Heroin relapse prevention with naltrexone implants: A randomised comparison with methadone treatment among inmates released from prison

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<td>6-MAM</td>
<td>6-monoacetylmorphine</td>
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<td>AE</td>
<td>adverse event</td>
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<td>ANOVA</td>
<td>analysis of variance</td>
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<td>BDI</td>
<td>Beck’s depression inventory</td>
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<td>CDAG</td>
<td>Cochrane drugs and alcohol group</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>CJ-DATS</td>
<td>criminal justice drug abuse treatment studies</td>
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<td>CREB</td>
<td>cyclic adenosine monophosphate response element binding protein</td>
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<td>DSM IV</td>
<td>Diagnostic and statistical manual of mental disorders</td>
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<td>EuropASI</td>
<td>addiction severity index, European version</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>i.m.</td>
<td>intramuscular</td>
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<td>ITT</td>
<td>intention to treat</td>
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<td>MMT</td>
<td>methadone maintenance treatment</td>
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<td>NAc</td>
<td>nucleus accumbens</td>
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<td>NIAAA</td>
<td>National Institute on Alcohol Abuse and Alcoholism</td>
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<td>NIDA</td>
<td>National Institute on Drug Abuse</td>
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<td>NIDDM</td>
<td>non-insulin dependent diabetes mellitus</td>
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<td>OMT</td>
<td>opioid maintenance treatment</td>
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<td>OR</td>
<td>opioid receptor</td>
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<td>RCT</td>
<td>randomised-controlled trial</td>
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<td>RR</td>
<td>relative risk</td>
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<td>SCL-25</td>
<td>Symptom check list 25 items</td>
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<td>sd</td>
<td>standard deviation</td>
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<td>SMART</td>
<td>sequential multiple assignment randomised trial</td>
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<td>TC</td>
<td>therapeutic community</td>
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<td>TLFB</td>
<td>timeline follow-back</td>
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<td>UROD</td>
<td>ultra-rapid opioid detoxification</td>
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<td>VTA</td>
<td>ventral tegmental area</td>
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Summary
Many prison inmates use opioids before incarceration and relapse rates upon prison release are high. Methadone maintenance has become the principal treatment modality for opioid addiction and it is increasingly implemented in criminal justice settings. More treatment options that can be initiated during incarceration and continued in the community are needed. Naltrexone implants constitute a novel treatment that has not been evaluated in a prison setting. Naltrexone implants have not been compared to opioid maintenance in a prospective study. A systematic literature review has been lacking.

In this thesis, the findings from a systematic literature review on sustained-release naltrexone, and the outcomes from a randomised-controlled trial (RCT) on naltrexone implants and methadone among pre-release prison inmates with heroin dependence are reported. Further, effects of illicitly used opioids during naltrexone implant treatment are described.

In the systematic literature review only one RCT of naltrexone depot for opioid dependence was found that met the inclusion criteria for assessment of treatment effectiveness. In that trial, Comer and colleagues reported a greater reduction in heroin use by a 384 mg naltrexone depot compared to a 192 mg depot or placebo injections. Although this indicates the effectiveness of naltrexone depot for opioid dependence, the overall evidence was found to be insufficient.

The prison study met several research challenges related to the criminal justice setting and the transition from prison to the community. These were related to interest and motivation during incarceration, random treatment allocation of inmates and aftercare following prison release. In spite of these challenges, the study found naltrexone implants and methadone to be of comparable effectiveness. Both treatments reduced heroin and illicit benzodiazepine use, and criminal activity during the six months after prison release. The reductions were found in the intention-to-treat analyses of all 44 participants and they were supported by the completer analyses. Subsequent analyses of opioid effects during naltrexone treatment revealed a larger than expected proportion of patients who had used opioids in spite of blood levels indicating satisfactory naltrexone release.
The findings from the prison study indicate that offering naltrexone implants to pre-release inmates is feasible and that this novel treatment is likely to reduce heroin use. If opioids are used during implant treatment their expected reinforcing effects are usually lacking.

Sammendrag [Norwegian]


I denne avhandlingen rapporteres det funn fra en systematisk litteraturgjennomgang på langtidsvirkende naltrexson. Dessuten rapporteres resultatene fra en randomisert kontrollert studie av naltrexson implantater sammenlignet med metadon vedlikehold blant heroinavhengige innsatte som løslates fra fengsel. Effekten av illegalt brukte opiater under naltrexson implantat behandling er også beskrevet.

Ved den systematiske litteraturgjennomgangen fant vi kun én randomisert kontrollert studie på naltrexson depot i behandling av opiatavhengighet som kunne inkluderes for evaluering av behandlingseffekt. I studien fant Comer og medarbeidere en større reduksjon i heroinbruk hos de som ble behandlet med 384 mg naltrexson depot sammenlignet med 192 mg eller placebo sprøyter. Til tross for at det ble funnet en fordelaktig effekt av naltrexson depot i behandling av heroinavhengighet, ble den samlede evidensen vurdert som utilstrekkelig.

Fengselsstudien viste spesifikke utfordringer vedrørende interesse og motivasjon under soning, tilfeldig fordeling av innsatte til behandling og oppfølging etter soning. Til tross for disse utfordringene kunne studien vise at naltrexson implantat behandling og metadon vedlikeholdsbehandling har sammenlignbar effekt. Begge behandlingsformene reduserte heroin- og benzodiazepinbruk og kriminalitet ved oppfølging seks måneder etter løslatelsen. Dette gjaldt blant alle 44 deltagere uavhengig om de startet behandling eller ikke og funnene ble støttet av analysen av deltakerne som fullførte studien. En senere analyse av opiatbruk
under naltrexon implantat behandling viste at en større andel enn forventet hadde brukt opiatet til tross for tilfredsstillende nivå av naltrexon i blodet.

Funnene fra fengselsstudien viser at det lar seg gjøre å tilby naltrexon implantat behandling før løslatelse og at denne behandlingen reduserer heroinbruk. Dersom opiatet brukes under behandlingen vil den forventete ruseffekten oftest utebli.
1. Introduction
1.1. Drug use and the prison setting
Heroin is the most commonly abused opioid and in the European Union an estimated 1.3 to 1.7 million individuals (about 0.5% of the adult population) are considered problem opioid users (EMCDDA 2008). Good prevalence data are difficult to obtain, but the United Nations Office on Drugs and Crime estimates similarly low opioid use prevalence of approximately 0.6% for the USA and of 0.25% when the whole world’s population is considered (UNODC 2008). Although affecting a relatively small group of the general population, the impact of illicit heroin use on the addicted individuals, their families and the community is often devastating.

The relationship between illicit drug use and criminality is well established (Sinha & Easton 1999). In inmate populations throughout the world substance abuse disorders are overrepresented compared to the general population (Fazel et al. 2006). In the Netherlands, as many as 79% of inmates report drug use before incarceration (EMCDDA 2007) and similar rates are reported for the USA with ca. 70% (Mumola & Karberg 2006) and for Norway with between 60 and 70% (Friestad & Hansen I.L. 2005; Ødegaard 2008). During incarceration, drug-involved offenders are likely to reduce the frequency of use and to change their preferred drug of abuse compared to outside of prison (Plourde & Brochu 2002; Shewan et al. 1994). The most frequently used drugs in prison are cannabis, followed by stimulants, benzodiazepines and opioids (Simpler & Langhinrichsen-Rohling 2005). In- and outside of prison, heroin users take a prominent part, because daily heroin use quickly leads to dependence with unpleasant withdrawal upon discontinuation. Maintaining daily heroin use is expensive, and hence often followed by acquisitive crime. Consequently, penal reactions are almost inevitable. Most heroin addicted offenders will be incarcerated at least once during their lifetime and a considerable number of them repeatedly (Dolan et al. 2005; Milloy et al. 2008). Thus, the criminal justice facilities are likely to become a stable institution in their otherwise rather disorganized lives. Incarceration provides stability for many individuals who fail to adapt to ordinary lifestyles when outside of prison. For heroin addicts, incarceration implies a major behaviour change. They are either forced to detoxify, or they continue injecting with high risk of acquiring blood borne diseases such as HIV and high risk of overdose, because access to syringe exchange programmes is limited and heroin or other illicit opioids are not continuously available (Lines et al. 2006a). Following prison release, many heroin-involved inmates will relapse within the first few months (Kinlock et al. 2002;
Nurco et al. 1991). During this time, the risk of overdose death is particularly high (Seaman et al. 1998; Ødegård et al. 2010).

Heroin-addicted offenders often circulate between the community, with daily drug use and subsequent acquisitive crime, and incarceration with forced abstinence or limited access to drugs. Thus, heroin addiction becomes a vicious circle for inmates and treatment providers. If inmates achieve abstinence during incarceration, they often fail to maintain it after prison release; and prison health services and community treatment providers have to re-define their positions continuously in order to facilitate recovery. Outside of prison the addicted individual may be largely unavailable for treatment, whereas during incarceration help including housing may be a clearly stated claim.

The unanimous conclusion of several reviews on criminal justice based treatment is that access to specialized addiction treatment services in prisons is seriously limited and that further programme evaluations are urgently needed (Cropsey et al. 2005; Pearson & Lipton 1999; Perry et al. 2006). These reviews also find that prison-based therapeutic communities (TC) that provide continuity of care after release have shown beneficial effects. Five year follow-up data for 576 TC participants in a US study show reduced drug relapse and criminal recidivism (Prendergast et al. 2004). In Norway, the Tyrili foundation provides treatment for incarcerated drug addicts (Johansen 2005). In Oslo, Tyrili applicants spend nine months in a prison-based therapeutic community and after release they are offered to continue in a TC outside of prison.

Drug-involved inmates wanting to initiate treatment during incarceration will often have to make an extra effort; because there are fewer treatment options in prison compared to the community and because the capacity of prison-based treatment seldom meets the demand. To initiate treatment however, incarceration may offer extraordinary possibilities such as a highly structured environment and reduced availability of illicit and prescription drugs. Large scale initiatives to substantially improve treatment possibilities in criminal justice settings are currently being undertaken (Wexler & Fletcher 2007).

