Malmö Treatment Referral and Intervention Study (MATRIS). Studies of opioid maintenance treatment in patients referred from a needle exchange program.

Bråbäck, Martin

2018

Document Version:
Publisher's PDF, also known as Version of record

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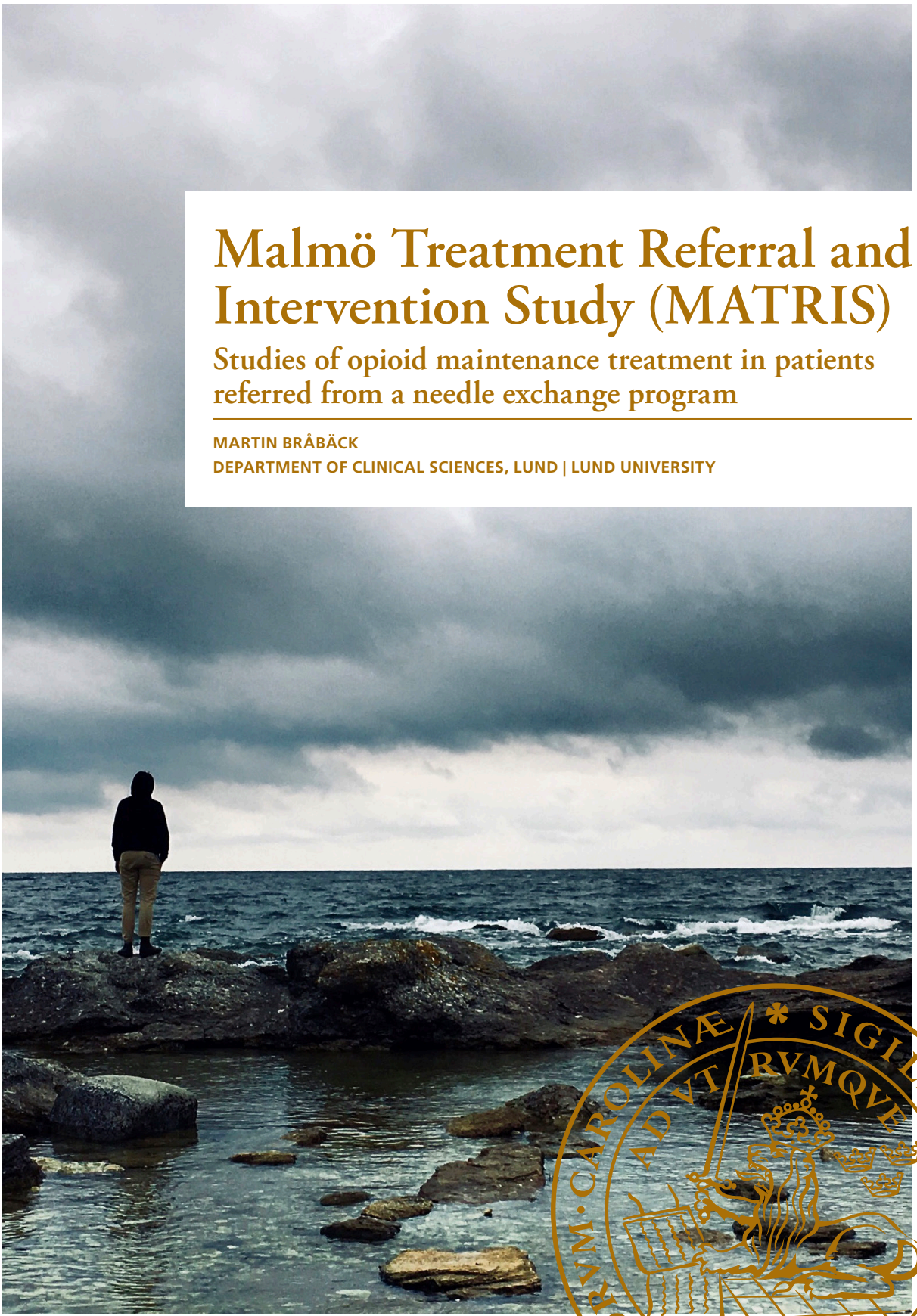

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Martin Bråbäck

LUND
UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Olof Palmes plats 1, Malmö, November 9th 2018 at 09.00 AM.

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Organization LUND UNIVERSITY	Document name DOCTORAL DISSERTATION
Faculty of Medicine Department of Clinical Sciences Lund Psychiatry, Lund, Sweden	Date of issue November 9th 2018
Author(s)	Sponsoring organization

Title and subtitle

Malmö Treatment Referral and Intervention Study (MATRIS). Studies of opioid maintenance treatment in patients referred from a needle exchange program.

Abstract

Background: Opioid maintenance treatment (OMT) with methadone and more recently buprenorphine is an evidence-based treatment for heroin dependence. Needle exchange programs (NEP) started in many countries in the 1980s to reduce the risk of HIV among people who inject drugs (PWID). NEPs have more recently been proposed as a potential conduit to treatment for drug dependence. The general aim of this thesis was to evaluate a model for referral of opioid-dependent individuals from a NEP to OMT and to evaluate the clinical course for these individuals starting OMT, regarding selected outcome measures.

Methods: Participants were included at the NEP in Malmö between October, 2011, and April, 2013. All participants were referred to a research facility for OMT run by the Addiction Centre Malmö. At the baseline assessment, participants were asked about substance use, psychiatric and medical history. The participants' health-related quality of life (HRQoL) was also assessed with the instrument EQ-5D. Patients were randomized to a strengths-based case management intervention (CMI) or a referral-only group (control). EQ-5D was repeated after 3 months of OMT. The clinical course with regard to retention in treatment, psychiatric diagnoses and inpatient care was assessed through patient records.

Results: Out of 100 potential study participants at the NEP who were invited to participate, 79 accepted to be included in the study. Of those, 75 turned up for study inclusion, baseline interview and randomization. Thirty-six participants were assigned to CMI and 39 to the control group. Seventy-one participants successfully started OMT. Among patients randomized, 95% of the intervention group and 94% of the control group started treatment. Thus, entry was not related to being in the control or intervention group. Of the patients who started OMT, a majority (82%) were still in treatment after 12 months. The EQ-5D visual analogue scale (VAS) measure for the whole study sample was considerably lower than a sample from a Swedish reference population. The EQ-5D VAS measure was found to significantly increase from baseline to 3 months into treatment. During the 3-year follow-up, 65% of participants were hospitalized for any psychiatric reason at least once. Using sedatives at baseline predicted hospitalization, and detoxification from sedatives, including benzodiazepines, was the most common cause. Seventy-two percent of the participants received a psychiatric diagnosis during the 3-year follow-up. When excluding substance use diagnoses, however, only 41% received a diagnosis with the most prevalent being anxiety disorders (27% of all participants).

Conclusions: Our results suggest that a NEP is a clinical setting that allows for efficient referral of heroin-dependent individuals to opioid maintenance treatment. Even in a NEP population, with a high degree of substance use problems and social instability, there was a significant improvement in HRQoL in the short term and, importantly, a majority of the participants were still in treatment after 12 months. Hospitalization was predicted by patients' baseline use of sedatives, and the most common reason for hospitalization during a 3-year follow-up was dependence on sedatives including benzodiazepines. This was also the most common psychiatric diagnosis apart from opioid dependence.

Key words Opioid dependence, opioid maintenance treatment, needle exchange program, health-related quality of life, methadone, buprenorphine/naloxone, psychiatric comorbidity

Classification system and/or index terms (if any)

Supplementary bibliographical information		Language English
ISSN 1652-8220		ISBN 978-91-7619-693-9
Recipient's notes	Number of pages	Price
	Security classification	

Signature  Date 2018-10-05

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Coverphoto by Lina Zetterman

Faculty of Medicine
Department of Clinical Sciences Lund

ISSN 1652-8220

ISBN 978-91-7619-693-9

Lund University, Faculty of Medicine Doctoral Dissertation Series 2018:125

Printed in Sweden by Media-Tryck, Lund University
Lund 2018

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III. Bråbäck M, Brådvik L, Troberg K, Isendahl P, Nilsson S, Håkansson A. Health Related Quality Of Life In Individuals Transferred From A Needle Exchange Program And Starting Opioid Agonist Treatment. Submitted.

IV. Bråbäck M, Brantefors A, Franck J, Brådvik L, Isendahl P, Nilsson S, Troberg K, Håkansson A. Polysubstance use – a major reason for psychiatric hospitalization in a cohort with opioid maintenance treatment referred from a needle exchange program. Submitted.

Abbreviations

APD	Antisocial personality disorder
CM	Strenghs-based case management
CMI	Strengths-based case management intervention
EQ-5D	An instrument developed by the EuroQoL group for assessment of health-related quality of life.
FDA	Food and Drug Administration
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
LAAM	Levo-Alpha-Acetylmetadol
MDD	Major depressive disorder
NEP	Needle exchange program
OMT	Opioid maintenance treatment
PWID	People who inject drugs
QoL	Quality of life
QUALY	Quality-adjusted life years
VAS	Visual analogue scale

Introduction

In 2015 it was estimated globally, that approximately 15.6 million people injected drugs (1). Opioid dependence has been found to contribute the most to the global burden of disease, due to premature death and disability, of all illicit substances included (2). The European Monitoring Centre for Drugs and Drug Addiction estimated that there were around 1.3 million high-risk opioid users within the European Union and that heroin was the most commonly used opioid (3). Opioid maintenance treatment (OMT) with methadone or buprenorphine has strong evidence for the treatment of opioid dependence (4). At the same time, in many countries potential patients still do not receive such treatment, illustrating the importance of finding new ways linking these individuals to treatment for opioid dependence. A needle exchange program (NEP) is one setting that has been suggested as a potential conduit to treatment for drug dependence (5). In this thesis we evaluated a model of referral from a NEP to OMT. The clinical course, with respect to specific outcome measures, was then evaluated for the subjects starting OMT.

