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

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Chapter 1.

Introduction: Heroin-assisted treatment in the Netherlands.*

Abstract

In this chapter the history of heroin-assisted treatment in the Netherlands is described. The first two sections present an overview of the prevalence of heroin addiction and the evolution of methadone maintenance treatment in the Netherlands. Since not all patients benefit from methadone maintenance treatment, other opioids were studied in small and uncontrolled experiments in Amsterdam, which is described in the third section. Sections four and five, respectively, summarize the international experience with heroin prescription in the United Kingdom and Switzerland, and the process that resulted in the decision to start heroin-assisted treatment in the Netherlands. The preparation and the design and goals of the heroin trials in the Netherlands are described in sections six and seven. The chapter concludes with an overview of the contents of this thesis.

* This is a slightly adapted version of the second chapter of Blanken et al. (2010): Heroin-assisted treatment in the Netherlands: History, findings, and international context. *European Neuropsychopharmacology,* 2010, 20 (supplement 2): S105-158.

1.1 Introduction

Heroin was introduced in the Netherlands in the autumn of 1972. During the first few years, its use was largely limited to the ethnic Dutch population and the route of administration was mainly through intravenous injection. A rapid upsurge in the number of heroin users was recorded around 1975 when Surinam, a former Dutch colony in the north of South America, became independent. At that time, almost half of the Surinamese population emigrated to the Netherlands, settling mainly in Amsterdam, Rotterdam, The Hague and some other urban areas. Young Surinamese men came to play a major role in the street trade of heroin, and many of them became users themselves. In this, however, they adhered to their own way of administering the drug, i.e. not injecting but inhaling (Grund and Blanken, 1993; Korf, 1995).*

Since then, the estimated number of heroin users has increased from 10,000 in 1977 to 20,000 in 1979 and 30,000 in 1983 (Schreuder and Broex, 1998). From 1984 on, the total number of problematic heroin users in the Netherlands was rather stable (Bureau NDM, 2008; Hoekstra and Derks, 1991; van Brussel et al., 1996). In the period 1993-1996 the number of heroin addicts in the Netherlands was estimated to 30,000 (range 27,000-33,000), whereas in 2006 this estimate was 33,000 (range 24,000-46,000) (Bureau NDM, 2008; Schreuder and Broex, 1998).

The general picture was one of a relatively stable population of problematic heroin users with a low incidence of new cases and a low mortality rate. This was also reflected in the fact that the mean age of the methadone maintenance population in Amsterdam had been increasing by approximately 10 months each year since 1984 (the mean age in 1984 was 28.2; the mean age in 1997 was 38.8; the mean age in 2007 was 47.4) and in the fact that the percentage of heroin dependent patients in methadone maintenance that were younger than 26 years dropped from 28% in 1985 through 3% in 1997 and 1% in 2007 (Buster and Reurs, 1998; GGD Amsterdam, 2007). This was a trend in the whole country with only 2% of the methadone maintenance patients younger than 26 in 2002 (LADIS, 2004).

* All references are presented at the end of this thesis, starting at page 149.

At the same time the ratio of injectors to inhalers had changed with a growing proportion of addicts using heroin mainly or exclusively by inhaling the vapours of heroin base that has been heated on aluminum foil *("chasing the dragon")* (Grund and Blanken, 1993). For example in Parkstad in the south of the Netherlands heroin injection went down from 33% in 1996 to 13% in 1999, whereas in Rotterdam the percentage of injectors went down from 15% in 1999 to only 10% in 2003 (Bureau NDM, 2008).

This stable, aging population of problematic heroin users was and still is served by a comprehensive treatment and health care system that provides services free of charge and has little or no waiting lists. The system includes various kinds of abstinence oriented treatment facilities (e.g. inpatient and outpatient detoxification, methadone reduction, residential treatment, therapeutic communities) as well as a wide range of facilities that do not focus on abstinence but rather on stabilization and harm reduction (e.g. methadone maintenance, needle and syringe exchange, work projects, sheltered housing, user rooms). It was estimated that, depending on the local circumstances, 65-85% of the problematic heroin users was in some form of contact with the treatment system at the time that the heroin trial was discussed (Schreuder and Broex, 1998; van Gageldonk et al., 1997).

Patients often begin treatment with the objective of becoming abstinent. In the course of their addiction and treatment career, however, many of those who did not quit the habit switch from abstinence treatment to some kind of harm reduction, primarily through participation in a methadone maintenance program, with or without the additional use of other pharmacological treatments (e.g. triple therapy for AIDS, antidepressants for a co-morbid affective disorder) and psychotherapeutic (e.g. counseling, skills training) or psychosocial (e.g. budgeting, housing assistance, work projects) interventions. In a study that was specially conducted as a preparation for the Dutch heroin trials, it was shown that all methadone maintenance programs in the Netherlands had at least some medical, psychotherapeutic and psychosocial treatment offered to their patients, but the nature, intensity and structure of this treatment offer varied much more than can be justified by variation in patient characteristics (Van der Lelij and Driessen, 1998).

