is small and the risks are controllable and manageable as long as heroin is provided in a medical, supervised treatment setting with strict treatment protocols.

8.1.3 Cost-benefit

For the Dutch and German heroin trials it has been shown that the program costs of HAT are substantially higher than the program costs of MMT, but these higher costs are offset by large savings due to stronger reductions in criminal activities - and, consequently, reduced law enforcement and reduced damage to victims - in HAT compared to MMT, resulting in a net savings per patient per year of almost € 13,000 in the Netherlands (Dijkgraaf et al., 2005) and € 8,000 in Germany (Graf von der Schulenberg and Claes, 2007). In the Swiss naturalistic cohort study annual HAT program costs were estimated at SFr 18,677 (€ 13,727) per patient, while the benefits were estimated at SFr 34,857 (€ 25,619), resulting in annual savings per patient in HAT of approximately SFr 16,000 (€
11,760 (Brehmer and Iten, 2001; Frei, 2001), including SFr 26,309 (€ 19,345) on criminality and legal system savings and SFr 6,245 (€ 4,592) for physical and mental health costs (Frei et al., 1998; Gutzwiller and Steffen, 2000).

8.1.4 Effectiveness

In chapter 7 it was shown that HAT, when implemented as routine clinical treatment in the Dutch addiction treatment system, remained an effective intervention (Blanken et al., 2010b) This confirms that the effectiveness of HAT can not be explained by a so-called "honeymoon effect" (i.e., changes in situations, like treatment may be accompanied by transient, positive outcomes among the individuals under observation) or a "Hawthorne effect" (i.e., the actual investigation itself influences the behaviour of the individuals under observation), as was concluded already in 2002: "In an analysis comparing the effect sizes between the first recruitment period (start 1998) and second recruitment period (start 2000) in Amsterdam and Rotterdam, no differences were found, indicating that 'Honeymoon' or 'Hawthorne' effects cannot account for the observed differences in response between the experimental and the control condition." (CCBH 2002: page 146). Moreover, the effectiveness of HAT as routine clinical treatment also indicates that the levels of control required for the RCTs are not indispensable to achieve treatment response among patients during routine treatment. These findings also confirm the results of the Swiss naturalistic cohort study (Rehm et al., 2001). Together, these two cohort studies, with over 2,300 treatment-refractory heroin addicts, show that HAT is also a feasible, effective, and generally safe treatment in routine clinical practice.

8.1.5 Long-term outcome

In the protocols of the original Dutch trials, after six months (inhalable) or 12 months (inhalable and injectable) heroin co-prescription was stopped for a period of at least two months, to investigate the effect of discontinuation of HAT. In chapter 2 it was shown that the majority of patients (82%) who had responded to six or 12 months HAT rapidly deteriorated and that the health and social status of the patients had returned to the dysfunctional baseline levels. Therefore, it was concluded that "medical co-prescription of heroin should be long
lasting to obtain stable positive outcomes“ (section 2.4; page 38).

Long-term retention in HAT was 55% after two years in Germany (Verthein et al., 2008), 50% after three years in Spain (Oviedo-Joekes et al., 2010c), and 40% after six years in Germany (Güttinger et al., 2003). In the Netherlands, four year retention amounted to 56% among patients who responded to 12 months HAT and seriously deteriorated during a two months discontinuation period of HAT, and thus were eligible for long-term HAT (Blanken et al., 2010a).

All studies on outcome of long-term HAT show that the improvements that were achieved within the first six to 12 months of treatment during the RCTs stabilized or even further improved in patients that remained in HAT. Patients in long-term HAT did better in terms of illicit heroin use and health, than patients not or no longer in HAT. In chapter 6 it was shown that patients in four years long-term HAT had an OR of 6.0 or more for continued treatment response compared with patients who were no longer in HAT. Among the patients in four years continued HAT, 70% had recovered from physical, mental and social problems, while 25% also had stopped illicit drug and excessive alcohol use.

Based on a seven-year period of HAT in Switzerland, mortality of patients in HAT was estimated at 1% per year, which was lower than the estimated death rate of 2.5-3% among Swiss opiate users in general. (Rehm et al., 2005) The standardized mortality ratio for patients in HAT was also lower than the standardized mortality ratio in an Australian meta-analysis (Rehm et al., 2005).