Background

History

Heroin was originally synthetized in 1874 and in 1898 marketed as cough suppressant. Quite early on, there were reports of heroin dependence and a ban for prescribing was introduced in the US in 1924 (6). Common routes of administration are intranasal, smoking or intravenous and the latter results in higher plasma peak levels (7). Early reports illustrate the clinical course of heroin dependence prior to methadone maintenance treatment with high relapse rates. In 1943, Pescor reported from a 6-month to 6-year follow-up of 4,766 individuals released from Lexington Addiction Research Center, Kentucky. Out of the released individuals, only 13.5% remained abstinent at follow-up, 7% were dead and the rest relapsed or were lost at follow-up (8). Another report described relapse rates for 1,881 patients released from Public Health Service Hospital at Lexington in the early 1950s who were referred to a New York City follow-up team. The follow-up was between 1-4.5 years

and the authors concluded that more than 90% of the patients relapsed within 6 months after discharge from hospital (9).

Opioid dependence

The risk of developing opioid dependence is due to an interaction between genetic influences, social factors and the pharmacological properties of heroin itself. The chemical composition of heroin is diacetylmorphine which due to its lipophilicity passes the blood-brain barrier considerably faster than morphine (10). Heroin has a short half-life of approximately 3 minutes and is then rapidly followed by formation of morphine with a half-life reported to be between 110-280 minutes (7). Heroin has, mainly through activation of opioid receptors, analgesic and depressive effects. The abuse potential is related to the euphoric effects in part explained by heroin's pharmacological properties with rapid uptake in the brain and its short half-life (11), pharmacological effects which probably at least to some extent explain why people who use heroin often proceed to intravenous administration.

Genetics also influence the vulnerability for developing dependence. In a family study, Merikangas et al. reported an up to 8-fold increase in risk to develop drug use disorders if having a family history of drug use disorder (12). In a study of over 3,000 male twins, Tsuang et al. reported that the genetic influence for the vulnerability of heroin abuse was higher than any other substance apart from alcohol, and was estimated to 54% of the total variance (13, 14).

Repeated intake of heroin results in increased tolerance and a potential withdrawal reaction if the intake stops. This usually results in continued substance use to avoid withdrawal. What usually started with positive reinforcement is later driven by negative reinforcement and the result is a chronic relapsing condition (15, 16).

The natural development of heroin dependence is usually characterized by a chronic course with periods of relapses with drug use interchanged by incarceration, hospitalization or treatment (17, 18).

Mortality

The mortality rates for people with heroin dependence are increased, the most common cause of death being overdose. The risk is higher after a period of abstinence due to diminished tolerance, or being out-of-treatment. Concomitant use of alcohol and benzodiazepines has been reported to contribute to increased risk of fatal overdose (19, 20). Other reported causes are acquired infections, including hepatitis and human immunodeficiency virus (HIV), but also suicide and increased exposure to violence (21). The increased mortality risk has been estimated to be between 13-63 times compared to the general population (21, 22).

A recent review and meta-analysis concluded that retention in methadone treatment was associated with reduced mortality due to both overdoses and other causes. The induction phase of methadone treatment and time closely after leaving treatment were however associated with an increased mortality risk (23).

Psychiatric comorbidity

In large epidemiological studies, lifetime substance use disorders and co-occurring psychiatric comorbidities have been estimated to between 30-60%, the most common psychiatric comorbidity being mood disorders, anxiety disorders and personality disorders (24-27). Reports regarding opioid dependence have shown even higher association with psychiatric comorbidity with between 44-86% of the subjects reporting lifetime psychiatric disorders, with major depressive disorder (MDD) being the most common disorder and antisocial personality disorder (APD) being the most common axis-II disorder (28).

Female gender has been associated with higher rates of mood and anxiety disorders and more severe mental health problems, while APD has been reported to be more common in men (29-31).

When looking at clinical samples, however, it is sometimes difficult to compare reports from different authors since some are conducted among opioid-using individuals and some in stable patients in opioid maintenance treatment (OMT). Different methods and instruments are used and organic psychiatric symptoms due to drug use can sometimes affect incidence and result in lower incidence rates after entering treatment (32, 33).

Brooner et al. reported that 47% of a sample of 719 individuals seeking treatment (OMT) had documented psychiatric comorbidity. The two most common diagnoses were APD (25.1%) and MDD (15.8%) (34). Studies from other treatment-seeking samples report even higher rates of comorbid non-substance use diagnoses, with up to over 70% reporting co-occurring axis-I diagnoses (MDD being the most common) and up to 65% reporting co-occurring axis-II diagnoses (APD being most common) (35-38).

In a sample from a needle exchange program (NEP) in Baltimore, Kidorf et al. found that 56% reported a lifetime non-substance use axis-I diagnosis or APD. Thirty-seven percent where diagnosed with APD and mood disorders were the most common axis-I diagnoses (39). Brienza et al. compared a sample of NEP participants with stable OMT patients with regard to rates of depression, and found significantly higher rates in the NEP sample (53.6% vs. 42.2%) (40). Psychiatric comorbidity, especially with both an axis-I disorder and APD, has been reported to be associated with greater substance use severity and elevated HIV risk in NEP participants (41).

The severity of psychological distress, above actual psychiatric diagnoses, seems sometimes to be associated with worse clinical course regarding certain clinical outcomes, for example psychological distress, criminality, substance use and treatment compliance (36, 42-46). However, when looking more specifically at OMT and outcomes like retention and opioid use, most studies do not report an association with psychiatric comorbidity (45-48).

Polysubstance use

Polysubstance use among individuals with heroin dependence is common (49) and associated with both psychiatric comorbidity (50, 51) and a higher HIV risk behavior (52). In some areas cocaine is reported to be the most common substance use disorder, followed by alcohol and cannabis (34). However, in the southern part of Sweden, the setting of the present study, cocaine is still not a commonly used substance among individuals with opioid dependence.

In a Swedish outpatient sample, cannabis and benzodiazepines were reported to be the most common co-used substances apart from opioids (53), and benzodiazepine use was also associated with dropout from treatment (54). When it comes especially to alcohol and benzodiazepine use, there is an increased risk for fatal and non-fatal opioid overdose (20). In individuals with opioid use disorder, alcohol use disorder has also been associated to an elevated risk of liver-related death (55). In individuals receiving OMT, alcohol use disorder has also been associated with greater risk for illicit drug use and early treatment termination (56). Cannabis use has not been associated with retention or use of heroin in OMT (57).

Among treatment-seeking opioid-dependent individuals or patients in OMT, between 46-77% report non-medical use of benzodiazepines (53, 54, 58, 59). This use in OMT has been associated with a higher degree of anxiety and depression but in these studies it has not been possible to assess whether this was due to a higher degree of psychiatric comorbidity or to the effect of benzodiazepine use itself (60, 61). Polysubstance-using individuals have also reported use of benzodiazepines for treating psychiatric symptoms due to withdrawal from alcohol or other drugs. It has also been reported that individuals in OMT sometimes use benzodiazepines to reach an intoxication effect in combination with methadone (58, 62-64).

Individuals in OMT, who continue to use benzodiazepines to a higher degree, report more social problems with homelessness and criminality, a higher degree of psychiatric symptoms, overdoses, risky injection behavior and use of other substances (60, 65). When looking at retention in treatment the results have been more mixed (54, 58, 59, 66). Benzodiazepines potentiate the sedative and respiratory depressant effect of opioids and have been reported in up to 80% of methadone- and buprenorphine-related deaths (58, 59).

Notably the misuse of other sedative substances such as pregabalin and zopiclone have been reported in individuals with opioid dependence and may be related to increased mortality (53, 67-72).

Quality of life

Apart from more traditional measures of treatment outcome such as abstinence from opioids or retention in treatment, some authors have called for the use of measurements of quality of life (QoL) or health-related quality of life (HRQoL) (73-75). Some authors advocate the use of QoL which they see as a more holistic assessment (75-77), others favour the use of HRQoL instruments and the possibilities for making cost-effectiveness analyses by calculating quality-adjusted life years (QUALYs)(78).

Several studies have reported that treatment-seeking individuals with opioid dependence report lower HRQoL when compared to the general population (79-82). Reported mental health scores are usually lower than for physical health (75). Enrolment and retention in OMT have repeatedly been shown to improve HRQoL scores (80, 83-90).

Factors that have been reported to be associated with lower HRQoL among individuals with opioid dependence have been female gender (79, 91, 92), higher age (93-95), comorbidity (psychiatric and/or physical) (85, 94, 96-102), and continued substance use (98). Improved HRQoL among individuals with opioid dependence have been associated with social support (103), housing conditions (101, 104), and decreased substance use (101).