The medical prescription of heroin was seen as a final treatment option, which was intended only for those chronic heroin dependent patients that had repeatedly failed in other available treatments, including state-of-the-art treatment in a methadone maintenance program. It is, therefore, crucial to have an adequate understanding of methadone treatment in the Netherlands and the results that were achieved with this treatment before the heroin trials were initiated (Van den Brink et al., 1999).

1.2 Methadone treatment in the Netherlands

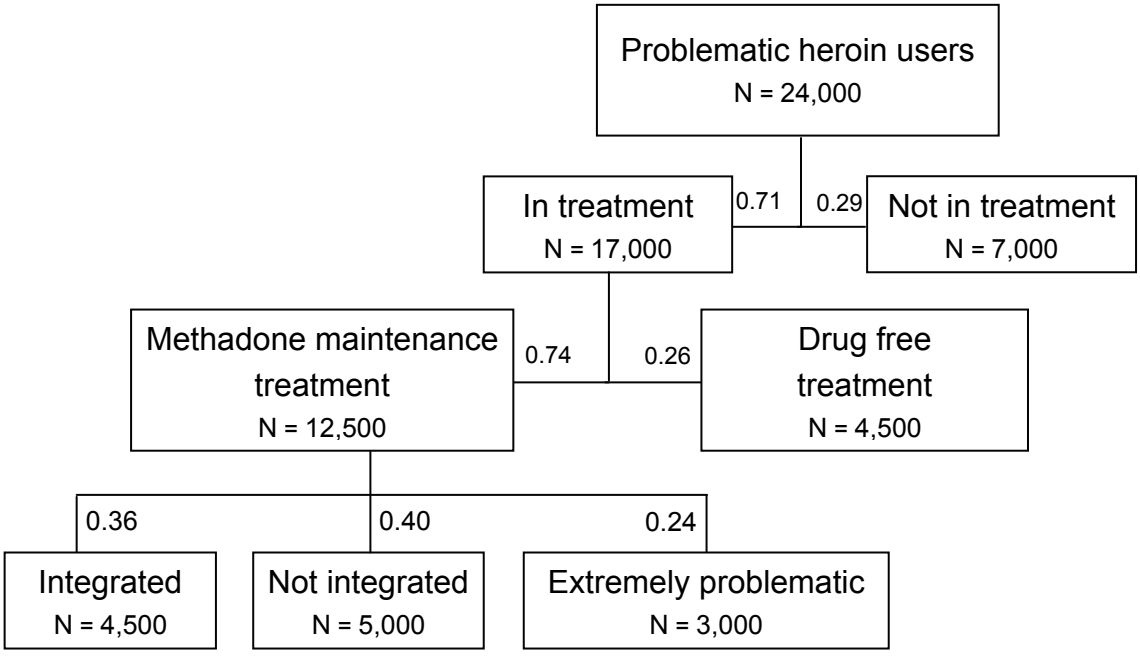
Methadone maintenance treatment for heroin addiction was introduced in 1965 in the United States (U.S.) (Dole and Nyswander, 1965). Prescription of methadone as a treatment method started in the Netherlands in 1968 (Geerlings, 1976; Trimbos, 1971). During the first few years, methadone was prescribed to morphine dependent patients. Following the introduction of heroin in the Netherlands in 1972, treatments with methadone were primarily directed towards achieving abstinence from heroin dependence. Generally, these methadone reduction programs suffered from high drop-out rates, and there was a serious threat that they would loose contact with many of the addicts. As a response to the rapid increase in the number of problematic heroin users during the late 1970s, and the introduction of HIV/AIDS in the mid 1980s, the aim of oral methadone prescription in the Netherlands shifted from achieving abstinence towards achieving stabilization and harm reduction. Prevention of risky behaviors and the provision of medical care through regular contact with the problematic users became the primary objectives of a methadone maintenance program in those patients who refused abstinence oriented counseling and were known to continue their use of illegal drugs. In a period of increasing risk of infection and increasing necessity - with regard to AIDS-prevention - to stay in contact with the problematic heroin users, the high drop-out rates in the methadone programs were seen as unacceptable by both treatment agencies and policy makers.

At the time that the heroin trials started, many of the Dutch methadone programs were so called 'low-threshold' maintenance programs, characterized by the absence of mandatory counseling, absence of sanctions in case of one or more drug positive urines, and relatively low dosages of methadone. These

programs were aimed at the reduction of health risks and improvement of the quality of life of those heroin dependent patients that were unable or unwilling to give up their drug use. Due to their low-threshold character, a high percentage of heroin addicts in the Netherlands (50-80%), including 'poor performers', were reached by these programs (Bieleman et al., 1995). In contrast, most methadone programs in the U.S. were 'high-threshold' programs, which targeted 'good performers', were aimed at achieving total abstinence from illicit opioids, and only reached 15-20% of the heroin using population (Office of National Drug Control Policy (ONDCP), 1998). Given these differences between the Dutch and the U.S. methadone efforts and the populations being served by them, results from American methadone evaluations could not simply be compared to those from Dutch programs.

Although no controlled studies on the effectiveness of the methadone treatments had been conducted at that time in the Netherlands, there was extensive clinical experience with dispensing methadone, and follow-up studies did provide some insight regarding their outcomes. In 1988, a survey was conducted on the dispensing of methadone in the Netherlands (Driessen, 1990). According to this study, the estimated number of problematic heroin users in the Netherlands was 24,000. Of these, an estimated 17,000 (71%) had been in contact with some treatment program at least once during the previous year (figure 1).

