Heroin-assisted treatment: from efficacy to effectiveness and long-term outcome
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Summary

General introduction
Since the introduction of heroin in the Netherlands in 1972, the number of heroin users has increased from approximately 10,000 in 1977 to an estimated 30,000 in 1984 after which the number of heroin users stabilised. This heroin using population is characterised by a relatively low mortality rate and low incidence of new cases. At the same time, the route of heroin administration changed from almost exclusive (intravenous) injection to primarily inhaling the vapours of heroin base heated on aluminum foil (chasing the dragon). Problematic heroin users were served by a comprehensive treatment system ranging from abstinence-oriented treatment facilities to facilities directed at stabilization and harm reduction. Methadone treatment programs were always available. With the increase of the population of problematic heroin users and the introduction of HIV/AIDS in the mid 1980s the focus of the methadone treatment programs shifted from high-threshold, aimed at complete abstinence from heroin, towards low-threshold, aimed at engaging and maintaining problematic heroin users in treatment, in order to stabilize or reduce their illicit heroin use, to reduce health risks and to minimize drug-related harm. As a result, during the late 1980s and early 1990s around 50-80% of the heroin addicted population was reached by the treatment system. However, not all heroin users benefited from treatment and it was estimated that around 8,000 problematic heroin users, although in methadone maintenance treatment, were not adequately regulated or extremely problematic. This led to a number of experiments involving substitution treatments with opioids other than oral methadone: intravenous morphine, intravenous methadone and oral dextromoramide (Palfium\textsuperscript{R}). The nature of these experiments (small-scale, uncontrolled, specific sub-groups) made it impossible to reach firm conclusions about the effectiveness of these treatments and their generalisability.

At the same time, in the mid 1990s, in Switzerland a large-scale naturalistic study was initiated on the effects of the medical prescription of intravenous heroin under supervision to treatment-refractory heroin addicted methadone maintenance patients. Although the results of the study were encouraging,
many questions remained unanswered. Due to the naturalistic, uncontrolled design of the study and the combination of heroin prescription with psychosocial support measures, no conclusions could be drawn with regard to the causal nature of the observed clinical improvements. In addition, differences in the dominant route of heroin administration between Switzerland (intravenous injection) and the Netherlands (inhalation) precluded generalization for the Swiss results to the Netherlands. In 1995 the Health Council of the Netherlands recommended a trial on the effects of medical prescription of heroin to severely heroin dependent patients with insufficient response to the available medical treatments. In December 1996, in concert with the Dutch Parliament, the Minister of Health, Welfare and Sport installed the Central Committee on the Treatment of Heroin Addicts (CCBH), with the task to report to the Minister on the intended and adverse effects of the experimental treatment with medically prescribed supervised use of pharmaceutical grade heroin.

After extensive consultation with national and international experts, and a number of commissioned pilot studies (e.g. development of a new formulation for inhaling pharmaceutical heroin), in 1997 the CCBH presented the protocols for two studies examining the effects of the medical prescription of injectable and inhalable heroin to severe, treatment-resistant heroin dependent patients to the Minister of Health, Welfare and Sport. The first treatment units opened in Amsterdam and Rotterdam (in 1998), later to be followed by treatment units in The Hague, Groningen, Heerlen and Utrecht (in 2002).

**Design of the study**

The primary objective of the heroin trials in the Netherlands was to evaluate both the intended positive and the harmful effects of 12 months maintenance treatment with oral methadone and co-prescribed heroin compared to a standard maintenance treatment with oral methadone alone in a population of chronic, methadone-refractory heroin dependent patients that were actively participating in a methadone maintenance program.

Only treatment-refractory heroin addicted patients in active methadone maintenance treatment were eligible for participation. Patients had to be at least 25 years old and meet diagnostic criteria for heroin dependence during the past
five years. In addition, in spite of regular participation in methadone main-
tenance treatment for at least the previous six months (with a prescribed
methadone dose of at least 50 mg (inhaling trial) or 60 mg (injecting trial) per
day for an uninterrupted period of at least four weeks in the previous five years),
the patients still used illicit heroin (nearly) daily and had poor physical or mental
health or poor social functioning.