Criminality

Out-of-treatment opioid-dependent individuals have been reported to more frequently commit crimes when compared to those being in treatment (105). OMT has been reported to reduce criminality (106, 107). Forced withdrawal from OMT upon incarcerated has been associated with a negative clinical course post-release, compared to continued OMT (108). It has also been reported that prisons can be a recruiting ground for opioid-dependent individuals and that OMT induction pre-release results in a higher treatment initiation and retention post-release (109).

Opioid maintenance treatment

Until the 1960s there were no long-term pharmacological treatment for opioid dependence beyond withdrawal treatment. At that time methadone was evaluated as a pharmacotherapy for heroin dependence at the Rockefeller University in New

York (110). In the 1980s, trials were done with buprenorphine as an option to methadone for the treatment of heroin dependence, and it was starting to be used on a larger scale in the 1990s (111). In the last 15 years, heroin has in some countries emerged as a treatment option for patients seen as refractory to standard treatment (112).

Methadone

Methadone is a mu opioid receptor agonist. It is rapidly absorbed after oral intake and has a high bioavailability. There is variability depending on individual factors but peak levels are on average seen 2-4 hours after oral intake and methadone has a long half-life which allows for once-a-day dosing (113-115).

In the early studies methadone was demonstrated to relieve patients of symptoms of withdrawal and craving for heroin. Increased tolerance due to adequate dosing of methadone was also demonstrated to result in a "narcotic blockade" or cross-tolerance resulting in patients becoming refractory to euphoric effects of heroin. These effect enabled patients to focus on social rehabilitation (116).

A follow-up of 17,500 patients admitted to methadone treatment in New York 1964-1971 reported high retention rates, increased employment and diminished criminality rates (117).

Results from the first double-blind comparison of methadone to placebo were reported by Newman in 1979. One hundred volunteers with heroin dependence were admitted to a hospital ward and stabilized on 60 mg of methadone. They were then randomized to two groups, one receiving continued treatment with methadone (on average 97 mg/day). The other group had their methadone dose reduced by 1 mg/day and eventually switched to placebo. After 8 months, 76% of the individuals receiving methadone were still in treatment, compared to only 10% of the controls (118).

There is now strong evidence for methadone's efficacy to retain people in treatment and to reduce their use of heroin (119). Methadone has also been shown to be superior to buprenorphine regarding retention in treatment (4).

Apart from effects on mortality (23) other effects reported in trials with methadone maintenance treatment have been reduced criminality (106, 107, 117, 120), reduced injection use and needle sharing (121) and reduced risk for HIV (122) and hepatitis C (123).

Buprenorphine

In contrast to methadone, buprenorphine is a partial agonist at the mu opioid receptor (124, 125). Buprenorphine was initially developed in the 1970s as an analgesic and its potential as a drug for opioid dependence was soon realized (126). Like methadone, buprenorphine has a long half-life, which makes once-a-day dosing possible, and a ceiling effect due to being a partial agonist, with safety implications since it reduces the risk for intoxications (127). Later, a combination product with buprenorphine-naloxone was developed to limit the risk for intravenous use by opioid-dependent individuals (128).

The first report of clinical use of buprenorphine for heroin dependence appeared in 1985 by Marc Reisinger, who concluded that buprenorphine was a promising alternative to the available treatments at that time, and encouraged further research (111).

The results from the first RCT were reported in 1992, when Johnson et al. concluded that 8 mg of buprenorphine were as effective as 60 mg of methadone (129). This has been followed by several RCTs, and a Cochrane review in 2014 concluded that buprenorphine was more effective than placebo at retaining patients in treatment and suppressing illicit opioid use. Buprenorphine was found to be equal to methadone with respect to suppressing illicit opioid use but inferior with respect to retention in treatment (4).

Levo-Alpha-Acetylmetadol (LAAM)

LAAM was approved for the treatment of opioid dependence by the Food and Drug Administration (FDA) in 1993. Its long half-life made alternate-day dosing possible. LAAM has been found to be comparable to methadone at retaining patients in treatment, and more effective at suppressing illicit opioid use (130, 131). Due to reported adverse events with cardiac arrhythmias (132), FDA and the European Agency for the Evaluation of Medicinal Products called for a removal of LAAM as first-line drug for opioid dependence (131).

Heroin

A Cochrane review from 2011 concluded that for treatment-refractory individuals, heroin alongside methadone increased retention in treatment, reduced intake of illicit substances and increase social functioning. Results from some included studies also reported reduced criminality (133). Due to an increase in reported adverse events, the authors recommended heroin treatment to be offered only to people who had failed regular maintenance treatment, and that it should only be

given in clinical settings that could ensure proper supervision and safety. Similar conclusions were made in a later review and meta-analysis by Strang et al. (112).

Needle exchange program

Needle exchange programs (NEPs) were established in many countries in the 1980s, mainly as a measure to prevent transmission of blood-borne infections among people who inject drugs (PWID). The first NEP was started in Amsterdam as a response to an outbreak of hepatitis B, and as a reaction to the HIV epidemic NEPs were started in many countries all over the world. In 2007, there were estimated to be between 11 and roughly 21 million PWIDs around the world, and intravenous drug use was important regarding transmission of HIV (134). In 2009 it was estimated that NEPs had been established in 82 countries, but that coverage varied substantially both regionally and nationally. The highest needle distribution was noted in the Australasia region and the lowest in sub-Saharan Africa (135). The services offered also vary from providing sterile injection equipment to offering more comprehensive services as well as other harm reduction interventions and health care.

In Sweden, two NEPs were established in Lund and Malmö in the 1980s but it was not until 2006 that a Swedish legislation was passed that allowed other regions to establish NEPs. The legislation also stated that apart from providing sterile injection equipment the programs should provide interventions with the aim of having the individual accept care and treatment.

When it comes to efficiency, several evaluations have been made of the impact of NEP for preventing HIV and HCV, and this has been described to be methodically difficult (136). There is however evidence supporting the effect of reducing injection risk behavior, which is a known risk factor for skin and soft tissue infections (137, 138). Sharing needles have also been estimated as the largest risk factor for infection with HIV or HCV among PWIDs (139, 140).

NEPs have been found to reduce HIV transmission by up to 48% (138, 141) and OMT with up to 54% (122). The effect of NEP on reducing HCV transmission has however been mixed (138). A recent Cochrane review and meta-analysis found that high NEP coverage in Europe resulted in lower acquisition risk by 56 %, a risk reduction that could not be found in North America. The authors also described an even higher risk reduction (74%) when NEP was combined with OMT (123). Authors have called for a combination of harm reduction measures - seeing them as part of a continuum and that NEPs could be a conduit to treatment for substance dependence (5, 142, 143).

Individuals attending NEPs often express interest and readiness for treatment for substance use, but when given referrals, the attendance rates are often low (5, 144).

There have been studies assessing referral and treatment enrolment and the results have been varying. Kuo et al. reported that 70% of the individuals with heroin dependence referred from a NEP entered treatment with LAAM (145). Riley et al. reported that 28% of the participants from a NEP in Baltimore who received methadone referrals entered treatment (146). Assessing more active referrals, Kidorf et al. reported that 40% of NEP participants who received motivational and economic incentives entered treatment with methadone, compared to 16% of the participants in the control condition (147). Strathdee et al. in a randomized design reported superior results from the intervention group receiving strengths-based case management (CM) and that 34% entered OMT within 7 days compared to 26% among controls (148). A dose-related effect of CM was also reported.

The Swedish experience

When methadone was introduced in Uppsala, Sweden, in 1966 by Dr Lars Gunne, the model developed by Dole and Nyswander was adopted (110, 120). To be included, the subject needed to have at least four years of documented opioid dependence, no advanced poly-drug abuse, tried several drug-free treatments, and be of at least 20 years of age, and the treatment could only be offered under voluntary conditions and not if arrested or serving a sentence (120). These criteria were not changed until 2005, and Uppsala served as a national methadone program for many years.

During 1979-1984, no new patients were admitted due to a change in government policy, but in 1983, the Swedish National Board of Health and Welfare decided that methadone maintenance treatment was again to be used for opioid dependence. As a result of the moratorium for admitting new patients, 41 out of 98 individuals on the waiting list had died when the program was re-started (149).

Important work has been done by Gunne and Grönbladh, evaluating the original national methadone program. In a controlled study comparing methadone to no treatment, published in 1981, 17 subjects were randomly assigned to methadone and 17 to no treatment. In the methadone group, 15 were still in treatment after two years and 12 were abstinent from illicit drugs and employed. In the control group, only one individual was abstinent, two were incarcerated and two had died (120).

In an evaluation of all 174 individuals admitted during 20 years of the National Methadone program, it was reported that with this model it was possible to achieve a high degree of abstinence and employment. Seventy-five percent stopped using illicit drugs. Over the years, the percentage of individuals studying or working was around 80% (150).

It was not until 1988 that a unit for methadone treatment was started in Stockholm. A program had started in Lund by 1990 and in Malmö by 1992. It was not until 2004 that Sweden's second largest city Göteborg started its own program.

Until 2005 the Swedish National Board of Health and Welfare restricted the number of available slots for methadone treatment in Sweden, and in 1999 it was estimated that perhaps as few as 10% of eligible individuals with opioid dependence were in treatment with methadone (151).