Figure 1 Drug treatment situation in the Netherlands
(Source: Driessen, 1990)



Among that group, approximately 4,500 had been in drug-free treatment and approximately 12,500 had received methadone on a regular basis, most of them for many years (mean time in program was approximately 8 years). According to the treatment staff of the methadone maintenance programs, 36% of the 12,500 methadone patients (*n* = 4,500) was well regulated (little or no illegal drug use, compliant with treatment, some social integration), 40% (*n* = 5,000) not adequately regulated (frequent use of illegal drugs, not fully compliant with treatment and low levels of social integration), and 24% (*n* = 3,000) extremely problematic (daily use of various illegal substances, physical and/or mental problems, high level of criminality, no social integration).

Furthermore, data from 1991 indicated that three-quarters (78%) of all methadone maintenance patients were still using heroin and more than a third (37%) was still using heroin on a daily basis (Driessen, 1992). At that time, nearly all methadone maintenance programs offered a broad spectrum of additional services, including psychosocial counseling, medical counseling and treatment, social work and, in some centers, psychotherapy. However, only a minority of the patients took part in one or more of these activities: 49% in social work, 28% in medical counseling, 13% in psychiatric counseling, 2% in psychotherapy, 2% in family therapy and 6% in group therapy (Driessen, 1992). These findings were confirmed by a subsequent study conducted in Amsterdam (Buster and Van Brussel, 1996). This study found that 5,545 problematic heroin users in Amsterdam had received methadone between 1994 and 1995 and that 65-70% of them was using heroin regularly or even on a daily base. This high level of illegal heroin use could not be (fully) explained by the low dosages of prescribed methadone, i.e. a daily dose of less than 50 milligrams. In fact, in 1995 in Amsterdam the average daily methadone dose was almost 60 milligrams (van Brussel et al., 1996).

In addition to the 11,500 patients in methadone maintenance programs in 1995, there were more than 1,400 drug-related admissions to general psychiatric hospitals and more than 3,000 drug-related admissions to addiction treatment clinics in the Netherlands (van Gageldonk et al., 1997). Finally, some outpatient drug-free treatment was provided by the Dutch Consultation Centers for Alcohol and Drugs.

At that time, methadone programs greatly differed in their treatment regimes, but no data were available on the relationship between methadone dose, the various forms of counseling provided in the programs, and the results of the treatment. However, data from the Amsterdam Municipal Health Service indicated that there had been an increase in the average daily methadone dosage from 43 mg in 1989 to 56 mg per day in 1995 (van Brussel et al., 1996), and similar developments had been reported in other cities in the Netherlands. This average was, however, much lower than the recommended dose in the U.S. (Parrino, 1992). According to their guidelines, the effective daily methadone dosage was 80 mg plus or minus 20 mg. However, a national survey showed that many programs in the U.S. had dose limits below these effective ranges and that many programs applied time limits for the maximum stay in the program (D'Aunno and Vaughn, 1992). Moreover, most of the patients that received methadone in the Netherlands were either unable or unwilling to give up their illicit heroin use, and higher methadone doses, which would prevent them from experiencing the euphoric effects of heroin, were often unacceptable to the patient (Korf et al., 1998). Consequently, prescribing higher doses of methadone was likely to result in high drop-out rates, thereby undermining one of the main aims of the Dutch methadone treatment system, which was to reach as many problematic users as possible for prevention, medical supervision and treatment. According to some evaluations, the effectiveness of this pragmatic approach was evidenced, among others, by the relatively small fraction of injecting drug users with AIDS in the Netherlands (12.4%) compared to the U.S. (24%) and Europe at large (38%) (Van Laar et al., 1995). In addition, mortality from drug addiction as a primary or secondary cause of death was quite low in the Netherlands where only 33 drug-related deaths were registered in 1995 (de Zwart and van Wamel, 1998). These data were corroborated by the stable and relatively small numbers of deaths from drug overdose reported in Amsterdam and Rotterdam among Dutch heroin addicts: 16 in Amsterdam and 14 in Rotterdam in 1996 (de Zwart and van Wamel, 1998).

Taken together, these findings suggest that in 1995: (1) methadone maintenance treatment was widely available in the Netherlands; (2) at least 50% of all problematic heroin users was enrolled in one of these programs; (3) methadone maintenance programs served a stable and aging population of chronic heroin

dependent patients with a long addiction and treatment career; and (4) a substantial number of the methadone patients was regularly using illegal heroin and other illegal drugs.

Approximately 8,000 of the 12,500 methadone maintenance patients were functioning less than optimally, exhibiting relatively low levels of medical and psychosocial functioning. Awareness of the limited success of these treatment efforts, in combination with the professional attempts to improve the living conditions of these chronically addicted patients, and the repeated calls for reductions in the public nuisance that resulted from their criminal behavior, led to various attempts to prescribe opioids other than oral methadone for the treatment of chronic, and especially treatment-resistant heroin dependent patients.

