IMPROVING MAINTENANCE TREATMENT OF HEROIN ADDICTION:
THE ROLE OF BUPRENORPHINE
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ABSTRACT

Background: Heroin addiction is a condition with high morbidity and mortality. The discovery of Methadone Maintenance Treatment (MMT) by Dole and co-workers 1964 represented the first major advance in the treatment of this condition. Through the work of Gunne et al in Uppsala, MMT was implemented in Sweden already in 1966. The use of this treatment has, however, been limited in Sweden. Some of the concerns have been related to safety issues. Methadone, a full opiate agonist, can lead to overdose and death due to respiratory depression. Buprenorphine, a partial opiate agonist, has a greater safety margin to overdosing, and therefore offers a safer alternative. Here, we studied efficacy of buprenorphine maintenance treatment (BMT) in the context of a comprehensive treatment package, and its place in a rational treatment strategy vs. methadone. We also examined the effects of buprenorphine on neuroendocrine hyperactivity in heroin addiction. Finally, we compared pregnancy outcomes in MMT and BMT pregnancies.

Aims: The following research questions were addressed: the efficacy of buprenorphine combined with psychosocial interventions; a comparison between “gold standard” MMT and a novel stepped treatment strategy using buprenorphine as first-line treatment; whether BMT leads to a normalization of the hyperactive HPA axis, and the possible link to negative affect; a comparison of fetal growth and neonatal outcomes in two consecutive case series consisting of BMT and MMT exposed pregnancies.

Methods: In two RCTs, with 40 subjects in study I and 96 subjects in study II, we measured retention in treatment, performed ASI interviews, and monitored illicit drug use by urine screens. In an experimental study, we used the metyrapone challenge (a chemically induced indirect stress provocation that measures HPA axis responsiveness), the Profile of Mood States self-report instrument and genotyping. The observational pregnancy study measured intrauterine growth, birth outcome, malformations, neonatal adaptation, neonatal abstinence syndrome (NAS) and infant mortality.

Results: Study I: 1-year retention was 75% and 0% in the buprenorphine and placebo groups, respectively (p= 0.0001). Urine screens were about 75% negative for illicit drugs in the patients remaining in treatment (subjects in buprenorphine group). Study II: Overall, 6-month retention was 78%. Stepped treatment and enhanced MMT outcomes were virtually identical. Among completers of stepped treatment, 46% remained on buprenorphine-naloxone. Proportion of urine samples free of illicit opiates increased over time and reached approximately 80% in both arms. Problem severity decreased significantly and uniformly in both arms. Study III: Although BMT appeared to normalize HPA axis response to metyrapone in heroin addicts, negative affect remained elevated in this group compared to healthy controls. Study IV: In the buprenorphine-exposed pregnancies NAS occurred in 19 cases (40.4%), only 7 (14.9%) needing withdrawal treatment, compared to 77.8% and 52.8% after intrauterine methadone exposure, respectively.

Conclusions: The combination of buprenorphine and intensive psychosocial treatment is safe and highly efficacious. A stepped treatment of heroin addiction appears equally efficacious compared to optimally delivered MMT. Together with prior data on the advantageous safety of buprenorphine, this suggests that broad implementation of strategies using buprenorphine as first-line treatment should be considered. Response to metyrapone was dampened in heroin addicts maintained on buprenorphine. Despite the normalized HPA axis function, increased measures of negative affect were seen in the buprenorphine maintained group, implying a dissociation of HPA axis responsiveness and affect in heroin addiction. Finally, our preliminary data suggest that buprenorphine may offer advantages during pregnancies complicated by heroin addiction.
LIST OF PUBLICATIONS

This thesis is based upon the following original articles referred to in the text by roman numerals:

I
Kakko J, Svanborg KD, Kreek MJ, Heilig M.
1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial.

II
Kakko J, Grönbladh L, Svanborg KD, von Wachenfeldt J, Rück C, Rawlings B, Nilsson L-H, Heilig M.
A Stepped Care Strategy Using Buprenorphine and Methadone Versus Conventional Methadone Maintenance in Heroin Dependence: A Randomized Controlled Trial.

III
Kakko J, von Wachenfeldt J, Svanborg KD, Lidström J, Barr C, Heilig M.
Mood and Neuroendocrine Response to a Chemical Stressor, Metyrapone, in Buprenorphine-Maintained Heroin Dependence

IV
Kakko J, Heilig M, Sarman I
Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series
LIST OF ABBREVIATIONS

ACTH  Adrenocorticotropic hormone
ANOVA  Analysis of variance
ASI  Addiction Severity Index
ASPD  Antisocial personality disorder
BMT  Buprenorphine Maintenance Treatment
BNST  Bed Nucleus of the Stria Terminalis
BDZ  Bensodiazepine
CI  Confidence Interval
CM  Contingency Management
CRH  Corticotropin-releasing hormone
CS  Composite Score
DNA  Deoxyribonucleic acid
Dnr  Record nr
DSM-IV  Diagnostic and Statistical Manual of Mental Disorders, 4th ed.
D2  Dopamine 2
FZ  Flunitrazepam
GnRH  Gonadotropin-Releasing Hormone
HPA axis  Hypothalamic-Pituitary-Adrenal axis
HPG axis  Hypothalamic-Pituitary-Gonadal axis
HSD  Tukey’s honestly significant difference
ISR  Interviewer Severity Rating
IUGR  Intrauterine growth restriction
i.v.  intravenous
KOR  kappa-opioid receptor
LAAM  Levo-alpha-acetylmethadol
LHPA  Limbic-Hypothalamo-Pituitary-Adrenal axis
MMT  Methadone Maintenance Treatment
MOR  mu-opioid receptor
NAS  Neonatal Abstinence Syndrome
NIH  National Institutes of Health
NMDA  N-methyl-D-aspartate
NOP  Nociceptin
OPRM1  mu-opioid receptor gene 1
PET  Positron Emission Tomography
POMS  Profile Of Mood States
PVN  Paraventricular nucleus
RCT  Randomized Controlled Trial
RP  Relapse Prevention
SD  Standard Deviation
SIDS  Sudden Infant Death Syndrome
s.l.  sublingual
SNP  Single Nucleotide Polymorphism
THC  Tetrahydrocannabinol
VTA  Ventral tegmental area
INTRODUCTION

1.1 BACKGROUND FOR THESIS

Methadone Maintenance Treatment (MMT) of heroin addiction was discovered by Dole and co-workers in the early 1960’s (Dole and Nyswander 1965). Although MMT was introduced in Sweden already 1966, its use has been restricted, and has not met the medical needs of the patient population. This was largely due to widespread resistance among the general public as well as policymakers, who disregarded the scientific evidence that emerged over the years to support the efficacy of this treatment. A regulatory gridlock resulted, which capped the number of patients in treatment. Safety concerns related to diversion of methadone further increased the resistance against broad implementation of MMT. During the 1990’s, there was, however, a dramatic increase in Sweden of deaths among heroin addicts, largely due to heroin overdose. Buprenorphine was introduced in Sweden 1999 for treatment of heroin addiction, and offered a promising alternative to methadone based on its partial opiate agonism: buprenorphine does not activate the receptors to a degree that can easily lead to overdosing (Robinson 2002). At its introduction in Sweden, documentation for efficacy of buprenorphine was limited to studies from the US, in which this medication had been used in relatively low doses, and with little regard for a comprehensive medical, psychological and social treatment combination. It was therefore of interest how buprenorphine would work in real Swedish clinical practice. What components should be added to the treatment framework to make it as effective as possible? And what about the relative efficacy of buprenorphine and methadone?

An additional question was how buprenorphine maintenance treatment (BMT) interacts with brain stress systems. An improved understanding of this interaction could help change the public opinion regarding maintenance treatment. Addressing the question, we focused our interest on possible effects of buprenorphine on the hyperactive Hypothalamic-Pituitary-Adrenal (HPA) axis, since earlier research has shown that heroin addicts have a hyperactive HPA axis, a state that is normalized by MMT (Kreek et al. 1984). We set out to investigate the hyperactive HPA axis as a possible biological substrate for craving, a key feature in the process leading to relapse to heroin abuse. This also directed our attention to a genetic factor possibly involved in opioid addiction, i.e. a single nucleotide polymorphism (SNP) in the gene coding for mu-opioid receptors (MOR).

Finally, during the course of this thesis project, we noted a baby boom among our female patients treated with buprenorphine. This came as a surprise, since pregnancies with patients maintained on methadone in Stockholm County had typically occurred only once or twice a year since the early 1980’s. At the time (2000), little was known about short-term effects of human in utero exposure to buprenorphine, with only about 35 cases reported in the literature. We therefore set out to investigate this matter in a comparison with in utero exposure to methadone.
1.2 OVERVIEW

1.2.1 Heroin Addiction

1.2.1.1 Nature of the problem

In 1997, the NIH Consensus Conference regarding effective medical treatment of opiate addiction concluded that “Opiate dependence is a brain-related medical disorder that can be effectively treated with significant benefits for the patient and society, and society must make a commitment to offer effective treatment for opiate dependence for all who need it.” The major benefits are reduced mortality, morbidity, criminality and use of other drugs (Anonymous 1998).

Once use of heroin has started, it is often escalated to abuse (repeated use with negative consequences), and thereafter addiction (with tolerance, withdrawal symptoms and compulsive drug intake). This chain of events will, however, not happen to everybody: 1 out of 3 to 1 out of 4 individuals who self-administers heroin will progress to addiction (Kreek et al. 2002). Once addiction is established, however, there are usually repeated cycles of cessation and relapse extending over decades, with 10% or fewer subjects showing spontaneous recovery. The follow up from the Lexington Addiction Research Center (Pescor 1941) remains the classical illustration of the natural history of opiate addiction as a disease. Among close to 5000 opiate addicts followed up for 6 months – 6 years, 7% were dead, about 13% were still abstaining, and remaining subjects had relapsed or were lost to follow-up.

Heroin is a short-acting opiate, which is rapidly metabolized to 6-acetyl-morphine and morphine, both of which are biologically active. Upon parenteral administration, blood levels of heroin and 6-acetyl-morphine will reach their maximal concentrations within minutes. The mean half-life of heroin after intravenous (i.v.) injection is three minutes (Inturrisi et al. 1984). This will lead to an “on-off” effect, which is fundamentally different from the steady-state effects associated with long-acting opioids.

Heroin addicts on the streets are taking heroin intermittently, which will lead to partial withdrawal before next dose. This pattern parallels intermittent exposure to escalating doses of morphine, a rat model used to study disturbances preceding or following development of opioid addiction. The effects of intermittent morphine treatment (injections twice daily) differs from the effects of constant morphine exposure (implanted pellets), and is probably a result of the partial withdrawal associated with intermittent drug administration of the short-acting opiate (Houshyar et al. 2003).

1.2.1.2 Development of addiction

Drugs of abuse produce their acute reinforcing effects by activating the mesolimbic dopaminergic system, the system mediating natural rewards. Opiates specifically increase the activity of dopamine-containing neurons in the ventral tegmental area (VTA) (Johnson and North 1992). Stimulation of MOR in the VTA removes tonic inhibition that these cells are normally under and therefore increases dopamine release in the terminal areas in Nucleus Accumbens (N.Acc). Of note, kappa opioid receptors (KOR) seem to have an opposite role, and their stimulation within the N.Acc decreases dopamine release (Spanagel et al. 1992).
Perhaps more important than acute drug effects in the normal brain are the long term changes that occur with prolonged drug abuse. Repeated “on-off” exposure to a drug of abuse will progressively lead to neuronal changes, which will change the activity in these networks. This will, in turn, lead to the complex physiological and behavioural changes that characterize addiction, such as tolerance, sensitization, withdrawal, craving, as well as cue- and stress-induced relapse (Kreek et al. 2002; Koob and Le Moal 2005).

Tolerance refers to a progressively diminished response to a constant dose of a drug after repeated exposure, which leads to dose escalation to reach the desired effect. Although MORs down-regulate in response to excessive agonist drive, tolerance may in part additionally be caused by dopamine 2 (D2) receptor downregulation; positron emission tomography (PET) studies have shown decreased D2 receptor availability among, for example, opiate addicts (Wang et al. 1997).