With respect to patients who discontinued long-term HAT, two things have to be emphasized. First, as was shown in chapter 6, negative reasons for discontinuation outnumber positive reasons. Similar results were reported from Switzerland, with the longest history of HAT, where 3.155 patients have been admitted to HAT between 1994 and 2007: Discontinuation of HAT was more often determined by negative ($n = 463$) than positive ($n = 299$) reasons. Moreover, the proportion of positive HAT discontinuations did not increase over time (Frick et al., 2010b). Second, the patients who discontinued HAT did not drop out of treatment completely; the majority was referred to MMT, and a small minority was referred to abstinence-oriented treatment. Given the results that patients who discontinued long-term HAT showed less favourable outcome than patients who continued long-term HAT, the question that remains to be an-
swered, is: Could the patients who discontinued HAT have been retained in HAT and, if so, would they have shown better long-term outcome?

Thus, the chronic nature of heroin dependence, the aging population of chronic treatment-refractory heroin addicts (with increasing problems in health and social functioning), and the positive status of patients in long-term HAT (compared with patients who discontinued long-term HAT), provide ample and convincing arguments to offer HAT to patients without a priori restrictions on treatment duration, for as long as needed and indicated.

8.1.6 Cochrane review of HAT

Just recently, The Cochrane Collaboration published a review on "Heroin maintenance for chronic heroin-dependent individuals" (Ferri et al., 2010), in which it was concluded that "the available evidence suggests a small added value of heroin prescribed alongside flexible doses of methadone for long-term, treatment-refractory opioid users" in terms of:

- increased treatment retention,
- decreased use of street heroin and other illicit substances, and
- decreased probability of being imprisoned.

Furthermore, the authors conclude that "due to the higher rate of serious adverse events, heroin prescription should remain a treatment of last resort for people who are currently or have in the past failed maintenance treatment" (Ferri et al., 2010; page 2).

This conclusion is based on a number of outcome parameters that were chosen by the reviewers; a strategy that can be questioned. This is especially true since the authors failed to report the results of the pre-specified primary outcome parameters that were used in the different RCTs, including the multidomain response index of the Dutch trials. The main overall finding of these RCTs is that all studies showed a significant and substantial positive effect of HAT over MMT on their primary outcome variable(s) (see Table 1 and Figure 1). Instead, the reviewers defined "treatment retention" and "relapse to street heroin use" as the first two primary outcome parameters. While treatment retention is an important process variable, the meaning of this variable is different for the different studies, because different HAT trials targeted different treatment-
refractory heroin addicts inside as well as outside the treatment system. The Canadian and (part of) the German trial focussed upon heroin addicts not in treatment and found positive retention rates for HAT compared to MMT; Canada: 88% versus 54%, Germany among "Nicht-Erreichten": 64% versus 41%. In contrast, the Dutch trials recruited treatment-refractory heroin addicts being actively treated in MMT and reported treatment retention rates for HAT and MMT of 68% versus 87% for inhaling addicts and 72% versus 85% for injecting patients. First of all, it should be emphasized that standard oral MMT in the Dutch trials resulted in very high 12-months retention rates. Second, it should be mentioned that most patients who discontinued HAT did not drop out completely, but were generally referred to MMT and continued treatment. Thus, treatment retention rates between the six RCTs can not be compared without referring to the different target groups and the different recruitment strategies for HAT.

The second primary outcome parameter analysed by Ferri et al. (2010) is "relapse to street heroin use", which ignores, not only the primary goal of treatment of chronic disorders, being improvement and not cure (see for instance O'Brien & McLellan, 1996), but also ignores the primary outcome parameters as defined in the German trial (reduction in the use of street heroin with at least 3 of 5 urine samples negative and no increase in cocaine use, or a 60% decrease in the number of self-reported days with street heroin use and no more than 2 days increase in cocaine use) and the U.K. trial (reduction of regular use of street heroin, defined as 50% or more of negative specimens on urinalysis). As was shown in Figure 1 (this chapter), RRs for these primary, predefined outcome measures were 1.25 (95%-CI: 1.14-1.38) and 2.75 (95%-CI: 1.60-4.73), respectively; effect sizes that do not justify the conclusion of Ferri et al. (2010; page 1) that there was only a "marginally significant protective effect of heroin prescription plus methadone for the use of street heroin".