1.3 Prescription of opioids other than oral methadone in the Netherlands

Three small-scale experiments were conducted in the Netherlands involving substitution treatment with opioids other than oral methadone (see Table 1).

Table 1. History of opioid maintenance treatment in the Netherlands

Year	Event
1964	Fist methadone maintenance treatment (MMT) in the U.S.
1968	Introduction MMT for treatment of morphine dependence in the Netherlands
1972	Introduction of heroin to the Netherlands
1978	Start experiment with morphine i.v. + amphetamines (*n* = 5)
1983	Start experiment with morphine i.v. + MMT (*n* = 37)
1990	Start experiment with methadone i.v. (*n* = 30)
1995	Start experiment with oral dextromoramide + MMT (*n* = 53)
1996	Installation Central Committee on the Treatment of Heroin Addicts (CCBH)
1998	Start RCT with heroin-assisted treatment (HAT)
2006	Start RCT with HAT + contingency management (CM)

MMT = Methadone Maintenance Treatment
HAT = Heroin-Assisted Treatment
RCT = Randomized Controlled Trial

1.3.1 Intravenous morphine

In the late 1970s, the consulting physician of a low threshold day-center for chronic heroin dependent patients in Amsterdam began prescribing intravenous morphine and amphetamines to five patients. In 1983 he published the positive results in the Dutch Monthly Journal of Mental Health (Havas, 1983) and negotiated with the Amsterdam Municipal Health Service (GG&GD) to extend his program (Derks, 1997). After a heated debate, and the closure of the dispensing program, the Minister of Health approved a morphine dispensing program for 37 patients.

The morphine dispensing program started in 1983 with a group of 37 extremely problematic heroin addicts and existed for a period of two years. Most of the patients received a combination of intravenous morphine and a basic dose of oral methadone. The results of the study suggested a beneficial effect (reduced levels of illegal heroine use and lower levels of criminality) for approximately half of the participants. However, these results could not simply be attributed to the co-prescription of intravenous morphine, because no control group was included in the study. Further compromising the results was the attrition of 11 participants who abandoned treatment within the first year because they were dissatisfied with morphine and/or they were suffering from histamine reactions following its administration (Derks, 1984, 1990). By 1993, 10 years after the start of the project which was supposed to run for only two years, seven of the original 37 patients were still receiving intravenous morphine, 14 patients had returned to oral methadone maintenance treatment, one was known to be drug-free and 15 had died (five committed suicide, six died from AIDS, two had developed lung cancer, two died of a drug overdose). These figures clearly indicated a high mortality rate. However, most of these deaths were not thought to be related to the program itself but merely reflected the severity of the pathology at entrance. The experimental program demonstrated that prescription of injectable opioids was feasible, that very little morphine leaked to the black market and that some of the patients did improve. When the experiment ended, no new patients were recruited because when given a choice, most patients preferred injectable methadone (van Brussel, 1997b).

1.3.2 Intravenous methadone

A second quasi-experiment started in 1990, when the Amsterdam Municipal Health Service (GGD) started prescribing intravenous methadone to 30 hardly manageable and severely addicted AIDS patients who were in a very poor health condition. Prescription had to be terminated for almost half of the participants because they failed to comply with the treatment regimen. The patients who continued this treatment developed a better relationship with the treatment staff and heroin use decreased considerably, although it did not stop altogether. According to the patients, injectable methadone did give a 'flash', but not as good as injecting heroin. Therefore, it was no surprise that the vast majority of the Dutch methadone patients were not interested in a program with injectable methadone (Jongerius et al., 1994).

1.3.3 Oral dextromoramide

A third experimental treatment program was conducted by the Amsterdam Municipal Health Service (GGD) in 1995. Oral dextromoramide (Palfium^{R}) was prescribed in addition to oral methadone to 53 severely addicted, non-injecting heroin users who had average addiction careers of 21 years, all of whom had not responded at all to earlier methadone maintenance treatment. The goal of this new treatment strategy was to alleviate the patients' suffering and to stabilize them. Unfortunately, the project was not systematically evaluated. However, the general impression of the project staff was that the treatment resulted in more adapted behavior on the part of patients and in improved relationships with the treatment services. A clinical evaluation suggested that heroin use decreased among most patients and that one patient actually stopped using altogether. Urinalysis results further revealed no increase in the illegal use of cocaine. Finally, termination of the prescription of those patients who had not benefited from the treatment did not cause problems (van Brussel, 1997a).

These attempts to improve the medical and psychosocial conditions of chronic, treatment-resistant heroin dependent patients show that there was an active debate regarding the medical prescription of opioids other than oral methadone since the early 1980s (see Appendix 1, page 165, for an example). However, until

the late 1990s, all experimental treatment programs were directed to very small groups of heroin dependent patients with rather specific needs, and the results of these experiments had not been adequately documented, leaving ample room for doubt regarding to the effectiveness of these treatments and their generalizability.