Opioid maintenance therapy (OMT), which has been shown to be effective in community settings, is still controversial in criminal justice settings. Although OMT is made increasingly available in European prisons (Stover et al. 2004), access is far from optimal or even lacks
completely in many parts of the world (Larney & Dolan 2009; Stallwitz & Stover 2007). Restricted access to OMT during incarceration includes highly developed countries such as the USA with a per capita prison population that is about 10-fold larger compared to Norway (UNDP 2009). However, a randomised-controlled trial suggested already in the 1960s that methadone maintenance (MMT) is effective to prevent relapse when initiated before prison release (Dole et al. 1969). Although prison-based methadone maintenance is available in a few US penal facilities (Tomasino et al. 2001), the next RCT on methadone maintenance conducted in the US criminal justice setting was reported only a few years ago (Kinlock et al. 2007). After several years of preparation, the criminal justice system in Baltimore finally approved conducting this trial (Prendergast 2009). In this RCT, heroin addicted inmates were randomly allocated to one of three groups: methadone start and counselling before release, referral to methadone treatment after release or counselling only. At one month follow up the methadone-before-release group was more likely to continue in community treatment and more likely to provide opioid negative urine tests. This study will be followed up by a larger multi-centre trial involving sites in several US American States and by another trial that evaluates the effects of buprenorphine.

A multicentre trial on sustained-release naltrexone to prevent relapse after prison release has also been suggested (O'Brien & Cornish 2006). Today, two RCTs evaluating oral naltrexone for criminal justice populations have been conducted (Cornish et al. 1997; Shearer et al. 2007). Two other non-randomised trials on oral naltrexone are reported (Brahen et al. 1984; Chan 1996). The Australian RCT by Shearer and co-workers struggled with low interest in participation and the trial was discontinued when the group randomly allocated to oral naltrexone failed to initiate treatment. The other three trials unanimously conclude on the feasibility of oral naltrexone for inmates when integrated into psychosocial support that enhances external motivation, e.g. work-release programmes and parole including follow-up by criminal justice staff. Although treatment attrition was still high in these trials, those who stayed on oral naltrexone were less likely to relapse to heroin and less likely to engage in criminal activity.

1.2. Opioid addiction

Frequent use of heroin quickly leads to addiction, which can be characterised as an ongoing compulsive and pathological use pattern that the individual maintains despite the awareness of the health damaging consequences (Hasin et al. 2006). In substance addiction or drug
dependence, the motivational system and the neurotransmitter dopamine have been found to have primary importance (Koob & Le 2008). Behaviours that increase dopamine levels such as the use of psychoactive substances will be linked to wanting and liking. The incentive sensitization theory postulates that repeated stimulation with psychoactive substances will be followed by neuroadaptation that may lead to a decrease in liking and an increase in wanting (Robinson & Berridge 2008). These motivational changes are believed to be maintained by substance induced genetic re-arrangements of neuronal functioning in the brain’s mesolimbic system (Nestler 2008). This system and the limbic forebrain (e.g. prefrontal cortex) are described as the brain reward circuit and play an important role in motivation (Wise 2002).

The brain reward circuit mediates the reinforcing effects of heroin through opioid receptors (OR) of dopaminergic neurons that are located in the nucleus accumbens (NAc) and ventral tegmental area (VTA) (Nestler 2001). In these neuroanatomical regions, heroin induces supraphysiological activation and thus constitutes a stimulus that is likely to become more salient than natural activating stimuli such as food intake, sex and child care (Volkow et al. 2004).

Immediate and long-term effects of heroin on neurons of the brain reward circuit are suggested. The immediate heroin effects consist of increased signalling of dopaminergic neurons in the VTA. This leads to increased dopamine release in the NAc and the prefrontal cortex which causes heroin-induced euphoria. The repeated exposure to heroin results in opioid receptor desensitization and down-regulation. In consequence, heroin tolerance is increased and dopamine release decreased unless larger amounts of heroin are taken. Long-term heroin exposure will eventually lead to long-term neuronal adaptation, such as altered gene transcription patterns (e.g. CREB), altered post-transcriptional mechanisms (e.g. changes in protein degradation) and changes in the synaptic structure of dopaminergic neurons in the NAc. These effects of heroin and other drugs of abuse in the brain reward circuit are suggested to form the neurobiological basis of drug addiction (Leshner 1997; Volkow & Li 2004).

The opioid withdrawal syndrome occurs after discontinuation of opioid intake. The principal symptoms are irritability, anxiety, muscular and abdominal pains, chills, sweating, sneezing, rhinorrhea and insomnia. Withdrawal is suggested to be a rebound in adrenergic hyperactivity in the locus coeruleus where heroin induces reduced signalling. The pre-synaptic alpha-2 noradrenergic agonists clonidine and lofexidine alleviate the opioid withdrawal syndrome.
(Gossop 1988; Strang et al. 1999). However, withdrawal symptoms are more reliably alleviated by repeated opioid use and thus withdrawal plays a major part in maintaining frequent heroin use and addiction (Gold 1993).

The strong reinforcing effects of heroin together with the unpleasant withdrawal syndrome support the understanding of the compulsive drug taking behaviour observed in opioid addicts. The more recent neurobiological findings have been integrated in an addiction medicine framework, in which drug addiction is regarded as a chronic relapsing disorder comparable to other chronic medical conditions such as non-insulin-dependent diabetes mellitus (NIDDM) and hypertension (O’Brien & McLellan 1996). In such chronic disorders, most medical treatment approaches will not be curative of the pathophysiology of the underlying disease. Nevertheless, medication can be an effective means to achieve important treatment goals such as symptom relief and substantial reduction of co-morbidity. The effects of medication are significantly enhanced by the individual’s motivation and ability to comply with other health promoting behaviours such as diet and training to reverse NIDDM, or reduced drug and alcohol use to significantly change an addicted lifestyle.

1.3. Opioid maintenance treatment with methadone or buprenorphine
Illicit opioids and mainly heroin remain the principal addictive drugs for which individuals seek treatment in the EU (EMCDDA 2008). The most widespread treatment approach is OMT with methadone or buprenorphine (Lobmaier et al. 2010). Methadone maintenance treatment was first described by Drs. Dole and Nyswander more than four decades ago (Dole & Nyswander 1965). This early medical approach is based on the biological principle of replacing the short acting heroin with the longer acting methadone. It also emphasizes that methadone is only the first, but maybe decisive step towards improving the social relations that had been impaired during several years of drug addiction (Dole & Nyswander 1980).

Since the late 1990s, the partial µ-OR agonist buprenorphine has become available for opioid maintenance treatment. When compared to methadone, the main advantage of buprenorphine lies in its ceiling effect which makes respiratory depression and fatal overdoses less likely. A potential drawback is a slightly lower treatment retention rate. Other important outcomes such as heroin use, non-opioid drug use and criminality have been found to be of comparable effectiveness for methadone and buprenorphine (Mattick et al. 2008).
Methadone and buprenorphine have longer half lives than heroin and reach their peak plasma concentrations later. When doses are increased slowly their sedative effect is markedly reduced and during long-term use with adequate and stable doses opioid-induced euphoria is usually lacking. With appropriate daily doses of methadone (between 60 and 120 mg) or buprenorphine (between 8 and 24 mg; or doubled doses every other day), individuals dependent on illicit heroin will rarely experience withdrawal including drug craving (WHO 2009). If heroin is used after the ingested dose, the desired euphoric effect is blocked. Therefore, during OMT the dependent individuals may be able to replace heroin seeking behaviour with other and more meaningful activities such as education or meeting friends and family. They may even be able to support themselves economically through regular work. Agonist maintenance treatment with methadone or buprenorphine facilitates behavioural changes and can help individuals to overcome their addicted lifestyles. However, both drugs are agonists at the μ-opioid receptors. Hence, they also have a rewarding effect, a black market value and if discontinued, their absence will lead to withdrawal including craving for opioids. Furthermore, the neuroadaptation caused by heroin use is unlikely to be reversed. Therefore, OMT cannot be considered curative of the physiological dependence on heroin. Notwithstanding these limitations, OMT has been shown to retain patients in treatment longer than in any other treatment modality. It is also effective in reducing heroin use, but in an extensive Cochrane meta-analysis no statistically significant advantages were found for criminal activity or mortality outcomes (Amato et al. 2005). In large longitudinal studies evaluating OMT however, significant reductions have been reported for heroin and poly-drug use, drug-related crime and mortality (Clausen et al. 2008; Gossop et al. 2003; Teesson et al. 2006).

1.4. Antagonist treatment with naltrexone
Another pharmacotherapy for opioid addiction is the use of antagonists at the opioid receptors. Naltrexone is the most prominent example and has been developed with substantial support from the US National Institute on Drug Addiction (NIDA) in the 1970s (O’Brien et al. 1975). Naltrexone binds to all three OR subtypes with the highest affinity for the μ-OR and lacks the rewarding effect of agonists (Gonzalez & Brogden 1988). Naltrexone competes with opioid agonists for receptor binding sites and due to its high affinity naltrexone effectively blocks agonist binding. It also displaces full agonists such as heroin and methadone from the receptors and may thus precipitate withdrawal. To avoid major withdrawal symptoms such as nausea, vomiting and psychosis, naltrexone treatment is either induced after accomplished
detoxification (four to seven days after last opioid intake) or during heavy sedation or general anaesthesia, which may be used to curtail withdrawal symptoms. Side effects of naltrexone treatment, such as nausea, muscle pain and headache are generally found to be transient and mild to moderate (Gonzalez & Brogden 1988). Although dysphoria during naltrexone treatment has been reported, the relationship is not well established (Miotto et al. 2002; Ritter 2002).

In literature reviews on oral naltrexone, randomised comparisons with OMT are scarce (Johansson et al. 2006; Minozzi et al. 2006). Only two trials are reported. An Iranian open-label RCT comparing 50 mg methadone and 5 mg buprenorphine daily with 50 mg oral naltrexone daily found superior treatment retention rates for methadone (Ahmadi et al. 2003). A Malaysian double-blind RCT comparing buprenorphine, oral naltrexone and placebo recently showed the superiority of buprenorphine maintenance (Schottenfeld et al. 2008). Of the 126 heroin-dependent participants, the group that was maintained on buprenorphine spent more time in treatment and relapsed later to heroin use than the groups receiving oral naltrexone treatment or placebo. For these outcomes, oral naltrexone was found to be inferior to placebo.

The main findings of about four decades of oral naltrexone research are the low patient interest in taking naltrexone and the high rates of early treatment dropout (Fram et al. 1989; Tucker et al. 2004). Pharmacologically however, naltrexone is an effective option to prevent relapse to opioid use, and may even have the potential to allow reversal of neuroadaptation. To improve patient compliance, NIDA proposed the development of sustained-release formulations already in the 1970s (Willette 1978). Investigations of early formulations showed significant adverse local tissue reactions and were discontinued (Chiang et al. 1985). Not before the late 1990s, several formulations have achieved approval for evaluation in clinical trials.

