A National Swedish Methadone Program 1966-1989

BY

LEIF GRÖNBLADH
Dissertation presented at Uppsala University to be publicly examined in Gunnesalen, Höghuset, Uppsala, Thursday, March 11, 2004 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

**Abstract**


Methadone Maintenance treatment of compulsive opioid addiction was started by the study of Dole and Nyswander (1965) and has subsequently been replicated in programs throughout the world. Methadone treatment has become the most effective modality for the treatment of chronic heroin addiction.

In 1966 a Swedish National methadone maintenance program was opened at the Psychiatric Research Center, Ulleråker hospital at Uppsala.

The aim of this thesis was to study the outcome of methadone treatment along various lines:
- An open randomised controlled study comparing the efficacy of methadone treatment and drug free treatment in 34 heroin addicts, 20-24 years of age.
- Before/after comparisons of rehabilitation among 345 heroin addicts admitted during the 23 years when this was a centralised National program.
- Retention in treatment.

**Study subjects, methods and treatment goals:** Subjects underwent an admission procedure when background data was collected through hospital records, and personal interviews. Therapeutic efforts focused on vocational rehabilitation, i.e. a return to full-time work or studies, hoping to make patients abandon their drug addict’s life-style and make them socially accepted and self-supporting.

**Results:** Thirty-four heroin addicts with a history of 4-8 years of heroin use were randomly assigned either to methadone treatment (17) or an untreated control group (17). The controls could not apply for methadone treatment until two years later. Outcome after six years observation showed that 81% became free of drug abuse, while the corresponding figure for the controls was only 1/17 (6%). The mean yearly death rate for the controls was 7.2%. Likewise, among the total material of 345 heroin addicts, 70-80% of the patients became engaged in work or studies, a significant increase compared with the situation before treatment (1.7%). The program was an effective reducer of illicit heroin use and criminality among its patients and prevented the occurrence of HIV infection among patients in long-term methadone treatment. The average one-year retention during 1967-1989 was 90% and cumulative retention showed that 29% were still in treatment 10 years after admission.

**Conclusion:** The present results emphasise the importance of vocational rehabilitation and support in a treatment strategy based on long-term maintenance therapy.

**Keywords:** heroin addiction, methadone maintenance treatment, rehabilitation, mortality, criminality and prostitution, retention, HIV-protection, treatment strategy

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ISSN 0282-7476
ISBN 91-554-5877-7

urn:nbn:se:uu:diva-4001 (http://urn.kb.se/resolve?urn=nbn:se:uu:diva-4001)
List of Papers

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1. Historical Remarks

1.1 Development of an illegal market for opioids in Sweden

Heroin was introduced on the Swedish illegal drug market in 1974 (Frykholm & Gunne, 1980). Before that time, opioid addiction occurred mainly among a minority of persons working in hospitals or pharmacies as well as iatrogenic cases who had been subjected to over-prescription following surgical or medical intervention. Around 1960 raw opium and later morphine base for iv injection was introduced on the Swedish illegal market. In 1967 a case-finding study localised 200 opioid addicts (Narkomanvårdskommittén, 1969) and an inventory of police registers also found the number of street opioid abusers to be low before 1965, whereas iv amphetamine addiction was high (Bejerot, 1975).

In 1979 the prevalence of hard-core drug users in Sweden was 15,000 (2,000 of them were heroin addicts); in 1998 there were 26,000 hard-core users (7,000 of them were heroin addicts; Olsson et al. 2001). Female heroin addicts were generally around 25% of the total population. There has been an increase in average age from 27 years in 1979, to 35 years in 1998. Before 1960 no specialised treatment for drug addiction existed outside the psychiatric hospitals. Privately founded therapeutic communities with no evidence-based treatment and with conflicting ideologies were established in the 1970ies. Many of them were closed down during the 1990ies due to poor outcome results and lack of financing.

1.2 Treatment of heroin addiction before Methadone Maintenance

1.2.1 Drug-free treatment

Before the advent of MMT, American studies reporting the outcome of drug-free treatment generally presented a low dividend of abstinent heroin addicts. For instance Pescor (1943) reported a follow-up of 4,766 patients released from the Lexington Addiction Research Center, Kentucky, with 13.5% abstinent, 7% dead and the remainder relapsed (39.9%) or lost to follow-up (39.6%) after 6 months to 6 years. Gerard et al. (1956) reported 80%
relapsed into regular or irregular heroin use and 13.3% abstinent within a year in a group of 247 heroin addicts treated in New York. Hunt and Odoroff (1962) in another report from Lexington, presented 1,912 heroin addicts, with 90.1% relapsed and 6.6% abstinent after 1-4½ years.