Meanwhile, the Swiss had started the medical prescription of supervised intravenous heroin to treatment-resistant methadone maintenance patients. However, no data were available in the Netherlands with regard to the medical prescription of heroin. Given these circumstances, the Committee on Pharmacological Interventions in Drug Addiction of the Health Council of the Netherlands (Health Council of the Netherlands, 1995) had to turn to the scientific evaluations of experiments with heroin in other countries, such as the United Kingdom (U.K.) (Hartnoll et al., 1980) and Switzerland (Uchtenhagen, 1994), when discussing the desirability of medical prescription of heroin to chronic, treatment-resistant heroin dependent patients. The following section summarizes these findings.

1.4 Heroin prescription prior to the Dutch heroin trials

Before the trials started in the Netherlands, several countries had already gained experience with the prescription of heroin to heroin dependent patients. This began in the late 1950s and early 1960s when individual physicians in the U.K. started to prescribe heroin to heroin addicts for maintenance purposes (Strang et al., 1994). In 1968, National Health Service (NHS) drug clinics took over responsibility for prescribing injectable heroin from the individual physicians who were no longer allowed to prescribe heroin to heroin dependent patients. During the late 1960s and early 1970s, the NHS clinics began to switch their prescription habits from injectable heroin to injectable methadone and since the mid-1970s to oral methadone (Mitcheson, 1994).

During this period of change (1972-1975), a randomized clinical trial was conducted comparing the effectiveness of medical prescription of injectable heroin (the old standard treatment) with medical prescription of oral methadone (the new standard treatment) (Hartnoll et al., 1980). The study population consisted of 96 patients with a mean age of 23.9 years (range 18 to 32 years), a mean addiction career of 5.9 years, and a history of daily heroin injection for at least three months prior to the study. All participants were strongly committed to continuing their drug

use. The prescribed heroin doses ranged from 30 to 120 mg and the oral methadone doses ranged from 10 to 120 mg daily, with most prescriptions ranging from 40 to 80 mg per day. The study produced equivocal results, in that there were no clear indications that one treatment produced better overall results than the other. Both treatments produced positive outcomes in certain areas and negative ones in others. Patients in heroin maintenance attended the clinic more regularly than did methadone patients. They also showed a greater reduction in illegal heroin use and criminal activities. In both groups, no significant changes were observed in work, housing, diet or physical complications due to drug use. While the majority of those who were refused heroin prescription continued to inject illegal heroin and only attended the clinic when they needed a specific service, approximately one-fifth was stabilized on oral methadone, and another fifth stopped all drug use (Mitcheson, 1994). According to the investigators, the results suggested that the preference for one particular approach depended on the priorities assigned to the various outcome domains: on the one hand, they could choose to help a small number of addicts stop using drugs by means of oral methadone; on the other hand, they could choose to try to help as many addicts as possible to improve their situation by means of injectable heroin. After the study most of the patients in the heroin prescription group were persuaded to convert to oral methadone, leading the investigators to conclude that a maintenance dose of injectable heroin for a limited period of time did not have adverse consequences with regard to the long-term status of the patients (Hartnoll et al., 1980). The authors noted that the findings provided no clear indication that one treatment was superior to the other. However, the findings were used by many to further replace injectable heroin maintenance by oral methadone maintenance. After a heated debate, many of the clinics simply refused to prescribe injectable drugs to new patients (Mitcheson, 1994). In 1994 only 1-2% of the estimated 75,000-150,000 heroin users in the U.K. received a prescribed supply of any injectable drug, and only a small proportion of these was receiving injectable heroin (Strang et al., 1994).

In 1994, the Swiss initiated a large-scale study on the effects of prescribing injectable and inhalable heroin, injectable and oral morphine, and injectable and oral methadone. The prescription program started as a comprehensive scientific

experiment and was completed in December 1996. Based on the positive results of a naturalistic follow-up study of 1,146 patients that received injectable heroin and the support it received in a national referendum on the issue (71% of the voters supported it and a majority did in all 26 cantons), the medical prescription of heroin could be continued. According to the reports produced by the investigators (Rehm et al., 2001; Uchtenhagen et al., 1996a, 1997; Uchtenhagen et al., 1996b), and an independent process evaluation conducted by the World Health Organization (WHO, 1999), the results of the Swiss heroin experiment have indeed been positive, with high treatment retention rates (89% after six months and 69% after eighteen months), dramatic reductions in the use of illegal drugs (heroin and cocaine) and impressive reductions in the level of criminal activities. Patients also experienced substantial and stable improvements in the domains of physical health, psychological well-being, housing and employment, and a substantial reduction in the number of contacts with drug users and the drug scene generally. It was also important that no public order problems were encountered and no fatalities could be ascribed to the experiment. Finally, a cost-benefit analysis revealed an overall net economic benefit of 32 U.S. Dollars (45 Swiss Francs) per patient day.

However, these results were all based on an uncontrolled one-group pre-post design. Within that design, baseline characteristics were compared with follow-up data of almost 800 patients who entered the project in 1994 and stayed in it for at least 18 months (69%), i.e. without the possibility to compare the pre-post changes of the experimental group with pre-post changes in a control group. It should be noted that the Swiss study does include four rather small randomized trials, with some of them using a double-blind procedure. Most of these studies were, however, not intended to evaluate the long-term effects of heroin prescription, but to investigate the short-term effects associated with the different experimental substances (intravenous heroin, intravenous methadone, and intravenous morphine) on recruitment, treatment retention, treatment compliance and side effects. The only randomized trial examining the long-term effects of heroin prescription was a small study conducted in Geneva (Perneger et al., 1998). In this study, 51 treatment-resistant heroin dependent patients were randomly assigned to intravenous heroin plus other health and psychosocial

services or to some other conventional drug treatment, usually oral methadone maintenance. After six months, almost all of the patients using legal heroin had stopped their illegal heroin use and their psychological and social functioning (measured by the frequency of suicide attempts and the level of criminal activities) was much better than was observed for those in the control group.