Sensitization refers to an increase in a drug effect with repeated drug administration, or alternately, a bigger response upon rechallenge with a smaller dose than what was used during the initial exposure. According to an influential theory, there are two major and potentially linked classes of drug effects that are sensitized by addictive drugs: psychomotor activating effects and incentive motivational effects (Robinson and Berridge 2003).

After prolonged abstinence, craving and drug relapse can be caused by acute re-exposure to small (“priming”) doses of the drug itself, drug-associated cues or stress (Shaham and Hope 2005). Craving is likely to be a heterogeneous category of phenomena: Reward craving refers to cravings for positively reinforcing drug effects, while relief craving refers to cravings for negatively reinforcing drug effects, i.e. drug actions to eliminate aversive affective states that arise in dependent individuals in the absence of drug (Heinz et al. 2003; Heilig and Egli 2006; Heilig and Koob 2007).

An influential model suggests that drug addiction, in addition to acute positively reinforcing drug actions, involves the development of an opponent process that is initiated to counter the acute effects of the drug, as originally hypothesized in the opponent process theory of affective regulation (Solomon and Corbit 1974). This opponent process persists after the drug has been cleared from the brain, but is now unopposed, resulting in a shift of the affective set point, a phenomenon labeled “allostasis” (Koob and Le Moal 2005). Thus, positively reinforcing drugs initially elicit positive affective and hedonic effects that are opposed by negative affective and anhedonic processes. The intense pleasure of the opiate drug "rush" or "high" would be opposed by aversive symptoms, which outlast the pleasurable effects. Acute withdrawal is a well recognized example of this phenomenon, and comprises both physical and affective components, i.e. subjective symptoms of negative affect. In addition, acute withdrawal is accompanied by recruitment of the brain stress neurotransmitter corticotropin-releasing hormone (CRH) (Weiss and Koob 2001). Relapse does, however, often occur long after physical withdrawal signs have
subsided. It is therefore likely that more persistent neuroadaptations lead to an increased sensitivity to negative affect that remains long after physical withdrawal phase is over, that is, during protracted withdrawal.

The region of the N.Acc and its neural circuitry may be an important neural substrate not only as classically described for aspects of drug addiction related to acute positive reinforcement, but also for aspects related to impaired reward function in the addicted state. Neuroadaptations within the reward circuitry of which the N.Acc is a key component would represent what has been labeled “within systems neuroadaptations” (Koob et al. 1989). In addition, other systems, such as the CRH system mentioned above, are recruited in the addicted state, representing “between systems neuroadaptations”. These are increasingly recognized as “anti-reward systems” (Koob and Le Moal 2005).

In summary, the addictive process typically starts out with impulsive drug abuse, motivated by pleasurable or positively reinforcing drug effects mediated by brain systems that normally mediate natural rewards. Over time, drug abuse transitions to a compulsive stage, in which drug seeking and taking is mainly for negative reinforcement, i.e. the removal of an aversive state experienced in the absence of drug, and caused by an up-regulated activity of anti-reward systems, otherwise involved in mediating negative affective states in response to stress.

1.2.1.3 Limbic-Hypothalmo-Pituitary-Adrenal (LHPA) axis

The stress response is regulated by the HPA axis: a stressor activates the paraventricular nucleus (PVN) of the hypothalamus, resulting in a release of CRH. This will lead to activation of the pituitary, resulting in a release of adrenocorticotropic hormone (ACTH). ACTH activates the adrenal cortex to produce cortisol, the hormonal endproduct of the HPA axis in humans (Reul and de Kloet 1985). Cortisol acts through glucocorticoid receptors found throughout the periphery, in the pituitary and hypothalamus, but also in limbic brain regions, such as the hippocampus and the amygdala. The hippocampus inhibits stress-induced HPA activation, whereas the amygdala may enhance glucocorticoid secretion. Limbic sites have minimal direct projections to HPA effector neurons of the PVN. Instead, hippocampal and amygdalar efferents relay with neurons in the bed nucleus of the stria terminalis (BNST) to access hypothalamic CRH neurons. It has been stated that the influence of the limbic system on the HPA axis in the end is determined by the balance and pattern of input from the respective structures (Herman et al. 2005).

1.2.1.4 CRH

Two distinct CRH systems exist in the brain: a hypothalamic CRH system, which is under negative feedback inhibition by glucocorticoids and an extra-hypothalamic, which is not. The latter system includes two primary sites; the central nucleus of the amygdala and the lateral BNST (Schulkin et al. 1998). Amygdalar CRH system activity is potently activated after administration of morphine and cocaine. Activation of this system observed at the time of withdrawal from morphine is responsible for aversion and anxiety related to this state (Maj et al. 2003). CRH is also a key mediator of relapse to heroin-seeking induced by stressors (Shaham et al. 1997).
1.2.1.5 Heroin Addiction, Hyperactive HPA axis and Maintenance Treatment

Heroin addiction is associated with a hyperactive HPA axis. Following stabilization in MMT, however, there is a normalization of this HPA axis reactivity (Kreek et al. 1983). There are also normal responses to metyrapone challenge in most steady-state MMT patients (Kreek et al. 1984).

The hyperactive HPA axis has been postulated as a possible biological substrate for craving. The effect of BMT on HPA axis reactivity, investigated with the metyrapone challenge, was thus far unknown, and was tested in study III.

1.2.1.6 Genetic influence

Three domains of factors that contribute to vulnerability to developing a specific addiction can be delineated: drug-induced effects, environmental influences and genetic factors (Kreek et al. 2002). Twin-, family and adoption studies show that vulnerability to drug addiction is a partially heritable condition under strong influence of environmental factors. Interestingly, opiate addiction appears to have the highest degree of heritability (Goldman et al. 2005).

A single nucleotide polymorphism (SNP) of potential functional relevance was discovered a decade ago in position 118 of the gene that encodes the MOR (Bond et al. 1998). The most common (i.e. “major”) allele carries an A in this position. This is replaced with a G (A118G) in the minor allele, with allelic frequencies ranging from 2 to nearly 50%, depending on the ethnicity of the population (Kreek et al. 2002). A significant association to opioid addiction has been found for the 118G SNP in some studies, e.g. in China (Szeto et al. 2001), and, as shown by our own research group, in a population from central Sweden, with up to 21% of the attributable risk for developing heroin addiction related to the presence of this polymorphism (Bart et al. 2004). The A118G exchange was originally proposed to confer an increased affinity of the receptor for the endogenous ligand beta-endorphin (Bond et al. 1998). Several more recent studies including one from the same group (Kroslak et al. 2007) have, however, failed to replicate this finding. It has also been reported that the 118G variant leads to decreased expression of the receptor (Zhang et al. 2005). The role of this genetic variant for opioid receptor signalling at the molecular level has thus become quite complicated. Nevertheless, consistent functional studies of this variant in humans (Wand et al. 2002) and of a corresponding variant in rhesus macaques (Miller et al. 2004; Barr et al. 2007; Barr et al. 2008) indicate that this variant is a gain-of-function mutation, that e.g. confers increased inhibitory tone onto the HPA axis, and increased reward from natural reinforcers.

This genetic variant is therefore of potential interest for pharmacogenetic effects of opioid agonists used in maintenance treatment. The frequency of the A118G SNP, and its impact on the results of the metyrapone challenge of BMT subjects was further analyzed in study III.
1.2.2 Maintenance Treatment

1.2.2.1 Maintenance Treatment

Maintenance treatment was originally conceived of as a comprehensive treatment of heroin addicts, who were offered a combination of pharmacological (methadone) and psychosocial interventions. Focus was on drug counselling and medical, psychiatric and socioeconomic problems (Dole and Nyswander 1965). Dole described the pattern that heroin use leads to, with fluctuations between the “high” in direct association with heroin intake, after 20-30 minutes followed by “straight”, and then “sick” if the person is not able to inject the next dose. He also described how a long-acting opioid, such as methadone, can stabilize this pattern (Dole et al. 1966). This has later been elaborated by Kreek, who described in detail how the “on-off” effect of short-acting opiates disturbs physiological functions on several levels, while the opposite occurs with “steady-state” administration of a long-acting opioid agonist, which does not disturb these functions, but instead enables a normalization of the functions disturbed by heroin abuse (Kreek 2000; Kreek 2003).

1.2.2.1.1 Pharmacological alternatives

1.2.2.1.1.1 Methadone

Methadone is an orally available synthetic opioid that is a full MOR agonist. It has a slow onset of action, and a long duration due to a long half-life, approximately 24 hours, which permits once-a-day dosing. In his original account of methadone actions, Dole described two properties of this therapeutic that made it particularly useful for maintenance treatment. First, the long half-life stabilized the disruptive fluctuations in MOR activation seen with short-acting drugs. This would eliminate the cravings experienced during the negative phases of these fluctuations. Secondly, the phenomenon of “narcotic blockade” was described; chronic administration of high methadone gave rise to a degree of opioid tolerance and cross-tolerance, which would render other MOR agonists, such as heroin, ineffective. This would further reduce the incentive for relapse (Dole et al. 1966).

The tolerance that is developed under MMT may, however, still leave some potential for additional MOR stimulation. Opioid receptor imaging with PET in long-term, methadone-treated former heroin addicts showed that specific binding of the tracer was lower by 19 to 32% compared with normal volunteers, which correlated with methadone plasma levels. A significant numbers of opioid receptors may therefore be available for function in their normal physiological roles (Kling et al. 2000). The study, however, utilized a nonselective MOR and KOR marker and therefore the receptor availability measure calculated does not refer to one but two receptor sites. Also, the study assumed that healthy subjects and methadone-maintained participants had similar regional MOR binding concentrations, which may not be the case (Zubieta et al. 2000). More recently, systematic pharmacological studies have convincingly demonstrated that methadone maintenance indeed potently and dose-dependently blocks the actions of heroin, and with a daily dose of 120mg, the heroin effects were completely eliminated (Donny et al. 2002).
Methadone has also a modest N-methyl-D-aspartate (NMDA) antagonist activity (Ebert et al. 1995). NMDA antagonists have been shown to prevent or attenuate the development of tolerance to opiates (Herman et al. 1995). This modest NMDA antagonism might explain, in part, the lack of development of progressive tolerance to methadone after stabilization on moderate to high doses (Kreek et al. 2002).

MMT as treatment for heroin addiction was discovered by Dole & Nyswander 1964. They started induction on low to moderate methadone doses, to avoid respiratory depression. As the patients developed tolerance, the doses were slowly increased, without the patients experiencing any opioid effects. All signs and symptoms of opiate withdrawal, as well as craving for heroin, disappeared, and the patients were able to concentrate on the psychosocial aspects of the treatment, yielding a high level of rehabilitation in this group of patients (Dole and Nyswander 1965; Dole et al. 1966).

In a classical double-blind study carried out between 1972 and 1975 in Hong Kong (Newman and Whitehill 1979) 100 heroin addicted volunteers were assigned at random to two groups: one group received methadone, while those in the other group were maintained on placebo. All subjects were provided a broad range of supportive services. After thirty-two weeks 76% of those receiving methadone were still in treatment, compared with 10% of the controls. At the end of the three-year project, the retention-rate for methadone subjects was 56%, compared to 2% in the placebo group. Similar outcomes have since been found in essentially every study carried out in this area.

MMT was implemented in Sweden already in 1966 by Prof. Gunne, who established a program that is still in operation. Gunne and his team performed a series of important studies, among which a classic RCT of MMT vs. waiting list showed a rehabilitation rate of 76% in the MMT-group, compared to 6% in controls (Gunne and Gronbladh 1981). This study also showed that MMT reduced both the high morbidity and mortality among heroin addicts. Another study from the same group reported mortality within a cohort of street heroin addicts. The mortality rate was 63 times higher than expected, compared with official statistics for a group with same age and sex distribution (Gronbladh et al. 1990). The group also reported that when patients in MMT were involuntarily discharged from treatment due to violation of program rules, they returned to the same high mortality as street addicts.