Programs including heroin addicts released on parole from the penitentiary system have reported somewhat better results. Admittedly, the California program of civil commitment produced only 13% with sustained community abstinence after first admissions in 200 male heroin addicts (Stephens & Cottrell, 1972). Diskind (1960) presented a group of 344 New York parolees, with 45% abstinent after 2-36 months. Excellent results were obtained in a group of 30 Californian physicians, 92% of which remained abstinent after 5 years of treatment. The risk to be struck off the medical register obviously contributed to this result. Vaillant (1973) published a 20-year follow-up of 100 narcotic addicts, which illustrates that, within the framework of a consistently organised probation program, 10 had become drug-free after 5 years. At the age of forty, 35 had become drug-free (although 10 of them were now receiving methadone maintenance treatment), 17 had died and 48 were continuous heroin abusers or lost to follow-up.

1.2.2 Programs providing iv morphine or heroin

Clinics delivering morphine for injection to heroin abusers were set up in the United States during the first decade of the 20th century, but were closed down during the 1920ies due to poor results on physical health and re-socialisation (Musto, 1973). In the United Kingdom heroin clinics were started in the 1950ies and although still maintained, have not been met with enthusiasm even in London. In an open 1-year study comparing injectable heroin and oral methadone, a majority of the patients in both treatment groups added illegal heroin and the abuse of non-opioids remained unchanged (Hartnoll, et al., 1980). Perneger et al. (1998) compared 27 heroin addicts who were given heroin for iv self-administration with a control group of 24, where most subjects were given oral methadone. There were no significant group effects on social or vocational rehabilitation or mixed drug abuse. Thus in both of the above studies the administration of heroin for iv use and MMT was a failure.
2. The original Dole-Nyswander MMT

2.1 Early application and development

In 1962 Dole and Nyswander at the Rockefeller University received a grant to investigate the problem of heroin addiction. They started their work by experimenting with iv morphine substitution to two patients who had used heroin for years. Since the half-life of morphine is 2 to 3 hours these patients required a morphine injection at least four times a day. The patients were found to be apathetic, sedated and remained preoccupied with drugs and injections. When their morphine tolerance increased, they required increasing doses administered at shorter intervals to remain comfortable (Dole & Nyswander, 1966; Dole, 1988). The research team instead turned their interest to the more long-acting, orally active methadone.

In their first report (Dole & Nyswander, 1965) twenty-two patients were stabilised on 5-150 mg daily of methadone. These patients reported a disappearance of their heroin-hunger, had only rarely urine samples positive for heroin and 14 out of the 22 (64%) became regularly employed. Ancillary services were available, but only a few patients presented any problems to be treated by psychotherapy. Dole and Nyswander found that when craving for heroin was eliminated by methadone, the patients began to function normally. They suggested that the basis of heroin addiction might be a metabolic disturbance and postulated that methadone produced its main effect by satisfying the craving for heroin and blocking the euphoria of heroin (the so called "narcotic blockade"). In 1988 Dr Dole stated: "The treatment is corrective, normalising neurological and endocrinological processes in patients whose endogenous ligand receptor function has been deranged by long-term use of powerful narcotic drugs."

Initially the inclusion criteria were a minimum of twenty years of age, a four-year history of heroin addiction with repeated failure in drug-free treatment and "freedom of choice", i.e. no legal compulsion to enter further treatment. Admissions were later on required to be more relaxed, to allow admission of 18-year-olds having only a two-year history of heroin use or mixed abuse, with few medical complications since methadone generally did not interact with other medication (Kreek, 1973). Research also confirmed that methadone was medically safe and patients did not experience euphoria or changed consciousness (Dole & Nyswander, 1980; Dole, 1988). Gunne and Holmstrand (1974) failed to confirm the existence of a complete
"narcotic blockade", but found that such a blockade was not essential for therapeutic success.

The successful outcome led to an expansion of programs and MMT now became the major public USA health initiative for the treatment of heroin addiction (Gearing & Schweitzer, 1974; Newman, 1977; Ball et al., 1988; Ball & Ross, 1991). A total of 91% remained in treatment for a year, whereas 8% were discharged due to behavioural problems, 1% left voluntarily and 70% were rehabilitated and "socially productive" (Gearing, 1970). In retrospect Dole and Nyswander (1976) found a reduction in one-year retention from 80% to 59% during the first 10 years of MMT in New York City. A major factor contributing to the increased dropout rate could have been the rapid expansion in patient numbers from 4,000 in 1970 to 35,000 in 1973 (Newman, 1977).

2.2 Methadone as a medication for substitution treatment

Methadone, (dl-4, 4-Diphenyl –dimethylamino-3-heptanone hydrochloride), is a synthetic analgesic opioid which was first developed in Germany during the Second World War and was released for research in the United States in 1947 (Isbell, Wikler, Eddy, 1947). As maintenance medication, methadone has distinct advantages compared with short-acting opiates like heroin. Oral methadone has a high bioavailability (around 80%) and elimination is generally slow, with a pH-dependent plasma half-life between 15 and 50 hours. A single dose in a stabilised person lasts between 24 to 36 hours (Kreek, 1979) without creating euphoria, sedation or analgesia. Instead the person can function normally and can perform any mental or physical tasks. Most importantly methadone relieves the persistent craving or “drug-hunger” that is considered to be a major reason for relapse into compulsory heroin addiction (Kreek, 1992).