It is also important to note that the Swiss experiment did not investigate the long-term effects of the prescription of heroin alone, i.e. without obligatory counseling and other psychosocial interventions. Thus, the Swiss experiments did not provide scientific information about the effect of the prescription of heroin per se, but more specifically about the feasibility, safety end potential effectiveness of a combination of supervised heroin prescription with psychosocial interventions. Consequently, it could not be excluded that the benefits of the Swiss heroin maintenance programs were at least partially attributable to the additional and partly mandatory psychosocial interventions (Perneger et al., 1998). Finally, it should be noted that the Swiss experiment with inhalable heroin in the form of heroin reefers (surrogate cigarettes) failed because of the low bio-availability (10-15%) of heroin from these *sugarettes:* 85-90% of the heroin burned in the process of smoking and never entered the body of the patient. In summary, the medical prescription of injectable heroin appeared to be both feasible and potentially effective in chronic, treatment-resistant heroin dependent patients, but only when the prescription was medically controlled, no take-home heroin was provided, and if psychosocial services were offered (Wodak, 1998). Three important questions remained unanswered:

(1) what is the relative contribution of heroin prescription in a combined pharmacological plus psychosocial intervention;
(2) what is the effect of participation in a scientific experiment on pre-post changes in some of the major outcome variables; and
(3) can we expect a positive effect of the prescription of inhalable heroin if adequate levels of bio-availability can be attained?

The latter question was crucial for the Netherlands with only a small minority injecting heroin and the majority inhaling heroin *(chasing the dragon).*

The Dutch study on the effectiveness of the medical co-prescription of heroin was designed to answer these questions with two randomized controlled trials

comparing the effects of a standard oral methadone maintenance program with similar programs using co-prescribed injectable or inhalable heroin, with drug administration at the clinic under medical supervision and no take-home dosages of heroin.

1.5 The decision to start heroin prescription in the Netherlands

We noted earlier, that the epidemiological situation in the Netherlands was characterized by a stable, aging population of problematic heroin users with long addiction and treatment careers. In addition, a substantial proportion of the Dutch heroin addicts was treatment-resistant, despite the existence of a comprehensive and easy accessible treatment system with many well-resourced methadone maintenance programs. These circumstances, together with the positive reports on the Swiss heroin experiment, led the Minister of Health to ask the Health Council of the Netherlands to formulate the conditions under which the prescription of heroin could become good clinical practice.

In its report, the Health Council concluded that the medical prescription of heroin to heroin dependent patients could have positive effects on the physical and mental condition and on the addictive behavior of patients. Medical treatment with heroin was regarded expedient if sound medical-scientific research could establish a positive balance between the effectiveness and harmful effects of such a treatment. In order to obtain the necessary data, the Health Council recommended a trial to be conducted in the Netherlands with severely heroin dependent patients with an insufficient response to the then available medical interventions (Health Council of the Netherlands, 1995).

In concert with the Dutch parliament, the government subsequently decided to prepare and to execute the study proposed by the Health Council. In December 1996, the Minister of Health, Welfare and Sport installed the Central Committee on the Treatment of Heroin Addicts (CCBH) with the task of reporting to the Minister on the intended and adverse effects of the treatment with heroin following the completion of a scientific study. After extensive discussions, the CCBH developed protocols to study the effects of the medical prescription of heroin (either through injection or by inhalation) to severe, treatment-resistant heroin

dependent patients. The protocols were developed in compliance with the guidelines for Good Clinical Practice, the Dutch law, and common medical-ethical standards regulating the conduct of medical-scientific research. Protocols were also developed for the development and testing of a stable and efficient inhalable form of heroin administration. The protocols of the study were also submitted for review to an international expert committee. In August 1997, the final protocols were presented to the Dutch Minister of Health. In January 1998, the International Narcotics Control Board (INCB) confirmed the estimates of the amounts of heroin that would be needed to execute the studies. Finally in July 1998, the first treatment units were opened.

1.6 Preparations for the heroin trials in the Netherlands

In order to start the experiment with supervised prescription of heroin to chronic, treatment-resistant heroin dependent patients several requirements had to be fulfilled.

First an estimate had to be made of the number of patients meeting minimal criteria to enter the study, i.e. the number of patients in methadone maintenance treatment not responding to an adequate dose of oral methadone (at least 50 or 60 mg for patients inhaling or injecting heroin, respectively). The study showed that many patients in methadone maintenance treatment were using much lower dosages either on their own request or based on the advice of the treating physician. However, in the larger cities in the Netherlands there were enough patients with an insufficient treatment response to adequate dosage of oral methadone (Korf et al., 1998).