Despite evidence that MMT is effective for opiate addiction, it has remained a controversial therapy, and attempts to establish alternatives have continued. For instance, an illustrative RCT compared MMT with psychosocially enriched 180-day methadone assisted detoxification. Despite the hope originally held by the authors, the ultraslow detoxification resulted in dismal outcomes, while MMT once again produced high retention, low heroin use rates and lower rate of drug-related HIV risk behavior than did detoxification (Sees et al. 2000). In fact, this study reproduced a pattern very similar to that found by both Newman and co-workers, and Gunne and his team: By 1-year, essentially no patients were retained in the non-pharmacological treatment arm, while more than 70% 1-year retention was observed in the group receiving MMT.
In summary, the Cochrane review from 2003 concluded that methadone is an effective maintenance therapy for heroin addiction as it retains patients in treatment and decreases heroin use better than treatments that do not utilize opioid replacement therapy. The studies included were more heterogeneous with regard to effects on criminal activity. Positive effects were reported in studies delivering highly structured treatment, but other less structured programs did not find effects on this parameter, and an overall statistically significant effect was not found (Mattick et al. 2003b).

1.2.2.1.1.2 LAAM

Levo-alpha-acetylmethadol (LAAM) is an analogue of methadone, also a full MOR agonist, with a longer half-life than methadone, 48-72 hours due to active metabolites, which permits less than daily dosing. Case reports of prolonged QT intervals in the electrocardiograms of patients receiving LAAM treatment, possibly with some associated clinical syndromes (Deamer et al. 2001), and the United States Food and Drug Administration warning issued 2001 about adverse cardiac events associated with the use of LAAM, have stopped the use of this medication in many countries.

There are, however, also reports about dose-dependent QT-prolongations and cardiac arrhythmias associated with methadone (Anonymous 2005; Iskandar et al. 2007). LAAM and methadone at clinically relevant concentrations can influence the human cardiac potassium channels, thereby providing a plausible mechanism for the adverse cardiac effects (Katchman et al. 2002). Prolonged QT intervals were not observed in a study where this was assessed in opioid dependent subjects receiving buprenorphine-naloxone (Baker et al. 2006). A recent RCT investigating the QT-interval effects of methadone, LAAM, and buprenorphine concluded that buprenorphine is associated with less QTc prolongation than LAAM or methadone and may be a safe alternative (Wedam et al. 2007).

1.2.2.1.1.3 BUPRENORPHINE

Buprenorphine is a mixed partial MOR agonist and KOR antagonist. It has a higher affinity for the MOR than typical full agonists, thus acting as a competitive antagonist if used at the same time as full agonists; therefore buprenorphine is also labeled as a relative or functional antagonist on the MOR.

Buprenorphine is also an agonist/partial agonist on nociceptin (NOP) receptors, a fourth member of the opioid receptor family, which does not bind prototypical opioids such as morphine. Activation of the NOP receptor system results in a marked functional anti-opioid action (Bloms-Funke et al. 2000; Lutfy et al. 2003; Ciccocioppo et al. 2007).

Buprenorphine has a slow onset of action, and a slow dissociation from the receptors, which permits dosing on alternate days, or even less frequently (Walsh and Eissenberg 2003). Plasma concentrations of buprenorphine are linearly related to dose, but a plateau is observed for the effects of buprenorphine on subjective measures and respiratory depression. Thus, buprenorphine has a ceiling effect at high doses. Single doses of buprenorphine up to 70 times the recommended analgesic dose are well tolerated by non-dependent humans (Walsh et al. 1994).
Early on, studies in rats and monkeys consistently predicted that chronic administration of buprenorphine would be less likely to produce physical dependence and withdrawal than treatment with full opioid agonists. Furthermore, animal self-administration studies showed buprenorphine to have a lower reinforcing value than full agonists. Initial human studies seemed to confirm those predictions (Lewis 1985).

Early human pharmacology studies with buprenorphine, as well as most of the early controlled clinical trials utilized a liquid buprenorphine formulation, while the marketed formulations today are sublingual (s.l.) tablets. To properly interpret the data generated by these studies, comparison of the bioavailability of buprenorphine in liquid and tablet forms is needed. A single-dose comparison study indicated that the bioavailability of the tablet formulation varied from 25-80%, and averaged roughly 50% that of the liquid formulation (Nath et al. 1999). Subsequent comparison studies showed that the blood level achieved by the tablet formulation approached 65-70% that of the liquid and suggested that the bioavailability of the tablet formulation improved with continued treatment (Compton et al. 2006). On chronic dosing, the bioavailability of the two formulations becomes comparable (Strain et al. 2004).

Data from a PET-study of MOR availability using $^{11}$C-carfentanil, a MOR-selective ligand, in heroin addicted volunteers, suggest that buprenorphine dose-dependently binds to MORs, reaching an approx. 90% receptor occupancy at 16 mg buprenorphine (liquid formulation) (Zubieta et al. 2000). As reviewed by Mattick (Mattick et al. 2004), clinical studies of buprenorphine that have used high doses of buprenorphine have consistently shown superior outcomes to those where low doses have been used. The PET study with carfentanil indicates that there is virtually no increase in MOR occupancy by buprenorphine between 16 mg and the maximal dose used clinically, 32 mg daily, prompting the question what mechanism might be providing the additional benefit. Although this could simply result from a depot effect, as pointed out above, buprenorphine is also an agonist/partial agonist at the NOP receptors. It is therefore possible that some of the additional efficacy of high buprenorphine doses might also be mediated through an activation of NOP receptors (Ciccocioppo et al. 2007).

Buprenorphine’s potential utility in the field of heroin addiction was first pointed out by Jasinski, who reported that buprenorphine is long-acting, produces a low level of physical dependence, is less toxic than other drugs used for maintenance therapy, and blocks the effects of narcotics (Jasinski et al. 1978). Reisinger in Belgium published the first report of promising clinical experiences with this new compound (Reisinger 1985). Several RCTs thereafter showed the efficacy of BMT. An early pivotal study compared 8mg buprenorphine to 20 or 60 mg daily of methadone, and concluded that buprenorphine was as effective as the 60 mg methadone dose (Johnson et al. 1992). An early multicenter RCT, where patients received various doses (1, 4, 8 or 16 mg/day) of liquid buprenorphine, combined with a one-hour weekly clinical counseling session, supported the safety and efficacy of buprenorphine. This study also showed progressively better outcomes with increasing buprenorphine doses. The authors proposed a sequential pharmacological treatment strategy beginning with buprenorphine, since this would offer patients and clinicians the widest subsequent treatment options (Ling et al. 1998).
In the Cochrane review (Mattick et al. 2004), the authors conclude that buprenorphine is superior to placebo in terms of retention and ability to suppress heroin use.

France was the first country to implement BMT for treatment of heroin addiction. This was done on a large-scale already in 1995, as an answer to a rapidly growing number of opiate overdose deaths, and also as a precaution caused by increased worries about possible methadone associated deaths. In France, all licensed physicians were allowed to prescribe buprenorphine without any special education or additional licensing. This led to a rapidly increasing number of opiate addicts under buprenorphine treatment in primary care (Fatseas and Auriacombe 2007). About 20% of all physicians in France are reported to use buprenorphine to treat about half of the estimated 150,000 problem heroin users. Opiate overdose deaths have declined substantially (by 79%) in France since the introduction of buprenorphine (Auriacombe et al. 2004).

*The efficacy of buprenorphine used in combination with intensive psychosocial interventions for treatment of heroin addicts in a Swedish treatment context was evaluated in a 1-year follow-up in study I.*

Because of its long half-life, buprenorphine may be used with less-than-daily dosing. In a clinical trial (Johnson et al. 1995) of daily versus alternate-day dosing with 8 mg buprenorphine, participants were randomly assigned to daily or alternate-day schedules of active medication administration. Primary outcome measures were retention in treatment and urine samples positive for opiates. There were no statistically significant differences between the dosing schedules on any of the outcome measures. The conclusion from that study was that an alternate-day dosing schedule can be effective in and acceptable to a substantial portion of patients. Another study (Eissenberg et al. 1997) assessed opioid withdrawal after an acute 72 h dose omission in buprenorphine-maintained patients (8 mg/day s.l.). The lack of subjective symptoms and physiological signs of opioid withdrawal during 72 h of acute dose omission supports the feasibility of less-than-daily dosing. A study investigating four dosing schedules, with up to 96-hour dosing, showed the feasibility and safety of twice weekly buprenorphine dosing (Petry et al. 1999).

1.2.2.1.1.4 NALTREXONE

Naltrexone is a nonaddictive, non-selective opioid receptor antagonist with some degree of MOR preference at lower doses. The half-life of naltrexone allows once-a-day administration. It significantly attenuates the effect of opiates to the extent that they lose their reinforcing properties (O'Brien et al. 1978). Since naltrexone does not activate opioid receptors and therefore does not dampen heroin craving, most patients, however, discontinue treatment and relapse. Studies combining antagonist treatment with behavioral management have shown that this treatment approach results in less than 15% 1-year retention in treatment of unselected heroin addicts (Kreek et al. 2002). A recent Cochrane Review (Munoz et al. 2006) concluded that no statistically significant benefit was shown in terms of retention in treatment or relapse results at follow-up for comparisons of naltrexone and placebo. Nevertheless, naltrexone has been shown to be effective in highly selected and motivated populations, such as physicians and professionals (Washington et al. 1984).
It is clear that compliance is the limiting factor for the use of naltrexone in maintenance treatment. An attempt to address this issue is to develop depot preparations of naltrexone, and reasonably successful short term outcomes were recently reported using this approach (Comer et al. 2006). It is unclear whether similar beneficial effects can be expected in the longer term, because patients ultimately need to return in order to receive additional depot injections. In addition, widespread use of subcutaneous naltrexone implants has evolved in clinics in Australia. There are until now no controlled data available to support the efficacy of this approach, and attempts to introduce this as a clinical treatment must therefore be viewed as problematic until such data are produced.

1.2.1.5 Heroin?

Heroin maintenance treatment has been suggested in different countries, specifically to reach heroin addicts who have not had benefits from regular maintenance treatment. This highly controversial issue has been studied in at least five RCTs, with varying results. Two of the studies reported that heroin maintenance can be seen as maintaining the status quo (Hartnoll et al. 1980) or that heroin maintenance is a feasible and clinically effective treatment (Perneger et al. 1998). Three studies actually did report some positive results. One of these found heroin maintenance to be more effective and probably as safe as methadone alone (van den Brink et al. 2003). One reported that heroin plus methadone was more efficacious than methadone alone looking at outcomes of physical health, HIV risk behavior, street heroin use, and days involved in crime (March et al. 2006). Finally, the third study reported that retention was higher in the heroin than in the methadone group, and the heroin group also showed a significantly greater improvement of physical and/or mental health and decrease in illicit drug use. However, and perhaps not surprisingly, more serious adverse events were found in the heroin group (Haasen et al. 2007).

The recent Cochrane review, with focus on prescription of heroin to heroin addicts, assessed the efficacy and acceptability of heroin maintenance versus methadone in retaining patients in treatment, reducing the use of illicit substances and improving health and social functioning. Four studies met the inclusion criteria for a total of 577 patients. The studies could not be analyzed cumulatively because of heterogeneity of interventions and outcomes. No definitive conclusions about the overall effectiveness of heroin prescription were possible (Ferry et al. 2006).

In summary, it is difficult to determine the role of heroin maintenance in the treatment of heroin addiction. On one hand, available data do seem to suggest that a minority of patients who do not succeed in MMT could achieve improved outcomes using this intervention. On the other hand, as explained above, the on–off profile of short acting opiates is what drives the brain pathology that underlies opiate addiction in the first place.

It can be noted that the question of whether heroin maintenance has a place in the treatment of addiction may be of limited relevance. The quality and outcomes of the MMT programs with which heroin maintenance has been compared has been far below what is possible. In several of the studies, the control groups consisted of patients who
were randomized back to the same treatment where they had already failed at least once. Given the serious neurobiological consequences of heroin use, and the difficult policy issues raised by the possibility of offering this as a medical treatment, a minimal conclusion is that this treatment should not be considered unless optimal MMT has been tried and failed.