The advantages with methadone as maintenance treatment are as follows:

- Methadone is orally effective
- Following tolerance development, methadone does not cause euphoria, or lethargy
- Methadone does not cause impairment in thinking, behaviour or function
- Methadone does not dull emotions and physical sensations
- Methadone diminishes the craving for heroin
- Maintenance treatment will continue to be effective without dosage increase
- Methadone is medically safe
Heroin addicts usually inject themselves several times a day. This means that the blood-level of heroin rises and falls rapidly, whereas the effect of methadone is generally stable for at least 24 hours.

2.3 Alternative pharmaco-therapies

In addition to MMT there are at the moment three alternative pharmacological treatments for heroin addiction in Sweden. **Naltrexone** is a long-acting opioid antagonist (T½ for naltrexone is 4 hours and for its active metabolite 6-beta-naltrexol T½ is 13 hours). This substance blocks heroin effects, including euphoria, and can therefore be used at early stages of the drug career to eliminate the rewarding effects of heroin. Later, when drug addicts have a compulsive dependence on heroin, with intensive craving, naltrexone is no longer useful due to its absence of effects on craving. This is reflected in a placebo-like retention rate, when chronic heroin addicts are given naltrexone (Kleber, et al., 1977). **Buprenorphine** is a partial agonist/antagonist, which produces less physical dependence than the pure agonist methadone. It owes its long duration of action partly to re-absorption and intestinal hydrolysis of the glucuronate. Attempts to increase the dose are limited by the antagonist effect, which has a preference for the kappa (κ) receptor. The mu (µ) receptor agonist effects are sufficient to block or reduce the craving for heroin and thus, patients tend to remain in treatment (Kakko et al., 2003). Buprenorphine seems to be a useful alternative treatment for heroin addicts who do not fulfil the acceptance criteria for MMT. **LAAM** (laevo-α- acetyl-methadol) is another opioid agonist, with an even longer duration of action than methadone, partly due to its active metabolites. It can be administered three times per week (generally Monday, Wednesday and Friday) and can be used in patients with compliance problems, who cannot be entrusted with take-home privileges (Borg et al., 2002). Due to its slow elimination it can easily be overdosed as a result of cumulation. It was recently found to prolong the electrocardiographically recorded QT interval, which might result in torsades de pointes and sudden death due to cardiac arrest (Deamer, et al., 2001). LAAM has not been used much in this country.
3. The Swedish MMT program

3.1 Introduction

The MMT program described in this thesis was early introduced in Sweden (Gunne, 1966) and this country has the oldest still functioning program in Europe. Its design remained unaltered, serving as a National program for 23 years. During five of those years, 1979-1984, there were no admissions of new cases due to a political debate around the legal prescription of a narcotic drug to addicts (Gunne, 1983, 1990; Johnson, 2003).

Acceptance criteria have remained the same over the 23 years and were first presented in Study I. These criteria are:

- At least 20 years old
- Not arrested, serving sentence or undergoing compulsory treatment
- A documented 4-year history of compulsive opioid misuse
- If non-opioid abuse exists it must be manageable
- At least 3 earlier attempts in drug-free treatment programs
- Signs of ongoing opioid abuse must be present on admission

3.2 Admission procedure

With patients' permission medical records, criminality registers, and other demographic register data were consulted to check whether applicants fulfil the admission criteria. During a semi-structured interview (Frykholm & Gunne, 1980) needle-marks and scars were inspected and urine samples taken to verify ongoing opioid use and to detect poly-drug abuse.

3.3 Inpatient phase

All patients participating in this study were admitted to a research ward at Ulleråker hospital, Uppsala. Following initial detoxification when clonidine, dextropropoxyphene or methadone was administered to reduce heroin withdrawal distress, medical examination and routine blood samples were collected.
All patients received their methadone induction as inpatients. Methadone dosing followed a schedule usually with 10-20 mg as first dose with an increase every other day until 60 mg was reached. Blood samples were taken to optimise an individual maintenance dose, ranging from 30 to 130 mg with an average of 80 mg (Holmstrand, Änggård, Gunne, 1978).

Patients were initially detoxified on an inpatient basis. Before methadone induction was initiated a negotiation took place between the patient, the hospital doctor and/or a clinical social worker to decide upon a suitable treatment plan, focusing on work or studies. Failures to reach an agreement could prolong the stay in the ward. Patients were taught how to apply for work and how to behave and look to be accepted by would-be employers. Patients were discharged when a suitable stabilisation dose of methadone had been reached, they had received a job, a place to live and a plan to solve economic problems was agreed upon. During the induction phase urine samples were delivered under the supervision of nurses 3 times a week.

3.4 The outpatient phase

After discharge from the treatment ward, patients were transferred to the outpatient team. The development of each individual patient was monitored by personal contacts, through visits to the patient's home, his/her visits to the outpatient clinic, telephone contacts, etc. Urine samples were collected 1-3 times weekly and sent to our laboratory for analysis by EMIT (Kaistha, 1977) and positives were confirmed by mass spectrometry (Oellerich, Külpmann, Haekel, 1977). To keep therapists informed about their continued vocational rehabilitation, patients regularly sent in their monthly salary verifications or certificate from their teachers. When patients had been employed, sick leaves were checked at the National Health insurance system, to validate the vocational rehabilitation. Whenever the outcome was found to be unsatisfactory patients could be readmitted to the hospital. Street prostitution was monitored by contact with the social welfare service or spontaneous reports from the police. If the methadone dose was not experienced as comfortable, a blood sample was taken to re-optimise the plasma level. The outpatient team also maintained contact with local doctors and social welfare services for updating of the treatment plan.