Second, more information was needed with regard to the medical, psychological and social services that were offered to patients in methadone maintenance treatment. A special study showed that most methadone maintenance programs offered additional treatments, but that there were large variations in the nature and intensity of these additional services (Van der Lelij and Driessen, 1998). As a consequence, it was decided to pre-stratify the randomization by treatment site.

Third, in order to assess the effect of newly established heroin prescription units on neighborhood safety and public nuisance, baseline assessments were

conducted in all neighborhoods where a new treatment unit was planned and follow-up assessments were organized to measure the positive or negative effects. In general, no negative effects were reported and some neighborhoods even reported reductions in acquisitive crime and other kinds of public nuisance.

Fourth, a new formulation had to be developed for inhaling the pharmaceutical heroin and new strategies had to be tested to distinguish the legal pharmaceutical heroin from the illegal street heroin. The development of inhalable heroin started off with a tablet containing equal amounts of heroin base and caffeine (the latter was added to improve bioavailability). It was then changed into a tablet containing a smaller amount of caffeine (1:3) based on complaints about sleep problems. Unfortunately, these tablets could not be produced in large amounts and tablets were replaced by capsules with the same content. When it appeared that some of the nurses showed allergic reactions (contact dermatitis) to the traces of heroin on the outside of the capsules (Hogen Esch et al., 2006), the capsules were replaced by sachets with the same content. For the use of injectable heroin, multi-dose vials were developed with 3 grams of freeze-dried heroin hydrochloride per vial. In addition to this pharmaceutical developmental work, a full program of pharmaco-kinetic and pharmacodynamic studies was carried out.

1.7 The heroin trials in the Netherlands

The primary objective of the heroin trials in the Netherlands was to evaluate both the positive and 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-resistant heroin dependent patients that were actively participating in a methadone maintenance program. Effects would be measured in terms of improvements in the physical and mental status, improvements in social integration and social functioning, and reductions in illicit drug use. This objective would be pursued separately and simultaneously for the prescription of injectable and inhalable heroin.

As a result of serious discussions and various (international) consultations, the selected design included two multi-center randomized controlled trials aimed to include 750 patients treated in six treatment units located in six different cities in the Netherlands. After an intensive debate, the Central Committee

on the Treatment of Heroin Addicts (CCBH) decided that a traditional randomized clinical trial was preferred over a pre-randomization or 'Zelen design' (Central Committee on the Treatment of Heroin Addicts, 1997; Zelen, 1979, 1990). Within these randomized trials, patient would be allocated to one of the following treatment conditions (see Figure 2):

(1) oral methadone during the first 12 months of the study in combination with a standard package of psychosocial interventions;
(2) oral methadone and co-prescribed heroin during the first 12 months of the study in combination with the same standard package of psychosocial interventions; and
(3) oral methadone and the same standard package of psychosocial interventions during the first six months of the study and a combination of oral methadone, co-prescribed heroin and the same standard package of psychosocial interventions during the second six months of the study.

The third condition was included to test whether 6 months of methadone plus co-prescribed heroin would be long enough to result in stable positive outcomes. In the RCT with inhalable co-prescribed heroin, eligible patients were randomly allocated to one of these three treatment conditions, whereas in the RCT with injectable heroine, eligible patients were randomly assigned treatment conditions (1) and (2) only, because the vast majority of the problematic heroin users in the Netherlands were *chasing the dragon* and it was expected that there would be very few injecting heroin users eligible for the injectable RCT.

Following this randomized treatment phase, all subjects would enter a naturalistic follow-up period. Patients assigned to 12 months methadone only would then be offered the opportunity to receive the experimental treatment of co-prescribed heroin, whereas patients assigned to six or 12 months co-prescription of heroin would return to the methadone maintenance program or to any other form of standard addiction treatment in order to test whether 12 months treatment with co-prescribed heroin would lead to a permanent positive effect. This applied to responders as well as non-responders to the experimental treatment with heroin. For the group of non-responders this termination of the prescription of heroin would be final and the same strategy was planned for those responders to

Figure 2. Design of the trials

Qualification and randomization			*Experimental study period*		*Follow-up period*
Route of administration	Phase I 4 - 8 weeks	Group	Phase IIa 6 months	Phase IIb 6 months	Phase III 6 months
INHALING	methadone	A	methadone	methadone	methadone + heroin
		B	methadone + heroin	methadone + heroin	most appropriate care *
		C	methadone	methadone + heroin	most appropriate care *
INJECTING	methadone	A	methadone	methadone	methadone + heroin
		B	methadone + heroin	methadone + heroin	most appropriate care *

* No medically prescribed heroin, except on individual medical indication.

the experimental treatment that did not deteriorate after termination of heroin prescription. However, responders to the experimental treatment with co-prescribed heroin that showed substantial deterioration in their functioning during the first two months following termination of the experimental treatment were allowed to start again with the experimental treatment.