Thus, in line with O'Brien & McLellan (1996; page 237/8), who stated that: "As with other chronic disorders, the only realistic expectation for the treatment of addiction is patient improvement, rather than cure. ( ) Successful treatment leads to substantial improvement in three areas: reduction of alcohol and other drug use; increases in personal health and social functions; and reduction in
threats to public health and safety." (O'Brien and McLellan, 1996), it can be concluded that the currently available RCTs have shown that - for chronic, treatment-refractory heroin-dependent patients - compared to (continued) MMT:

- HAT does result in impressive reductions in illicit heroin use, and modest reductions in cocaine use and use of other drugs and alcohol (all RCTs);
- HAT does result in improvements in mental and physical health (Germany, the Netherlands, Spain, and Switzerland) and social functioning (Canada, the Netherlands, Spain, and Switzerland), and may reduce mortality (Switzerland); and
- HAT does result in reductions in threats to public health and safety (Canada, the Netherlands, Spain, and Switzerland) (see also: Lasnier et al., 2010).

8.2 For which patients does HAT work?

On the group level, HAT is more effective than (continued) MMT in treatment-refractory heroin dependent patients. However, not all patients benefited from HAT. It is therefore important to study predictors for treatment response in order to improve patient-treatment matching and the efficiency of treatment trajectories.

8.2.1 Previous abstinence-oriented treatment

In chapter 3 it was shown, in both heroin trials in the Netherlands, that clinical characteristics were generally not predictive of treatment outcome and not relevant for patient-treatment matching. The one exception was a history of abstinence oriented treatment: patients with at least one abstinence-oriented treatment episode in their treatment career were more likely to respond to HAT compared to MMT. This finding was confirmed in the German heroin trial (Haasen et al., 2010). We speculated that "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." (section 3.4; page 49). More recently, it was reported from the Canadian NAOMI-trial that
motivation at the start of treatment did not predict treatment retention or time to treatment discontinuation (in HAT nor MMT) (Nosyk et al., 2010). However, patients in HAT with a high motivation had a significantly higher probability of becoming a treatment responder than patients with low motivation (OR = 4.8; 95%-CI: 1.8-12.4) (Nosyk et al., 2010). Unfortunately, there was no information whether highly motivated patients were more likely to have a clinical history of abstinence-oriented treatment.

Given these converging results, it is tempting to redefine treatment-refractory heroin dependence in terms of patients who failed in both MMT and abstinence-oriented treatment. There are, however, two important reasons not to do so.

First, there is convincing evidence that heroin dependence is a chronic disorder, with episodes of abstinence frequently and often repeatedly followed by relapse (Leshner, 1997; McLellan et al., 2000; O'Brien and McLellan, 1996). Given the chronicity of the disorder, the goal of treatment has shifted from total abstinence (i.e., cure) to stabilization and improved health and functioning (i.e., care) (Haasen and van den Brink, 2006; Van den Brink and Haasen, 2006; Van den Brink and van Ree, 2003). About 50–60% of patients begin re-using within 6 months following treatment cessation, regardless of the type of discharge, the patient characteristics or the particular substance(s) of abuse (McLellan et al., 2005; page 449), and studies of abstinence rates at 1 year after completion of treatment indicate that only 30-50% of patients have been able to remain completely abstinent throughout that period (O'Brien and McLellan, 1996; page 237/8). In an impressive 33-year follow-up study of heroin addicts in the U.S. it was shown that only 22% of the patients were abstinent at any given time point throughout those 33 years. Moreover, even among addicts that had been abstinent for a period of at least five years, a quarter subsequently relapsed into heroin use (Hser et al., 2001).

Second, the outcome of (inpatient) abstinence-oriented treatment is generally disappointing (Mattick et al., 2009; Sees et al., 2000). In a review, comparing five heroin detoxification trials (n = 380), the percentage of patients achieving initial, seven days of heroin abstinence varied from 4% to 12% for outpatient detoxification, 24% for inpatient detoxification, and 58-60% for rapid detoxi-
fication with or without sedation (Digiusto et al., 2005). Recently, the efficacy of naltrexone-induced rapid detoxification with or without anaesthesia was studied among heroin dependent patients, with a repeated history of unsuccessful abstinence oriented treatments, but with a social network including non-opioid users and relatively few problems in, for instance, physical and mental health and social functioning. One month after rapid detoxification with naltrexone, 46% of the patients (irrespective of anaesthesia) showed evidence of re-instated illicit heroin use (de Jong et al., 2005), and after 16 months only one quarter of this good-prognosis sample was still abstinent (de Jong et al., 2004).