This comprehensive program thus offered medical as well as psychosocial support.
4. Aims of the present study

The overall aim of the present study was to document the outcome effects of a National Swedish methadone maintenance treatment program along various lines:

- A randomised controlled study comparing the efficacy of methadone and drug-free treatment (I, II)
- The impact of methadone treatment on mortality rates in comparison with waiting-list controls (III)
- Long-term protection of methadone against HIV-infection (IV)
- Before/after comparison of rehabilitation variables (II, V)
- Elucidation of the situation of female heroin addicts (V)
- Retention rates (VI)
5. Materials and Methods

5.1 Subjects
A total of 349 (243 male) opiate addicts were admitted during 1966-1989. Due to missing data three female and one male were excluded from further analysis. A total of 66 heroin addicts who were referred to the program during this period did not fulfil the acceptance criteria. These subjects were not accepted for treatment and were not studied further. In Study I there is a cohort of 17 subjects aged 20-24 years who fulfilled acceptance criteria but, by random assignment, were not given MMT. Due to the design in Study I and Study II, eight of these controls were transferred to MMT after 2 years and another 2 after 5 years of observation and serving as controls.

Study III presents another cohort of untreated controls: during the 5-year period of no intake 98 waiting list controls were studied for mortality rates. Those who survived were eventually accepted for MMT. All participants could be traced throughout the studies.

5.2 Randomised trial (Study I, II)
All physically healthy heroin addicts between 20-24 years of age who were referred to the MMT during 1973-1979 were consecutively included in this study. Three subjects, one with ongoing hepatitis and two with acute endocarditis were exempted from randomisation for ethical reasons and were given MMT.

The investigation was approved by the Clinical Ethics Committee of the University of Uppsala. In order to keep the number of subjects at a minimum, yearly assessments between the experimental and control group were plotted in a sequential analysis model (Bross, 1952). Intake of new subjects was interrupted when differences between pairs in the experimental and control group were significant at the 5 percent level, which occurred when 17 subjects in the experimental group and 19 in the control group had been included in the trial. It was later found that two of the controls had managed to receive methadone from private practitioners and thus had to be excluded. Variables studied were vocational adjustment (work and studies), criminal activity (yearly number of sentences), illicit drug use (as monitored by urine tests) and effects on health status and survival. Those who were
given MMT were monitored by weekly interviews and by monthly paycheck stubs from those who were employed and school certificates from those studying.

The controls who were not given MMT were traced by their contacts with other clinics, through social workers, by National criminality registers and mortality registers. In addition 13 out of 17 subjects within the control group visited our clinic as in- or outpatients during the six follow-up years. All participants could be localised at predetermined time points of the follow-up period.

After discharge from the hospital, patients were transferred to the outpatient team. The frequency of follow-up contacts varied between patients and was adjusted to the individual need of each person. Contacts were sometimes maintained through telephone calls as some patients lived at a distance of up to 400 miles from the hospital. When the outcome was found to be unsatisfactory, patients could be re-admitted to the hospital. The outpatient team also maintained contacts with local doctors, usually GPs, doctors at infection clinics and social workers in the subjects living region.

Methadone doses were dispensed by a local pharmacy. Take-home dose privileges of up to one week were granted only those who could verify that they had regular work and functioned without misuse of drugs.

Illegal drug use was monitored both by contacts and by regular urinary drug screening for opiates, amphetamines, barbiturates, bensodiazepines, cannabis and cocaine. If there was a concern about heavy drinking behaviour, the urine was also tested for alcohol. Urine specimens were delivered 3 times a week to the local pharmacy, from where they were sent to the laboratory. During scheduled visits to the clinic each subject was asked to deliver urine specimens under observation by trained nurses. The subjects receiving MMT in this study were subjected to the same clinical procedures as other patients in the National program.

5.3 Mortality rates (Study III)

Matching the personal identification numbers of each subject against the National Mortality register was made to record the deaths in this study. Forensic pathologists had subjected all deaths to a post mortem and autopsy reports were examined in association with subjects’ medical records. The presence of drugs involved in these cases was investigated by analyses at laboratories of forensic medicine.
5.4 HIV prevention (Study IV)

Subjects admitted to the National methadone programme before 1984 (Study IV) were HIV tested and retested yearly 1985-1990 for antibodies. Blood tests were taken when patients came for regular counselling to the hospital. Subjects living far away from Uppsala were asked to deliver blood tests at a local clinic or department of infectious diseases.

5.5 Female heroin addicts (Study V)

By patient interviews, validated by social workers, female heroin addicts lives were elucidated.