As already mentioned, patients in the experimental condition would be offered both methadone and heroin in combination with a standard package of psychosocial services, whereas patients in the control condition would be offered only methadone in combination with a similar package of psychosocial services. Continued methadone maintenance was chosen as the control condition because it constitutes the most extensively researched substitution treatment that was available. Heroin was chosen as the experimental compound because it was shown to be superior to other opioids in terms of its appeal to clients, treatment retention, treatment compliance, and safety in the Swiss trials (Uchtenhagen et al., 1997). The rationale for the combination of methadone and (co-prescribed) heroin in the experimental condition was that methadone, with its longer half life, could prevent withdrawal symptoms when the patient would not be able to take his or her medical heroin. Both methadone and heroin were provided free of charge. Dosages would be individually titrated with a maximum of 400 mg of pharmaceutical grade heroin per administration and a maximum of 1,000 mg of pure heroin per day in a treatment regimen with a maximum of three administrations per day and a treatment setting that allows treatment sessions seven days per

week. In general, patients would have to administer the heroin themselves either through self-injection or by *chasing the dragon*. Patients that were assigned to the injecting protocol were allowed to switch to inhaling as their route of administration, but patients assigned to the inhaling protocol were not allowed to move to injecting. No heroin take-home dosages were allowed and no other illicit drugs were prescribed to study participants.

Patients in the experimental and control condition were offered similar packages of psychosocial interventions, including individual counseling, group counseling, housing and budget assistance, participation in work projects and standard medical and psychiatric treatment. These additional treatments were available, although in varying degrees and combinations, in all cities (Van der Lelij and Driessen, 1998). Because of the differences in availability of additional treatments between cities, it was decided to pre-stratify random assignments according to city.

It was anticipated that stabilization or cessation of illicit drug use due to the experimental treatment would be accompanied by improvements in physical and/or mental health status and improved social functioning and integration. In the *primary* outcome variable, however, attention had to be paid to the way in which these different outcome domains were related. Two approaches were considered. The first was based on the view that the most significant benefit from treatment in this specific population, and arguably the most difficult to achieve, was social integration and rehabilitation. Previous studies suggested that improved social integration and rehabilitation was preceded by an initial reduction or stabilization of illicit drug use and illicit activities and improvements in physical and mental health status. In this view, social integration and rehabilitation would be the most relevant primary outcome. In the second approach, no assumptions were made regarding the hierarchical or sequential order of the different outcome domains. In terms of a primary effect measure, this implied the use of a composite index score that would simultaneously refer to improvements in illicit drug use, physical and mental health status and social functioning. In addition the question had to be answered whether the primary outcome variable should be dimensional or categorical. The first is often expressed in terms of differences in mean levels of improvement between experimental and control group(s), whereas the second is

commonly expressed in the difference in response rates between experimental and control group(s). In both cases, however, the difference that is considered clinically relevant and the statistical analyses should be determined prior to the start of the trial (European College of Neuropsychopharmacology, 1995). After a long debate, it was decided that the primary outcome of the study should be a dichotomous, multi-dimensional composite index and that 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 ≥ 40% improvement in at least one of the three inclusion domains (i.e. physical health, mental health, social functioning) from baseline to the 12 months end-point, and
(2) the improvement was not at the expense of serious deterioration (≥ 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).

Secondary outcome measures included treatment completion, and stable or sustained response (i.e., the percentage of patients who became a responder prior to the 12 months end-point and remained responder during the course of the trial).

1.8 Content of the thesis

This thesis presents the results of the Dutch trials on the efficacy, safety, and (long-term) effectiveness of heroin-assisted-treatment for chronic, treatment-refractory heroin addicts. In *chapter 2,* the main results of the two randomized clinical trials testing the feasibility, safety and efficacy of heroin-assisted treatment compared to continued methadone maintenance treatment are presented.

Once it had been concluded that supervised medical co-prescription of heroin to treatment-refractory heroin addicts was more effective than and probably just as safe as methadone alone, the question arose, whether there were patient characteristics that were predictive of a differential response to either methadone or methadone plus heroin treatment. The answer to this patient-treatment-matching question is pursued in *chapter 3*.

The next two chapters address factors that may be relevant for the process that is responsible for the success of heroin assisted-treatment. *Chapter 4* presents qualitative data on patient experiences regarding this new treatment, and describes patient perspectives on the function of heroin. In *chapter 5,* the effect of heroin-assisted treatment on craving and illicit heroin use and the relationship between these changes and overall treatment outcome is studied.

By the time the heroin trials in the Netherlands were finished, it was decided to follow the cohort of treatment-refractory heroin addicted patients that had participated in the trials. *Chapter 6* presents the four year follow-up data.

After the positive results of the two randomized controlled trials, due to political, administrative and legal complications it took the Netherlands another seven years, i.e. till the end of 2009, to implement heroin-assisted treatment as a routine last-resort treatment for patients that do not benefit from methadone maintenance treatment. In 2003, a naturalistic study was started to see whether the results from the randomized controlled trials could be replicated in routine clinical practice. The results of this study are presented in *chapter 7*.

In the final *chapter 8* the major results from the previous chapters will be summarized and discussed in light of the results of other trials on heroin-assisted treatment conducted in Europe and Canada. The chapter addresses the key results of the following research 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 concludes with some major challenges for the near future to further improve the quality and effectiveness of heroin-assisted treatment in terms of treatment retention, illicit drug use, physical and mental health and social functioning, including criminality.