Patients were randomised into one of three treatment groups: (1) oral
methadone during the first 12 months of the study; (2) oral methadone and co-
prescribed heroin during the first 12 months of the study; and (3) oral metha-
done during the first six months of the study and a combination of oral
methadone plus co-prescribed heroin during the second six months of the
study. In all three groups, patients were offered a comparable standard package
of psychosocial interventions. Since the prevalence of injecting heroin use is
rather low in the Netherlands, the study among the injecting heroin users was
restricted to the first two treatment groups.

A dichotomous, multi-dimensional composite index was chosen as the
primary outcome of the study and the difference in the percentage of responders
according to the composite index between the experimental and control condition
should be at least 20% in order to be clinically relevant. Patients were considered
as responders if:

(1) they showed \( \geq 40\% \) improvement in at least one of the three inclusion
domains (i.e. physical health, mental health, social functioning) from base-
line to the 12 months end-point, and

(2) the improvement was not at the expense of serious deterioration (\( \geq 40\% \)) in
any of the other domains, and

(3) the improvement was not accompanied by a substantial increase (> six
days/month) in the use of stimulant drugs (i.e., cocaine or amphetamine).

**Efficacy of heroin-assisted treatment compared to standard methadone maintenance treatment**

In *chapter 2*, the main results of the two open label randomized controlled trials,
comparing the effectiveness of 12 months medical and supervised co-
prescribed injectable or inhalable heroin plus methadone, compared to 12
months oral methadone alone were presented. Although 12 months treatment completion rates were high (ranging from 68-87%) in all groups, retention was significantly better among patients in methadone maintenance treatment (MMT) than among patients in heroin-assisted treatment (HAT). In spite of the somewhat lower treatment retention, HAT was significantly more effective than MMT both in the inhalable heroin trial (difference in response = 22.8% (95%-CI: 11.0-34.6%); Number Needed to Treat (NNT): 4.4 (95%-CI: 2.9-9.1)) and in the injectable heroin trial (difference in response = 24.3% (95%-CI: 9.6-39.0%); NNT: 4.1 (95%-CI: 2.6-10.4)). Furthermore, it was shown that HAT was about as safe as MMT, with few Serious Adverse Events related to the prescribed heroin and no fatalities related to the study medication. Finally, the majority (82%) of treatment responders rapidly and substantially deteriorated in the two months after the protocolised discontinuation of co-prescribed heroin after the 12 months experimental study period.

The main conclusions of the second chapter were: (1) in treatment-refractory methadone maintenance patients, medical and supervised co-prescription of inhalable as well as injectable heroin was more effective than standard oral methadone maintenance treatment, in terms of physical health, mental condition and social functioning; (2) HAT was probably as safe as oral MMT; and (3) medical co-prescription of inhalable or injectable heroin should be long-lasting in order to obtain stable, long-term positive outcomes.

**Patient-treatment matching**

Although, chapter 2 had shown that HAT was more effective than continued MMT, a substantial proportion of treatment-refractory heroin addicted patients did not respond to HAT. In addition, even though it has been documented that HAT is more cost-effective than continued MMT, treatment costs were considerable. Therefore, chapter 3 investigated whether specific patient characteristics were predictive of a differential response to either co-prescribed heroin treatment or ongoing oral methadone treatment.

Of 44 patient characteristics (relating to sociodemographic background, physical health, mental status, social functioning, and addiction (treatment) career, as well as current drug use), only one differentially predicted treatment
response. Patients with a history of one or more abstinence-oriented treatments had much better response rates in HAT (60.5%) than in MMT (23.8%), while patients without previous abstinence-oriented treatment had comparable response rates in HAT and MMT (39.2% and 37.5%, respectively). Further explorations of possible differences between patients with or without previous abstinence-oriented treatments did not reveal any clear-cut differences between these two groups of patients. As a post hoc explanation of this finding, it was suggested that patients with a history of abstinence-oriented treatment might have learned to comply better with the strict treatment regimen of HAT. In addition, it was also hypothesized that they were better motivated to take part in demanding interventions such as HAT.