5.6 Retention in treatment (Study VI)

Retention in treatment was calculated in three different ways. The 1-year and 3-year retention of newly admitted subjects was recorded during the first 23 years of the National methadone program. In addition, the yearly percentage of subjects staying in treatment for several follow-up years was recorded.

5.7 Statistical analyses

When data are continuous, t-test was performed. For categorical data, following the recommendation of Siegel (1956), chi-square tests with Yates correction for 4-fold tables were used. The MacNemar test for significance of changes were calculated when treatment effects were tested. In Studies I, and II sequential analysis (Bross, 1952) was used, which enabled the investigator to interrupt the study as soon as group differences with significance at the 5 percent level were reached.

Survival estimates (Study III, IV) for groups were made by the product-limit method (Kaplan & Meier, 1958) supplied by the SAS Institute (1988). The log-rank test was used to calculate differences in survival between groups. Survival analysis was chosen since it can handle the inclusion of subjects for inter-individually different lengths of time.

In Study VI the calculation of yearly and long-term retention rates is described.
5.8 Ethical considerations

All information about patients was in accordance with current secrecy regulations. Steps were taken to protect the identity of the deceased. All persons working in the MMT program have been under obligation to preserve secrecy.
6. Results and Discussion

6.1 Randomised Controlled Trial (RCT)

Studies II and I present the outcome of an open randomised experimental study where a group of methadone treated patients (n=17) were compared with a group (n=17) that received drug free treatment. The randomised part of the study was closed after two years of observation when those initially assigned to the control group became eligible for entry to MMT. After two years 12/17 (71%) in the methadone group were no longer using heroin or other drugs and were either employed (n=10) or in education (n=2). The overall outcome from this RCT with a six-year follow-up is presented in Table 1.

Table 1. Success vs failure in the treatment of 34 street heroin addicts, 20 to 24 years old, who were randomised (year 0) to MMT or drug-free control treatment and followed for six years. The controlled part of the study was concluded after 2 years. During years 3-6 the percentage successfully rehabilitated could no longer be defined within a shrinking control group.

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
<th>No drug abuse</th>
<th>Drug abuse</th>
<th>In prison</th>
<th>In hospital</th>
<th>Excluded</th>
<th>Dead</th>
<th>N (% successful)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>MMT</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17 (0%)</td>
<td>17 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Drug-free</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17 (0%)</td>
<td>17 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>MMT</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>17 (53%)</td>
<td>17 (6%)</td>
<td></td>
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<tr>
<td>1</td>
<td>Drug-free</td>
<td>1</td>
<td>15</td>
<td>17</td>
<td>17 (53%)</td>
<td>17 (6%)</td>
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<tr>
<td>2</td>
<td>MMT</td>
<td>12</td>
<td>5</td>
<td>2</td>
<td>17 (71%)</td>
<td>17 (6%)</td>
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</tr>
<tr>
<td>2</td>
<td>Drug-free</td>
<td>1</td>
<td>15</td>
<td>2</td>
<td>17 (71%)</td>
<td>17 (6%)</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>MMT</td>
<td>21</td>
<td>1</td>
<td>4</td>
<td>25 (84%)</td>
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<td></td>
<td></td>
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<tr>
<td>3</td>
<td>Drug-free</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>25 (84%)</td>
<td>9</td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>MMT</td>
<td>20</td>
<td>1</td>
<td>4</td>
<td>25 (80%)</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
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<td>25 (80%)</td>
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<tr>
<td>5</td>
<td>MMT</td>
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<td>4</td>
<td>25 (80%)</td>
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<td>5</td>
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<td>2</td>
<td>25 (80%)</td>
<td>9</td>
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<tr>
<td>6</td>
<td>MMT</td>
<td>22</td>
<td>1</td>
<td>4</td>
<td>27 (81%)</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Drug-free</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>27 (81%)</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Eight of the controls reapplied for MMT and were accepted.
2) Two of the controls reapplied for MMT and were accepted.
3) Cessation of drug abuse was always associated with vocational rehabilitation, i.e. full-time work or studies.
4) Four exclusions for rule violations were subsequently recorded as treatment failures, due to continued drug abuse.
The table shows great differences in death rates between the treatment groups: All 6 deaths occurred in the control group. Among the controls only 1/17 (6%) managed to stop his drug taking and resume work. Drug-free treatment thus gave 6% rehabilitated, while MMT reached 71% in two years (p<0.01). During the remaining follow-up period the rehabilitation rates were 80-84% among the methadone treated subjects. The results of this study illustrated the superior efficacy of MMT over drug-free treatment.

There are two earlier RCT studies comparing the efficacy of methadone maintenance treatment with a control group receiving drug-free treatment (Dole et al., 1969; Newman & Whitehall, 1979). Dole and colleagues studied 28 male imprisoned heroin addicts, of whom 12 were randomly assigned to methadone treatment, whereas 16 was a waiting list control group. Both groups were followed for 12 months. One subject dropped out of each group. Outcome showed that six of the 12 subjects (50%) in the methadone group were employed or at school but in the untreated control group 15/16 (94%) relapsed to street heroin addiction. These results agreed well with our 1-year findings (see Table 1.).