Buprenorphine was introduced in Sweden in 1999, and not regulated by the same legislation as methadone until 2005. In addition to abolishing the restriction of number of treated patients, the Swedish National Board of Health and Welfare in the new legislation lowered the threshold for OMT from four to two years of documented opioid dependence, which was further lowered to one year in 2009. OMT is only allowed at special psychiatric addiction treatment services certified by the Swedish National Board of Health and Welfare. The combination product of buprenorphine/naloxone was introduced in Sweden in 2007.

In 2003, Kakko et al. reported a trial comparing buprenorphine to placebo in 40 heroin-dependent individuals who did not fulfil the Swedish inclusion criteria for methadone maintenance. Both groups also participated in cognitive-behavioral group therapy and individual treatment plans for collaboration with the social services regarding issues of housing and occupation. Out of the 20 individuals randomized to a fixed dose of 16 mg of buprenorphine, 15 were still in treatment after one year. Among the controls, all dropped out within two months, and four patients were reported dead at follow-up (152).

In a report from 2007, Kakko et al. demonstrated that a stepped-care approach starting with buprenorphine/naloxone retained heroin-dependent individuals to the same degree as methadone maintenance. In addition, it demonstrated the feasibility of a low-threshold approach without prior inpatient treatment, social stability or treatment induction in regular outpatient clinics (153).

Aims

General aims

The general aim of this thesis was to evaluate a model for referral of opioid-dependent individuals from a NEP to OMT and to evaluate the clinical course for individuals starting OMT regarding specific outcome measures.

Study-specific aims

Study I

The aims of the study were to 1) assess effectiveness of a syringe exchange program for referral of heroin-dependent patients to evidence-based treatment with methadone or buprenorphine (buprenorphine-naloxone), and to 2) assess, in a randomized controlled design, the potential add-on effect of a strengths-based case management intervention, with respect to successful treatment entry in OMT.

Study II

The primary aim was to evaluate the effect of OMT with respect to 1-year retention for the heroin-dependent individuals who successfully started treatment as described in study I.

Study III

The aim of this study was to investigate changes in HRQoL (measured with EQ-5D) from baseline to three months into treatment, and whether it was related to baseline characteristics or drug use. The study sample was also compared to a sample from the general population regarding HRQoL.

Study IV

This study was a 3-year follow-up of the same cohort studied in study II and III. The aims were to study prevalence and reasons for psychiatric hospitalization and potential predictors, and to investigate concurrent psychiatric diagnoses (including other substance dependence diagnoses apart from opioid dependence) during follow-up.

Material and methods

Setting

The Malmö Treatment Referral and Intervention Study (MATRIS) took place in the city of Malmö, located in the region Skåne in the southernmost part of Sweden. The population, roughly, is in Malmö 300,000, and in Skåne 1.3 million.

The NEP in Malmö is located in the hospital area and run by the Department of Infectious Diseases. The NEP is staffed by nurses, assistant nurses, social workers and it is also possible for attendees to get an appointment with a physician and/or a midwife. Apart from distribution of injection equipment it offers basic medical care, risk reduction strategies and psychosocial support. The individuals attending are identified by their social security number and are regularly tested for HIV, hepatitis B and hepatitis C (HCV). Vaccinations are offered for hepatitis A and hepatitis B. At the time of the study approximately half of the 1,000 enrolled individuals at the NEP stated their main drug to be heroin. A previous study estimated that the other half mainly consisted of amphetamine users (154). The NEP participants made approximately 7,000 visits a year and roughly 50,000 syringes and 100,000 needles were distributed annually. A majority of the individuals enrolled at the NEP were anti-HCV positive, in contrast the HIV prevalence close to zero (155).

The Addiction Center Malmö is also situated in the hospital area and has three inpatient units and an emergency room. At the time of the study it also had two outpatient clinics for OMT. Because of the study, a new research facility for OMT was started which was also managed by the Addiction Center Malmö. The research facility was initially situated in the hospital area but later relocated approximately three kilometers from the NEP.

Study design

MATRIS was a two-group randomized controlled trial (RCT) where all participants were included at the NEP in Malmö and referred to the same research outpatient clinic for OMT. Patients were randomized to a strengths-based case management intervention (CMI) or a referral-only group (control group). Participants were

included between October 21, 2011, and April 1, 2013. Due to relocation of the OMT clinic, inclusion was temporarily stopped for five months in 2012.

Potential participants in MATRIS were at first approached by staff at the NEP and asked whether they were interested to take part in a study that might result in OMT. If interested, the participants were within days scheduled to one of two social workers for informed consent, formal inclusion, baseline assessment and randomization. The social workers were part of the MATRIS research team and specially trained in case management.

The randomization schedule was computer-generated by an external statistician not involved in other parts of the trial. It was stratified for age and participants were assigned randomly after the baseline assessment by the next numbered sealed opaque envelope.

At the baseline assessment participants were asked about substance use, psychiatric and medical history. The participants' HRQoL was also assessed with the instrument EQ-5D developed by the EuroQol group (156). They also left a hair sample for later analysis for substance use. If the participant was randomized to the intervention group she/he was offered CMI in direct connection.

The CMI was brief, semi-structured and adapted to the patient needs. The sole purpose of the intervention was to increase the chance that the participant appeared at the appointment at the OMT outpatient clinic one week after the baseline assessment. During the CMI, which on average lasted 30 minutes, strengths and resources were explored by the case manager and participant. Enquiries were made about the nine life domains (life skills, finance, leisure, relationships, living arrangements, education/occupation, health, internal resources, and recovery) in accordance with the strengths-based case management model which previously has been shown to enhance linkage to treatment (157-161). To explore possible support in the participants' social network, a relationship map was used. The most common help the participants in our study asked the case managers for was reminding them of the appointment at the OMT outpatient clinic through a text message or a phone call.

The participants who were randomized to the control group only received an appointment at that OMT outpatient clinic one week after the baseline assessment.

At the appointment at the OMT outpatient clinic, participants left a urine sample for toxicology screening and were medically evaluated to see whether they were eligible for OMT according to the Swedish legislation. If the toxicology screen was positive for opioids and the participant was deemed eligible for OMT, treatment was usually initiated 4 days after the medical assessment. Choice of OMT medication was outside of the study protocol.

The protocol was approved by the Regional ethics review board in Lund, Sweden. The study was also registered at clinicaltrials.gov: Malmö Treatment Referral and Intervention Study

(MATRIS), NCT01457872, https://clinicaltrials.gov/ct2/show/NCT01457872.

A power calculation was performed on the assumption that 50% of the participants in the control group and 75% in the intervention group would enter treatment. A calculation of 80% power with a 95% confidence interval resulted in a target number of 130 participants. It turned out, however, to be virtually no difference between the groups and significantly higher treatment initiation rates than we had anticipated. Due to diminished participant inflow the inclusion process was therefore stopped after inclusion of 75 participants.

Participants

Eligible participants for MATRIS were individuals attending the NEP in Malmö, with heroin as their main drug of abuse, and who had made at least two NEP visits prior to study start. In order to make the recruitment process easier and more effective, the individuals enrolled at the NEP were divided into four age groups. The recruitment then started with the youngest (20-30 years) and oldest (51 years and older), followed by the two remaining groups (31-40 and 41-50). The number randomized to each group was balanced to be representative of how the age distribution at the NEP was among enrolees reporting heroin to be their drug of choice. Exclusion criteria were pregnancy, already being in treatment, severe unstable psychiatric condition or inability to understand and provide informed consent.

When retrospectively interviewing the staff at the NEP it was reported that approaching NEP enrolees consecutively was difficult because the staff were sometimes were busy with other patients or due to the fact that the potential participant was too intoxicated or did not want to stay for information. A naturalistic post-hoc attrition and feasibility analysis (presented in the Results section) was therefore conducted. This was done by going through all patient records at the NEP for the study period and comparing patients who were approached to patients who were not approached. This was done regarding age, gender and frequency of NEP visits.

Study outcomes and statistics

Study I

A successful transfer of participants from NEP to OMT initiation at the outpatient clinic was the primary outcome. This was measured as the number of patients who started OMT, and secondly, a potential add-on effect from CMI was tested for. Fisher's exact test was used to test for differences regarding treatment entry rates between the randomized groups, along with the measure of the odds ratio with 95% confidence intervals.

Potential baseline predictors regarding treatment entry were analyzed using Fisher's exact test for binary variables and Student's t-test for continuous variables. To adjust for potential predictors, logistic regression was used.

For the post-hoc attrition and feasibility analysis, when making a comparison between recruited study participants and NEP enrolees not approached for participation, chi-square test was used for comparison of gender and Mann-Whitney for age and number of NEP visits.

Study II

Primary outcome was 1-year retention in treatment measured as the number of patients still in treatment after this time. Data was collected from patient records and the proportion of participants still in treatment after 1-year was reported. A survival analysis was performed with the number of days in treatment as the time-dependent variable.

Study III

The outcome measure was HRQoL measured using the instrument EQ-5D at baseline and three months into treatment.

EQ-5D assesses health and functioning through five different life domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three different severity levels. As a result 243 different health states can be determined from the scores, and Swedish experienced based value sets (162) were used to calculate EQ-5D index values for each health state. The EQ-5D index value can be between 0 and 1 where the first corresponds to dead and the latter to full health. There is also a VAS scale included in the EQ-5D where respondents rate their overall health between 0-100.

To measure difference over time, two new variables were constructed; 1) EQ-5D index difference which was the difference between EQ-5D index at baseline and at three months, and the 2) EQ-5D VAS difference which was constructed in the same manner.