Thus, the disappointing results of abstinence-oriented treatments (often in less severe dependent heroin addicts, with a seemingly better prognostic profile) and the chronicity and severity of heroin dependence, indicate that abstinence-oriented treatments in the HAT target population of chronic, treatment-refractory heroin addicts will result in low success rates and high relapse rates. Therefore, previous attempts at heroin detoxification and other forms of abstinence-oriented treatments, should be precluded as an extension of the definition of treatment failure for HAT.

8.2.2 Other patient characteristics: Motivation, gender and psychiatric comorbidity

In addition to the modifying effect of previous abstinence-oriented treatment on treatment response, a limited number of specific patient characteristics have been explored, in the German and Canadian heroin trials.

First, as already mentioned in the preceding section, (baseline) motivational status did not predict retention or time to discontinuation in either HAT or MMT. However, while patients were retained in HAT regardless of motivational status, motivated patients showed a more favourable response to treatment in terms of decreases in crime and illicit drug use (OR = 4.8; 95%-CI: 1.8-12.4). According to Nosyk et al. (2001; page 161) "HAT successfully retains opioid dependent patients who otherwise may not have been attracted into existing treatment options, and may enhance the odds of successful rehabilitation among patients motivated for treatment."
Second, in another post hoc analysis of the Canadian trial, it was shown that male and female patients did not differ in retention and overall clinical response (i.e. improvement in illicit drug use and/or criminality) in HAT or MMT (Oviedo-Joekes et al., 2010a). HAT was more effective than MMT in retaining both male patients (RR = 1.55; 95%-CI: 1.24-1.92) and female patients (RR = 1.74; 95%-CI: 1.25-2.43). However, in terms of overall clinical response, HAT was more effective than MMT among heroin addicted men (RR = 1.54; 95%-CI: 1.14-2.08), but not among heroin addicted women (RR = 1.19; 95%-CI: 0.81-1.74). It should be noted, however, that the number of female patients was relatively small resulting in a broad 95%-CI and a non-significant finding. In the Dutch trials, gender was neither a predictor of outcome nor a patient-treatment matching variable (Blanken et al., 2005; Blanken et al., 2010b).

Third, in post hoc analyses of the German trial, among a sub-sample of patients for whom (CIDI) psychiatric diagnoses were available (n = 626 out of all 1.015 patients) it was shown that HAT had a better outcome than MMT concerning improvement of health and reduction of illicit drug use, regardless comorbid psychiatric diagnosis. However, the effects in the comorbidity group were not as strong as in the non-comorbidity group. It is unclear why Schäfer et al. concluded that "the results of our study indicate that psychiatric comorbidity can be considered an additional inclusion criterion for HAT" (Schäfer et al., 2010; page 94). It seems more warranted to conclude that psychiatric comorbidity should not be seen as a contra-indication for HAT.

Finally, Haasen et al. (2009) have shown that HAT was more effective than MMT both among patients with and without comorbid alcohol dependence (assessed with ASI composite score or CDT-blood measure), in terms of improvements in health and illicit drug use. Moreover, HAT was more effective in reducing alcohol intake during treatment than MMT, which is most likely caused by the more frequent testing for sobriety in HAT (three times daily) than in MMT (once daily) before heroin and methadone were dispensed (Haasen et al., 2009).
8.2.3 Treatment failure as criterion for HAT

All six RCTs thus far were targeted at chronic, heroin-addicted patients with a history of treatment failures. Canada (completely) and Germany (partly) aimed at treatment-refractory heroin addicts that were not in treatment at the time of recruitment. The other trials (and part of the German trials) aimed at patients currently in MMT who did not benefit sufficiently from this treatment. However, the nature of the targeted population did not seem to affect the outcome of HAT with similar effects in patients currently in MMT and patients currently not in treatment (Haasen et al., 2007). Interestingly, post hoc analyses of the German trial revealed that patients without previous maintenance experience also did better in HAT than in MMT with respect to illicit drug use, but not with respect to health. This raises the question whether failed treatments should be defined in terms of failed maintenance treatments exclusively or that it could also be defined in terms of failed abstinence-oriented treatments (AOT), as an alternative option for failed MMT. In this case, treatment failure would be defined as "failed in MMT or failed in AOT," whereas in the extension that was rejected in the previous section, failed treatment was defined in terms of "failed in MMT and failed in AOT". Although the question whether or not treatment failure should be defined in terms of "failed in MMT or failed in AOT," can only be answered in a prospective controlled trial, it is important to consider the higher costs and medical risks of injectable heroin prescription when offering HAT to patients without previous MMT experience.