In the Newman and Whitehall study (1979) the first 100 consecutive admissions of male heroin addicts were included in the experiment. Subjects were admitted to a treatment unit for two weeks and were stabilised on individual methadone doses. They were then randomly assigned to a methadone program or a placebo program. The placebo group was gradually withdrawn by a daily 1 milligram reduction of methadone dose until they dropped out or reached 0 milligram. Both groups were then observed for three years and outcome results were focused on retention in treatment. At the end of study, five subjects were in treatment in the control group corresponding to 10 percent while 38 (76%) stayed in the methadone group. The Newman and Whitehall study showed the superiority of methadone over placebo on treatment retention.

6.2 Rehabilitation

The primary treatment goal within the National methadone maintenance program at Ulleråker was a rapid return to working life, to socialise patients and improve their self-confidence. At the five-year follow-up 70-80% of the patients in treatment were engaged in paid work or full-time studies, a significant increase compared with the situation before treatment when 2.5% of men and 0% of the women had a job, total 1.7% (Study V). In order to record the potential for regular work, Study VI reported not only the 1.7% with paid jobs for at least 6 months during the year before entering MMT, but in addition also 12% who participated in unpaid vocational training before entering MMT, and while receiving money from Social Welfare. During the first 5 years of treatment the percentage employed with regular
job on the open labour market or full time studying increased to between 71% and 81%.

The stability of outcome data is illustrated in Study II, where it is shown that over 14 years the proportion working or studying remained at 80%. In addition, 10% were registered as unemployed, but were prepared to take any job that was offered.

Other studies have shown similar effects on vocational rehabilitation. In an early study of 100 heroin addicts admitted to MMT, the employment rate increased from 21% on admission to 65% after one year in methadone treatment (Maddux & Desmond, 1979; Maddux & MacDonald, 1973).

In the DARP studies Simpson and Sells (1982) reported an increase from 33% employed before treatment to 58% after 3 years in MMT in a cohort of 895 heroin abusers. Thus, MMT in various studies has proven a marked rehabilitative power.

An important sign of change in life-style was noticed, since patients no longer continued to live together with drug-abusing partners. The proportion of subjects living in a stable drug-free relation was increased from 8% to 50% after five years in treatment while drug addicted partners were abandoned.

Among the 102 female heroin addicts, 70% had earned their money to finance the heroin through prostitution. This figure was reduced to 3% during the first follow-up year, but on year 5 one excluded woman and two in treatment relapsed into occasional prostitution behaviour (Study V).

6.3 Drug abuse during MMT

Regular urine tests showed that initially only one third of the subjects became altogether free of drug and alcohol abuse. It is assumed that MMT specially reduces the craving for opioids, while not interfering with other types of dependence. For this reason drug abusers with severe poly-substance drug habits are best avoided, through selective acceptance criteria. When non-opioid abusers are admitted, which happens all the time, the heroin dependence is regarded as dominating and patients declare themselves able to handle non-opioid habits, after receiving an MMT-induced reduction of craving for heroin. Still, the single dominating reason for involuntary discharge from our treatment program is repeated and increasing non-opioid poly-drug abuse, which occurred in 57 subjects (16.5%; Study VI). Partly due to this policy of discharge, following repeated warnings in cases of increasing poly-drug abuse, we did not experience a rise in such abuse. The only exception to this was a subgroup of 74 HIV positive patients, some of them with incipient AIDS symptoms, who had to control their anxiety by aid of bensodiazepine medication. During the first year in treatment 40% had an occasional relapse of heroin use (less than once per
month), which was reduced to 10% during the initial 5 years of MMT (Study V).

Condelli and Dunteman (1993) examined a sample of 526 patients admitted to MMT. The rate of heroin use decreased to 17% during long-term continuous methadone treatment. In the Drug Abuse Reporting Program (DARP) study Simpson and Sells (1982) found that 44% of 895 patients in MMT reported no use of illicit narcotics during the first treatment year (self-reported data). In the Ball and Ross study (1991) there was an association between heroin use and methadone dosage. Among patients on doses over 71 milligrams per day, no heroin use was detected, but patients on doses below 46 milligrams were 5 times more likely to use heroin than those given higher doses. According to Ball and Ross the length of stay in MMT was associated with reduction in heroin use. Powers and Anglin (1993) demonstrated that in 933 heroin addicts receiving MMT, the illicit opioid use decreased but misuse of alcohol and cannabis were moderately increased.

Dole and Joseph (1978) compared methadone maintenance treatment in New York City in 1969 with a control group receiving no treatment, and found at 12-month follow-up that subjects in the control group were 92 times more likely to use heroin than those in the methadone group.

Around 25% in the Swedish MMT were heavy consumers of alcohol and were offered special treatment for their drinking habits. Ball and Ross (1991), Dole and Nyswander (1965), McGlothlin and Anglin (1981) reported that of patients in MMT, 15-40% had alcohol-related problems.