1.2.2.1.1.6 Comparing MMT and BMT

Several RCTs have investigated the relative efficacy of buprenorphine and methadone. Both studies using fixed doses of buprenorphine (8mg, liquid formulation) (Johnson et al. 1992) or tablet (8mg) (Pain et al. 2000) or flexible dosing procedures (mean dose 8.9 mg daily, liquid formulation) (Strain et al. 1994), or tablet (11.2mg) (Mattick et al. 2003a) showed no statistically significant differences in reducing illicit opioid use and maintaining patients in treatment, when compared to 60 mg methadone daily (fixed doses), or flexible mean doses (mean dose 54-57.3 mg). In a long-term (1 year) fixed-dose study, BMT (8 mg daily, liquid formulation) was compared with MMT (30 or 80 mg daily). Patients assigned to high-dose MMT performed significantly better on measures of retention, opioid use, and opioid craving than either the buprenorphine or the low-dose methadone group. Performance on these measures was virtually identical between the latter two groups and BMT at 8 mg/d appeared to be less than optimally efficacious (Ling et al. 1996).

In a meta-analysis comparing the efficacy of burpenorphine and methadone, the authors found that there was a substantial variation in outcomes in the different trials, which might be due to differences in dose levels, exclusion criteria and provision of psychosocial treatments. When the retention analysis was limited to the studies that tested 8 mg or more of buprenorphine in liquid formulation there was no statistically significant difference. The authors discuss that it is possible that a modest change in buprenorphine dose may have resulted in substantially different outcomes (Barnett et al. 2001). Another meta-analysis also found a relative equality in the efficacy of buprenorphine and methadone (West et al. 2000).

The Cochrane Review (Mattick et al. 2004) reported that the meta-analysis indicates that methadone is statistically significantly better than buprenorphine in retaining patients in flexible dosing approaches. It also discusses the possible influence on retention in treatment of too slow induction onto buprenorphine. The authors conclude that buprenorphine is an effective intervention for use in the maintenance treatment of heroin addiction, but it is not more effective than methadone at adequate doses.

In the Cochrane Review, High dose buprenorphine was defined as 8 mg per day, and Very high dose as 16 mg buprenorphine per day. Likewise, presumably to avoid accumulation and adverse events, the methadone doses studied have typically been lower (<80mg/day) than those known to be optimally effective clinically. In study II, we compared High dose methadone (flexible dosing up to 120 mg daily) with High dose buprenorphine, which in this context was up to 32 mg daily. The study also investigated the efficacy of a stepped regime using buprenorphine as first-line choice, with a fast switch to methadone if needed, compared with “gold standard”; enhanced MMT.
### 1.2.2.2 Problems with maintenance treatment

Three decades ago, a system of treatment for heroin addiction was proposed under the acronym STEPS (sequential treatment employing pharmacologic supports), which rejected the dichotomous assessment of treatment "success" or "failure" in favor of the expectation of partial and temporary improvements. In this model, small steps were expected to bring the addict to an abstinent and well-functioning state, if possible (Goldstein 1976). This view is similar to the modern view of addiction as a chronic relapsing disorder, not unlike e.g. hypertension or diabetes, which can be managed with varying degrees of success without necessarily being cured (McLellan et al. 2000).

Although both MMT and BMT are highly effective when treating heroin addicts, neither of the treatments can be expected to help everybody. Estimates of the proportion of patients who are helped by maintenance treatment vary. For instance, Senay (Senay 1983) reported that methadone is effective for one-third to one-half of patients enrolled in methadone programs, while, according to De Leon, subgroups of methadone clients can be broadly classified into three functional levels, and the proportions of a clinic population in each group may be estimated to be 20% (High), 40% (Medium) and 40% (Low-Marginal) (De Leon 2003). Some possible reasons for this low level functioning are discussed in the following sections. On the other hand, it should be kept in mind that data from the Gunne group suggest a somewhat different picture, in which close to 80% of patients in this program ultimately achieved stable social function (Gunne et al. 2002).

#### 1.2.2.2.1 Psychopathology

Almost half of patients in maintenance treatment can be expected to fulfill criteria for a psychiatric diagnosis other than drug abuse or dependence (Strain et al. 1991). Patients with higher levels of psychopathology respond less well to treatment (McLellan 1986). The most common diagnoses among heroin addicts are depression, anxiety and antisocial personality disorder (ASPD) (Corty et al. 1988), which is echoed in the context of maintenance treatment. In a cross-sectional study, half of the MMT patient population was found to be suffering from depression, with higher depression scores seen in patients abusing or using prescribed benzodiazepines (BDZs) (Peles et al. 2007). In a sample of MMT patients, a large proportion of subjects exhibited severe depression and anxiety, and a majority was classified as "psychiatric cases". Depression and anxiety were strongly related to personal distress, and personal distress levels were correlated with BDZ use (Darke et al. 1994b). One out of four patients received a current diagnosis of ASPD. The most common symptoms of ASPD among MMT clients were unlawful behaviours, recklessness and aggressiveness. Of note, subjects with a current diagnosis of ASPD had been retained in treatment as long as other clients and could, surprisingly, respond to MMT as well as other clients (Darke et al. 1994a).

#### 1.2.2.2 Neurocognitive dysfunctions

A study performed in Russia, where drug abusers are traditionally using only one drug (as opposed to polydrug abuse) showed that heroin addicts exhibited significantly more disadvantageous decision making and longer deliberation times while making risky decisions than control groups (Fishbein et al. 2007). In another study, performance of
MMT patients was compared to controls without substance abuse histories. The wide range of impaired cognitive functions was striking (Mintzer and Stitzer 2002). To differentiate the effects of a history of long-term opioid (or polydrug) abuse from the effects of MMT itself, performance of a newly recruited group of currently abstinent former opioid abusers was studied and compared to the groups investigated above. Performance of the abstinent abusers fell between that of the MMT clients and controls on many measures, suggesting that MMT may be associated with additional impairment over and above that associated with long-term abuse (Mintzer et al. 2005).

As a partial opioid agonist, buprenorphine can be expected to produce less impairment in psychomotor and cognitive performance than methadone. In an RCT assessing whether patients under BMT performed better than patients under MMT in cognitive tests measuring psychomotor performance, buprenorphine produced less impairment of cognitive functions, a difference that, according to the authors, is especially relevant when it comes to driving ability and social functioning (Soyka et al. 2005). Another study evaluated dose-related effects of repeated administration of the buprenorphine-naloxone combination product (8/2, 16/4, 32/8 mg, s.l. tablets) in opioid-dependent volunteers on performance, following a period of 7-10 days of dosing at each level. Results revealed minimal impairment in performance as buprenorphine-naloxone dose was increased four-fold (Mintzer et al. 2004).

1.2.2.2.3 Alcohol and maintenance treatment

Patients in MMT exhibit a high prevalence of alcohol problems, which in itself can constitute a threat against continuing treatment: drinking problems among patients undergoing MMT are associated with an increased risk of relapse into illicit drug use and with discharge from treatment (Stenbacka et al. 2007). One study reported that half of the MMT patients had actual or potential drinking problems, and that patients who abused alcohol also tended to use BDZ (Stastny and Potter 1991). Another study reported that one-fifth of the sample met criteria for alcohol dependence. Co-morbid alcohol use problems were associated with symptoms of somatization, obsessive-compulsive behavior, depression, phobic anxiety, and psychosis (Elbassel et al. 1993)

Alcohol consumption has, by some investigators, been reported to increase further under MMT (Bickel et al. 1987; Ottomanelli 1999) which may represent a serious limitation in the long term clinical use of this compound. The agonistic activity of methadone at MOR could be the origin of this effect, since some animal experiments suggest that MOR agonists increase self-administration of alcohol (Hubbell et al. 1986; Hubbell et al. 1993). As pointed out above, buprenorphine is also an agonist at NOP receptors. Extensive animal data indicate that NOP agonism leads to suppression of alcohol drinking, and in fact NOP agonists are in development for treatment of alcoholism (Heilig and Egli 2006). Experiments using alcohol preferring rats recently showed that low doses of buprenorphine increased ethanol consumption by stimulating MORs, whereas high buprenorphine doses markedly and selectively decreased it, through actions at NOP receptors. These data suggest that high dose buprenorphine might offer advantages over methadone with regard to co-morbid alcohol use problems (Ciccocioppo et al. 2007).
1.2.2.2.4  Bensodiazepines and maintenance treatment

BDZs are commonly used and abused by patients in maintenance treatment, which can be problematic in many ways. For instance, BDZ use/abuse has been suggested as a major risk factor for depression in this population (Peles et al. 2007), although it is of course difficult to know whether the BDZ use is causing the affective symptoms, or whether the causation is the other way around.

The short-acting BDZ flunitrazepam (FZ) is a major BDZ of choice for heroin addicts (Woods and Winger 1997). In a study on violent juvenile offenders, the main self-reported reason for FZ abuse was to change the perception of reality and achieve feelings of increased power and self-esteem (Daderman and Lidberg 1999). Based on forensic evaluation of another small group of offenders (who were not heroin addicts), it was suggested that FZ may induce transient states characterized by severe hostility and lack of empathy, i.e. features otherwise typical of psychopathy. FZ use was also associated with anterograde amnesia, leading to a transient dissociative state (Daderman et al. 2002). It is important to note that these small studies have been carried out in criminal offenders with pre-existing antisocial traits, and it is therefore unclear whether these effects of FZ generalize to subjects without this type of susceptibility. However, as noted above, up to 25% of heroin addicts do have ASPD.

A study assessing BDZ abuse in an Israeli MMT clinic reported that almost half of the patients who abused BDZs during their first month of treatment ceased to do so after 1 year, while 1 out of four who had not abused BDZs at the beginning of MMT did so after 1 year in treatment. FZ was the most commonly abused BDZ (Gelkopf et al. 1999). Another Israeli study reported that BDZ abusers were found more often to be polydrug abusers, and they had higher self-rated psychopathology and psychological distress scores (Bleich et al. 2002). The same was found in a study investigating BDZ use/abuse/dependence among BMT-patients in France. Problematic users of BDZ had higher depression and anxiety levels, which correlated to quality of life impairment (Lavie et al. 2008).

1.2.2.2.5  Diversion, abuse and safety risks of methadone

The overwhelming safety concern regarding methadone is death due to respiratory suppression, or “overdose”. The lethal dose of methadone is estimated at 50 mg for an opiate-naïve adult (Ghodse et al. 2004). Deaths attributed to methadone should, however, be considered in the context of co-intoxication with other drugs: 70% of fatal intoxication victims who had obtained methadone for MMT died from methadone co-intoxication with illicit drugs, suggesting the high risk of death among persons who continued use of illicit drugs during methadone treatment (Shah et al. 2005).

Deaths attributed to methadone occur both in and outside of treatment. A study reported that the vast majority, 69%, of deaths attributed to methadone occurred in subjects not in MMT at the time of their death. Among the deaths that did occur while in MMT, about half occurred during the dose-finding period of MMT. Further apparent risk situations are methadone intake in addition to that received for MMT, and i.v. injection of methadone (Vormfelde and Poser 2001).
The number of deaths attributed to opioid overdose increased in both Australia and the UK between 1985 and 1995, and was substantially higher per capita in Australia than in the UK. Methadone accounted for a higher proportion of opioid overdose deaths in the UK (50%) than in Australia (18%). A plausible hypothesis for these differences is that the greater availability of methadone maintenance in the UK contributed to both the lower overall rate of opioid overdose mortality, and the greater relative contribution to this mortality by methadone (Hall et al. 2000).

1.2.2.6 Diversion, abuse and safety risks of buprenorphine

The large-scale, unregulated prescription of buprenorphine in France has been accompanied by extensive diversion, and injection abuse (Obadia et al. 2001). Diversion leading to i.v. use of buprenorphine may occur in up to 20% of French buprenorphine patients, and has led to various infections but only rare cases of overdose, and then only in combination with sedative-hypnotic drugs (Auriacombe et al. 2004). When buprenorphine misuse by injecting drug addicts was assessed in a Swedish survey of needle exchangers, a vast majority of heroin addicts reported intake for withdrawal treatment or self-detoxification. Euphoria seeking was more common among amphetamine addicts (Hakansson et al. 2007).

In a French calculation (Auriacombe et al. 2001), the authors counted the number of deaths attributed to buprenorphine or methadone from 1995 to 1998 in France in relation to the estimated number of French patients who received either buprenorphine or methadone, and reported the risk of death attributed to methadone as more than 10 times higher than that attributed to buprenorphine (Fatseas and Auriacombe 2007). Another French report discussed a series of 34 deaths involving buprenorphine in France: buprenorphine was “clearly” responsible for only four of these; most deaths involved its intake with other drugs, especially BDZs and antipsychotics (Pirnay et al. 2004).