A closely related criterion of failed maintenance treatment relates to the medication prescribed as maintenance treatment. Although up to this date most trials exclusively targeted patients who failed in methadone maintenance treatment, also patients who failed in buprenorphine maintenance treatment (BMT) should be considered to be eligible for HAT, since BMT is becoming a widely available and proven effective maintenance treatment for heroin dependency (Mattick et al., 2008).

To summarize, based upon the available evidence with respect to patient-treatment matching, it can be concluded that HAT should continue to target chronic heroin addicted patients who have failed in outpatient substitution treatment. In order to further improve the efficiency of HAT, patient-treatment
matching studies should shift focus from phenotypic, clinical patient characteristics towards endophenotypic and genetic patient characteristics. For instance, among alcohol dependent patients it has been shown that different polymorphisms of the gene encoding the mu-opioid receptor OPRM1 differentially predict relapse and time to heavy drinking after treatment with naltrexone (Oslin et al., 2003). At the time of writing, data that have been collected among 200 patients in HAT are analyzed in terms of possible genetic differences in allelic frequencies of polymorphisms in genes encoding for opioid (mu, kappa, delta, and sigma) and cannabinoid receptors (CB1 and CB2) and their endogenous ligands involved in opiate addiction (promelanocortin, prodynorphin, proencephalin, and pronociceptin) between patients who have and who have not benefited from treatment with co-prescribed heroin.

8.3 How does HAT work?

In the final report of the Dutch heroin trials, it was already stated that it is "likely that the observed effects of the co-prescription of heroin are closely associated with the behavioural changes connected with and resulting from the medical co-prescription of heroin; behavioural changes that could not be induced in this chronic, treatment-resistant population by the prescription of methadone alone." (CCBH, 2002; page 147). In chapters 4 and 5 data were presented on the patients' perspective on HAT and the course of subjective heroin craving and illicit heroin use during HAT, respectively. Although these data do not offer direct answers to the question "How does HAT work?" they do give some insight in the underlying processes responsible for the success of HAT.

Participation in HAT offers the patients an opportunity to disengage their daily life structure from the illicit drug scene. However, not all patients succeed to discontinue or strongly reduce their illicit heroin and cocaine use. This may be related to the function that heroin has in their life. As argued in chapter 4, there is some indication that patients who - in addition to the negative reinforcing effects of heroin - still experience heroin's positive reinforcing effects, are more likely to respond to HAT (6 out of 7 patients) than patients who only experience the negative reinforcing effects of heroin (9 out of 17 patients). If this relationship between experiencing positive reinforcing effects from heroin and
treatment response would be found in larger samples as well, this could indicate that patients who are (still) able to experience these positive reinforcing effects are also patients who are able to experience positive reinforcing effects from behaviours other than drug use. In this respect, it would be worthwhile to study if elements from the Community Reinforcement Approach (Roozen, 2005; Roozen et al., 2004) or Contingency Management interventions aimed at behavioural goals other than drug use (Lussier et al., 2006), could stimulate patients in HAT to withdraw from the illicit drug scene and move towards a lifestyle with decreased illicit drug use and regular, non drug-related activities that are also experienced as positive and reinforcing.

In a previous study with double-blind heroin-dose variations it was shown that heroin craving was associated with the prescribed dose of heroin, with higher doses being related to lower craving levels (Rook et al., 2006). Although the association between heroin craving during treatment and treatment response in the small-sample sub-study reported in chapter 5 was not significant, heroin craving could be a useful measure to assess the adequacy of the prescribed heroin dose, and an early indicator of the patient's response to HAT. In a study among alcohol dependent patients (changes in) craving predicted time to relapse to any drinking after treatment (Oslin et al., 2009) and the authors suggested that different craving patterns during treatment may define different subtypes of alcohol dependent patients that differentially respond to treatment. In order to further elucidate the role of heroin craving and to investigate whether the treatment response to HAT can be optimized, small-scale, prospective studies should be conducted in which the course of heroin craving during treatment and its association with treatment response is further explored.