The majority of research on sustained-release naltrexone is based on cases (Brewer 2002; Hulse et al. 2003; Hulse & O’Neill 2002), small samples (Comer et al. 2002; Sullivan et al. 2006; Waal et al. 2003; Waal et al. 2006) or cohort studies without a planned-comparison group (Carreno et al. 2003; Foster et al. 2003; Gölz & Partecke 2000; Hulse et al. 2004a; Hulse et al. 2005). Although prone to bias, these results unanimously indicate that sustained-release naltrexone is beneficial for selected groups. The two Norwegian pilot studies that
investigated naltrexone implants were conducted without a control group. In the first study, implants were purchased from the US based Wedgewood Pharmacy and ten volunteers received at least one and a maximum of four implants that released naltrexone on average 30 to 80 days (Olsen et al. 2004). At ten months follow-up, six participants had not relapsed to heroin use, but two patients had experienced local site reactions and their implants were surgically removed (Waal et al. 2003). The second study investigated single (three months) and double (six months) naltrexone implants imported from GoMedical Inc., Perth, Western Australia. Eight of the 13 volunteers reported no heroin use at eleven months follow-up and only one patient developed a tissue reaction at the implant site that needed surgical revision (Waal et al. 2006).

In a Spanish sample of 156 outpatients that consisted largely of heroin smokers living with a partner and having stable work, self-reported drug use was found to be reduced during the twelve months follow-up (Carreno et al. 2003). Patients received an average number of 2.3 Wedgewood one-month implants before opting for oral naltrexone. Retention in treatment was reported to be high with 80% of patients still attending the private clinic at six months and 65% at twelve months. In a British study investigating the same implant, the results from 101 patients indicate a low opioid relapse rate of 23% at twelve weeks follow-up (Foster et al. 2003). All patients attending the private clinic started naltrexone implant treatment during rapid detoxification. After their first implant, all patients could choose to continue the treatment on implantable or oral naltrexone. As the costs of the procedure and the implants had to be paid by the patients, some were reported to choose the low-cost option oral naltrexone for economic reasons.

Similarly positive findings are reported from a German study investigating a locally produced six-weeks implant (Gölz & Partecke 2000). Following detoxification, 69 patients received one or more implants and another 39 received oral naltrexone. Naltrexone compliance in the self-selected groups was improved when the implant treatment was made available during the course of the study. Opioid relapse rates were pooled for both groups and reported to be 19% after one and 30% after three months. Twelve months after detoxification and naltrexone induction, 47% of the patients on implantable or oral naltrexone had relapsed. The follow-up period for both treated groups was on average 18 months (range 44) with shorter periods for the implant treatment that became available later on in the study. Based on months in follow-
up, the implant group spent 60% of their time opioid abstinent and the oral naltrexone group 40%.

In Australia, a cohort of about 360 patients who had undergone ultra-rapid opioid detoxification (UROD) with subsequent naltrexone implant treatment during 2001-02 was retrospectively investigated using a database record-linkage design. Four research questions were investigated and naltrexone implant treatment was generally associated with favourable outcomes: Firstly, non-fatal opioid overdoses leading to emergency department presentations were reduced six and twelve months after implant treatment compared to the six months before treatment (Hulse et al. 2005). However, an increase in non-fatal overdoses caused by sedative drugs was reported for the period after implant treatment start. They occurred mainly during the ten days following naltrexone induction and should therefore be considered UROD-related rather than caused by the naltrexone implants. Secondly, the mortality rates during the three years following naltrexone implant treatment were found to be comparable with the mortality of an MMT cohort who had started treatment during 2001-02 (Tait et al. 2008). However, as the results are not based on a prospective and controlled trial, the direct comparison between the two groups is limited and therefore the results need to be interpreted with caution. Thirdly, hospital admission rates for mental health problems were found to be reduced during the almost two years after naltrexone implant treatment in comparison to time before treatment (Ngo et al. 2007). The reduction in admission rates was not found for mood disorders. Also, the risk of mental health related hospital admissions and length of stay were unchanged when comparing before and after treatment. Fourthly, drug-related morbidity and hospital admissions following naltrexone implant treatment were compared to a cohort who had received MMT (Ngo et al. 2008a). Hospital presentations for non-fatal overdoses from opioids decreased in the naltrexone implant cohort but not in the methadone maintenance cohort. However, non-fatal overdose-related presentations from other drugs than opioids increased in both cohorts. Also, in the naltrexone implant cohort hospital presentations increased for conditions that were unrelated to overdose or to non-opioid drug use.

Despite insufficient evidence, treatment with unregistered depot and implant formulations (often in private clinic settings) is available in several countries such as Australia, China, Egypt, England, Germany, Portugal and The Netherlands. The proponents of sustained-release naltrexone strongly advocate its efficacy despite the lack of rigorously controlled clinical trials (Brewer 2008). Another important unanswered question in naltrexone research
concerns therapeutic blood levels. It is still unclear at which naltrexone level a clinically relevant amount of heroin is blocked and to what extent. Blood levels of 1 - 2 ng/ml are suggested to block the effects of 25 mg heroin (diacetylmorphine) on the basis of single case reports and human laboratory studies (Brewer 2002; Chiang et al. 1985; Comer et al. 2002; Navaratnam et al. 1994; Resnick et al. 1974).

1.5. Ethical considerations when conducting treatment research in prison
Scepticism and hesitation towards clinical research that involves drug-involved inmates may be justifiable, because coercing prisoners into clinical trials has an infamous history. In the US, opium had been prohibited through the Harrison Narcotic Act since 1914 and in the following decades many addicts were sent to prison. When in 1935 the “United States Narcotic Farm” opened its doors in Lexington, it was given a dual role as prison and as hospital (Campbell et al. 2008). The goal was to provide treatment and nothing less than complete rehabilitation of both the incarcerated and the volunteering addicts. Moreover, Lexington had a laboratory known as the Addiction Research Center, where medical and criminal justice staff pursued another ambitious goal: finding the permanent cure for addiction. The inmates were recruited to research that included seminal laboratory studies, such as the identification of opioid receptors, the first application of methadone in humans in 1948, and of buprenorphine just before the Farm and the Research Center were shut down in 1974. In the same year, NIDA had been created and the Farm’s Addiction Research Center became NIDAs intramural programme (Kosten & Gorelick 2002). NIDA supported the development of naltrexone and sustained-release formulations from the very beginning (Bradford et al. 1976). This work was a continuation of the results from the laboratories at the Narcotic Farm, where the first application of an supposed opioid antagonist (cyclazocine) in man was reported (Martin et al. 1966). In the mid 1970s, closing the Narcotic Farm had become necessary because coercive drug research with inmates was then considered unethical and thus had to be banned. However, the experience from four decades of drug research with incarcerated individuals has also helped to outline guidelines on the special ethical considerations that are granted inmates today to protect them from coercive research (OHRP 2003). These guidelines for involvement of prisoners in research recommend investigating addiction treatment in prison populations, because substance use, abuse and addiction are overrepresented there. The main features of the guidelines are that:

- First contact between inmate and researcher is established entirely voluntary, which usually implies info through prison staff (health care or correctional).
• Participation is voluntary and independent of the terms of the sentence, e.g. access to visitors, exercise and release on parole.
• All inmate information collected by researchers is handled confidentially.

Quasi-compulsory addiction treatment as alternative to a pending prison sentence is available in many European countries including Norway and in the US (Sletnes 2005; Stevens et al. 2005). All the different national approaches emphasize the individuals’ possibility to choose between punishment and treatment. In general, clinical research aims at improving health care and voluntary participation is considered crucial (Rickham 1964). Offering improved health care through clinical research in criminal justice settings may have particular implications for voluntary participation, because the gap between health care that is provided in prisons compared to the community is widely acknowledged (Taxman et al. 2007). When implemented in criminal justice settings, clinical research to improve treatment particularly aims at narrowing the health care gap between prison and the community. Some argue that this effort should be taken further: The authorities may even have an obligation to provide better health care in prisons than in the community, because they have an extraordinary responsibility for the individuals that are incarcerated, i.e. forced into a high risk situation by the authorities (Lines 2006b). However, unless research had a very strong rationale or sufficient evidence for making health care provided in criminal justice settings more available or better than in the community, it would hardly meet support in the public opinion as it would be perceived as coercive.
2. Aims of this thesis

Treatment with naltrexone implants has become available for use in research during the last decade. Previously, heroin involved offenders have been found to benefit from oral naltrexone treatment upon community re-entry. The effects of naltrexone implant treatment for opioid dependence have not been investigated in a prison population.

The aims of this thesis are:

a) To present a systematic review of the literature on sustained-release naltrexone and to assess its effectiveness for heroin dependence.

b) To evaluate the feasibility and effectiveness of naltrexone implant treatment in a randomised comparison with methadone treatment among heroin addicted inmates after prison release.

c) To assess opioid use during naltrexone implant treatment and to evaluate the opioid effects experienced.

Both published (see appendix) and unpublished data are reported in the thesis.
3. Methods and findings

3.1. Literature review (Paper I)

Aims
A systematic review of the literature was conducted to evaluate the effectiveness and safety of the available sustained-release naltrexone formulations.

Methods
Two search strategies were developed: The first search identified reports to assess effectiveness of sustained-release naltrexone for opioid dependence and was restricted to randomised-controlled trials. The second search identified any report of the use of sustained-release naltrexone in humans to assess safety. All retrieved references eligible for inclusion were independently assessed by two authors regarding relevance and potential risk of bias. For RCTs, the methodological quality was assessed according to predefined measures in accordance with Cochrane standards. Outcome measures were predefined and data were extracted independently by two authors. Any disagreement was resolved by consensus, if necessary by discussion with a third author.

Statistical analyses
Meta-analyses were performed when appropriate for all predefined outcomes using review management software (RevMan 4.2.) available online. Relative risks (RR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes. Statistical heterogeneity between studies was assessed with Chi squared tests which indicate a confidence interval and a p-value to measure the probability of heterogeneity. Low p-values indicate significant heterogeneity and thus a variation in effect estimates that should be considered beyond chance. Further, RevMan calculates I-squared statistics indicating grades of heterogeneity ranging from zero (none) to one (a lot).

Results
Seventy four primary reports were obtained in full text and assessed for eligibility. To assess safety, 17 reports were included in the review. Only 1 of 17 reports was included to assess the effectiveness of sustained-release naltrexone for opioid dependence.
**Effectiveness**

In the one report by Comer and colleagues, 60 heroin addicted outpatients were randomly allocated to one of three treatment arms in a double-blinded fashion (Comer et al. 2006). The double depot naltrexone injection (384 mg) was found to be more effective than the single depot (192 mg) or the placebo injection. The group receiving the double naltrexone dose showed a trend towards better treatment retention and dropped out significantly later than the groups receiving the single dose or placebo. Further, the double dose group scored “needing heroin” on a visual analogue scale significantly lower compared to placebo. On average, plasma levels in the double dose group were maintained above 1 ng/ml throughout the eight weeks study period.

