Sustained release naltrexone for opioid dependence: Effectiveness, safety, and clinical feasibility

Nikolaj Kunøe

2010
'First you will come to the Sirens who enchant all who come near them. If any one unwarily draws in too close and hears the singing of the Sirens, his wife and children will never welcome him home again, for they sit in a green field and warble him to death with the sweetness of their song. There is a great heap of dead men's bones lying all around, with the flesh still rotting off them.'

'Therefore pass these Sirens by, and stop your men's ears with wax that none of them may hear; but if you like you can listen yourself, for you may get the men to bind you as you stand upright on a cross-piece half way up the mast, and they must lash the rope's ends to the mast itself, that you may have the pleasure of listening. If you beg and pray the men to unloose you, then they must bind you faster.'

_Homer, The Odyssey_

*book 12, line 1*

Translation: Samuel Butler (1898) / The Perseus Project
Acknowledgements

The last five years have been something of a personal Odyssey to me, beset with its own Schylla and Charybdi, unexpected turns of events, and not least vital cast members. This is the section where the latter receive honorable mention, and the rest are all but forgotten.

Professor Helge Waal designed the original trial and secured funding for it and a trial in prison settings, and provided excellent supervision to an often impatient candidate.

My colleague, Philipp Lobmaier, who generously agreed to conduct implantations on all naltrexone patients in the Greater Oslo area including those participating in my trials. Familiarity with patients, trial medication and its instruments put him in a unique position to conduct follow-up interviews whenever I was absent due to traveling.

The trial participants, who realized the potential of the treatment and volunteered to try it - sometimes having to defy the skepticism of addiction professionals charged with their care.

Øistein Kristensen, John-Kåre Vederhus, and Bjørg Hjerkinn for being a second SRX trial site in Kristiansand, Southern Norway, contributing extra participants to the trial.

The South-Eastern Norway Regional Health Authority for funding for the initial 3 years of the trial via the Centre for Addiction Treatment, Oslo University Hospital.

The Norwegian Centre for Addiction Research at the University of Oslo, which under Research Director Jørgen Bramness, continued to support these studies through to publication and defence.

Professor Michael Gossop for sharing his vast knowledge and experience in scientific publication.
My family for providing a backdrop of stability and security that has permitted me to live a fuller, richer life than one could otherwise expect.

And not least, my partner Agnete, my Penelope of the last few years, whose love and wisdom continues to inspire me every day.
Summary

Dependence on heroin or other opioids is a serious disorder that increases the risk of physical disease, mental disease and death. Heroin dependent patients completing inpatient treatment have a high risk of relapsing to opioid use once they leave controlled environments and return to their community. Naltrexone is a drug with the ability to block heroin and other opioids, but clinical studies of the treatment have generally shown that patients are not able to take naltrexone tablets with sufficient regularity for the medication to have the intended effect. Sustained release formulations of naltrexone may address this problem, but little is known about its effectiveness, safety, and clinical feasibility in the treatment of opioid dependence.

This thesis investigated the above topics by:
1) Conducting a systematic review of the literature on sustained release naltrexone.
2) Comparing patients randomly allocated to either naltrexone implants or no implants in addition to their ‘treatment as usual’ aftercare.
3) Describing the prevalence of opioid use among naltrexone implant patients and the drug ‘high’ experienced following such use.
4) Observing and describing the proportion of first-time naltrexone implant patients retained in naltrexone implant treatment.

The literature review found that an insufficient amount of research had been published on sustained release naltrexone to conclude on its safety or efficacy in the treatment of opioid dependence. The treatment RCT found that naltrexone implants greatly reduced opioid use and craving, was well accepted by patients and was generally well tolerated. Just over half of naltrexone implant patients tried opioids, most of whom felt no effect of use. About half of patients who started treatment with naltrexone implants were retained in naltrexone implant treatment when re-implantation was due.

These findings suggest that sustained release naltrexone is an effective treatment for opioid dependent patients who seek abstinence from opioids. Naltrexone implants seem to have an
acceptable level of safety for this patient group, and is clinically feasible in terms of retaining patients in the treatment and blocking opioid ‘high.’
Sammendrag (Norwegian summary)


Denne doktorgraden tok sikte på å undersøke ovenstående ved å:
1) Foreta en systematisk gjennomgang av litteraturen på langtidsvirkende naltrekson
2) Sammenligne resultatene til heroinavhengige som ble randomisert til å motta eller ikke motta naltreksonkapsler i tillegg til sin vanlige oppfølging etter institusjonsopphold.
3) Beskrive forekomsten - og rusopplevelsen av opioidbruk blant pasienter med naltreksonimplantat.
4) Observere og beskrive andelen av opioidavhengige med førstegangs naltreksonimplantat som ble videreført til en andre behandlingsperiode med naltreksonimplantat.