Although this result suggested that previous abstinence-oriented treatment could be considered as an additional inclusion criterion, it was argued that it would be preferable to enhance patients' motivation through, for instance, Motivational Interviewing (Miller, 1996).

**A patient perspective on heroin-assisted treatment**

In order to learn more about patient factors that may predict treatment response in HAT, *chapter 4* presented the results of a sub-study, in which a series of open interviews (at the start of HAT, after two, six and 12 months of HAT and two months after discontinuation of HAT) were held with 24 patients, in the HAT centers in Groningen and Rotterdam. The open interviews addressed patients' experiences in terms of: (1) their subjective experience with the prescribed pharmaceutical grade heroin, (2) the changes in patients' life structure and perceived availability of heroin during HAT as well as after discontinuation of HAT, and (3) the function and reinforcing effects of heroin in their lifes. Based upon the qualitative accounts of the patients, it became clear that although patients differed in their appreciation of the quality and effects of the prescribed heroin, they all experienced the positive aspects of the assured heroin availability, which enabled many of the patients to strongly reduce or discontinue their involvement in illegal activities (like committing petty crime, drug dealing or sex work) and to improve their daily life structure. Patients differed in their accounts of heroin's functionality in their lifes. All patients recognized the negative rein-
forcing effects of heroin, i.e., the potency of heroin to avoid or remove negative states, like withdrawal, anxiety or stress. However, there were also patients who clearly articulated heroin's positive reinforcing effects, like 'feeling good'. This last group, the so-called pleasure appraisers, were more likely to have improved control over their illicit drug use and to have responded to HAT, when compared with the so-called mood managers, who only reported heroin's negative reinforcing effects.

The results of this qualitative study, among a small sample of patients in HAT, suggested that psychosocial interventions, like cognitive behavioural therapy (CBT; an intervention addressing the behaviour reinforcers of, in this case, illicit drug use) and contingency management (CM; a potentially effective intervention in promoting changes in life structure and non-drug related activities) should be considered as additional interventions for patients in HAT.

**Craving and illicit heroin use during heroin-assisted treatment**

*Chapter 5* reported on the second sub-study conducted in The Hague and Heerlen comparing 36 HAT patients with 37 MMT patients in terms of the course of heroin craving and illicit heroin use, during 12 months treatment. In addition, the relationship between heroin craving and illicit heroin use, as well as the association between craving and illicit heroin use on the one hand and multidomain treatment response on the other hand, was analysed, for patients in HAT and MMT.

Among patients in HAT (but not among patients in MMT) there were strong reductions in both illicit heroin use and heroin craving, which had been reached within the first two months of treatment. Illicit heroin use and heroin craving were significantly associated both among patients in MMT and in HAT. The expected association between illicit heroin use and multidomain treatment response was only found in MMT-patients and not in HAT-patients. This unexpected finding was probably due to the small sample size and low statistical power, since a post hoc analysis of the total intent-to-treat sample of the full-scale RCT showed a significant association between illicit heroin use and multidomain treatment response among patients in MMT as well as among patients in HAT.
It was argued that participation in HAT, with a guaranteed treatment offer of high quality, pharmaceutical grade heroin, might result in stable consumption patterns of co-prescribed heroin. Consumption of co-prescribed heroin, in turn, might become a form of automatized drug use behaviour, which is not likely to be disrupted and will, thus, invoke little heroin craving. The observed reductions in heroin craving during HAT, it was hypothesized, might also reflect a reduction of salience attributed to heroin by patients in HAT, given the stable perceived availability of co-prescribed heroin.

**Outcome of long-term heroin-assisted treatment**

*Chapter 6* presented the outcome of long-term HAT that was offered to the patients with a positive response to HAT and who had seriously deteriorated during the two months discontinuation of HAT (according to the protocol of the RCT). Among this selective sub-sample of 149 patients, four-year treatment retention amounted to 56%. It was shown that treatment response remained high for as long as patients continued long-term HAT, compared with patients who had discontinued long-term HAT. The proportion of patients without (physical, mental and social) health problems increased from 59% at the end of the first year HAT, to 70% after four years HAT. Moreover, one out of four patients who continued long-term HAT for four years were free of health problems and had discontinued illicit drug use as well as excessive alcohol use.