**Safety**

Seventeen reports were included and among them were six RCTs; only one of six investigated an opioid dependent population. Opioid dependent samples were investigated in nine of eleven non-randomised trials; implants were used in the majority of the trials and most lacked a control group or did not systematically report safety outcomes. This substantially limited the safety assessment of the implants.

However, when considering the safety outcomes reported from naltrexone depot treatment for alcoholism, we found frequent, but mild to moderate and transient side effects such as nausea and headache. Safety outcomes related to injection site reactions of the depot compared to placebo injections were largely similar and gave little reason for concern, but we found a statistically significant disadvantage of the naltrexone depot compared to placebo for two of eight adverse event (AE) outcomes (see Figure 1).
Figure 1: Comparison of lower dose naltrexone depot and placebo injection in the treatment of alcoholism: Selected safety outcomes

<table>
<thead>
<tr>
<th>Study or outcome</th>
<th>Naltrexone: events/N</th>
<th>Placebo: events/N</th>
<th>RR (fixed)</th>
<th>Weight %</th>
<th>RR (fixed) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome 1: one or more injection site reaction</strong></td>
<td>123/167</td>
<td>103/166</td>
<td>100.00</td>
<td>1.19 [1.02, 1.38]</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.25 (p = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome 2: injection site related AEs, pooled</strong></td>
<td>247/668</td>
<td>205/664</td>
<td>89.14</td>
<td>2.60 [1.33, 3.06]</td>
<td></td>
</tr>
<tr>
<td>Kranzler 1998</td>
<td>16/30</td>
<td>4/10</td>
<td>8.26</td>
<td>1.20 [1.03, 1.39]</td>
<td></td>
</tr>
<tr>
<td>Kranzler 2004</td>
<td>247/668</td>
<td>205/664</td>
<td>100.00</td>
<td>1.18 [1.02, 1.36]</td>
<td></td>
</tr>
<tr>
<td>Garbutt 2005</td>
<td>18/210</td>
<td>19/209</td>
<td>0.94 [0.51, 1.74]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>281/908</td>
<td>228/883</td>
<td>89.14</td>
<td>1.20 [1.03, 1.39]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi² = 0.63, df = 2 (p = 0.73), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.24 (p = 0.02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.01 0.1 1 10 100

Favours naltrexone depot  Favours placebo injection
3.2. Challenges in clinical research involving problematic drug users in criminal justice settings (Paper II)

Aims
The various challenges in the study were analysed and solutions to the problems suggested.

Methods
In the open-label trial inmates were randomly allocated to naltrexone implants or methadone treatment. Candidates for the trial were suggested by prison staff or health services and then offered an info visit. Trial information that included the research staff’s contact details was made available in written form in brochures and posters. Participation was requested voluntarily and all candidates, relevant treatment providers and prison staff were informed orally and through written informed consent that participation was entirely independent of terms of the sentence, i.e. access to media, visitors, training or exercise, transfer to other sections or prisons and parole conditions. Further, study participants were systematically informed that the Norwegian methadone programme regulations apply; i.e. methadone initiation is scheduled through home community social services and approved by central OMT authorities. Research staff could not guarantee treatment approval, however the importance of methadone initiation before prison release for the success of the trial was emphasized. During the screening process, the candidates’ statements on heroin use before imprisonment were logged in order to distinguish between non-eligible and non-interested inmates. Whenever possible, the inmates’ plans to cope with heroin abstinence at community re-entry were noted. The reasons for dropout from the methadone and naltrexone implant group were compared and possible differences in sample characteristics were analysed.

Statistical analyses
Continuous outcomes were compared using t-tests or rank methods if the assumption of normal distribution was violated. Binomial outcomes were compared using Chi squared statistics with Fisher’s Exact Test for small groups. Statistical significance was tested two-tailed at the conventional level of \( p=0.05 \).

Results
During one and a half years of recruitment, only 46 of 111 eligible inmates signed informed consent. Two of the 46 withdrew consent after random treatment assignment and did not provide complete baseline data. The 65 eligible inmates who refused participation had usually
undergone forced detoxification upon imprisonment. Challenges were the low interest, the randomised study design and aftercare. These were related to criminal justice settings in general and more specifically to clinical addiction research which extends beyond prison release.

**Low interest and ambivalence**

In contrast to heroin addicts in the community, treatment motivation of heroin-involved inmates is influenced by prison setting specific factors such as forced detoxification and a changing juridical status. Usually upon incarceration, inmates on remand await their charges before they are court sentenced to a certain number of weeks, months or years in prison. The date of regular prison release is not set until the charges have been accepted; and only then the time to a possible parole application becomes predictable. These changes in juridical status during several months of incarceration are likely to affect the inmates’ motivation to engage in any treatment that stretches beyond release and includes aftercare, as offered in our study.

After spending weeks or months of their sentence, the inmates reported satisfaction with their drug free state and were eager to maintain it after prison release, most frequently by relying on their own resources. Some intended to apply for residential treatment or OMT, however hardly any stated more than vague plans for community re-entry.

Prison staff was supportive of the trial and granted prison access at any time. Information was also spread through word of mouth by prison social workers, health services and core prisoners. Nonetheless, prison walls constitute a significant barrier that does not facilitate contact between researchers from the outside and the inmates. More continuous contact appears crucial to properly inform the inmates, to best understand their own expectations and to appropriately meet their fluctuating motivation and ambivalence. However, regular meetings with eligible inmates could not be achieved for several reasons: Inmates could be moved to other sections in the same prison or even to other prisons without further notice. Thus, they became subject to different routines, i.e. the scheduled time to spend on exercise, in the court yard and for other activities. Further, arranging info meetings with groups of inmates from several different prison sections depends on significant support from criminal justice staff: security must be evaluated continuously, inmates must be accompanied by staff and the meetings should be scheduled without affecting other activities.
Treatment preferences and random allocation to treatment

When introducing the trial to eligible inmates, random allocation to the two fixed interventions was extensively discussed. Frequently asked questions were “Why random allocation?”, “Why is buprenorphine no option?”, “When do I get the first methadone dose?” and “What happens if I am in an emergency situation and need pain relief or anaesthesia while I am on the naltrexone implant?”

All 46 consenting inmates were asked which of the two fixed interventions they hoped for before random allocation. As expected the largest proportion (43%) stated methadone maintenance, while 35% hoped for the naltrexone implant and 22% stated no preferred intervention. Participants were likely to refuse treatment initiation if the random allocation failed to meet their expectations. Two inmates even withdrew consent. Among the 44 inmates with complete baseline data, there was no statistically significant difference between the 17 dropouts and the 27 treatment starters on core characteristics such as age, total time spent in prison and heroin use before current incarceration. Interestingly, reasons for dropout in the two groups differed. In the naltrexone arm, all eight who did not start treatment were dissatisfied and refused the randomly allocated treatment. However, dissatisfaction with randomly allocated treatment was also reported in the methadone arm and five of eleven participants refused to start methadone treatment. The remaining six non-starters could not be granted the support needed for MMT by the social services in their home community (see Figure 2).

Beyond the prison walls: preparing release and scheduling aftercare

To prepare inmates for release with study treatment initiated and aftercare scheduled proved difficult and required substantial effort. Release dates were uncertain for virtually all participants, either due to new verdicts pending or in anticipation of parole approvals. Also, during the study recruitment period, the urgent need of prison capacity in Norway had resulted in shortening sentences during incarceration in order to meet the increased demand. Inmates, who had originally been sentenced to six months or more in prison, could get their sentence reduced by ten days; if originally sentenced to twelve or more months the reduction could be by 20 days. These post court-room reductions could result in earlier than expected release dates, and since they were not granted to all inmates, they also contributed to the uncertainty of the release dates in our study.
Dropout from methadone occurred quickly and frequently: two of eleven methadone starters experienced side-effects and discontinued before prison release; another four were no longer receiving methadone on average 41.5 days (sd 55.7, range 113) post release. Dropout occurred mostly due to difficulties in daily meeting for dose pick up. Daily meeting was not required in the naltrexone implant group. Re-incarcerations occurred similarly often in both treatment groups, and was not more frequent than among those who had never initiated the per-protocol treatment.

3.3. Naltrexone implant treatment compared to methadone in pre-release inmates: findings from the prison study at six months follow-up (Paper III)

Aims

To investigate the feasibility and treatment effects of naltrexone implants and methadone on the use of heroin and other illicit drugs, and criminality after prison release. The hypotheses were that naltrexone implant treatment would reduce heroin use significantly more than methadone, and further that both groups would improve while in treatment in terms of reduced criminal activity and reduced non-opioid drug use compared to baseline. Finally, we hypothesized that symptoms of depression and anxiety would not increase in participants receiving naltrexone implant treatment compared to methadone and to baseline.

Methods

Design and sample

The study used a randomised-controlled, open-label design. The target population comprised opioid dependent inmates awaiting prison release. Exclusion criteria were clinically significant liver impairment, currently untreated major depression or psychosis, and pregnancy. Inmates who volunteered and signed informed consent were randomly allocated to naltrexone implant treatment or methadone maintenance.

Interventions

Methadone treatment was provided according to standard Norwegian programme regulations: Community social services had to support and file the participants’ application, which then had to be approved by the regional OMT authorities before the first methadone dose could be received in prison. Based on the experience from two previous pilot studies, participants received implants containing approximately 2.2 g of naltrexone, which is released at therapeutic levels for five to six months (Waal et al. 2003; Waal et al. 2006). The site in the
subcutaneous tissue of the lower, lateral abdominal wall where the implants were surgically inserted was inspected upon stitch removal, usually one to two weeks after surgery.

Assessments
The main outcome measures were heroin and non-opioid drug use and criminal activity, which were assessed with the European version of the Addiction Severity Index (ASI) for the time preceding the current incarceration (Kokkevi & Hartgers 1995). The ASI assesses seven domains of interest, among others education and employment situation, substance use history and criminal activity. The interview is designed for research and clinical use and requires three days training. Levels of reliability and validity have been found to be satisfactory (McLellan et al. 1992; McLellan et al. 1985).