Statistical analysis using Students t-test was made to see whether there was a statistically significant increase of the 'EQ-5D difference' or 'EQ-5D VAS difference' over time.

Linear regression was used to assess potential baseline predictors for change of 'EQ-5D difference' or 'EQ-5D VAS difference'. The characteristics analyzed as independent variables were sex, age, randomization group, being responder in treatment (defined as more than 80% negative toxicology screens for opioids or other illicit substances for the first three months in treatment), previous suicide attempts, and previous overdoses.

Group comparisons at baseline were made using Mann-Whitney.

Study IV

Primary outcome was psychiatric hospitalization during a 3-year follow-up of the participants starting OMT, including potential predictors for hospitalization. In addition, psychiatric diagnoses during the same period were studied. The data was collected from study report forms and from a review of patient records.

Hospitalized patients were compared to non-hospitalized patients, and participants with a psychiatric diagnosis were compared to participants with no psychiatric diagnosis.

In order to identify potential predictors at baseline, comparisons were made using Chi-square test for binary variables, and the Fisher's exact test if there were less than five subjects in one category. Mann-Whitney's test was used for continuous variables. Finally, a regression analysis was used to adjust potential predictors for one another.

A multiple regression analysis was made to identify baseline predictors for time to first hospitalization when controlling for baseline use of buprenorphine (buprenorphine and buprenorphine-naloxone were grouped together) and sedatives-hypnotics (benzodiazepines, 'z drugs', and pregabalin were assessed together as sedatives-hypnotics).

Since discharge from OMT often is a predictor of poor clinical course (163) we wanted to control for discharge from OMT with regard to hospitalization. Therefore, a Cox regression proportional hazard analysis with time-varying co-variates was made.

Results

Study I

Out of 100 potential study participants who were approached by staff at the NEP, 79 were willing to take part in the study. Out of those, 75 turned up for study inclusion, baseline interview and randomization. Thirty-six participants were assigned to CMI and 39 to the control group. Seventy-one participants then successfully started treatment. Among patients randomized, 95% of the intervention group and 94% of the control group started treatment. Thus, entry was not related to being in the control or intervention group (unadjusted OR=0.92 [0.12-6.89] and adjusted OR=0.96 [0.12-7.83]).

When conducting the post-hoc attrition and feasibility analysis it was found out that 72 patients had not been approached by the NEP staff. A comparison to patients who started treatment showed that the patients not approached had made significantly fewer visits to the NEP (2.0 vs. 10.7, $p<0.001$), and were younger ($p=0.03$).

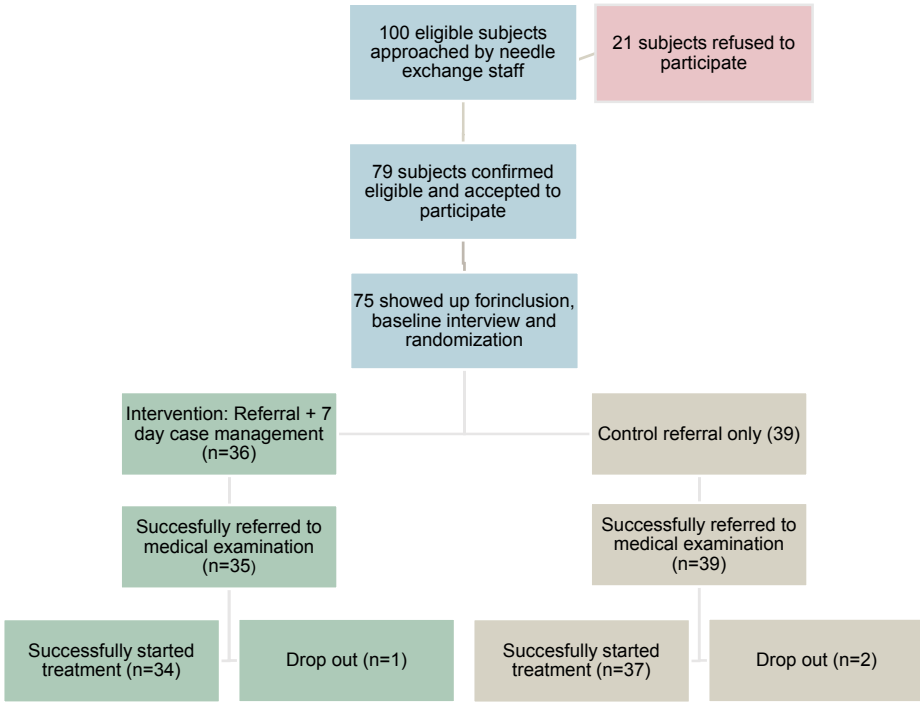

Figure 1
Study profile over the referral process from NEP to OMT.

Study II

Of the 71 patients who started OMT, 67 (94%) were still in treatment after three months, 63 (89%) after six months, and 58 (82%) after 12 months.

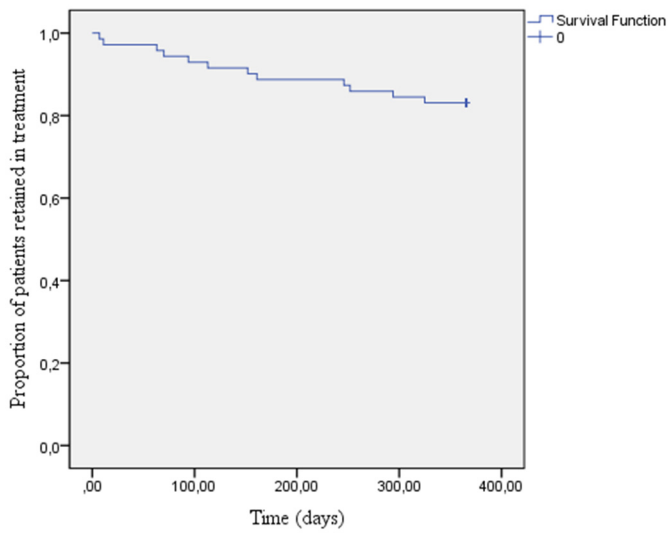

Figure 2
Proportion of patients still in treatment over time.

Study III

At baseline the mean EQ-5D VAS for the study sample was 47.3 (0 being 'the worst health you can imagine', and the highest rate 100 'the best health you can imagine'). The highest percentage of reported problems were from the domains of anxiety/depression and pain.

Participants reporting to be prescribed drugs for a psychiatric condition had significantly lower mean EQ-5D index values at baseline (0.66 vs. 0.76, p=0.024). Participants reporting previous suicide attempts were found to have significantly lower mean EQ-5D VAS scores (36.5 vs. 51.8, p=0.022).

A linear regression analysis showed less improvement in EQ-5D index score over time for participants reporting previous overdoses (-0.10, p=0.025). No significant change of EQ-5D index score difference was found over time. The EQ-5D VAS difference was found to significantly increase over time with a mean of 10.94 (p=0.008) for the whole group.

Study IV

During the 3-year follow-up, 65% of the participants were hospitalized for a psychiatric reason at least once. Substance-related reasons were the most prevalent and hospitalization for detoxification was found in 59% of the participants. Detoxification from sedatives/hypnotics was the most common substance-related reason and was found occurring for more than half (52%) of the study participants.

Sedative-hypnotic use and buprenorphine use at baseline, respectively, were found to significantly predict hospitalization. When controlling for one another in a logistic regression model, hospitalization was only significantly predicted by baseline use of buprenorphine (OR 4.2, CI 1.2-14.5 p=0.025) and not by sedatives-hypnotics (OR 3.1, CI 1.0-9.8 p=0.052).

When using a multiple regression analysis to predict time to first hospitalization from baseline use of sedatives-hypnotics and buprenorphine, these variables significantly predicted time to first hospitalization ($F=9.9$, $p<0.0005$, $r^2=0.226$). Both variables added significantly to the prediction ($p<0.05$).

A Cox proportional hazard regression was performed with time to discharge as a time-varying covariate. Discharge from OMT was found to predict hospitalization (OR 2.0, CI 1.0-3.9 p=0.039) when controlling for baseline use of sedatives-hypnotics (OR 2.6, CI 1.2-5.7 p=0.015) or buprenorphine (OR 2.3, CI 1.3-4.3 p=0.005) which were also significant predictors for psychiatric hospitalization in this analysis.

Seventy-two percent of the participants received a psychiatric diagnosis, i.e. including a comorbid substance use disorder in addition to opioid dependence, during the 3-year follow-up. When excluding substance use diagnoses however, only 41% received a diagnosis, the most prevalent being anxiety disorders (27% of all participants). We could not identify any baseline characteristic predicting a non-substance use diagnosis.

Discussion

All results presented in the previous sections were analyzed from the same cohort of out-of-treatment heroin-dependent individuals recruited at the NEP in Malmö and referred to the OMT outpatient clinic. The participants initiating OMT were then followed for three years. The first study was an RCT and the three following were prospective observational studies.

The studies in the present thesis provide three main themes: 1) the referral from NEP and treatment initiation at the OMT outpatient clinic described in study I and retention in treatment described in study II, 2) short-term outcome including quality of life, studied in study III, and 3) the role of substance use in the long-term outcome, the consequences of which were mainly analyzed in study IV. Below is a general discussion of methods and results from the studies according to these themes.