1.2.2.3 Enhancement of maintenance treatment: Evidence Based Best Practice

As has already been pointed out, maintenance treatment is a combination of pharmacotherapy and psychosocial interventions. The immediate introduction of these services leads to significantly higher retention and more comprehensive and effective treatment (Anonymous 1998). However, psychosocial interventions alone, without pharmacological maintenance, continue to be offered as a mainstream treatment option in heroin addiction. While several Cochrane reviews have explored the efficacy of pharmacotherapy for opiate addiction, it is only recently that a systematic review focused on the role of psychosocial interventions alone. The authors concluded that the available evidence is limited and heterogeneous, and that at present, psychosocial treatments alone are not adequately proved treatment modalities or superior to any other type of treatment (Mayet et al. 2005).

Many techniques can be tried to enhance maintenance treatment. In the following sections, we will discuss psychosocial interventions that are evidence-based.
1.2.2.3.1 Psychotherapy/ Family therapy

Psychotherapy can be used, both individually as well as in group therapy. RCTs have shown favourable outcomes, both from supportive-expressive psychotherapy (Woody et al. 1987; O'Brien et al. 1995), and cognitive-behavioural psychotherapy (Scherbaum et al. 2005). A recent meta-analysis of family therapy in treatment of substance dependence indicated a robust effect size. The meta-analytic evidence favored family therapy over individual counseling or therapy, peer group therapy, and family psychoeducation (Stanton and Shadish 1997).

1.2.2.3.2 Contingency Management

A meta-analysis conducted on contingency management (CM) interventions in MMT confirmed that CM is effective in reducing supplemental drug use. Significant moderators of outcomes included type of reinforcement provided (take-home doses, vouchers), time to reinforcement delivery, the drug targeted for behavioral change, and number of urine samples collected per week (Griffith et al. 2000). The dose of medication can also be used as reinforcer, either by itself (O'Brien et al. 1995) or in combinations with other reinforcers, such as vouchers or take-home doses: studies have shown further improvements by the combinations (Dallery et al. 2001; Preston et al. 2000). There is also an effect with reinforcer magnitude (Dallery et al. 2001).

1.2.2.3.3 Intake procedure and Structure

The effect of assessment and intake procedures on the outcome of MMT was investigated in a natural experiment in which a single methadone clinic admitted patients by a rapid intake procedure, and patients who had been on a waiting list and underwent formal assessment interviews. Outcome measures were frequency of illicit drug use, and risk of dropping out or being expelled from treatment. Subjects admitted after prolonged, formal assessment were twice as likely to use heroin during the first six months of treatment, and were more likely to leave treatment, both voluntarily as well as involuntarily (Bell et al. 1994). In an experiment to increase retention in treatment, investigators changed the intake procedure into a MMT-program, offering contact with a physician and other treatment staff on the day of arrival to the clinic, with the assessments finished and medication started within that same first day. The rapid intake group showed higher retention at each follow-up, and confirmed the original hypothesis; decreasing delays at intake significantly increases the retention rate (Woody et al. 1975).

A study examined the effects of setting limits on continued drug abuse in patients receiving methadone maintenance. Subjects were randomly assigned either to structured treatment (drug use exceeding set limits resulted in methadone withdrawal) or to unstructured treatment (no consequences of continued drug use). The structured treatment resulted in significantly less drug use and greater retention (McCarthy and Borders 1985). In contrast, Caplehorn (Caplehorn et al. 1993b) reported that patients assigned to a strongly abstinence-oriented program were four times more likely to leave treatment in the 6 months of treatment than those subjects assigned to a more laissez-faire program. An interesting bi-phasic approach was described by Gunne (Gunne et al. 2002), where a succession of an initially highly structured and controlled treatment...
paradigm, followed by an adaptive model supporting a gradual increase in patient autonomy, seems to be beneficial, with a steady high retention.

1.2.2.3.4 Dosing

Studies have repeatedly shown that there is a strong association between methadone dose and in-treatment heroin use (Bell et al. 1995; Caplehorn et al. 1993a; Hartel et al. 1995) as well as retention in treatment (Johnson et al. 2000), which also holds true for buprenorphine (Mattick et al. 2004). When patients in a methadone clinic were given knowledge and control of their own doses, a small group of patients did raise their doses systematically, and these patients tended to decrease illicit opiate use. Patients and staff overwhelmingly preferred an open-dose self-adjustment system over the usual procedure of dose management by professional staff and dose changes achieved by negotiation (Goldstein et al. 1975).

A study showed that outcomes in MMT are dose-dependent also with regard to the intensity of psychosocial interventions: Patients were randomly assigned to one of three treatment groups for a 6-month clinical trial: (1) minimum methadone services (MMS) - methadone alone with no other services; (2) standard methadone services (SMS) -- same dose of methadone plus counseling; or (3) enhanced methadone services (EMS) -- same dose of methadone plus counseling and on-site medical/psychiatric, employment, and family therapy. While methadone treatment alone (MMS) was associated with reductions in opiate use, two-thirds of these subjects had to be "protectively transferred" from the trial. This was significantly different from the 2 out of 5 of SMS subjects and 1 out of 5 of EMS subjects who met the criteria. The addition of basic counseling was associated with major increases in efficacy; and the addition of on-site professional services was even more effective (McLellan et al. 1993).

1.2.2.3.5 The buprenorphine-naloxone combination

Buprenorphine has been investigated in combination with the opioid antagonist naloxone, with the goal of decreasing abuse and diversion. The addition of naloxone in a 4:1 ratio does not change the bioavailability or effects of a 16 mg buprenorphine dose administered sublingually as two 8 mg tablets (Harris et al. 2004). When the buprenorphine-naloxone combination was tested in an RCT within the context of office-based treatment of opiate addiction, results showed that the combination is efficacious, safe and well tolerated, with no difference between groups that received buprenorphine alone or in combination with naloxone in overall adverse events, and with equivalent reductions in craving (Fudala et al. 2003).

However, when injected by subjects who are not addicted to opioids, the addition of naloxone attenuates the opioid agonist effect of buprenorphine (Weinhold et al. 1992). This is also the case if the combination is taken intravenously by individuals dependent on short- or long-acting opioids, where a precipitated withdrawal is seen, further reducing the abuse potential (Mendelson et al. 1999; Johnson and McCagh 2000).

To compare abuse of buprenorphine and buprenorphine-naloxone among untreated i.v. drug addicts, a survey was distributed to attendees at a Helsinki needle exchange program. More than 75% said they used i.v. buprenorphine to self-medicate addiction
or withdrawal. Most had tried the buprenorphine-naloxone combination intravenously, but 80% said they had a "bad" experience. Its street price was less than half that of buprenorphine alone (Alho et al. 2007). This parallels the results of a laboratory study where morphine maintained opiate addicts had the morning dose of morphine omitted on the test day, and were instead given i.v. doses of buprenorphine alone or with naloxone. Subjects reported the amount of money they were willing to pay for next dose of the same: the participants were willing to pay less than half the amount for the buprenorphine-naloxone 4:1 combination in comparison with 2 mg buprenorphine (Mendelson et al. 1999). When a buprenorphine-naloxone combination was introduced in New Zealand, already 1991, to reduce i.v. abuse of buprenorphine (as an analgesic), participants in a survey performed one year after the introduction of the combination reported that they would pay less for the combination product, and that the combination was their least preferred injectable opioid (Robinson et al. 1993).

Thus, a context that provides low thresholds into treatment, rapid intake, high initial structure in treatment followed by an adaptive approach, and a framework consisting of high doses of both pharmacological and psychosocial evidence-based interventions seems likely to be the optimal context in which maintenance treatment should be offered. This is also quite descriptive of the treatment context provided in study II.

1.2.3 Maintenance treatment and pregnancy

1.2.3.1 HPG axis and hypothalamic amenorrhea

Menstrual cycles are regulated by the Hypothalamic-Pituitary-Gonadal (HPG) axis. In short, Gonadotropin-Releasing Hormone (GnRH) is released from the hypothalamus, and stimulates the pituitary to produce and secrete gonadotropin, which in turn serves as a stimulus for ovulation. A pulsatile GnRH release is required to maintain gonadotropin synthesis and secretion. GnRH is under opioid control; a majority of women with hypothalamic amenorrhea exhibit a persistent slow frequency of GnRH pulses that reflects excessive hypothalamic opioid tone. The ability to change the pattern of GnRH secretion is an important factor in the maintenance of cyclic ovulation, and loss of this function leads to anovulation and amenorrhea (Marshall et al. 2001).

1.2.3.2 HPG-axis, Heroin Dependence and MMT

Both heroin addiction and methadone treatment is commonly associated with amenorrhea and appears to be related to an alteration of the hypothalamic mechanisms controlling gonadotropin secretion. In an early study, more than one-half of former heroin addicts receiving MMT had experienced menstrual abnormalities while taking heroin or methadone (Santen et al. 1975). Another study showed that MMT was associated with a longer and more variable cycle length. Methadone use more than doubled the risk of amenorrhea, while injection drug use almost quadrupled it (Harlow et al. 2003). Another study evaluated whether cycle length was more regular during MMT than during heroin use. Cycle length begun to normalize during MMT, and 59% of women with secondary amenorrhea prior to the study started to menstruate. MMT, despite interfering with menstrual function in an absolute sense, seemed to interfere less than illicit heroin abuse (Schmittner et al. 2005).
1.2.3.3 Pregnancy and maintenance treatment

MMT is considered to be the “gold standard” treatment of pregnant heroin addicts who cannot achieve a drug free state. This is based on more than 35 years experience, showing the benefits of this treatment. These include reduced maternal morbidity and mortality and promotion of fetal stability and growth (Kandall et al. 1999). MMT is, however, associated with a neonatal abstinence syndrome (NAS), which often requires treatment of the newborn (Kaltenbach et al. 1998).

As buprenorphine was introduced for treatment for heroin addiction, pregnancies where the fetus was exposed to buprenorphine in utero occurred. Some of the early reports emerged from Austria (Fischer et al. 1998; Fischer et al. 2000; Schindler et al. 2003). These were small series of case reports, demonstrating that BMT in opioid-dependent pregnant patients was efficient and well tolerated by both mother and fetus. Meanwhile, there were also case reports coming out from France, but most of the reports were published in French journals. A review (Johnson et al. 2003) summarized the 21 reports published so far, representing approx. 15 evaluable cohorts of infants. Of 309 infants, NAS had been reported in 62% infants with 48% requiring treatment. However, more than 40% of these cases were confounded by illicit drug use. The authors concluded that buprenorphine appeared to be safe and effective in both mother and infant, with a NAS that may differ from methadone both qualitatively and quantitatively.

Results from the first RCTs comparing BMT to MMT in the treatment of pregnant opioid addicts (Jones et al. 2005; Fischer et al. 2006) suggested that buprenorphine is not inferior to methadone on outcome measures assessing NAS and maternal and neonatal safety. As both these studies had limited power to detect differences, the cohort studies that emerged in parallel offered some complimentary information:

In a French multicenter observational study, 260 infants born to opiate-addicted mothers on MMT or BMT were followed prospectively. Major findings were that three-quarters of the newborns developed NAS, half of them were treated (Lejeune et al. 2006). A recent study from Finland reported 67 buprenorphine-exposed pregnancies. The pregnancies and deliveries were uneventful, 76% of the newborns had NAS, and severe NAS with need for treatment was seen in 57% (Kahila et al. 2007). A recent Austrian study (Ebner et al. 2007) included 53 neonates born to opioid-maintained mothers. The mothers received methadone, slow-release oral morphine or buprenorphine throughout pregnancy. Irrespective of maintenance treatment, all neonates showed APGAR scores comparable to infants of non-opioid dependent mothers. No difference was found between the three maintenance groups regarding neonatal weight, length or head circumference. Sixty percent of neonates required treatment for NAS [68% in the methadone-maintained group, 82% in the morphine-maintained group, and 21% in the buprenorphine-maintained group].