Depression and anxiety during incarceration were self-reported on Beck’s Depression Inventory (BDI) and the Hopkins Symptom Check List (SCL-25). The BDI consists of 21 items that are scored from zero to three resulting in a max score of 63 points. A cut off value of 21 points has been suggested to distinguish cases of severe depression from non-cases in the original publication (BECK et al. 1961). The BDI has been reported to have good psychometric properties in drug dependent patients (Schaefer et al. 1985). The SCL-25 consists of ten items measuring anxiety and 15 items on depressive symptoms (Derogatis et al. 1974). All items are scored from one to four, summed up and then divided by 25. Cut off values that indicate clinical significant depressive symptoms are suggested to lie between 1.5 and 1.8 (Nettelbladt et al. 1993; Sandanger et al. 1998; Winokur et al. 1984). The final score can be used for screening and indicates general psychiatric distress. Side effects possibly related to naltrexone, such as headache, nausea, vomiting, anxiety / restlessness and muscle pain, were rated on a questionnaire from zero (not at all) to three (a lot) for the preceding week.

All assessments were repeated six months after prison release. Heroin use was then additionally assessed by timeline follow-back, TLFB (Sobell L.C. & Sobell M.B. 1992). This interviewing technique uses a calendar method to assess the number of days with drug use during a given period, e.g. six months. In illicit drug users, TLFB has been found to have good reliability and high concordance with objective measures of drug use (Fals-Stewart et al. 2000). In case of re-incarceration during the follow-up period, drug use was assessed for the
time preceding the new prison sentence, whereas for criminal activity the baseline values were imputed.

Hair samples were analysed with liquid chromatography tandem mass spectrometry at the Division of Forensic Toxicology and Drug Abuse at the Norwegian Institute of Public Health (Hegstad et al. 2008).

Statistical analyses
For the intention-to-treat (ITT) analyses missing data were replaced with baseline observations, regardless of whether treatment was initiated or not. Mixed within-between subjects analyses of variance (ANOVA) were performed on heroin and illicit non-opioid drug use and criminal activity. Kaplan-Meier survival analyses were performed on days to heroin relapse (Kaplan & Meier P. 1958); missing data was replaced on the assumption of heroin relapse on day one following prison release. Differences between the groups were assessed with the log-rank test. For the completer groups, outcomes were analysed with t-tests for normally distributed data. If the assumption of normality was violated rank methods were used, i.e. the Mann-Whitney U test for between groups comparisons and the Wilcoxon signed-rank test for pre-post, within group comparisons. For pre-post comparison of dichotomous outcomes in two groups the McNemar test was used. All statistical significance was tested two-tailed at the conventional level of p=0.05.

Results
Of the 46 individuals who volunteered for the trial, 27 initiated the randomly allocated treatment: 16 of 24 in the naltrexone group and 11 of 22 in the methadone group. Figure 2 gives an overview on study enrolment, drop-out, treatment initiation and follow-up. Two of the 19 individuals who did not initiate study treatment withdrew consent. They were excluded from the analyses and not contacted for follow-up. An overview on characteristics of the final sample is given in Table 1. On these characteristics, there were no statistically significant differences between the groups.
Table 1: Baseline characteristics of study participants by randomly allocated group

<table>
<thead>
<tr>
<th></th>
<th>Methadone, n=21</th>
<th>Naltrexone implant, n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (sd)</td>
<td>35.4 (6.6)</td>
<td>34.9 (7.4)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1 (4.8)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Heroin debut age, mean years (sd)</td>
<td>23.3 (6.2)</td>
<td>23.4 (7.1)</td>
</tr>
<tr>
<td>Regular poly drug users, n (%)</td>
<td>18 (85.7)</td>
<td>20 (87)</td>
</tr>
<tr>
<td>Current sentence length, mean months (sd)</td>
<td>8.5 (5.7)</td>
<td>10.3 (5.0)</td>
</tr>
<tr>
<td>Years in prison during lifetime, mean (sd)</td>
<td>5.0 (4.6)</td>
<td>4.7 (4.0)</td>
</tr>
<tr>
<td>Homeless before sentence, n (%)</td>
<td>10 (47.6)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Heroin use† (sd)</td>
<td>25.0 (9.2)</td>
<td>27.8 (5.0)</td>
</tr>
<tr>
<td>Amphetamine use† (sd)</td>
<td>9.5 (11.9)</td>
<td>11.0 (12.9)</td>
</tr>
<tr>
<td>Benzodiazepine use† (sd)</td>
<td>15.9 (12.5)</td>
<td>14.5 (11.7)</td>
</tr>
<tr>
<td>Criminal activity† (sd)</td>
<td>20.3 (12.1)</td>
<td>18.5 (12.1)</td>
</tr>
</tbody>
</table>

Note: † indicates mean number of days during last month before imprisonment.
Figure 2: Number of inmates screened, enrolled, dropped out, treated and followed up

172 inmates screened → 61 non-opioid users

111 eligible → 65 not interested

46 consented and randomly allocated

22 allocated to methadone maintenance

1 dissatisfied & withdrew consent

21 in ITT analyses

11 received first dose

4 dissatisfied with allocation

1 dissatisfied & withdrew consent

24 allocated to naltrexone implants

23 in ITT analyses

6 involuntary dropouts

7 dissatisfied with allocation

16 received implant

8 followed up, 3 dropouts

5 followed up, 5 dropouts

Per-protocol:
5 completers
10 not initiated
6 discontinued

7 dropouts

13 followed up, 3 dropouts

Per-protocol:
13 completers
7 not initiated
3 discontinued
The intention-to-treat sample

The ITT analyses were performed on the 44 participants who were randomly allocated. For 18 of 44 participants, missing data at six months follow-up were replaced by baseline values assuming an unchanged situation, i.e. relapse to frequent drug use and criminal activity following prison release. Of these 18 participants, ten had been allocated to the naltrexone implant group and eight to the methadone group. Nine of the 44 participants had been re-incarcerated during follow-up and were interviewed in prison. The analyses showed a statistically significant reduction in heroin and benzodiazepine use, and criminal activity at six months follow-up for both groups (Figure 3). Naltrexone implant treatment and MMT were found to be comparably effective on these drug use outcomes and criminal activity. No advantage of one treatment over the other was detected.

Figure 3: Drug use and crime in the ITT sample at baseline (before imprisonment) and six months follow-up by group

![Graph](image)

Note: Bars indicate mean days per month, whiskers are standard deviations.
The * indicates a statistically significant reduction (i.e. effect of time) in the analyses of variance. There were no statistically significant differences between the two groups.

The survival analysis performed on days to heroin relapse showed no difference between the treatment groups (see Figure 4). Relapse to frequent heroin use during the six months following release was evident in 13 of 21 participants in the methadone group and in 7 of 23 in the naltrexone group.
Note: Missing data for four participants in each group were imputed on the assumption of relapse on the first day after prison release. There was no statistically significant difference between the two groups (Chi squared 3.56; p=0.059). The mean time to relapse in both groups was 95.0 days (95% CI 68.0, 122.0).

The survival analysis was modified and then repeated twice: Firstly, when data was imputed assuming relapse on the second day after release, this less conservative approach showed a statistically significant risk reduction for heroin relapse in the naltrexone group compared to methadone (Chi squared 4.04; p=0.044). The naltrexone group relapsed on day 112.8 (mean; 95% CI 80.8, 144.8) whereas the methadone group relapsed on day 68.5 (mean; 95% CI 32.9, 104.2). Secondly, when analysing the convenience sample (i.e. omitting the eight individuals who had missing data on heroin relapse) a statistically significant advantage of naltrexone on heroin relapse rates (Chi squared 4.33; p=0.038) was found. In this scenario, the naltrexone group relapsed on day 136.1 (mean; 95% CI 106.7, 165.5) whereas the methadone group relapsed on day 84.2 (mean; 95% CI 43.6, 124.8).

The completer sample
The treatment per-protocol sample comprised 13 participants in the naltrexone and five in the methadone group (see Figure 2). All 18 individuals still received the study medications when meeting for follow-up. A statistically significant reduction in use of heroin and non-prescribed
benzodiazepines was found in both groups compared to baseline (Table 2 and Figure 5). The reduction in criminal activity was borderline significant. The methadone group reported greater reductions in amphetamine use than the naltrexone implant group. Seven completers were re-incarcerated on average 94 days (sd 71.3) into the follow-up period, 5 of 13 in the naltrexone and 2 of 5 in the methadone group. The re-incarceration rates between the completer groups did not differ.

Table 2: Drug use and crime in the completer sample at baseline (before imprisonment) and 6 months follow-up

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone group, n=13</th>
<th>Methadone group, n=5</th>
<th>Within groups, p-values</th>
<th>Between groups, p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>at follow-up</td>
<td>baseline</td>
<td>at follow-up</td>
</tr>
<tr>
<td>Heroin</td>
<td>26.5 (6.3) 4.9 (11.2)</td>
<td>26.0 (6.5) 4.8 (8.6)</td>
<td>&lt;0.001</td>
<td>0.474</td>
</tr>
<tr>
<td>Illicit Benzo</td>
<td>14.0 (14.3) 9.4 (12.6)</td>
<td>18.8 (12.5) 4.0 (5.5)</td>
<td>0.031</td>
<td>0.526</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>12.1 (14.1) 11.2 (11.0)</td>
<td>6.0 (13.4) 1.0 (2.2)</td>
<td>0.659</td>
<td>0.021</td>
</tr>
<tr>
<td>Criminality</td>
<td>18.9 (13.7) 12.5 (13.5)</td>
<td>24.0 (8.2) 11.4 (12.4)</td>
<td>0.055</td>
<td>0.934</td>
</tr>
</tbody>
</table>

Note: Values indicate mean days per month with standard deviation in brackets. Rank-method statistics were used, i.e. the Mann-Whitney U test for comparisons between the two groups and the Wilcoxon signed-rank test for comparisons within both groups. Criminality data was imputed for re-incarcerated individuals.
Figure 5: Drug use and crime in the completer sample at baseline and follow-up by group.

Note: Bars indicate mean days per month, whiskers are standard deviations. The * indicates a statistically significant reduction in both groups. Reduction in amphetamine use was greater in the methadone than in the naltrexone group. No between groups differences on the other outcomes were found.

Depression and anxiety were self-reported on the BDI and Hopkins SCL-25 during incarceration and again six months after release. Only data from completers were analysed and no differences were found. The naltrexone group scored on average 11.9 on the BDI before treatment start and 12.3 after six months. The methadone group scored on average 16.2 before treatment start and 12.8 after six months. With the BDI cut-off value of 21 or more points indicating depression, 2 of 13 participants in the naltrexone group were defined as cases at follow-up compared to 1 of 5 MMT participants. There was no change from baseline. On the Hopkins SCL-25, the naltrexone group scored on average 1.45 at baseline and 1.86 at follow-up. The MMT group scored on average 1.84 at baseline and 1.75 at follow-up. With the cut-off score of 1.75 or more indicating clinical significant depression / anxiety, 6 of 13 participants were defined as cases in the naltrexone group at follow-up, compared to 1 of 4 in
the MMT group. In the naltrexone group at follow-up, the number of cases had not increased significantly compared to the 3 of 12 cases found at baseline (McNemar test $p=0.375$).