Our outcome results demonstrate that this National methadone program was an effective reducer of illicit heroin use. We did not experience a rise in non-opioid misuse except in a subgroup of 74 HIV-infected subjects, sometimes with early AIDS symptoms. The HIV positive patients were increasingly high consumers of benzodiazepines.

6.4 Criminal activity in MMT

The year before methadone treatment 82% of men and 76% of female subjects were sentenced due to criminal activity. At the 5-year evaluation the criminal activity for the male subjects had decreased to 12%, for the ex-prostitutes this figure was 7.4% and for non-prostituted women 9.1%. Among the continually criminal patients, 36 (10.4%) were excluded from MMT due to imprisonment.

Dole and Nyswander (1968) followed 750 subjects in MMT during four years. Since entry in MMT 88% of the patients showed arrest-free records. The remainders were arrested mainly on suspicion of loitering. A total of 5.6% were guilty of criminal offences and were convicted. In the randomised study of Newman and Whitehall (1979), addicts receiving placebo had twice the number of convictions during their enrolment in the study compared with
the subjects undergoing MMT. Also the Leman et al. study (1993) in their evaluation of 51 subjects in MMT who were followed for one year reported that 89% had no criminality activity. These findings confirm the efficacy of MMT to reduce criminality in various program settings.

6.5 Mortality rates

Study III demonstrates a 20-year evaluation of the mortality of subjects in MMT (n=166) compared with a waiting list control group (n=115). The mortality of 115 untreated street heroin addicts was 63 times that expected, when compared with official statistics for a matched group of this age and sex distribution. The death rate of the street addicts was 7.2% per year. As reported in Study I, the 17 randomised controls had the same death rate (7.2%).

Subjects who entered methadone treatment showed a mortality rate reduced to 8 times that expected.

As presented in Study III sixteen patients (14 male) died while undergoing methadone treatment which corresponds to a death rate of 1.4% per treatment year.

This study confirms that methadone treatment had a major impact on the survival of heroin addicts.

6.6 Protection against HIV infection

In study IV presents patients admitted to MMT before 1983 and who were asked to perform a HIV antibody test. Two female individuals living with heroin abusing men were found to be HIV positive. Of those admitted during 1984-86, 16% were HIV positive, while during 1988, 59% of the newly admitted were positive. Despite this rise in seroconversion among street addicts, none of the long-term treated patients in the Swedish methadone programme developed positive HIV tests after admission.

Hartel et al. (1988) reported that American patients who entered MMT before 1983 and remained in treatment for several years had significantly lower rates of AIDS and HIV infection than patients admitted after 1983. Novick et al. (1990) followed 58 heroin American addicts who had used heroin for an average of 10 years before entering MMT. Before MMT, 91 percent were engaged in needle sharing. After participation in MMT, none of the subjects seroconverted to HIV infection. Concerns have been expressed about the discovery of the even more widespread epidemics of Hepatitis B and C among Australian injecting heroin abusers as noticed by Bell et al. (1990). In response many governments around the world have expanded and
developed new methadone maintenance programs, Gossop and Grants (1991), Uchtenhagen (1990). Also Moss et al. (1994) found MMT to be protective against HIV infection in a cohort of 681 opioid injecting abusers in San Francisco in a follow-up from 1985 to 1990. Subjects who spent less than one year in MMT were about three times more likely to test positive for HIV than those who stayed at least one year in treatment.

Study IV showed that the Swedish program had prevented the occurrence of new cases among the MMT patients. Unfortunately the Swedish Board of Health and Welfare has maximised the number of patients who are permitted to be accepted. At the present time less than 10% of all Swedish street heroin addicts are being treated.

6.7 Female heroin addicts

Female heroin addicts were found to finance their heroin by prostitution (70%) or criminal activity (30%). Two thirds also financed their male partner's heroin use. During the time period of study, there was no system of pimps organising the sexual exploitation of several girls, but each girl had a boy-friend for her personal protection, who was mostly dependent on her for delivery of heroin or money. These boy-friends might sometimes disappear or be imprisoned and were then regularly replaced by another boy-friend. Prostitutes usually had 5-8 customers per day and some of them built up contacts with regular customers, who had to pay more. Prostitution money was used only for heroin, whereas money for food and housing was obtained from the social bureau, where the female addicts claimed that they had no income. Clothes and paint for make-up were regularly stolen in department stores. The street prostitutes actually made $110,000 per year and those with regular customers $177,000 per year.

6.8 Retention in treatment

Study VI shows the retention in treatment. The average one-year retention rate during 1967-1989 was 90% (range 80-100%). Cumulative retention showed that 29% were still in treatment 10 years after admission.