The recent Cochrane report, including only RCTs, found three trials with 96 pregnant women. Two compared methadone with buprenorphine and one methadone with oral slow morphine. Authors conclusions were that they didn't find any significant differences between the drugs compared both for mother and for child outcomes; the trials retrieved were too few and the sample size too small to make firm conclusion about the superiority of one treatment over another (Minozzi et al. 2008).
A study not included in the Cochrane report was the recently reported RCT from the Czech Republic. The group of patients included 147 i.v. heroin addicted pregnant women. The maintenance treatment started during the first trimester of pregnancy. Finally, 47 heroin addicted women without maintenance treatment, 32 women maintained on methadone and 38 women maintained on buprenorphine were enrolled in the study. Patients were included if they did not smoke more than 10 cigarettes a day, and proved absence of other addictive substances, thereby offering a better possibility to evaluate the impact of the medication per se, than the earlier reports where the results were confounded by illicit drug use or nicotine. The lowest birth weight, the highest number of newborns with intrauterine growth restriction (IUGR) and the most numerous placental changes were found in the group of heroin addicted women. The differences compared to the two groups receiving maintenance treatment were statistically significant. The severity and course of NAS were most severe in newborns of women from the methadone group (Binder and Vavrínkova 2008).

Although the clinical impression is that BMT-exposed pregnancies seem to be associated with both lower degree and frequency of NAS than MMT-exposed pregnancies, only the Czech study has, this far, been able to demonstrate this difference. While waiting for large RCTs investigating the matter, we studied a population based cohort consisting of all consecutive pregnancies in Stockholm County 1982-2006 where the mother had been either buprenorphine- or methadone-maintained due to heroin addiction, to see if the this study, showing the naturalistic course, would provide us with some complimentary information (study IV).

Nota bene: The discussion of buprenorphine in the context of pregnancy is solely referring to the formulation of buprenorphine alone. The buprenorphine-naloxone combination is not approved for use during pregnancy.
2 AIMS

The overall aim of this thesis was to evaluate the role of the partial opioid agonist buprenorphine in treatment of heroin addiction in the context of a multimodal treatment program. To achieve this objective more specific aims were:

The aim of study I was to evaluate the efficacy of buprenorphine in combination with psychosocial interventions chosen according to evidence-based best practice, in a group of people with heroin addiction at an early stage (1-4 years of documentation) and without abuse of or addiction to other drugs.

The aims of study II were to investigate a stepped strategy with buprenorphine as first-line treatment, to find predictors of who would need either buprenorphine or methadone, to further enhance the treatment delivery framework by adding additional components, and to explore the outcome of a markedly simplified intake procedure (low thresholds to highly structured treatment).

The aims of study III were to investigate HPA axis reactivity after maintenance treatment with buprenorphine, using the metyrapone challenge. For comparison, HPA axis reactivity was examined in two groups of healthy controls, either receiving or not receiving an acute dose of naltrexone. To assess a possible correlation between neuroendocrine response and affect, mood ratings were obtained in parallel with hormone levels. Finally, because genetic variation at the mu-opioid receptor gene (OPRM1) is associated with heroin addiction and differential HPA axis reactivity, we assessed the contribution of this variant to our results.

The aim of study IV was to compare fetal growth and neonatal outcomes after in utero exposure to buprenorphine or methadone.
3 MATERIALS AND METHODS

3.1 ETHICAL COMMITTEE APPROVALS

The Karolinska South human subjects ethics committee approved Study I (Dnr 294/99), Study II (Dnr 373/03), and Study III (Dnr 374/03). The Karolinska Regional Ethics Committee considered Study IV to be a quality improvement project (Dnr 2007/996-31/3), which therefore did not need an ethical committee approval.

3.2 PATIENTS

3.2.1 Study I (Buprenorphine vs. placebo)

To this randomized placebo-controlled trial we screened all consecutively admitted inpatients in the chemical-dependence units of Addiction Centre South, Stockholm. Four hundred and forty patients were screened for trial eligibility. Patients with 1-4 years documentation of heroin dependence (DSM-IV), and absence of codependence on alcohol, amphetamines, cannabinoids or benzodiazepines were offered to participate in the study. After obtaining their written informed consent 40 individuals were included, thus yielding a highly selected study population.

3.2.2 Study II (STEP vs. methadone)

To this two-site randomized double dummy-controlled trial, we received 130 self-referral prescreening forms. A doctor’s appointment was scheduled, a screening evaluation was carried out, and written informed consent was obtained. The inclusion criteria were heroin dependence (DSM-IV) >1 year, age >20 years and acceptance of the stated treatment principles. Ninety six patients were included, presumably yielding a highly unselected study population.

3.2.3 Study III (HPA axis and buprenorphine)

An experimental laboratory study, comparing responses to metyrapone challenge in 20 buprenorphine maintained heroin addicts; and 20 healthy volunteers, 10 receiving a single 50mg naltrexone dose (NTX+), and 10 who received no naltrexone (NTX-). Patients were 16 males and 4 females, aged 30-38 years, heroin dependent (DSM-IV) and relapse-free under buprenorphine maintenance minimum 6 months. Healthy volunteers were 9 males and 11 females aged 36-49 years with no history of addiction.

3.2.4 Study IV (Pregnancy and maintenance treatment)

A naturalistic population based comparison of consecutive, prospectively followed buprenorphine-exposed pregnancies in Stockholm County, Sweden, to retrospectively analyzed consecutive methadone-exposed pregnancies. In this study we included all pregnancies in Stockholm County complicated by heroin addiction undergoing maintenance treatment; 47 pregnancies occurring in 39 women with BMT 2001 - 2006, and 35 pregnancies occurring in 26 women with MMT 1982-2006.
3.3 METHODS

3.3.1 Procedures Study I

Participants were randomly assigned to either active treatment or placebo, and received fixed dose medication under double blind conditions throughout the 1 year follow up. All patients were admitted to an inpatient unit during the first week, when half of the subjects received a one week’s induction on buprenorphine (8mg day 1, 16 mg thereafter), whereas the other half received buprenorphine in tapering doses for the first 6 days, in accordance with the clinic’s standard treatment for heroin withdrawal. Patients were discharged after 1 week in hospital, but had to return to the treatment unit daily for supervised administration of medication for at least 6 months. After this time the frequency of visits was agreed with individual patients, but the daily medication dose was kept constant throughout the study.

Within 4 weeks of inclusion, patients started a 12 session course of manual-based behavioral therapy, which used cognitive behavioral therapy principles and focused on relapse prevention (RP) as described by Marlatt (Larimer et al. 1999). The RP model suggests that both immediate determinants (e.g., high-risk situations, coping skills, outcome expectancies) and factors that are not immediately apparent (e.g., lifestyle, cravings) contribute to relapse. Many of these factors are examples of what animal studies have shown to reinstate drug-seeking behavior: stressors, drug-associated cues, and priming effects of drug itself. The RP model uses intervention strategies that allow the therapist and client to address each step of the relapse process. Specific interventions include identifying specific high-risk situations for each client and enhancing the client's skills for coping with those situations, managing lapses, and restructuring the client's perceptions of the relapse process.

In addition to the group-based behavioral therapy, throughout the study, patients were offered 45 min individual counseling sessions every week in the treatment unit. Finally, individual treatment plans were developed in collaboration with social services departments to address issues of housing and occupation.

At baseline, and every 3 months, subjects remaining in treatment were assessed using the Addiction Severity Index (ASI) (McLellan et al. 1992). The ASI is a semi-structured interview used to assess the severity of treatment problems found in alcohol- and drug-abusing patients. ASI is a reliable and valid instrument, and it has found a wide range of both clinical and research applications (McLellan et al. 1985). It has been reported that interrater reliability is higher for ASI composite scores than for the raw interviewer severity ratings (Alterman et al. 1994). However, we have consistently found these two measures to correlate at rates in excess of 0.9, making this distinction less relevant. A possible reason for this is the small number of raters used in our studies.

Patients also delivered supervised urine samples thrice weekly. Urine samples were analyzed by the SWEDAC-accredited Clinical Pharmacology Laboratory at Karolinska University Hospital. Screening was made with the EMIT kit (Beckman Coulter, Bromma, Sweden), with cutoff values for opiates of 300 ng/ml, central stimulants of 300 ng/ml, cannabinoids of 300 ng/ml, and BDZs of 100 ng/ml. All screening-positive
samples were validated and quantified using SWEDAC-accredited liquid chromatography–mass spectrometry. Cocaine was not analyzed because the use of this substance is extremely rare in clinical heroin populations in Sweden.

The primary endpoint of the study was 1-year retention in treatment and analysis was by intention to treat. Secondary outcomes were drug free urine samples and ASI severity ratings, both analyzed in completers only.

3.3.2 Procedures Study II

Upon arrival to the outpatient clinic, each patient was randomized to MMT or stepped treatment. Random assignment was by the research pharmacy, insulated from trial staff. Blinding was achieved using the individual patient packs containing four identical-looking sublingual tablets containing buprenorphine-naloxone or placebo, in combinations yielding the desired dose, and one capsule of the respective dose of methadone hydrochloride or its placebo. A double-blind 24-day induction phase provided uniform dose escalation and stabilization for both arms (MMT: 10 days to reach 70 mg/day of methadone; stepped therapy: 2 days to reach 16 mg/day of buprenorphine-naloxone). To avoid precipitating withdrawal, medication was given upon the appearance of withdrawal symptoms, ≥8 hours after the last heroin intake.

After induction, allocation codes were communicated to the sites. Based on the criteria given below, the local trial leader or designee wrote orders for 2-week intervals, blinded for the patient. Patterned after a prior report (Johnson et al. 2000), “transitions” were possible in intervals of 2 weeks. A transition was a dose increase or, in subjects receiving 32 mg/day of buprenorphine-naloxone, switching to methadone. Criteria for transitions were the following—with the preceding 2 weeks: ≤2 missed visits, self-reported insufficient blockade of craving, self-reported withdrawal symptoms on nadir, or any urine sample positive for illicit opiates and no signs of overdosing (cognitive impairment, sedation, respiratory depression). MMT was allowed transitions in 10-mg increments to 120 mg/day. Stepped therapy allowed transitions, in 8-mg increments, to 32 mg/day. If this was insufficient, a rapid switch followed; patients received 50 mg/day of methadone the day after the last buprenorphine-naloxone dose, followed by 10-mg increases every second day to 90 mg/day. After this, the methadone maintenance therapy followed protocol above.

Patients met with case managers at least weekly for counseling and to provide information for dose adjustments. A slip (self-reported drug intake or any positive urine sample) led to the progression of 1) a dose increase; 2) if insufficient (i.e., indicators of slip/relapse continued to occur), or the maximum dose had been reached, intensified counseling to two and then three times a week. When 4 weeks’ stability in treatment had been achieved, defined by all-negative urine tests, but no earlier than after 3 months, patients were allowed take-away doses for weekends. With additional completed 4 weeks of stability, take-away doses were dispensed twice weekly, and after an additional 4 weeks of stability, once weekly. In case of relapse, daily supervised administration resumed.
Patients were withdrawn from the study if they were absent from scheduled visits for more than a week; verbally or physically threatened or abused staff or patients; dealt drugs; or engaged in illicit drug use which by the responsible physician was deemed to endanger medical safety, e.g., intake of repeated high doses of BDZs. Patients participated in group relapse prevention therapy (RP; see above). Supervised urine samples were obtained in conjunction with the initial assessment visit and during the study.

On inclusion, as well as after 3 and after 6 months, problem severity was assessed using the ASI.

The primary outcome, retention in treatment, was analyzed by intention to treat. Analyses of secondary outcomes, ASI severity ratings and the proportion of urine samples negative for illicit opiates were planned for completers only.

### 3.3.3 Procedures Study III

To assess the endocrine stress-response, the standard metyrapone challenge was carried out in stable buprenorphine maintained subjects (stable in treatment >6months), and in healthy volunteers. To generate a positive control, HPA axis reactivity was also examined in another group of healthy volunteers after an acute dose of naltrexone, because it has been described that opioid antagonists activate the HPA axis (Del Campo et al. 1994; Wand et al. 1998). The metyrapone challenge is a clinical neuroendocrine test to explore the HPA axis and, for instance, the magnitude of reactivity to this “chemical stressor”. The cortisol synthesis inhibitor metyrapone selectively blocks 11-beta-hydroxylation in the adrenal cortex for a few hours. In the single-dose test, this leads to an abrupt lowering of plasma cortisol levels, and thereby an abrupt cut-off of the normal negative feed-back control by this glucocorticoid, which usually provides inhibition both at the level of the hippocampus, and at the hypothalamic and pituitary sites. Therefore, there is a surge of hypothalamic CRH which acts on the anterior pituitary, causing an increase of processing and release of the proopiomelanocortin peptides, ACTH and beta-endorphin. In healthy humans, there is a rise in both ACTH and beta-endorphin levels following the abrupt lowering of cortisol levels by metyrapone (Kreek 2003).