Hair analyses were available for 18 of the 44 participants. When compared to the results from self-reported heroin use, 13 of the 18 pairs (72%) were concordant. Of the five pairs that were not concordant, one participant in the MMT group reported relapse, but the heroin metabolite 6-MAM was not detected in hair. The remaining four participants did not report relapse, but 6-MAM was detected in their hair samples. Three were receiving naltrexone treatment and one MMT.

*Adverse events and side effects in the naltrexone implant group*

During the six months follow-up period, none of the 16 naltrexone implants was surgically removed due to site reactions. One participant requested the removal due to nausea approximately five months into follow-up. He had then relapsed to infrequently injecting heroin and had repeatedly failed to meet for appointments, making implant removal not feasible. Another two participants reported itching and skin rash at the implantation site, which resolved with oral antihistamines on the one and oral antibiotics on the other occasion. At 9 and respectively 14 months after treatment start, two participants had implant remains removed on their own request, citing cosmetic reasons. Infrequently reported symptoms such as headache and nausea were considered side effects that were possibly related to naltrexone, but not to the implant-site or surgical procedure.

On average 12 days (sd 6.1) after treatment start, only 8 of 16 participants had completed the self-report side effects questionnaire. The highest average score on the 0 to 3 scale was rated for headache (0.88) followed by trouble sleeping (0.75), reduced appetite (0.75), irritability (0.57) and nausea (0.50). During the first month in treatment, none of the participants rated the symptoms as 3, worrying them “a lot”. Missing data on side effects limits the analyses of the development over time. However, the narratives of the majority of participants who met for follow-up supported the questionnaire data. Participants did usually not relate the reported symptoms specifically to the naltrexone implant and experienced those side effects reported as little troublesome.
3.4. Opioid use despite naltrexone blockade: Effective overriding? [Paper IV]

**Aims**
To investigate the possible overriding of the blockade provided by naltrexone implants with opioids. It was expected that participants would test the blockade only a limited number of times and that hardly any participant would use opioids frequently.

**Methods**
Any opioid use by participants receiving naltrexone implant treatment was assessed, and whether or not they reported experiencing a euphoric effect (i.e. got high). Data from the prison study were pooled with data from two outpatient studies. A total of 60 participants who had received a naltrexone implant for the first time were included in the analyses. Fourteen of the 60 were women, 42 were discharged from inpatient treatment settings and 18 came from the prison study.

*The outpatient studies*

The aim of these two studies was to evaluate the effects of naltrexone implant treatment in outpatients recently discharged from long term residential treatment or short term hospital-based detoxification. Participants were recruited from inpatient units in south-eastern Norway. In both the pilot and the randomised-controlled outpatient study, the control condition consisted of regular aftercare following discharge such as counselling, medication with oral naltrexone, OMT, or other treatment modalities. Participants in both groups were free to choose their treatment from the existing alternatives in their home community and in cooperation with local social services. Naltrexone implants were given as a supplement to usual aftercare. Naltrexone implant treatment was initiated before discharge. In both studies, the structured interview Addiction Severity Index was the principal tool to assess drug use. Hair samples were taken in the RCT only. Both studies were approved by the South Norwegian Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. The studies were funded by the Southern Norway Regional Health Authority and registered publicly at http://clinicaltrials.gov, identifier NCT00269607 (pilot) and identifier NCT00521157 (RCT).

The first, unpublished study was a non-randomised pilot using a matched-controlled design with patients volunteering for implant treatment and a comparison group, who was matched on key variables such as age, gender and onset of opioid dependence. As enrolment was going
slow, the study was discontinued when twelve participants were included. Six had initiated naltrexone implant treatment and all six are included in this data analyses. In the second study, 56 patients were enrolled and randomly allocated to one of two groups. The outcomes for the naltrexone implant group were advantageous at six months follow-up (Kunoe et al. 2009). Group crossover was optional at six months follow-up, resulting in 36 participants eligible for the current analyses. All of them had started naltrexone implant treatment for the first time during the total of twelve months follow-up.

Measurements and definitions of opioid use and effect
In all three studies included in the current analyses, self-reported use of heroin, buprenorphine, methadone and prescription opioids was analysed separately and then combined in an ‘all opioids’ category. Opioid use was categorised as ‘high frequency’ in case of five or more days of use during follow-up and as ‘low frequency’ in case of four or less days of use, allowing comparisons of two groups of users. Special attention was given to buprenorphine during data collection and analyses as buprenorphine has relatively high µ-OR affinity and was therefore regarded as the opioid with the greatest potential to override the naltrexone blockade. In accordance with this assumption, buprenorphine was pointed out as a possible pain reliever in case of a medical emergency on an implant carrier’s card, which was provided for all participants. Outcome variables such as use of non-opioid drugs, health status, social functioning, and crime were also assessed.

During the follow-up interview, the participants were asked to describe their experienced opioid-related euphoria or ‘high’. Patients were also asked about opioid tolerance and withdrawal symptoms according to DSM-IV diagnostic criteria. Reported statements were then rated independently by two researchers on a scale from zero ‘no high’ to three ‘full high’, with one indicating ‘uncertain high’ and two ‘some high’. In case of disagreement, the higher rating was chosen. For every participant who reported opioid-related euphoria, information on opioid type and dosage, and extra hair- and blood samples were requested. Naltrexone blood levels were plotted against the implant’s release profile described earlier (Hulse et al. 2004b; Ngo et al. 2008b). For ethical reasons, an agonist challenge paradigm to directly assess the extent of blockade override was not conducted.
Statistical analyses
Analyses of variance (ANOVA) controlling for gender and age were performed post-hoc for within group (i.e. opioid use over time) and between groups comparisons (i.e. high vs. low frequency use). If the assumption of normal distribution was violated rank methods (e.g. Spearman’s rho) were used instead. Chi squared statistics were used for binomial outcomes, with Fisher’s Exact Test for small groups. All statistical significance was tested two-tailed at the conventional level of p=0.05.

Results
The full sample of 60 participants had a mean age of 33.7 (sd 8) years. Mean duration of heroin use was 6.7 (sd 4.5) years, poly-drug use was 10.4 (sd 7.4) years and injecting drug use was 9 (sd 8) years. Mean time spent in prison was reported to be 3.8 (sd 6.3) years and years of completed education were 11 (sd 2). Five participants did not attend follow-up and their data were collected by telephone interview with them or with significant others. No fatal drug overdoses were reported in the cohort and no individual had opioid withdrawal or increased tolerance that would indicate current dependence. Sixty blood samples were taken throughout the 180 days follow-up period and in 95% of samples the naltrexone and 6-beta naltrexol levels were found to be above 1 ng/ml.

Opioid use pattern, effect and factors associated with override
Testing the naltrexone blockade with opioids was reported by 34 (57%) individuals: 19 had mostly used heroin, nine buprenorphine, five morphine tablets and one methadone. The individuals who had used mostly buprenorphine to test the blockade reported more pre-naltrexone experience with illicit buprenorphine and with OMT than the non-using individuals. The opioid users were more likely than the non-users to also use cannabis, amphetamines and illicit benzodiazepines during the study period. They also injected drugs more often and committed more acquisitive crime than the non-users.

Sixteen reported high frequency use and at follow-up this group had returned to levels of use comparable to those reported before treatment start. Five injected mainly buprenorphine. The 18 participants who reported low frequency opioid use typically tested the naltrexone blockade at the beginning and again at the end of the implant period. At follow-up they reported an opioid use reduction.
Of all 34 participants who had used opioids, nine reported feeling ‘some’ or ‘full high’. One non-fatal overdose was reported. Nineteen users did not feel any effect while three were uncertain about the effect. The remaining three users did not make a statement. The nine users who reported override of the naltrexone blockade differed from the 22 users who did not achieve an opioid effect. During the study period, the override group had used more illicit benzodiazepines and more opioids, particularly buprenorphine.

4. Discussion
4.1. Findings and limitations
4.1.1. Literature review [paper I]
The one study on depot naltrexone showed a dose dependent benefit in terms of reduced heroin use and increased treatment retention. The methodological quality was considered good with low risk of methodological bias. The primary outcome measures that allowed calculation of effect estimates were treatment retention (number of participants) and time to drop out (days in treatment). Opioid positive urine samples were reported on a group level in the original article, but the number of samples per participant was not available. Group based urine samples are likely to be biased towards individuals that were compliant with urinalyses. This issue was addressed in the original article by imputing missing data on the assumption of positive urine samples. However, this procedure may overestimate heroin use. For the Cochrane review, calculation of an effect measure from urinalysis was not recommended by the CDAG and thus not performed. According to Cochrane standards, a single RCT is considered insufficient evidence to conclude on treatment effectiveness.

For naltrexone implants, two randomised-controlled trials on the Australian naltrexone implant have recently been reported (Hulse 2009; Kunoe et al. 2009). Both trials support the effectiveness of this implant to reduce heroin use, compared to treatment as usual in the Norwegian setting and compared to oral naltrexone or placebo in the Australian setting. These studies will be included in an update of the systematic literature review.

The strength and also the major limitation of systematic Cochrane reviews lie in the exclusion of non-randomised studies (Cochrane Handbook 2008). For example, in systematic reviews of pharmacotherapies that are frequently investigated in RCTs such as antipsychotics, this restriction may be highly relevant in order to assess the specific effect of the medication in a direct comparison with strong internal validity and a very low risk of bias. A meta-analysis of
150 double-blind RCTs with more than 21000 patients investigated the claimed advantage of newer antipsychotic drugs compared to older drugs such as haloperidol (Leucht et al. 2009). In this systematic review, the newer antipsychotics were not found to be better than the first-generation drugs, although open-label studies have systematically reported their advantages. Such studies were, however, excluded from the meta-analyses according to the standards of the Cochrane collaboration. When these strict methodological standards are applied to review an unconventional treatment, the evidence from RCTs is likely to be scarce; in the case of sustained-release naltrexone, only one RCT could be included to assess effectiveness. Furthermore, in the experimental design of randomised trials, strict patient inclusion and exclusion criteria are usually applied. This procedure in itself will introduce bias, because it is likely to attract a study population that differs from the average patients attending drug treatment services. An example from alcoholism research is reported, in which a single exclusion criterion (from a list with common criteria) was sufficient to exclude half of the 1484 alcohol dependent patients that had been identified in a representative US population sample (Blanco et al. 2008). Studies with high internal validity such as RCTs may have a low risk of bias, but they are also likely to have rather poor external validity which limits the generalizability of the findings to average community populations.