Abstinence from all drugs including methadone may not be an appropriate treatment goal for a majority of heroin addicts (Cf Ward, Mattick and Hall, 1998). Longer stay in treatment is associated with better overall outcomes (Ball & Ross, 1991; Simpson & Sells, 1982). Although the initial good results in the American studies were soon followed by a drop in 1-year retention below 60% (Dole & Nyswander, 1976; Strain et al., 1993) the Swedish experience demonstrate a remarkably high and stable retention rate during 23 years of observation. Our results may have to do with the high
and stable rate of vocational rehabilitation. In our neighbouring country, Denmark, MMT was received with great enthusiasm during the 1970ies and around 5,000 heroin addicts were included in treatment. However, most of the Danish patients were given an early retirement pension. After a while they took up new kinds of drug and alcohol abuse and a few years later there was an epidemic of suicides among heroin ex-addicts and a rise in methadone-related deaths outside the treatment programs (Ege, 1996; Kontaktudvalget, 1979).
7. General Discussion

Background data for 345 subjects (102 female) showed significant differences between male and female heroin addicts. The women more often had heredity for mental disturbance, came more often from broken homes, had more school problems including truancy and received more hospital treatment for overdoses. It was also noted that more female heroin addicts had stitch marks from iv injections into the jugular veins revealing a desperate injection technique when arm veins had been used up. The prostitutes differed both from the males and from non-prostituted women. The prostitutes had a lower age at heroin debut, were earlier subjected to hospital detoxification and had more treatment periods for drug abuse, while male heroin addicts spent more time in prison. Thus, female heroin addicts represent a selection of socially frustrated individuals, with a particularly severe degree of drug dependence, partly as a result of high and regular access to heroin. Despite this sinister background, they have a better survival expectancy compared with the male heroin addicts. While male street heroin addicts have a death rate of 9.1% per year (70 times the expected), the death rate among female addicts was 4.2% per year (47 times the expected).

Over the last 35 years MMT has grown from a small research project to an effective treatment method. However ambivalence toward MMT still remains among both public and treatment professionals, making it difficult for Swedish heroin addicts to receive this treatment.

Among interesting differences in treatment outcome between the National Swedish and the American programs is the stability in retention over the years in the Swedish version. Unfortunately, this has changed during the nineties, when MMT was subdivided in 4 different programs with different treatment goals. This development will have to be subjected to future studies of treatment strategies and outcome.

Significant program factors of the treatment strategy in this National MMT can be summarised as follows:

- Inpatient induction
- Comprehensive treatment team with full-time medical doctor, nurses, university trained counsellors, psychologist, program director and administrators
- Methadone dispensing at a local pharmacy
- Urine sampling adjusted to treatment progress
• Patients with specific mental disorders such as anxiety and major depressive disorder receive additional treatment

The present results emphasise the importance vocational rehabilitation and supports a treatment strategy based on long-term maintenance therapy. Although 13% could be voluntarily discharged with a maintained low mortality rate, a majority of heroin addicts relapse into heroin use, criminality and prostitution when methadone is untimely and involuntarily discontinued.
8. Conclusions

This National Methadone Program was in operation for 23 years. Outcome from these years has shown stable and positive results:

- An average yearly retention of 90%
- A significant decrease in drug abuse, criminality and prostitution compared with the situation before treatment
- An increasing involvement with drug-free partners, while drug-abusing partners were abandoned
- Protection against HIV infection
- A dramatic reduction in mortality of those staying in treatment
- Patients in work or study increased to 70%-80%, transforming a majority of the heroin addicts to law-abiding, tax-paying citizens.

When the Swedish National Methadone system was split up into four different programs starting 1988 and concluded 1990, some programs switched into a different more confronting treatment with an ensuing rise in mortality rates and drop in vocational rehabilitation. The data presented here will provide a background for further study and analysis of the optimal treatment policy.
Acknowledgements

The present studies were carried out at the Psychiatric Research Center, Ulleråker hospital, Uppsala, Sweden.

This thesis would never have been realised without the collaboration of many persons.

First and foremost my supervisor, Professor emeritus Lars Gunne, for his never-ending support and patience, constructive criticism and good friendship throughout the years.

Associate professor Lennart S Öhlund, for his enthusiasm, continuous advice and support.

Professor Frits-Axel Wiesel, head of the Department of Psychiatry, for good advice and support.

Professor Karl-Gunnar Götestam for inspiring guidance during the final part of this research.

My colleagues at the methadone program in Uppsala: Solveig Dansson, Lisbeth Skoglund, Kerstin Eriksson, Ingemar Holmlöf, Gunilla Svedström, Erica Olsson, Maria Edholm, Annica Rhodin, Hanna Ljungvall, Berit Skottheim, Christina Bessner, and Bo Sparrenhöök for support in the clinical work and good friendship.

Mari-Louise Aarflot for all tests at the laboratory.

Lottie Söder, secretary of the department, for her helpfulness.

Marianne Andersson for assistance in the library.

Lars-Håkan Nilsson, head of the clinic, for support and for giving me the opportunity to complete this thesis.

The staff at the treatment ward for good caring of the patients.

Associate Professor Tommy Lewander together with colleagues at the doctoral program at Ulleråker for advice and sharing their experiences with me.

My gratitude also goes to all those patients who participated in this national methadone program.

Finally, my wife Ingegerd, our daughter Alfhild and son Carl for patience and encouragements during all the years. Thank you!
References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to October, 1985, the series was published under the title “Abstracts of Uppsala Dissertations from the Faculty of Medicine”.)