Referral from NEP and initiation of OMT

This study of referral of heroin users from a NEP to OMT showed that a majority of the included participants successfully started OMT. Furthermore, a 12-month follow-up of the participants who started OMT showed that a majority were still in treatment at that time. Study I was a two-group RCT assessing a potential add-on effect of a strength-based CMI on treatment initiation rates. There were high rates of referral and treatment initiation for both groups, and treatment initiation was unrelated to intervention status. In study II, which was a prospective observational study of participants who started OMT, a majority of the participants were still in treatment after 12 months, at a percentage comparable to other OMT clinics in Sweden.

The high referral and treatment initiation rates from NEP to OMT, and the high retention in treatment, were somewhat surprising since the numbers were higher compared to some previously published data from the US. In two different studies from Baltimore on the referral of heroin-dependent individuals from NEP to OMT, no more than 40% entered OMT even after receiving CMI or motivational and monetary incentives (147, 148). However, Kuo et al. did report that 70% of heroin

dependent individuals entered treatment with LAAM when referred from a NEP in Baltimore and that 84% were in treatment after 90 days (145).

Neufeld et al. reported that individuals referred from NEP to OMT had poorer 12-month retention compared to other referrals (35% vs. 56%). However, no association with outcome could be seen when adjusting for baseline characteristics known to be associated with worse outcome such as drug use severity as measured by substance use and injection behavior (164). NEP populations have been reported to have a high degree of drug use severity and psychiatric problems when compared to other out-of-treatment opioid-dependent individuals (34, 39, 165, 166), which could explain a worse treatment response.

The participants in our sample also reported a high degree of drug use severity reporting injection on average 21 of the last 30 days prior to study inclusion. A majority reported previously defined overdoses and the use of other substances apart from heroin, mainly other opioids, sedatives, alcohol and cannabis. Almost a third reported previous suicide attempts and a high degree of criminality and social instability. It is therefore unlikely that our high retention rate is explained by being a population with a lower degree of problems at baseline.

Predictors for retention have been studied and longer tenure in treatment has been associated with older age, female gender, less use of non-opioid drugs or alcohol, higher methadone dose, and satisfaction with treatment (115, 167-180). In our setting, when it comes to non-opioid drugs, another study has shown that especially non-prescribed benzodiazepine use in treatment has been associated with higher degree of drop-out from treatment (54), whereas in studies from other settings, the results have been more inconsistent, either with an association with poor treatment outcome and/or shorter tenure in treatment (65, 66) or not associated with lower retention rates (58, 60). There is also some evidence that involvement in the criminal justice system is associated with a negative treatment outcome (168, 174, 181, 182). Studies have also shown that longer waiting times are associated with lower rates of treatment entry (183-186) and that rapid intake is associated with higher or no change in retention rates (183, 184, 187-189).

It may be assumed that a high degree of baseline problems ought to be predictors for a negative clinical course and potentially negative with respect to retention. On the other hand, in the present sample there was a very short time from study inclusion at the NEP to treatment initiation at the OMT outpatient clinic which could in part explain the high treatment initiation and retention rate. Initially the ambition was to report predictors from our sample since we thought there were several ‘candidate’ predictors at baseline from what is known from previous reports. We could, however, not find any statistically significant predictors (unpublished results), possibly due to the high retention rates but more probably due to the relatively low number of included participants.

In conclusion, the results suggest that a NEP is a clinical setting that allows for efficient referral of heroin-dependent individuals to OMT. A majority of the participants starting OMT were still in treatment after 12 months. These results suggest that NEPs should be regarded not only as a means for reducing negative effects of injection drug use, but also a potential gateway to treatment for drug dependence. Future studies should address the feasibility of similar referrals to other settings, for example emergency wards (190), criminal justice settings (191, 192) or peer outreach programs (193).

Quality of life

In study III, which was a prospective observational study, the patients reported a significantly lower mean EQ-5D VAS score at baseline when compared to a sample from the Swedish general population. In particular, participants reporting previous suicide attempts had significantly lower EQ-5D VAS, and having a prescribed psychiatric medication was associated with a lower EQ-5D index score. Higher EQ-5D index and VAS scores at baseline were significantly associated with having less problems with benzodiazepine use during the first three months of treatment. Participants reporting previous overdoses showed less improvement of EQ-5D index scores over time. However, the sample as a whole did show a significant increase of the EQ-5D VAS over time, indicating that OMT had a beneficial effect with regard to HRQoL also in this sample of rapidly transferred NEP participants.

As far as we know, this is the first time HRQoL is reported as an outcome in a population recruited at a NEP and transferred to OMT in a rapid, low-threshold manner. As stated above, our sample had lower HRQoL than a sample from the general population but also when compared to a sample of homeless people in Sweden (194). The sample from the general population reported the most problems from the domain of pain, while our sample and the sample of homeless individuals reported the most problems from the domain of anxiety/depression. A weakness of the comparison with the general population is that the sample provided by the EuroQoL group is from the late 1990s (195). The sample of homeless individuals however is more recent, from 2006. Our findings are also in accordance with previous studies reporting opioid-dependent individuals to have lower HRQoL than the general population (79-82, 97).

Since psychiatric problems/comorbidity is common in the opioid-dependent population (28, 34, 196) and linked to lower HRQoL (94, 96, 97), the findings that previous suicide attempts and being prescribed a psychiatric medication were associated with lower HRQoL at baseline, were not surprising. EQ-5D have previously been reported to be responsive to reductions in illicit drug use during

OMT (197). We did not find any association between reductions in opioid use and HRQoL, however, and higher HRQoL at baseline was associated with less use of benzodiazepines in treatment. Since benzodiazepine use has been linked to more psychiatric problems, this finding was not surprising as it may reflect an underlying psychiatric disorder or a negative effect of benzodiazepine use in itself. Overall, most of the participants reported using sedative-hypnotics, including benzodiazepines during the last 30 days prior to the baseline interview, and only a small minority could be classified as responders during the first three months.

Despite having only a minority of responders in the short term, we report an increase of HRQoL for the whole group during the same time which is in accordance with other studies reporting improvement of HRQoL during OMT (80, 83-86, 198). The finding that a large proportion of our sample were using illicit substances during the 3-month follow-up, and still reported improved HRQoL, is an interesting finding and might reflect the fact that patients and staff do not always agree upon what is treatment success, a point that has been raised by others (73, 74, 199). The results create new hypotheses and future studies could complement the HRQoL measurement with a qualitative study to try to get a better picture of what is important for the patients regarding quality of life, or using alternative instruments. The EQ-5D was chosen since it has been validated for heroin-dependent individuals (200), is sensitive to use of illicit substances (197) and allows for estimates of quality-adjusted life years (QUALYs). Some authors argue that these factors make HRQoL preferable to measuring QoL (78). Other authors however argue for the use of QoL instruments, which they considered a broader concept not just measuring health and functioning in different life domains (75-77).

In summary, we found a significant improvement of HRQoL in the short-term despite having a population troubled by a high degree of psychiatric problems, social instability and polysubstance use.

The role of substance use in the long-term outcome

In study IV we found that most participants received at least one psychiatric diagnosis apart from opioid dependence. Dependence on sedative-hypnotics was the most prevalent followed by anxiety disorders and mood disorders. When looking at psychiatric hospitalization, detoxification from benzodiazepines was the most common cause for inpatient treatment. Psychiatric hospitalization was predicted by baseline use of buprenorphine and sedative-hypnotics when controlling for treatment status. The latter group included benzodiazepines, ‘z drugs’ and pregabalin, but benzodiazepines was the major problem. All of the small group of

participants reporting baseline use of pregabalin also reported use of benzodiazepines.

The finding that polysubstance use was common and had a negative impact was not surprising since this is a common clinical problem. It has previously been reported for opioid-dependent patients (51, 58, 201), and associated with increased risk for both fatal and non-fatal overdoses (20) and worse clinical outcomes with more psychiatric symptoms, social problems and polysubstance use (60, 61, 65, 202). Given the increased risk for such problems by the concurrent use of opioids and benzodiazepines, the increased use of inpatient services was not unexpected.

It is more difficult to understand why buprenorphine use at baseline predicted hospitalization, since intuitively it should be safer than full opioid receptor agonists. It has also been reported buprenorphine is used among heroin-dependent individuals mainly for self-treatment of withdrawal when used without prescription, as opposed to producing euphoria (154).

Psychiatric hospitalization was selected as a primary outcome since it was thought to reflect psychiatric severity, although it is rarely reported in studies of the heroin-dependent population.

In a Swedish register linkage study of psychiatric hospitalization in ex-prisoners with substance use problems, hospitalization was predicted by sedative use, previous hospitalization, suicide attempts, depression and anxiety (203). We also reported a negative impact of sedative use at baseline on psychiatric hospitalization. In a study from Australia, psychiatric hospitalization was studied, using linked hospital records, in a cohort of 1,184 heroin dependent individuals prior to and after rapid opioid detoxification and following oral naltrexone. They concluded that treatment reduced the risk for psychiatric hospitalization and that admissions peaked three months prior to treatment (204). In another study using hospital records, Ngo et al. found that patients with psychiatric comorbidity had a higher risk for drug-related hospitalization prior to methadone treatment compared to patients without psychiatric comorbidity. They found, however, substantial reductions in hospitalization rates post-treatment and that depression and anxiety had a protective effect against drug-related hospitalization (205). In our study, substance use at baseline predicted hospitalization but not factors linked to psychiatric problems. Treatment of sedatives/hypnotics dependence was the most common inpatient diagnosis co-occurring with opioid dependence.