In these studies, craving measures preferably should be extended from self-report to more implicit and less conscious processes that may relate to cue-reactivity, attentional bias and the salience of illicit heroin (and other, non-prescribed drugs, like cocaine) (Field and Cox, 2008; Rosenberg, 2009). As was hypothesized in chapter 5, it might well be that given the stable availability of high-quality, pharmaceutical grade heroin, heroin loses at least some of its salience for some of the patients in HAT (Goldstein and Volkow, 2002). If this were the case, this may explain why some patients succeed in disengaging
their daily life from the illicit drug scene, as described in chapter 4, while others did not. In addition, it would be important to study among patients for whom heroin craving does not reduce and who continue to use illicit heroin, and cocaine as well, if they display automatic action-tendencies to approach illicit heroin (and cocaine), and, if so, if these tendencies can be re-trained in a direction away from approaching illicit heroin and cocaine. This intervention (attentional bias modification training) has shown to be potentially effective in alcohol-dependent patients in terms of overall treatment response and prevention of relapse (Schoenmakers et al., 2010).

8.4 How to improve the way HAT works?

8.4.1 Additional psychosocial interventions

In most HAT trials, pharmacological treatment was supplemented by a standard offer of psychosocial support in HAT as well as MMT. The German trial formed an exception by simultaneously randomising patients to either HAT or MMT and to either "psycho-education plus individual counselling" or "case management and motivational interviewing". Although different in content, the two psychosocial interventions were very similar in terms of intensity. The main finding was that type of psychosocial intervention was not related to the primary outcomes, i.e., improvement in health and illicit drug use (Haasen et al., 2007).

One of the most promising psychosocial interventions in the treatment of heroin and cocaine addiction is Contingency Management (CM) (Dutra et al., 2008). CM is a proven effective intervention to change behaviour by providing incentives for meeting verifiable behavioural goals, like abstinence in cocaine or illicit heroin use (Griffith et al., 2000; Lussier et al., 2006; Prendergast et al., 2006), but also improving clinic attendance and medication compliance (Lussier et al., 2006). In 2003 an RCT was initiated in The Netherlands, to study the efficacy of CM as an add on treatment to HAT, targeting cocaine use. In a cross-over design, patients in HAT were first randomized to either HAT supplemented with cocaine-CM for six months ($n = 115$) or HAT only for six months ($n = 110$). After six months, cocaine-CM in the experimental group was discontinued and patients continued with standard HAT, whereas patients who received standard HAT were switched to HAT plus cocaine-CM for six months.
The primary outcome parameter is cocaine use (urinalysis), and secondary outcome parameters are treatment retention and treatment response. The last patients will finish the study by November/December 2010 and results will be available in 2011. Thus far, the trial is successful in obtaining 75-80% of all planned urine-sample submissions in both treatment groups.

### 8.4.2 Alternative and additional treatment options

Given the high costs (although outweighed by the financial benefits) and the slightly increased medical risks of overdose and seizure (although controllable and manageable) of HAT and the fact that around 50-55% of the patients do not respond to HAT (see chapter 8), additional treatment options for heroin dependent patients should continue to be explored, in order (1) to reduce the costs of HAT, (2) to further increase the medical safety of HAT, and (3) to address the needs of patients that do not benefit from HAT. Potential options include different routes of administration of the prescribed opiate or the use of opiates other than heroin. The following options will be discussed: oral and intranasal ("snorting") administration of heroin, and prescription of hydromorphone or oral (slow release) morphine.