When systematically reviewing sustained-release naltrexone treatment, our suggestion to open study inclusion criteria for non-RCTs in the assessment of effectiveness was rejected by the Cochrane Drugs and Alcohol group. Hence, we were not allowed to consider all the available evidence in our review. On the other hand, the non-randomised trials on sustained-release naltrexone for opioid dependence that we excluded were usually prone to bias. Reports from small samples in single-group pilot studies do not allow direct comparisons (Hulse & Tait 2003; Waal et al. 2003; Waal et al. 2006). Even larger studies with groups of 50 or more patients lacked properly controlled conditions and thus effectiveness assessment could not be performed (Gölz & Partecke 2000). In two trials with comparison groups, the enrolment procedure was prone to selection bias, because patients were recruited from private clinics, where they chose and paid for the experimental treatment: rapid detoxification with subsequent naltrexone implant treatment (Colquhoun et al. 2005; Foster et al. 2003). In another trial, patient follow-up was conducted by telephone interview only and dropout was not accounted for in the analyses resulting in a high risk of attrition bias (Carreno et al. 2003). Importantly, the drawbacks of the above described non-randomised trials would not be resolved by a random allocation procedure alone. Both attrition and detection bias can be
accounted for in well-conducted longitudinal studies by complete reporting of drop outs, performing intention-to-treat analyses and if possible, blinding the outcome assessors for the treatment modality.

As sustained-release formulations require a minimally invasive procedure, we intended to specifically assess the safety of such naltrexone formulations in the systematic literature review. For the safety assessment non-randomised studies were accepted by the Cochrane Drugs and Alcohol group. The main results indicated transient, mild to moderate side effects related to the drug naltrexone. Depot formulations appeared to cause more injection site related side effects than the placebo injections. In line with these findings, the FDA issued a warning in December 2008 for the naltrexone depot Vivitrol® after several reports of injection site reactions.

4.1.2. The prison study

*Challenges during trial implementation* [Paper II]

Interest in participation among eligible inmates was low, despite ample information and a low threshold for face-to-face information meetings. Offering regular group meetings during incarceration could have improved interest. However, frequent meetings will rely on research staff who spends substantially more time in the prison and who is integrated to a large extent in the prisons’ daily routines. On the other hand, such engagement from research staff may threaten their independent role.

Random allocation to methadone and naltrexone is a challenging task due to their distinct pharmacology. A direct comparison had hardly been attempted with one example reported from an Iranian outpatient setting (Ahmadi et al. 2003). Randomly allocating prison inmates was earlier found to be particularly challenging, because the play of chance that randomisation implies had been perceived as extremely unfair and was therefore rejected (Erez 1985). Methadone maintenance treatment is still controversial and not optimally implemented in criminal justice settings. Inmates in the experimental group received naltrexone implants which unlike methadone lack a rewarding effect. Thus naltrexone is likely to be considered the most favourable pharmacotherapy by criminal justice staff, in contrast to the inmates receiving treatment. In line with findings for heroin addicts in the community, we expected the inmates to prefer methadone to naltrexone.
Aftercare preparation and follow-up were impeded by the need to coordinate researchers with criminal justice staff, prison health services and community treatment providers. For trial participation, the time frame of two months time to release was chosen as inclusion criteria. The objective was to be able to prepare treatment initiation and multidisciplinary group meetings. This time frame proved too short, especially for the methadone group which needed more extensive preparation before receiving the first dose.

The scarce evidence on the effectiveness of addiction treatment programmes in criminal justice settings may be due to particular barriers encountered there, e.g. scepticism towards pharmacological strategies to treat addiction in general and maintenance treatment with agonists that have abuse potential in particular (McMillan & Lapham 2005; Zamani et al. 2009). Another barrier may lie in the limited acknowledgement of addiction as a chronic brain disease in the general population, which is also evident in health care services and the criminal justice system. The definition of addiction as a disease implies the need for a criminal justice health care approach that goes far beyond forced detoxification upon imprisonment and a zero tolerance policy in case of relapse. Therefore, efforts to implement clinical addiction research in criminal justice settings, where usually punishment is exerted as the principal promoter of changing deviant behaviour, may be less likely to succeed compared to addiction specialist services.

Dropout before and after treatment start occurred frequently and indicates that a self-selected sample was recruited. On the one hand, random allocation to the fixed interventions contributed to the high attrition rates. Treatment preference appeared to be an important selection factor in our sample, although there were no differences on socio-demographic or drug use characteristics, neither between naltrexone and methadone groups nor between treatment starters and dropouts. On the other hand, methadone as a control condition was attractive and contributed therefore to inmates accepting the experimental condition to a larger extent. Despite initial scepticism quite a few participants changed their mind and started naltrexone treatment. Offering methadone in our RCT may in fact have contributed significantly to the rather large proportion in the naltrexone group accepting the experimental treatment. However, it cannot be ruled out that random allocation to the fixed interventions has resulted in selective attrition and thus it may have failed to limit selection bias in our small sample. To reduce the risk of selective attrition, we could have allocated the control group to oral naltrexone instead of methadone. A direct comparison of naltrexone tablets with
implants in a double-blind, double-dummy randomised trial has now been reported in an outpatient community setting in Australia (Hulse et al. 2009). This design appears as the reasonable first choice also for criminal justice settings. However, we opted against it for two reasons: the low patient interest in naltrexone treatment is well known and offering only naltrexone would have made the trial virtually impossible to complete during the funding period of three years. Further, the effectiveness of methadone in community settings is well established and there is every reason to assume that it produces comparably good results in criminal justice settings. OMT in general must be made easier available to more inmates and we assumed that our trial with methadone as a control condition would contribute to improvement.

Finally, more advanced strategies such as sequential, multiple random assignments (SMART) could have been attempted in order to meet participants’ preferences to a larger extent. Supposedly, more inmates would have performed better throughout the follow-up if we had succeeded to better match the treatment with their preferences. Adaptive treatment strategies have been suggested to be useful for the investigation of chronic disorders such as drug addiction (Murphy et al. 2007). They allow for re-routing participants to receive the most appropriate treatment, which is adjusted throughout the study course according to pre-defined variables such as responsiveness or preference and motivation. An important limitation of SMART strategies is that two-group, fixed intervention trials are still needed for the confirmation of findings. Additionally, multiple randomisation will by definition result in allocating to more than two groups, which implies the need for testing of multiple hypotheses and thus larger samples (Bauer 2008).

*Outcomes at six months after prison release* [Paper III]

Both treatment groups showed reductions in the use of heroin and illicit benzodiazepines and in criminal activity after prison release, at six months follow-up. For these outcomes, and for time to heroin relapse, patients allocated to naltrexone implants and methadone treatment showed similar levels of reductions in problem scores, and in these respects the two treatments may be regarded as being of comparable effectiveness.

The two study groups showed different treatment performance. In the naltrexone implant group treatment retention was higher than in the methadone group, but naltrexone acceptance was lower. Some methadone group participants also refused to initiate treatment due to non-
acceptance, but the main contributing factors to unsatisfactory methadone initiation were the programme’s application process that relied on community treatment providers and the complicating prison routines. Retention in the methadone treatment programme was low. This may have been due to the requirement of daily dose pickup which proved difficult to comply with for many individuals. The differences in treatment retention at six months may be partly attributed to the very different formulations of the two medications. All participants who started treatment in the naltrexone implant group were receiving this treatment six months after prison release: none had the implant surgically removed. For participants who started methadone treatment, the majority were not receiving medication at six months after release.

Only two of our initial hypotheses predicted our findings. We expected reduced drug use and reduced criminal behaviour in both treatment groups compared to baseline. We were not able to conclude on the other hypotheses, as our study sample was small and attrition high. For heroin use reduction, there was no statistically significant advantage of naltrexone over methadone. This finding was influenced by missing data at follow-up, which were imputed on the assumption of a worst case scenario. Also, we failed to contribute to the question of whether or not naltrexone can cause depression because dropout after treatment start was high. In a study published a few years ago, no association between depression and naltrexone effects was found; on the contrary, depressive mood improved among those who were compliant with oral naltrexone (Dean et al. 2006).

Hair analyses were available for 41% of the ITT sample and supported the self-reported drug use outcomes to a large extent. However, hair analyses as an objective method of drug testing is not yet established and results are vulnerable to pre-analytical handling of the samples. The extent of drug use that results in reliable and sensitive findings in hair needs further investigation. Although separate analyses of hair segments that are suggested to correspond to one month were planned, this approach appeared not feasible. Therefore, findings from the hair analyses were not published together with the self-reported drug use outcomes.

Relying only on self-reported drug use data for the time prior to prison may have resulted in recall bias. More importantly, it may have given inmates the possibility to claim opioid addiction in order to receive methadone although they may not have used opioids regularly. Methadone diversion is a known problem in the community and its black market value is supposedly even higher in prison. Opioid addiction was diagnosed retrospectively for the time
before the current incarceration, because proper assessment would have needed substantially more manpower. Prison health services usually have limited resources and although screening all inmates for eligibility upon imprisonment was planned, it proved not feasible.

4.1.3. Overriding the naltrexone blockade by injecting opioids? [Paper IV]

Opioid dependent patients who received sustained-release naltrexone implants showed a mean reduction in opioid use during treatment. This reduction was unevenly distributed. Almost half of the naltrexone patients did not use opioids at all. However, more than half of the sample challenged the antagonist effects of naltrexone at some point during the six month treatment period. More interestingly, about a quarter of the sample challenged the blockade repeatedly, and 15% reported having used opioids on at least 90 days during the 180 day study period.

This repeated use of opioids despite receiving naltrexone is difficult to understand. The majority of opioid use took place when naltrexone levels were above the therapeutic limit of 1-2 ng/ml of naltrexone. This suggests factors other than naltrexone concentrations were important to opioid use.