When excluding substance-related comorbidity, mood disorders and anxiety disorders were the most common, which is in line with previous reports. The rates were in the lower end of what has been reported in other studies using lifetime diagnoses and SCID (28, 34, 45). When compared to another study using record linkage reporting lifetime prevalence of both outpatient and inpatient psychiatric

diagnoses, our rates were overall higher (205). This possibly illustrates the difficulties with comparing comorbidity not only due to different settings but also because of different screening instruments. We used the patient records to identify psychiatric diagnoses for each participant for the 3-year follow-up from the time they were included in the study. This approach allowed for a high degree of certainty regarding the available diagnoses but had the disadvantage of underestimating potential diagnoses that could not be validated due to current substance use. For example, less than 1/10 of patients in our sample were diagnosed with ADHD, or a personality disorder, whereas other studies have reported considerably higher rates, e.g. for personality disorders, with antisocial personality disorder being the most prevalent (28, 34). When it comes to ADHD it has been found to be more prevalent in the substance-using population, however with a wide range of prevalence estimates depending on the populations and methods used (206). In a recent study from Norway, 1/3 of a sample of OMT patients screened positive for ADHD (207). Patients with substance dependence and co-occurring ADHD have been reported to have increased psychiatric comorbidity, HIV-risk behavior and more hospitalizations (206, 208). For patients in OMT, co-occurring ADHD has been associated with greater addiction severity and more psychiatric comorbidity (206, 209).

Our conclusion is that in our sample, polysubstance use was the most important predictor for a worse clinical course as measured by hospitalization. We did not find any significant differences between patients with a non-substance psychiatric diagnosis and those without regarding baseline characteristics.

Methodological considerations

The small sample size is a limitation of the study. Due to diminished patient inflow the study inclusion was terminated prematurely. The treatment entry rates for both randomization groups were however considerably higher than expected when performing the original power calculation. Therefore it is unlikely that there would have been a significant difference between the randomized groups with regard to treatment entry in OMT. The sample sizes of the follow-up studies also suffered from the premature inclusion stop.

Inclusion was also stopped for five months due to a move of the OMT outpatient clinic. The first clinic was in close proximity to the NEP, whereas the new facility was situated on the other side of the town, approximately 3 km from the NEP. Transportation has been reported to be a potential barrier to referral (143) but since the referral and treatment initiation rates remained high this does not seem to have had any impact on the outcome.

At the time of the study there was a waiting list for OMT in Malmö and most other parts of Skåne. To avoid that individuals started at the NEP only in order to get OMT, as this was not the scope of the study, eligible individuals had to have made at least two visits to the NEP prior to study start. One cannot rule out the possibility that the waiting list situation affected the results. Other studies have, however, reported low attendance rates when NEP participants expressing a wish for treatment were given referrals to treatment (5, 144, 146, 210).

It was not always possible to ask and include the NEP participants in a consecutive manner as stated in the protocol. It was found that 72 patients had not been approached by the NEP staff and that they were on average younger and had made fewer visits to the NEP when compared to included NEP participants. This is a clear limitation to our model for treatment referral from NEP, and more research is needed to find efficient ways of referring also younger and less frequent NEP participants to treatment. Future studies should also more thoroughly study the NEP population regarding not only demographics, but maybe also from a qualitative aspect to get an idea of what patients perceive as obstacles for treatment referral.

General conclusions

Our results suggest that a NEP is a clinical setting that allows for efficient referral of heroin-dependent individuals to opioid maintenance treatment, which is presently the most effective treatment for this patient population.

Even in a NEP population with a high degree of substance use problems and social problems, there was a significant improvement in HRQoL in the short term and, importantly, a majority of the participants were still in treatment after 12 months.

The most common reason for hospitalization during a 3-year follow-up was dependence on benzodiazepines and similar sedatives, and this was also the most common psychiatric diagnosis apart from opioid dependence. Hospitalization was indeed predicted by patients' baseline use of sedatives.

The most common non-substance use diagnoses were mood and anxiety disorders. The rates of ADHD and especially personality disorders were lower than expected, possibly due to difficulties in diagnosing a population with a high degree of current polysubstance use.

Clinical implications

Based on the present results, the model for linkage of heroin-dependent individuals from NEP to OMT has the potential of improving substance use services for this patient group. Thus, NEPs should not only offer services focused on preventing blood-borne diseases and general health, but also be organized to provide an effective link to treatment for drug use disorders.

Barriers to treatment have traditionally been high in many clinical settings, and in a global perspective they are still significant. Due to high-threshold criteria for OMT, waiting lists are common at many sites and there are often strict requirements for social stability and detoxification before treatment initiation. This often leads to a need for initial inpatient treatment which produces further delays. By removing barriers to treatment that may negatively influence referral and treatment initiation, more patients could access the benefits of treatment and patients who today are out-of-treatment might be reached. While important issues such as homelessness, polysubstance use and psychiatric comorbidity should always be addressed, the present results suggest that patients can safely start OMT even in an out-patient setting with fewer exclusion criteria. It therefore seems reasonable to stabilize the patients in OMT first, before addressing other issues.

While it was safe to allow for a rapid start of outpatient OMT in this NEP population and treatment retention was comparable to regular OMT programs, there was a negative impact of polysubstance use, especially benzodiazepines. Evidently, this is a clinical aspect that needs special attention in clinical care of this population. It is hypothesized that a reduction in benzodiazepine use has the potential of reducing mortality, psychiatric morbidity and possibly also the increased need for inpatient treatment. In addition, current polysubstance use constitutes a barrier to diagnosing important psychiatric comorbidity and providing adequate treatment and support. Inpatient services for individuals with current polysubstance use are often a great help to stop using drugs, but are rarely offered in hospital settings due to the high costs. This is an area that needs more research in cooperation with municipal social services.

Implications for future research

The linking of heroin-dependent individuals from NEPs to OMT needs to be further studied also in other clinical settings. Candidate settings for studying such models could be for example the criminal justice system, emergency rooms or maybe naloxone outreach programs. When it comes to linkage from NEPs, one group that was left out in the present study was the population with primary amphetamine dependence which constituted approximately half of the enrolled NEP participants. Questions for future research may include the possibility of linking also individuals with amphetamine dependence to treatment, and what that treatment offer should be (154).

Polysubstance use is common, also in the OMT population (49, 53, 211). Further research ought to focus on how to better help patients not only dependent on opioids but also on other substances. In the present work, especially benzodiazepine dependence turned out to be a problem associated with a negative clinical course. Research should therefore focus on how to better address polysubstance dependence.

Populärvetenskaplig sammanfattning

Injicering av opioiden heroin medför stora risker för användaren. Själva injektionen kan medföra olika slags infektioner och heroinet kan vara uppblandat med andra substanser, ha en okänd styrka och medföra risk för exempelvis överdosering. I Sverige är det personer som använder opioider, ett samlingsnamn för t ex. heroin och morfin, som löper störst risk att avlida av narkotikaöverdos.

För att minska spridning av infektioner som HIV och hepatit i samband med injektion startades sprutbyten på många ställen i världen under 1980-talet, detta för att narkotikaanvändare skulle använda ren injektionsutrustning och inte dela med andra. Även i Malmö och Lund startade sprutbyten på 1980-talet som försöksprojekt men inte förrän 2006 kom lagstiftning som tillät sprutbyten på andra platser.

För personer som blivit beroende av heroin finns sedan slutet på 60-talet vetenskapligt utvärderad läkemedelsassisterad behandling (LARO) med metadon och sedan 1990-talet även buprenorfin. Behandlingen medför framförallt minskad överdödlighet men även minskat heroinanvändade och mindre spridning av infektioner. I Sverige har tillgängligheten till läkemedelsassisterad behandling varit låg vilket på många håll resulterat i långa väntetider. Att använda sprutbytesprogram som en väg in i behandling kan verka logiskt men har tidigare endast undersökts i enstaka studier från USA och med varierande resultat.

Syftet med denna avhandling var att undersöka om det går att använda sprutbyte som en väg in i läkemedelsassisterad behandling med metadon eller buprenorfin. Vi har därefter följt upp de patienter som började för att se hur många som stannade kvar i behandling, hur deras självrapporterade livskvalitet förändrats på kort sikt samt kartlagt i vilken utsträckning patienterna har andra psykiatriska sjukdomar, inklusive substansberoende, och för vilka diagnoser som patienterna vårdats på sjukhus under uppföljningstiden på tre år.

Arbete 1

I första delarbetet ville vi se om det gick att överföra personer som använde heroin och hade kontakt med sprutbytet till läkemedelsassisterad behandling med metadon eller buprenorfin på en särskild beroendemottagning. Avsikten var att utvärdera en modell där hälften av patienterna erbjöds extra stödinsatser med syftet att öka chansen för att de skulle infinna sig på beroendemottagningen.

Sammanlagt 75 patienter på sprutbytet i Malmö tackade ja till att delta i studien. Av dessa lottades 39 till kontrollgruppen som endast fick en läkartid på beroendemottagningen en vecka senare för ställningstagande till läkemedelsbehandling. De övriga 36 patienterna erhöll, i tillägg till läkartid, erbjudande om extra stödinsatser (case management), i syfte att öka sannolikheten att patienten kom till läkarbedömningen. Den vanligaste stödinsatsen i gruppen som erbjöds detta var SMS-påminnelse om läkartiden på beroendemottagningen eller att de bad om att bli uppringda en viss tid innan.