In a small pilot study (with only two patients in HAT) it was found that, although the pharmacokinetic profile and bioavailability of orally administered heroin was inferior to intravenously administered heroin, the pharmacodynamic profile of oral heroin administration, in terms of "flash" and "high" effects, was acceptable for the patients (Gyr et al., 2000). In a large, naturalistic cohort study \( n = 365 \) Frick et al. showed that oral administration of heroin is feasible, safe (in terms of the number of serious adverse events: 0.032 SAE in the first and 0.007 in the second application year for oral administration \textit{versus} 0.043 SAE per application year for intravenous administration) and effective (in terms of treatment retention: two-year survival rates > 80%, compared to a one-year survival rate of 70% in intravenous HAT) (Frick et al., 2006; Frick et al., 2010a). Although no data are available on the clinical effectiveness of orally administered heroin, these feasibility studies make orally administered heroin tablets an interesting candidate for further testing in controlled trials, as a potential alternative for the prescription of injectable or inhalable heroin.
Intranasal administration of heroin might be a second acceptable and safe alternative. Cone found similar pharmacokinetic and pharmacodynamic properties for intranasally administered ("snorted") heroin compared to intramuscular administered heroin (Cone et al., 1993). However, Mitchell et al. reported a somewhat less intense effect for intranasal heroin spray compared to intravenous heroin in terms of speed and magnitude of peak plasma morphine and 6-monoacetylmorphine (6MAM) concentrations, but withdrawal suppression and positive effects were at least as strong for intranasal compared to intravenous administration and all subjects gave favourable appraisals of the intranasal diamorphine spray, citing advantages including ease of use, the avoidance of needle hazards, and reduced stigma (Mitchell et al., 2006). Comer et al. compared intravenous with intranasal heroin administration and concluded that, although intranasal heroin is less potent than intravenous heroin, the reinforcing effects and subjective ratings for both routes of administration were quite comparable (Comer et al., 1999). Overall, these studies suggest that, compared with intravenous administration, intranasal administration of heroin produces somewhat lower blood concentrations and a slower onset of action, coupled with an adequate bioavailability and positive drug effects, that can be easily controlled by the "snorting" patient (Cone, 1998). The intranasal heroin dosages in these studies varied from 12 mg (Cone, 1998), through 40 mg sprayed heroin (Mitchell et al., 2006) to 100 mg (Comer et al., 1999) snorted heroin. However, it is unknown whether higher dosages, as are common in supervised HAT, of intranasal heroin are tolerated by patients.

Hydromorphone is another opiate agonist with potential effectiveness in the treatment of chronic, heroin dependent patients. In the Canadian NAOMI trial, a small \( (n = 25) \) group of patients was prescribed injectable hydromorphone (a registered medicinal product for pain management) instead of injectable heroin, in a randomized, double-blind design. The majority of hydromorphone patients thought they had possibly (32\%) or definitively (32\%) received heroin and no patients thought they were definitively receiving hydromorphone. Moreover, hydromorphone was similarly safe and effective (in terms of treatment retention and illicit drug use) as prescribed heroin (Oviedo-Joekes et al., 2010b).
Although in general, sustained- or slow-release oral morphine treatment (SROM) seems inferior to MMT and buprenorphine treatment (Giacomuzzi et al., 2006), there are indications that SROM might be effective in patients who do not tolerate or do not respond favourably to oral methadone. In two studies, MMT patients were switched to SROM, showing positive outcomes in social functioning, health, craving and a higher preference for oral morphine (78%) over methadone (22%) (Mitchell et al., 2004), and improvements in opioid withdrawal symptoms and craving for heroin (Kastelic et al., 2008). Thus far, SROM was explored in small, non-randomized studies and has not been directly compared with (injectable or inhalable) HAT. In addition, it should be noted that morphine-levels after oral heroin administration were higher ($C_{\text{max}}$) and peaked faster ($t_{\text{max}}$) than after oral morphine administration, thus making oral morphine less likely a suitable candidate in a treatment context where injectable or inhalable heroin is already prescribed.

8.5 Conclusion

Medical prescription of heroin - alone or in combination with oral methadone - to chronic heroin addicts with insufficient benefit from methadone maintenance treatment or other treatments for heroin dependence, currently in or out of methadone maintenance treatment, has proven to be a feasible, safe and efficacious treatment in six RCTs, in six different countries with over two thousand patients. Two large cohort studies in Switzerland and the Netherlands further support the effectiveness and safety of HAT as a routine, last resort clinical treatment option for treatment-refractory heroin dependent patients.

For the near future, there are some major challenges to further improve the quality and effectiveness of HAT in terms of treatment retention, illicit drug use, physical and mental health and social functioning, including criminality. Early 2011 we will know if contingency management is an effective add on psychosocial intervention for HAT in improving cocaine use, treatment retention and treatment response. In addition, studies are needed on the efficacy and safety of alternative modes of heroin administration, e.g. oral or intranasal heroin administration. In order to further improve the efficiency of HAT, patient charac-
teristics at the endophenotypic and genetic level should be studied to identify potential predictors for patient-treatment matching. And, finally, for treatment-refractory heroin addicted patients who do not respond sufficiently to HAT, there remains the need to continuously explore the effectiveness of other psycho-social (e.g., drug user rooms), pharmacological (e.g., hydromorphone) and other innovative medical interventions (e.g., deep brain stimulation or other neuromodulation techniques) to at least stabilize and if possible improve their health situation and quality of life and to minimize the potential harms caused by ongoing illicit heroin use.