The override phenomenon has earlier been reported for single cases in oral naltrexone treatment which is subject to considerable uncertainty regarding medication compliance (Brewer 2002; Haas et al. 1976). Recently, two case-reports of override during sustained-release naltrexone treatment were published. A patient treated with the Russian two months implant Prodetoxon® experienced a non-fatal overdose after having injected very large amounts of heroin (Kruptisky et al. 2007). Another patient used nasal oxycodone with effect during treatment with the injectable Vivitrol (Fishman 2008). Although our sample of naltrexone implanted patients is larger, the results are far from conclusive. Our data were collected after drug use had taken place and we did not have the opportunity to observe objective opioid effect measures such as pupil diameter or vigilance. Our findings need further investigation, because despite the pharmacological blockade that naltrexone provides, opioid injection and even overdoses may occur among implanted addicts. Although the majority is unlikely to use opioids frequently or to experience an effect, some patients will relapse and of these, some will report an effect.
Possible explanations for override may lie in pharmacogenetic aspects of naltrexone (Haile et al. 2008; Mitchell et al. 2007) or in gender differences that might affect treatment response (Suh et al. 2008). It must also be kept in mind that the participants in our studies received implants pending the validation for human use. Therefore, variation in production standards and naltrexone release rates might have occurred and allowed opioid effects in some individuals but not in others. Since claimed override has occurred across the various batches of implants that were imported from Australia, and since the majority of blood analyses showed naltrexone levels above 1 ng/ml, these concerns appear unfounded. However, blood naltrexone levels should be monitored frequently also in future studies investigating formulations not validated for human use.

Another limitation of our data lies in the fact that it is unknown if the experienced effects in our sample were actually caused by the injected opioids. In our population, the reported effects were usually smaller than anticipated and they may have been triggered by a mix of memories, expectations and frequent injecting of benzodiazepines. The role of the high-affinity partial agonist buprenorphine is still unclear; our data indicate that it may have been more effective for overriding than illicit heroin. However, for a more thorough investigation a human laboratory setting is needed that allows recording of objective agonist effect measures and application of intravenous drugs.

4.2. Our findings in the light of other research

Substitution treatment in prison has recently been reviewed and the authors conclude that methadone maintenance provided during incarceration reduces heroin and syringe use, improves health and supports social stabilisation (Stallwitz & Stover 2007). In a French observational study, about 80% of the investigated opioid-involved offenders were receiving OMT upon prison entry (Marzo et al. 2009). The study design limits the interpretation of effect measures. However, maintenance treatment with methadone or buprenorphine did not appear to have a beneficial impact on the re-incarceration rates during the three years follow-up. In Australia, Dolan and colleagues have conducted a randomised-controlled trial on methadone maintenance during four months of continuous incarceration (Dolan et al. 2003). They found a significant reduction of heroin injecting among methadone maintained inmates compared to waiting list controls. All 382 participants were contacted again for another follow-up four years after (Dolan et al. 2005). Although re-incarceration rates and drop-out from the initial methadone treatment were high in this cohort, longer periods with MMT were
associated with improved outcomes on mortality and criminal activity. Improved outcomes during methadone and buprenorphine maintenance in the New York City jail system have been reported recently (Magura et al. 2009). In this randomised trial, inmates started OMT before release. Independent of treatment condition, they were likely to meet for the three months follow-up in the community and to report reduced heroin use. Buprenorphine appeared more acceptable than methadone in terms of higher intention to continue treatment also after release and more favourable drug-related outcomes.

For pharmacotherapies other than methadone, conclusions for criminal justice populations cannot yet be drawn due to scarce evidence. A systematic Cochrane review on criminal justice system-based substance abuse treatment identified only one RCT on a pharmacological intervention for heroin dependence (Perry et al. 2006). In the report, oral naltrexone plus counselling was compared with counselling only among 51 parolees in an open-label RCT (Cornish et al. 1997). Participants in both treatment groups met biweekly for counselling with their parole officer. During the follow-up after prison release, the oral naltrexone group showed significantly less heroin use and re-arrests compared to the counselling only group. However, treatment retention rates at six months follow-up were comparable in both groups. Around 30% of the participants dropped out of treatment during the first study month with no differences between groups. In the Australian prison system, an open-label RCT on oral naltrexone compared to agonist replacement therapy was conducted (Shearer et al. 2007). Only 9 of 68 eligible inmates in the oral naltrexone arm initiated treatment. Random allocation failed because of low interest and the trial was discontinued.

Since few RCTs on pharmacological treatment for heroin addiction during transition from prison to community aftercare have been conducted, the reduction in heroin use that we found together with the challenges that we identified and described are important contributions. For the large-scale RCT that was conducted on methadone maintenance in the US prison system, results at three, six and twelve months after release are now available (Gordon et al. 2008; Kinlock et al. 2008; Kinlock et al. 2009). The findings indicate improved drug counselling attendance and increased treatment retention if methadone is started before prison release compared to counselling only or MMT referral upon release. The group of inmates who started methadone before release was also less likely to use illicit opioids or to engage in criminal behaviour than the counselling only group. In contrast to our findings, enrolment was substantially higher and attrition rather low.
Also in the US, 13 multi-site studies targeting drug-involved offenders are currently being conducted. The Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) were started in 2002, funded by the National Institute on Drug Abuse (NIDA) and several supporting agencies such as the US Department of Justice and NIAAA (Wexler & Fletcher 2007). This large scale initiative includes assessment of offender problems, measurement of progress in treatment and recovery, HIV and hepatitis reduction and implementation of planned interventions which link criminal justice and drug abuse treatment. Six of the 13 studies apply a randomised-controlled design and aim at testing of hypotheses, such as assessing the advantages of specifically improved community re-entry strategies compared to usual procedures.

4.3. Implications

4.3.1. Ethics

The urgent need for more clinical substance abuse research in criminal justice settings has been pointed out by Charles O’Brien in a comment on the first large-scale RCT investigating methadone for opioid addiction among American prison inmates before release:

“Concern over the rights of prisoners often goes to the point of believing that no person under legal restraint can provide free and informed consent to a study. The intention is to protect, but the result is that the subjects are deprived of the right to volunteer for studies and to receive potential benefits from new treatments.” (O’Brien 2008)

The individuals’ right to choose between treatment and punishment is also considered crucial in the drug courts that are increasingly implemented. In this quasi-compulsory treatment approach, the individuals’ autonomy is secured by informed consent. A multicentre trial was conducted in several European countries to compare quasi-compulsory inpatient treatment with a group receiving the same intervention voluntarily, and comparable reductions in drug use and criminal behaviour are reported (Uchtenhagen et al. 2008). Another important finding is that the participants’ motivation to change was not negatively affected by the choice of treatment instead of prison.

The ethics of coercing inmates into treatment have recently been discussed. It has been argued that mandated treatment of addiction might be ethical (Caplan 2008), but this argumentation
has met objections (Buchman & Russell 2009). Interestingly, when Caplan judged court-mandated treatment an ethical coercive means, he explicitly referred to naltrexone and argued that pharmacotherapy with an antagonist may re-instate the individual’s autonomy, which is to some extent impaired by addiction (Caplan 2006). It is doubtful that autonomy can be re-instated by pharmacotherapy and court-mandated naltrexone treatment has met strong critique (Caplan 2007; Hall et al. 2008; Stancliff 2007). In our opinion, any treatment modality should be based on free and informed consent which must be carefully implemented especially in court-mandated, compulsory or quasi-compulsory treatment. In line with O’Brien’s comment we think that achieving informed consent is possible in criminal justice settings. It implies that individuals must have understood the possibility to withdraw from treatment at any stage; which was found to occur in the prison study. Offering unregistered pharmacotherapy in compulsory treatment is unethical.

In the prison study, two substantially different pharmacotherapies among volunteers were compared. On the one hand, addictive methadone that needed to be ingested under supervision every day. On the other hand, heroin-blocking naltrexone that was surgically inserted and not connected to any compulsory aftercare. In contrast to our approach, the other three RCTs on oral naltrexone for inmates used a design that might be considered quasi-compulsory (Brahen et al. 1984; Chan 1996; Cornish et al. 1997). Pharmacotherapy was integrated with psychosocial support that enhances external motivation, such as work-release and parole including follow-up by criminal justice staff. We aimed at informing as many eligible inmates as possible and since many rejected participation, they appeared autonomous and capable of making decisions that influence their lives after prison release. Since methadone start before release could not be guaranteed, MMT can hardly be considered a potent enough incentive to judge our study design quasi-compulsory. Nevertheless, we expected methadone to be more attractive than naltrexone implant treatment. Therefore, MMT was made available through voluntary group cross-over after the trial’s first six months, but still on the condition of an approved application to Norwegian OMT authorities.

The prison study has been criticized (Ruyter et al. 2009). Firstly, it was stated that the prisoners might have been subject to coercion by improved access to methadone - which was not the case. Secondly, it was argued that the study was unethical because non-participants were not receiving study treatment. According to our evaluations, clinical research would be impossible if the study treatment should be offered to all possibly interested parties. Further,
those who rejected trial participation were systematically informed of the possibility to apply for ordinary OMT which is available in Norwegian prisons subject to waiting lists.

4.3.2. Future research with naltrexone implants
In previous criminal justice research, beneficial effects have been reported for methadone and oral naltrexone, but implants have not been used and the two pharmacotherapies have not been directly compared. The previous trials show important commonalities with our RCT: pharmacological interventions reduce drug use and criminal activity among inmates in prison settings and after release. These reductions are also found in RCTs involving individuals in the community. Also, as shown in community settings for several decades, agonist maintenance is more attractive than naltrexone.

Future studies on naltrexone implants should investigate the blood levels that block clinically relevant amounts of heroin; pharmacokinetic studies in healthy volunteers are lacking. Longitudinal randomised studies in criminal justice and community settings are needed to compare the effects of naltrexone implants and available standard treatment such as OMT. Important outcome measures are mortality, heroin and other drug use, time in treatment and extent of rehabilitation. Target populations that benefit from naltrexone implant treatment need to be defined further.

5. Conclusions
The systematic review of the literature conducted in 2007 did not find sufficient evidence to conclude with the effectiveness of sustained-release naltrexone treatment for opioid dependence. However, several RCTs have subsequently reported heroin use reductions during naltrexone implant treatment. This finding is supported by cohort studies and case reports. The prison study reported in this thesis found naltrexone implants and methadone treatment to be of comparable effectiveness in terms of self-reported reductions in heroin and illicit benzodiazepine use and criminality. The study is too small to conclude on possible advantages of one treatment modality over the other. Further research on pharmacotherapy in drug-involved criminal justice populations is urgently needed. Such studies should be planned according to the challenges that were met in this study. Access to prison-based methadone maintenance in Norway should be facilitated. The effectiveness of sustained-release naltrexone to block opioid effects and to prevent high rates of immediate opioid relapse and overdose after prison release should be investigated further.
References


Brewer C (2002). Serum naltrexone and 6-beta-naltrexol levels from naltrexone implants can block very large amounts of heroin: a report of two cases. Addict Biol; 7, 321-323.


**Appendix**

Papers I, II, III & IV