Av de patienter som deltog i studien infann sig alla utom en på beroende-mottagningen och de extra stödinsatser som den ena gruppen fick resulterade inte i bättre överföringsgrad för den gruppen.

Tolkningen som görs är att det viktigaste var den konkreta länken mellan sprutbytet och beroendemottagningen som möjliggjorde snabb överföring och behandlings-start.

Resultaten visar att det går att överföra patienter från aktiv heroinanvändning och kontakt med sprutbyte till evidensbaserad läkemedelsbehandling inom beroendevården. Genom att använda sprutbytet som kontaktyta kan vi nå en grupp som inte är aktivt behandlingssökande eller som inte lyckats ta sig in i behandling på traditionellt sätt.

Arbete 2

I arbete två följde vi upp de patienter som överförts från sprutbyte till LARO-behandling för att se hur stor andel som kvarstannade i behandling, s.k. retention. Av dem som startade så var en majoritet (82%) kvar i behandling efter 12 månader. Detta är jämförbart med andra LARO-mottagningar i Sverige trots att patienterna i denna studie överfördes från sprutbyte till behandling på mycket kort tid, med förenklat utredningsförfarande och utan krav på social stabilitet.

Arbete 3

skattade sin livskvalitet högre innan behandling jämfört med de som fortsatte att I detta arbete avsåg vi att undersöka om patienterna, trots snabb överföring från sprutbyte till behandling, upplevde att livskvaliteten ökade i behandling på kort sikt samt om det var relaterat till drogfrihet, psykiatrisk samsjuklighet eller sociala faktorer. Vi jämförde också patienternas resultat med ett stickprov från den svenska normalbefolkningen. Patienterna skattade sin livskvalitet med ett särskilt frågeformulär (EQ-5D) innan behandling på sprutbytet samt efter tre månaders LARO-behandling. Resultaten visade att den skattade livskvaliteten var högre efter tre månaders behandling jämfört med resultaten innan behandling. Användande av psykiatriska läkemedel och tidigare självmordsförsök var kopplade till lägre skattad livskvalitet. Patienter som huvudsakligen varit drogfria under tre månader i behandling använda narkotika i behandling.

Jämfört med den svenska genomsnittsbefolkningen skattade patienterna sin livskvalitet betydligt lägre, även jämfört med en tidigare svensk studie av hemlösa.

Arbete 4

De 71 patienter som påbörjade LARO-behandling följdes upp efter 36 månader. Genom granskning av medicinska journaler kartlades vilka diagnoser som patienterna hade men också för vilka eventuella psykiatriska sjukdomar och problem de fick vård på sjukhus. Det visade sig att en majoritet (65%) vårdats på sjukhus vid åtminstone ett tillfälle under uppföljningstiden. Problematiskt användande av receptbelagda lugnande läkemedel var den vanligaste orsaken till inläggning på sjukhus. Det fanns också ett samband med användning av denna typ av läkemedel innan LARO-behandlingen och behovet av vård på sjukhus under uppföljningstiden.

En majoritet (72%) erhöll också en annan psykiatrisk diagnos utöver opioid-beroende. Den vanligaste icke-substansrelaterade diagnosen var ångestsyndrom.

Sammanfattningsvis ger forskningsstudierna stöd för att sprutbytesverksamhet inte bara kan fungera som smittskyddsåtgärd för patienter med heroinberoende utan som effektiv väg in i behandling. Genom att använda sprutbytet som kontaktyta kan man nå en grupp som inte är aktivt behandlingssökande eller som inte lyckats ta sig in i behandling på traditionellt sätt. Trots snabb överföring av patienter från sprutbyte, utan krav på drogfrihet eller socialstabilitet, stannar patienterna i behandling i lika hög utsträckning som i mer traditionella LARO-program i Sverige. Patienternas livskvalitet ökade då de kom in i behandling trots en hög grad av psykiatrisk samsjuklighet. Användning av lugnande receptbelagda medel innan behandling var kopplat till behov av slutenvård (vård på sjukhus). Beroende av sådana preparat var också den vanligaste diagnosen kopplat till slutenvård under uppföljningstiden och bör observeras.

Slutsatsen är att denna överföringsmodell sannolikt kan implementeras på fler sprutbyten för att öka tillgängligheten till LARO-behandling för personer som använder heroin, och möjligen också för att nå fler individer som inte annars hade kommit i kontakt med beroendevården.

Acknowledgements

First of all I would like to thank all the patients who participated in the studies and made this thesis possible. Since the making of this thesis really was a team effort I would like to take the opportunity to express my deepest gratitude to the many persons helping out, supporting, inspiring and making it worthwhile and possible.

First of all I would like to thank my main supervisor Anders Håkansson. As I remember it, we started to talk about the idea that resulted in this thesis at an annual meeting of the College on Problems of Drug Dependence together with Mats Berglund. This was a long time ago and I may be incorrect but I think we did the original sketch for what was going to become MATRIS on a napkin. I have always enjoyed our discussions and I am very grateful for your continued support, patience and your usually very optimistic view on things when I at times have been more pessimistic. I could not have had a better supervisor! Thank you also Mats Berglund. It was always an inspiration to be with you on different meetings and I will never forget how you taught us to mingle in the morning during the poster sessions. I am also grateful to you for sending me to the Rockefeller University in New York to initiate a collaboration with Mary Jeanne Kreek. She is one of the true pioneers when it comes to opioid maintenance treatment research and a person that made me especially interested in research regarding opioid dependence.

I would also like to thank my co-supervisors Louise Brådvik and Johan Franck for your patience, sharing your vast knowledge and for helping me improve my writing skills.

To be able to do the studies in this thesis, a new research clinic (nowadays LARO Matris) had to be started and the studies would not have been possible without the past and present staff there. I would especially like to thank Katja Troberg, Pernilla Isendahl, Suzan Nilsson, Cristof Broman and Malin Skarland – the start-up crew. A special thanks to Katja who as the head of the research clinic managed us through some difficult times, not the least for keeping up the spirit when we ran out of money and faced a close down. Later also contributing as a co-author together with Suzan and Pernilla.

Thank you also to the past and present staff at the needle exchange program in Malmö. I would especially like to thank Tina Hansson, Britta Sjöström and Magnus

Andersson who worked at the needle exchange from its start during the 80s and took part in preparations for the study and were crucial for the execution of it.

Thank you to Marianne Alanko and Anna Jerkeman for good collaboration. I hope we keep collaborating in the future.

I would also like to thank the organizations responsible for financing the studies. First of all the National Swedish Research Council for Working Life and Social Sciences. Thank you also to Region Skåne for sponsoring the research facility, Lund University, Psychiatry Skåne and Sweden´s southern healthcare region for grants that enabled me to finish writing this thesis.

A special thanks also to the prior and present staff at LARO Hasselgatan for being so patient when I was off from my clinical work and doing research.

I would also like to express the gratitude to all my colleagues at Addiction Center Malmö for covering for me when not being present for clinical work. I would like to especially thank Anna Hultgren who through the years stepped in for me at LARO Hasselgatan and LARO Matris when I was trying to focus on research.

I would also like to thank the present director of the Addiction Center Malmö, Karina Stein and her predecessors Bengt Sternebring, Håkan Rosén and Åsa Magnusson for giving me support and opportunities to do research alongside my clinical work.

A thank you also to Jonas Berge for sharing our expertise in statistics.

Thank you to my other co-authors Lars Ekström and Anna Brantefors.

Finally I would also like to express my gratitude to family and friends…

Thank you to Bitte, My och Lina for support from the beginning of this journey. A special thanks to My for being my personal IT support and helping out with technical matters regarding the figure in paper I. Thank you Lina (and Måns) for letting me use the picture!

Thank you Erik, Hanna, Anna for friendship, support and letting me be part of your families. Petrus, you belong here too. I do appreciate our conversations about human existence. Thank you Magnus for taking my mind off research when discussing literature and life.

Last but not the least, thank you to my parents Lena and Lennart for their love, support and encouragement through the years. I would also like to thank my amazing sister Frida, you are the best!

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Printed by Media-Tryck, Lund 2018 NORDIC SWAN ECOLABEL 3041 0903

Malmö Treatment Referral and Intervention Study (MATRIS)

Heroin dependence is associated with high mortality. Opioid maintenance treatment (OMT) with methadone or buprenorphine has strong evidence for the treatment of opioid dependence. At the same time, in many countries potential patients still do not receive such treatment, illustrating the importance of finding new ways linking these individuals to treatment for opioid dependence. A needle exchange program (NEP) is one setting that has been suggested as a potential link to treatment for drug dependence. In this thesis we evaluated a model of referral from the NEP in Malmö to an outpatient clinic for OMT. Our results suggest that a NEP is a clinical setting that allows for efficient referral of heroin-dependent individuals to OMT. Furthermore, even in a NEP population with a high degree of substance use problems and social problems, there was a significant improvement in quality of life in the short term and, importantly, a majority of the participants were still in treatment after 12 months.

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Psychiatry
Department of Clinical Sciences, Lund

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2018:125
ISBN 978-91-7619-693-9
ISSN 1652-8220