To assess a possible correlation between neuroendocrine response and affect, mood ratings were obtained in parallel with hormone levels, using the established Profile of Mood States (POMS) self-report instrument (McNair et al. 1971). The POMS is a widely used instrument to assess transient (state-dependent) mood changes, originally divided into six dimensions: depression, tension-anxiety, anger, fatigue, confusion and vigor. Normative data from the general population have been provided (Moore et al. 1990; Nyenhuis et al. 1999).

Finally, we assessed the contribution to our results of a genetic variant at the OPRM1 gene locus, by performing genotyping of the A118G SNP. DNA was purified from whole blood using standard methods. Genotyping of the A118G SNP was performed by a TaqMan allelic discrimination assay using the ABI PRISM® 7900HT Sequence
Detection System (Applied Biosystems Inc., Foster City, CA, USA) following the manufacturer’s protocol. Briefly, 10 ng DNA was amplified in a final volume of 10 µl containing 0.5 µl of 20X MGB probe and primers, 5 µl of 2X TaqMan Universal PCR Master Mix in a 384-well microplate format (Applied Biosystems Inc., Foster City, CA, USA). Amplification conditions were 50°C for 2 min then 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 60°C for 1 min. 15% of the samples were genotyped in duplicates as a quality check, with complete concordance.

### 3.3.4 Procedures Study IV

The basis for this study is the existence since 1982, at Karolinska Hospital Huddinge, of a single specialized antenatal care clinic for women in Stockholm county whose pregnancies are complicated by substance abuse disorders (Larsson et al. 1982). This clinic has followed standardized procedures since its inception. Upon referral of a pregnant woman with heroin addiction with maintenance treatment, a meeting is convened of an interdisciplinary team, consisting of a psychiatrist, a pediatrician and a gynecologist/obstetrician, midwives, and medical social workers specialized in working with pregnant women with substance abuse disorders. The team follows the women throughout the pregnancy. The antenatal care clinic works closely together with addiction medicine units, social services and obstetrics and child care throughout the county. All pregnant women receive intensive psychosocial support during the maternity care period.

The case series analyzed in Study IV represents all heroin dependent pregnancies in Stockholm County that received maintenance treatment between the years 1982 – 2006. The MMT cases were analyzed retrospectively from medical records. Data for the BMT cases were prospective. Since the introduction of buprenorphine (Subutex) in Sweden in 1999, the same pediatrician (author IS) met all but five women during the second trimester (average 26th week of gestation) to inform them about possible buprenorphine effects on the fetus, and to obtain their consent for participation in the study. All pregnancies were followed to delivery at the antenatal clinic, and all children were born at the Karolinska University Hospital Huddinge.

After delivery, newborn infants were cared for together with their mothers on the maternity ward in order to promote attachment. The pediatrician examined and assessed the children on a daily basis and the emergence of NAS was evaluated by the midwife on the ward every 3 to 4 hours using the scoring system developed by Finnegan and colleagues, in wide international use both for clinical and research purposes (Finnegan et al. 1975). Among other applications, the Finnegan-scoring system is well established as a basis for pharmacological therapy of the infant. When pharmacological treatment of the infant was needed, the infant and the mother were moved to the neonatal care unit in the same hospital.

Descriptive characteristics (age, weight, height) of the mothers at the beginning of the pregnancy, opioid maintenance treatment duration, other medical prescriptions, smoking habits at 32 weeks of gestation (number of daily smoked cigarettes), dichotomous data (twin pregnancies, miscarriages, development of pre-eclampsia, occurrence of IUGR, occurrence of serological markers for viral infections as Hepatitis...
and HIV) were extracted from the Swedish standardized antenatal medical records, which have remained the same over the 25 years of this study. Data for the newborn infants were extracted from the medical records and consisted of delivery mode, anthropometric measures, APGAR score at one, five and ten minutes, occurrence of NAS; medical treatment and postnatal stay at hospital.

Following the neonatal period, outcome information on infant mortality in sudden infant death syndrome (SIDS) during subsequent three months was collected from medical records.

3.4 STATISTICAL ANALYSES

3.4.1 Study I
Retention in treatment and actual survival (i.e. number of days staying in treatment, and number of days staying alive, respectively) were analyzed with Cox’s proportional hazard regression analysis with treatment status as the predictor variable. In both cases, patients who completed 365 days of treatment were regarded as censored observations. ASI severity and composite scores fulfilled criteria for homogenous variances, and were analyzed with repeated measures ANOVA, treating dropouts as missing values. Comparisons between individual time points were done with Tukey’s honestly significant difference (HSD) test for unequal samples. Data were analyzed using Statistica version 6.0 for Windows.

3.4.2 Study II
The primary outcome, retention in treatment, was analyzed by using Cox proportional hazard regression, with age, duration of heroin use, and gender as covariates. The assumption of proportional hazards was tested by using the time-dependent covariate test because this has good power for detecting nonproportionality. Noninferiority for censored survival data are commonly tested with a single time point comparison and this approach was used here.

Secondary outcomes were only analyzed for completers. Among these, ASI severity ratings were analyzed with repeated measures ANOVA, with treatment as a between-subjects and time as a within-subjects factor. The other secondary outcome in completers was the proportion of urine samples negative for illicit opiates. The total number of scheduled urine sampling time points in completers varied between 48 and 54, with the majority submitting 52 samples. To equalize this, the study period was divided into six 1-month blocks, within which the proportion of clean samples was calculated for each subject. Missing samples were treated as positive. The proportion of clean samples was analyzed using two-way ANOVA, with treatment as between-subjects and block number as the within-subjects factor. The same approach was used for BDZs and tetrahydrocannabinol (THC). Very few subjects had any central stimulant use, and this parameter was not further analyzed.
Finally, within the stepped therapy arm, a logistic regression analysis was used to evaluate whether gender, age, or severity or duration of dependence would predict switching to methadone. All analyses used Statistica 7.0 (StatSoft, Tulsa, Okla.).

3.4.3 Study III
Cortisol and ACTH data were analyzed separately by ANOVA using the general linear model module of Statistica, with repeated hormone values as a within subjects factor, group and sex as within subjects factors, and age and BMI as covariates. POMS scores were subjected to a factor analysis. Principal component factors were extracted, and rotated using normalized Varimax-rotation. Repeated measures ANOVA was carried out, with factor scores on the respective factor as dependent variable, time as repeated measures / within subjects factor, and group as between subjects factor. Post hoc comparisons were preformed using Newman-Keul’s test. OPRM1 genotype frequencies were compared between groups using Yates corrected \( \chi^2 \)-test. STATISTICA 7.0 (StatSoft, Tulsa, Oklahoma) was used for all analyses.

3.4.4 Study IV
For statistical analyses, averages and standard deviation were used to describe population data. For group comparisons, one way ANOVA was used for continuous variables. To control for the significant difference in age between mothers in the BMT and MMT groups, respectively, this variable was additionally included as a covariate. A similar approach was used to determine whether treatment category (BMT or MMT) contributed to neonatal outcomes over and above its effect on length of pregnancy. Fishers Exact test (two-tailed) was used for frequency variables. To eliminate the potential confound of assessing multiple pregnancies from the same women, additional analyses were carried out restricting the population to one randomly selected pregnancy from each of the women who had multiple children. Results did not differ, and therefore the results for all pregnancies are presented. STATISTICA 7.0 (StatSoft, Tulsa, Oklahoma) was used for all analyses.
4 RESULTS

4.1 STUDY I

The primary outcome retention in treatment was significantly better in the buprenorphine group than placebo (Figure 1), with 75% one-year retention in the buprenorphine group.

![Figure 1](image)

Data for the secondary outcome, ASI problem severity ratings and composite scores could only be obtained while patients stayed in treatment. Because all controls had dropped out before the first assessment at 3 months, the only assessment of the secondary outcome variable was whether baseline problem severity had fallen during treatment with buprenorphine in comparison with baseline untreated scores. To make this comparison, we did an intention-to-treat analysis, with data from patients who had dropped out as missing values. Results from a repeated measures ANOVA showed a highly significant reduction in ASI scores over time in the buprenorphine group. Use of illicit drugs in the buprenorphine group was rare; results from thrice-weekly supervised urine analyses showed that a mean of 75% of samples obtained were negative for the substances analyzed.

Finally, we noted a significantly higher mortality in the controls, among whom four people died during the study period, versus none in the buprenorphine group (Cox’s regression, p=0.015).
4.2 STUDY II

The primary outcome, retention in treatment, was virtually identical between arms, with overall six-month retention of 78% (Figure 2). A hypothesis of stepped therapy being inferior to methadone maintenance treatment with regard to the proportion of subjects retained could be rejected.

Figure 2

In stepped treatment, the final breakdown of the intention-to-treat group was 11 of 48 dropouts, 17 of 48 nonswitcher completers and 20 of 48 switcher completers. By comparison, in the methadone maintenance treatment arm, 10 of 48 were dropouts, and 38 of 48 were completers (Table 1). Neither age, gender, duration of heroin use, nor baseline aggregate ASI severity ratings significantly predicted whether subjects in stepped therapy remained on buprenorphine-naloxone or switched to methadone.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Final daily dose (mg±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMT</td>
<td>38</td>
<td>110.0 ±13.2 mg methadone</td>
</tr>
<tr>
<td>STEP, non-switchers</td>
<td>17</td>
<td>29.6 ± 4.7 mg buprenorphine</td>
</tr>
<tr>
<td>STEP, switchers</td>
<td>20</td>
<td>111.0 ±11.7 mg methadone</td>
</tr>
</tbody>
</table>
Overall, problem severity as measured by the ASI decreased over time. When ASI subscales were analyzed, reduction in total problem severity was mostly attributable to a reduction over time of drug-related problems. However, a significant reduction of problems related to occupation was also found already at this early stage of treatment. Other ASI subscales were not significantly affected.

Overall, the proportion of urine samples free of illicit opiates over time increased significantly, with 80% of tests being negative during the final month of the study. No difference between the two groups was found. Similar results were obtained for BDZs and THC.

### 4.3 STUDY III

Cortisol production by metyrapone administration was adequately suppressed in all study group, and metyrapone induced suppression of cortisol did not affect the groups differentially.

There was a significant response of ACTH to the metyrapone challenge and main effect of group. A differential response of ACTH between the groups was shown by a highly significant interaction term. Post hoc comparison showed that both the naltrexone and the buprenorphine group differed from the control group. Specifically, healthy controls challenged with naltrexone showed higher responses, while buprenorphine maintained heroin dependent patients showed lower responses than untreated healthy controls.

The frequency of the 118G allele was 20.0% in heroin addicts, but only 7.5% in healthy volunteers, yielding a trend for a statistical significance ($\chi^2=2.64; p=0.10$). To exclude the possibility that the different 118G allele frequency contributed to the metyrapone challenge results and psychological ratings, all analyses were replicated excluding 118G carriers. Following exclusion of 118G carriers, response over time, main effect of group and the interaction remained significant. However, on post hoc analysis, while the naltrexone group still robustly differed from both untreated controls and buprenorphine maintained subjects, the buprenorphine maintained group and untreated controls no longer differed. In a breakdown of the buprenorphine maintained heroin dependent group by genotype, it was clear that responses indistinguishable from healthy controls were seen in 118A homozygous subjects, while carriers of the 118G allele essentially lacked an ACTH response to metyrapone (Figure 3).