It was concluded that, unless there is a compelling medical or social contra-indication, heroin co-prescription should be continued as long as possible and necessary among treatment-refractory heroin addicted patients.

**From randomized controlled trials to routine clinical practice**

After the heroin-assisted treatment RCTs (RCT-HAT) were completed, the first patients were recruited for routine heroin-assisted treatment (Routine-HAT), starting in 2003. *Chapter 7* presented a systematic comparison of patients who were offered 12 months RCT-HAT \((n = 193)\) with patients who were offered 12 months of Routine-HAT \((n = 345)\). First, it was shown that patients in Routine-HAT were very similar to patients in RCT-HAT, although they were two years
older, reported somewhat more physical and mental health problems (non significant) and expressed a significantly higher need for treatment. Also, the proportion of injecting patients was lower in Routine-HAT (22%), compared with RCT-HAT (39%). Twelve-month treatment retention was very similar for patients in Routine-HAT (79%) and RCT-HAT (70%) and there were only small and clinically non-significant differences in attendance rates and heroin dose variations. Co-prescribed heroin treatment remained a safe treatment, also in Routine-HAT: Among the 345 patients, there were seven fatal SAEs, but none was related to the study medication. Twelve months treatment response in Routine-HAT amounted to 55% (comparable with 51% treatment response in RCT-HAT) and the reduction of cocaine use was somewhat more pronounced in Routine-HAT than in RCT-HAT. Finally, two models were constructed to predict treatment retention and treatment response on the basis of (baseline) patient characteristics in RCT-HAT, but these models could not be validated in Routine-HAT.

It was concluded that HAT in the transition from strictly controlled RCTs to routine clinical treatment remained a safe and effective intervention for chronic, heroin addicted patients who functioned poorly and who had not benefited sufficiently from other substitution treatments. It was also emphasized that treatment procedures should be well-described in treatment guidelines and HAT should be monitored regularly, in order to guarantee the quality and safety of heroin-assisted treatment in the long run.

**Heroin-assisted treatment: Discussion and conclusion**

In *chapter 8*, the results that were presented in the preceding chapters, were summarized and discussed in a broader context and in the light of the international literature on HAT and related topics. In the first section, it was concluded that - based on all the available evidence - HAT can be considered to be a safe, effective, and cost-effective treatment, and that this is also true for HAT as a routine, long-term clinical treatment. In the second section, it was concluded that - despite the repeated finding of better outcomes in patients with previous experience in abstinence-oriented treatment - no additional inclusion criteria are needed to obtain successful outcomes in HAT. In the following
sections, some potential mechanisms of action of HAT and possible ways to further improve its outcome were discussed, such as the use of additional psychosocial interventions (like Contingency Management) and the possibilities of other routes of heroin administration (oral or intranasal) or alternative opiate agonists (like hydromorphone).

**Conclusion**

On the basis of the presented studies, conducted in the Netherlands and corroborated by findings of RCTs from five other countries, it was concluded that heroin-assisted treatment (either alone or in combination with oral methadone) has proven to be a feasible, safe and efficacious treatment for chronic, heroin addicted patients who have not benefited sufficiently from methadone maintenance treatment (or other treatments for heroin dependence). In addition, it was concluded that the effectiveness and safety of heroin-assisted treatment as a last resort, routine clinical treatment option for treatment-refractory heroin dependent patients was supported by two large cohort studies. To further improve the quality, effectiveness and efficiency of heroin-assisted treatment, the effectiveness of *add on* psychosocial interventions should be studied, as well as the safety and effectiveness of alternative modes of heroin administration, and the potential of endophenotypic and genetic predictors for patient-treatment matching. Finally, there remains the urgent need to explore the effectiveness of other psychosocial, pharmacological and new medical interventions to at least stabilize and if possible improve the health situation and quality of life and to minimize the potential harms caused by ongoing illicit heroin use, for patients who do not benefit sufficiently from methadone maintenance treatment nor from heroin-assisted treatment.