8.6 Epilogue: From trials to routine treatment

On 4 February 2002 the results of the two randomized controlled trials were presented to the Minister of Health. Although the results were very positive and the Minister of Health openly and unrestrictedly supported the conclusions and recommendation of the committee that was responsible for the execution of the study on 12 March 2002, this was not the start of routine heroin-assisted treatment in the Netherlands (see Table 3, next page).

The results of the study and the recommendation of the Minister of Health to implement the findings into routine clinical care were scheduled for 17 April 2002 to be discussed in the Dutch parliament. However, on 16 April 2002 the Dutch Government had to resign because of the Dutch involvement in Srebenica in former Yugoslavia in 1995.

General elections were planned with the populist party of Pim Fortuyn as one of the new participants. On 6 May 2002, one week before the elections, Pim Fortuyn was assassinated and during the elections, on 15 May 2002, his party became the second largest of the country. A new Government with the populist party as one of the coalition members was formed. In that period, heroin-assisted treatment was hardly on the agenda. However, this Government lasted only a few months and in December 2002, the interim Government decided to make a first step in the process to implement heroin-assisted treatment in the Netherlands. As described in chapter 7, a naturalistic study was started to see whether the results
Table 3. History of HAT in the Netherlands after the presentation of the HAT RCT results

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>4 February 2002</td>
<td>Presentation of the results of the RCTs to the Minister of Health</td>
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<tr>
<td>12 March 2002</td>
<td>Positive response Minister of Health: HAT* should be implemented</td>
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<tr>
<td>16 April 2002</td>
<td>Fall of the Government about role of the Dutch army in Srebrenica</td>
</tr>
<tr>
<td>6 May 2002</td>
<td>Assassination of populist party leader Pim Fortuyn</td>
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<tr>
<td>15 May 2002</td>
<td>Victory populist party of late Pim Fortuyn: no further steps in HAT</td>
</tr>
<tr>
<td>15 October 2002</td>
<td>Fall of the Government due to problems in populist party</td>
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<tr>
<td>December 2002</td>
<td>Start naturalistic effectiveness study HAT</td>
</tr>
<tr>
<td>23 January 2003</td>
<td>Installation Committee Implementation HAT (CIBH)</td>
</tr>
<tr>
<td>15 May 2003</td>
<td>Report CIBH: advice 15 treatment units and 1000 treatment slots</td>
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<tr>
<td>July 2003</td>
<td>Start registration procedure heroin as medicinal product</td>
</tr>
<tr>
<td>December 2005</td>
<td>Registration dossier presented to Medicine Evaluation Board</td>
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<tr>
<td>May 2006</td>
<td>Start study with HAT + Contingency Management for cocaine use</td>
</tr>
<tr>
<td>21 December 2006</td>
<td>Registration heroin as a medical product for heroin dependence</td>
</tr>
<tr>
<td>18 July 2009</td>
<td>Law change permitting heroin prescription as routine treatment</td>
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* HAT = heroin-assisted treatment

from the RCTs could be replicated in routine clinical practice. In addition, the interim Government installed a special advisory committee on the implementation of heroin-assisted treatment. In May 2003, this committee recommended the implementation of 15 heroin dispensing units in 13 different cities in the Netherlands with a total of 1,000 treatment slots (Commissie Invoeringsaspecten Behandeling Heroïneverslaving, 2003). However, routine heroin-assisted treatment would become much easier if heroin was registered as a medicinal product by the Netherlands Medicines Evaluation Board (MEB) and would become possible only after some changes in the Dutch narcotics law. Preparation of the dossier for the MEB started in July 2003, the dossier was presented to the MEB in December 2005, and registration of heroin as a medication for the treatment of chronic, treatment-refractory heroin dependent patients took place on 21 December 2006.
Meanwhile, as already mentioned, in May 2006 another study was initiated, testing the additional effect of contingency management for cocaine reduction in patients receiving heroin for the treatment of their heroin addiction. On 18 July 2009, the Dutch narcotic law was changed and from that time on heroin-assisted treatment can be offered as a routine treatment. In December 2010, approximately 700 patients were in heroin-assisted treatment in 15 treatment units in the Netherlands.