Although the POMS has been described to assess mood in five domains, an inspection of the scree-plot indicated that a three-factor solution best described the underlying structure in our data. These three factors together explained 46.2% of the variance. Inspection of these items suggested that Factor 1, which accounted for 17.1% of the variance, could be labeled ‘Negative affect’, and consisted of depressed mood, irritability and hostility, which seemed intercorrelated. Factor 2, which accounted for 17.4% of the variance, could be labeled ‘Positive affect’, and received loadings from factors that express elevated mood, and factors that express vigor, or energy. Factor 3, contributing 11.7% of the variance, received contributions from items that express ‘Fatigue and confusion’, and was called accordingly. This factor was not of interest for the current study, and was not further analyzed.
ANOVA of factor scores on ‘Negative affect’ yielded a highly significant group effect. Post hoc analysis showed that the buprenorphine maintained group differed from both untreated controls and naltrexone treated healthy subjects with a higher ‘Negative affect’, while the two latter were indistinguishable.

ANOVA of factor scores on ‘Positive affect’ also showed a significant group effect. Here, post hoc analysis showed that the naltrexone group deviated from the other two groups with a lower ‘Positive affect’.

Figure 3

4.4 STUDY IV

No significant baseline differences between the groups emerged, with the exception of BMT subjects being significantly younger. Overall, smoking was much more common in the cohort examined here compared to pregnant women in the general population.

The medication dose (mean) given to the subjects during pregnancy was 15.4 mg, for the BMT group and 71.3 for the MMT group. The occurrence of illicit drug use (opiates or cannabis) after recognition of pregnancy, confirmed by patient report or urine screening, occurred in 15/47 cases (31.9 %) in the BMT group and in 17/35 cases (48.6 %) in MMT group; information was missing in 2 cases in the MMT group. This difference was not statistically significant.

Children born to MMT mothers had significantly lower birth weight than those born to BMT subjects. Since a near-significant trend for a lower gestational age at birth was found in the MMT group (p=0.06), we also examined whether treatment category influenced birth weight when gestational age was controlled for as a covariate. As expected, gestational age as covariate contributed in a highly significant manner to birth weight. When controlling for this covariate, the effect of treatment group to influence birth weights was markedly weakened and remained only at a trend level (p=0.07).
The frequency of newborns with any NAS was almost two fold higher in the MMT group compared to BMT (p=0.0008). Severe NAS (i.e. at a level necessitating pharmacological treatment) was more than three fold higher in the MMT group (p=0.0004). Accordingly, average length of stay in the hospital was considerably longer for the MMT group (p=0.0009).
5 DISCUSSION

5.1 MAIN FINDINGS REGARDING MAINTENANCE TREATMENT

In Study I we showed that the combination of buprenorphine and intensive psychosocial treatment is highly efficacious in the treatment of heroin addiction. One year retention in the treatment group was 75%. Problem severity was greatly reduced, specifically in the areas of drug use, crime and occupation. Urine screens were about 75% negative for illicit opiates, central stimulants, cannabinoids and BDZs in the patients remaining in treatment.

The intensive and highly structured treatment model was combined with a non-confrontational and empathetic staff. A combination of defined criteria for involuntary discharge, combined with a willingness to mainly initiate support efforts on signs of destabilization, could have been especially effective in the study setting.

The study population was highly selected, with a relatively short period of heroin addiction (1-4 years) and without co-dependence on other drugs, thus representing a group of patients that could be expected to be relatively easier to treat. It was, however, remarkable to find that retention was very poor in the controls: Although the controls received a treatment which had a higher quality than what the ordinary treatment system in Sweden could offer at that time, with intensive psychosocial support as well as access to an inpatient unit which the patients could contact at any time to receive support and where admission could be offered within one day if needed, no patient remained in treatment beyond 2 months. Apart from being an RCT providing evidence that the addition of buprenorphine to intensive psychosocial treatment is highly efficacious, this study also shows that psychosocial treatment alone does not work in treatment of heroin addiction, not even in an early stage.

Study II investigated a stepped strategy for treatment of heroin addiction, capitalizing on the advantageous properties of both buprenorphine-naloxone and methadone. Primary as well as secondary outcomes for stepped treatment and MMT were virtually identical. The noninferiority of stepped treatment was formally demonstrated on the primary outcome, which was particularly encouraging given that the comparator MMT arm yielded a set of outcomes that compares favorably with any previously published studies of heroin addiction (Mattick et al. 2003b).

In this case, the study population was highly unselected, with a relatively long period of heroin addiction (mean 10 years) and patients were included in the study regardless of co-dependence on other drugs, thus representing a group of patients that could be expected to be relatively difficult to treat.

We used the same treatment framework as in study I, but improved it further: The pharmacological treatment was combined with behavioral methodology based on close monitoring of illicit drug use by supervised urine sample collection, reinforcement of treatment compliance by contingency management, and relapse prevention group therapy—all methods known to improve treatment (Carroll et al. 2001; Kakko et al. 2003; Schottenfeld et al. 2005). In this study, the patients were, however, not offered inpatient treatment for problems associated with addiction; the entire study was performed in an outpatient setting. We used higher doses of medication than what has traditionally been used, an unusual combination of rapid intake, a low threshold for inclusion and a nonconfrontational approach on one hand,
with a highly structured treatment program on the other. Finding a balance between patient autonomy and structure in the treatment of heroin addiction has been raised as a key factor in determining outcomes (Caplehorn et al. 1993b).

5.2 MAIN FINDINGS REGARDING NEUROENDOCRINE CORRELATES AND GENETICS

A main finding of this study is an unexpected double dissociation of endocrine response and negative mood following metyrapone challenge. The buprenorphine-maintained heroin addicts showed an attenuated HPA axis response to metyrapone compared with control subjects, whereas the response of the group that received naltrexone was markedly increased. In contrast, negative affect did not differ between the untreated control group and the group of healthy volunteers given naltrexone but was more intense in the buprenorphine group. The buprenorphine and the control groups did not differ in positive affect, whereas naltrexone-treated healthy volunteers reported lower scores on this dimension.

Unexpectedly, the HPA axis response of our buprenorphine-maintained subjects to metyrapone was actually subnormal, a pattern that is somewhat different from what has typically been reported with methadone-maintained individuals. Importantly, carriers of the OPRM1 118G allele contributed disproportionately to the dampening of ACTH response in the buprenorphine-maintained group and basically lacked a response to the challenge (Figure 3). The OPRM1 118A/G variation has previously been shown to confer differential HPA axis response to naltrexone (Wand et al. 2002). The suggestive finding of a more potent HPA axis suppression by buprenorphine in 118G carriers is in general agreement with these data and can be thought of as their mirror image.

A single dose of the opiate antagonist naltrexone predictably increased the activity of the HPA axis in healthy volunteers. The ability of naltrexone to activate the HPA axis was established early on (Kosten et al. 1986). This is presumably the result of removing inhibitory tone of endogenous opioid peptides acting to suppress HPA axis activity both at a pituitary and hypothalamic level (Kreek et al. 2002). To the extent that exaggerated activation of the HPA axis constitutes a risk factor for relapse, these data suggest caution in treating heroin dependence with naltrexone. Additional caution may be prompted by the present finding that naltrexone administration suppressed positive mood. This may in part be related to an ability of naltrexone to block MORs in the VTA, leading to a decrease in dopaminergic tone (Spanagel et al. 1992; Johnson and North 1992). Reduction of positive mood by naltrexone presumably is an undesirable effect and may be related to known compliance issues with this medication.

We did not directly assess measures of craving, because this would not be meaningful in healthy volunteers without a history of opiate abuse. However, we measured negative affect, which can be assessed in heroin addicts and healthy control subjects alike and which in the former population has been shown to correlate with craving for opiates and relapse (Bradley et al. 1989; Childress et al. 1994; Janiri et al. 2005). Furthermore, recruitment of negative affect has been postulated as an important anti-reward mechanism in the development of addiction (Koob and Le Moal 2005). Our data suggest that a direct contribution of the HPA axis to negative affect and craving related to this mood state is unlikely.
An alternative or complementary possibility is that negative affect in heroin addicts is primarily the result of increased activity in extrahypothalamic stress circuits that initially may result from but over time become relatively independent of the exaggerated HPA axis activity in these subjects. In particular, a recruitment of CRH signaling within the extended amygdala is a candidate anti-reward mechanism that might initially be driven by a hyperactive HPA axis (Schulkin et al. 1998; Makino et al. 2002) but subsequently become largely autonomous and contribute to a transition from impulsive to compulsive drug use. Dysregulation of this circuitry has been hypothesized as being particularly slow to return to homeostasis and may confer a negative affective state that persists long into stable maintenance treatment (Koob and Le Moal 2005).

Our study indicates that the exaggerated HPA axis response to metyrapone previously reported in untreated heroin addiction is normalized by 6 months of successful BMT. The buprenorphine finding is in agreement with previous data indicating a similar ability of methadone to achieve such a normalization (Kreek et al. 1984). Given the potential for chronic HPA axis hyperactivity to cause hippocampal and other pathology, this would appear to be an important aspect of buprenorphine’s as well as methadone’s therapeutic properties.

5.3 MAIN FINDINGS REGARDING MAINTENANCE TREATMENT AND PREGNANCY

Children of buprenorphine treated mothers showed normal growth during pregnancy, while the height and weight of children with intrauterine methadone exposure was significantly lower at birth. A major component of this difference was attributable to a shorter gestational time for mothers in MMT. Both the incidence and severity of NAS was lower among children of buprenorphine treated mothers, and their length of hospital care was shorter.

When reviewing the literature, an interesting pattern emerges: in studies where low doses of medication were used, there was often a high degree of concomitant illicit drug use. These studies also reported a high degree of NAS (Johnson et al. 2003). In contrast, when high doses were used, illicit drug use was under better control and the degree of NAS was low (Jones et al. 2005). In a study that excluded subjects with illicit drug use to exclude the confound from this factor, the frequency and severity of NAS was higher in MMT-exposed pregnancies compared to BMT-exposed pregnancies (Ebner et al. 2007). In the only RCT this far with power sufficient to detect differences in this regard (a study that also excluded patients with illicit drug use), NAS was significantly worse after MMT exposure. Both MMT and BMT however showed better outcomes than continued heroin addiction when looking at birth weight, the number of newborns with IUGR and the number of placental changes. Thus, successful clinical management of substance use seems to be key to lowering NAS rates.
6 CONCLUSIONS

6.1 CONCLUSIONS AND CLINICAL IMPLICATIONS

The combination of buprenorphine and intensive psychosocial treatment is safe and highly efficacious, and should be added to the treatment options available for individuals who are addicted to heroin.

A stepped treatment of heroin addiction as described here appears equally efficacious compared to optimally delivered MMT. Together with prior data on the advantageous safety of buprenorphine, this suggests that broad implementation of strategies using buprenorphine as first-line treatment should be considered. These should be combined with systematic follow up of outcomes, and provisions for rapid transfer to methadone in cases where this is indicated.

In contrast to exaggerated HPA axis responsiveness reported in untreated heroin addiction, response to metyrapone was subnormal in heroin addicts maintained on buprenorphine. When controlling for genetic variation at the OPRM1, 118G carriers were responsible for this hyporesponsiveness while 118A homozygous subjects were normoresponsive, suggesting altered pharmacodynamics depending on this SNP. Despite the suppressed neuroendocrine stress reactivity, increased measures of negative affect were seen in the buprenorphine maintained heroin dependent group, implying a dissociation of HPA axis reactivity and affect in heroin addiction.

Data from our non-randomized comparison of buprenorphine and methadone treatment of opiate addiction during pregnancy suggest that buprenorphine may offer advantages for maintenance treatment of pregnant heroin addicts.

6.2 IMPLICATIONS FOR FUTURE RESEARCH

This thesis prompts the following questions for future research:

How do we optimize treatment for individuals who do not respond to the stepped treatment strategy? Specifically, what approaches can be developed for individuals in very early stage of heroin abuse/addiction, or individuals who drop out of treatment, irrespectively of how enhanced it might be from the providers’ point of view? What is the users’ point of view, in this regard?

Is there a link between heroin addiction, HPA axis hyperactivity and hippocampal degeneration, and does maintenance treatment have protective effects in this regard?

The influence of genetics on pharmacodynamics (pharmacogenetics) is a new field of great interest, adding possibilities to personalize pharmacological treatment according to genetic variation.

And finally, long term effects of in utero exposure to maintenance treatment need further investigation, especially studies controlling for confounders.
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8 REFERENCES