Resultatene av litteraturgjennomgangen viste at det var utført for lite forskning av god kvalitet til å kunne konkludere noe sikkert om denne typen behandling. Den randomiserte sammenligningen av naltreksonimplantat etter døgnbehandling fant at denne behandlingsformen ga betydelig reduksjon i opioidbruk og hadde et akseptabelt nivå av bivirkninger og hendelser for denne pasientgruppen.
Litt over halvparten av pasientene med naltreksonimplantat prøvde opioider i løpet av behandlingsperioden, men kun et fåttall oppga at de fikk noen rusvirkning av det.
Omtrent halvparten av pasientene med naltreksonimplantat klarte å fortsette med en implantatperiode nummer to.
Funnene i avhandlingen tyder på at langtidsvirkende naltrekson er en effektiv behandlingsmåte for opioidavhengige som ønsker avhold fra opioidstoffer. Behandlingsmåten ser ut til å ha et akseptabelt nivå av bivirkninger for denne pasientgruppen og er praktisk gjennomførbar i forhold til potensielle for gjentatte behandlinger og virkningen av opioidbruk.
Contents

1. List of papers 13

2. Aims 15

3. Background 17
   3.1. Relapse in opioid dependence 17
      3.1.1. Biological mechanisms of relapse 18
      3.1.2. Behavioral mechanisms of relapse 19
      3.1.3. Cognitive and motivational relapse mechanisms 19
      3.1.4. Social mechanisms of relapse 20
   3.2. Naltrexone and its role in the prevention of relapse 21
   3.3. Naltrexone formulations for clinical treatment 22
      3.3.1. Oral naltrexone treatment 22
      3.3.2. Sustained release naltrexone 23

4. Research questions 27

5. Methods and materials 29
   5.1. Systematic review of the literature 29
   5.2. Clinical studies 31
      5.2.1. Demographics 32
      5.2.2. Instruments and outcomes 33
         5.2.3. Design 38
         5.2.4. Ethical and regulatory aspects 39
         5.2.5. Statistical analyses and power analyses 39
   5.2.1. Demographics 32

6. Main findings 43
   6.1. Efficacy and adverse events in the literature 43
   6.2. Effectiveness and adverse events in a randomized comparison 43
1. List of papers

**Paper 1:** Lobmaier P., Kornør H., Kunøe N., Bjørndal A., 2008.

Sustained release naltrexone for opioid dependence (review)


Naltrexone implants after inpatient treatment for opioid dependence: a randomised controlled trial


Challenges to antagonist blockade during sustained release naltrexone treatment

Addiction (accepted draft). *(Published in Addiction (9) 2010. 105, 1633-39; doi: 10.1111/j.1360-0443.2010.03031.x)*


Retention in naltrexone implant treatment for opioid dependence (draft accepted for review)

*(Published in Drug & Alcohol Dependence 2010. 111: 166-69; doi:10.1016/j.drugalcdep.2010.03.021)*
2. Aims

Recovery from opioid dependence is complicated by patients’ tendency to relapse shortly after achieving abstinence in a detoxification clinic or similar inpatient settings. Maintaining abstinence from opioids could be facilitated by use of naltrexone, an opioid antagonist that blocks the action of heroin and other opioids. Oral naltrexone has shown limited effectiveness in clinical settings due to problems with feasibility; more precisely, it is difficult for patients to maintain daily intake of the medication. Sustained release naltrexone formulations represent a potential solution to this problem.

The purpose of this thesis is to increase the scientific knowledge on clinical treatment with sustained release naltrexone by addressing the following research aims:

- Investigate the effectiveness of sustained release naltrexone in preventing relapse among opioid dependent patients who complete inpatient treatment.

- Assess the safety of naltrexone implant treatment for opioid dependence.

- Evaluate the feasibility of using naltrexone implant as a treatment for opioid dependence in clinical settings.
3. Background

Opioid dependence is a debilitating disorder on an individual, family, and societal level. An estimated 15.6 million people worldwide experience the considerable reduction in quality of life and the increased risk of death associated with regular heroin use (United Nations, 2007; Stein et al. 1998; Zanis & Woody, 1998; Darke et al. 2006; Ravndal & Amundsen, 2009). Families of heroin users struggle with the immediate emotional and economical consequences of use. Communities must cope with the wider consequences of use like criminal activity, loss of productivity, and high consumption of health and social services (Mark et al. 2001).

On a neurobiological level, opioid dependence is caused by the repeated intake of opioid drugs which includes heroin, morphine, codeine, methadone, and many more. Opioid receptors exist as a separate class of receptors within the nervous system, with different subtypes (e.g. mu, kappa, delta) and endogenous opioid molecules that bind to them, acting as neurotransmitters. The opioid receptor system is involved in a wide range of CNS functions, many of which are related to motivation, sedation, and pain relief (Simon, 2005). Opioid drugs (or ‘agonists’) activate opioid receptors causing sedation and drug ‘high’ amongst other effects. The ‘high’ experience is thought to originate from a subsequent release of dopamine in an area of the midbrain called the nucleus accumbens (NAcc). Dopamine release in NAcc is implied in most addictive states (Wise, 1980). With regular intake of opioids, the sensitivity of the opioid receptor system decreases and equivalent dosages slowly cease to have their original effect (Yoburn et al. 1989; 1990). This is known as ‘tolerance’ and is a main symptom of opioid dependence (APA, 2000).

3.1. Relapse in opioid dependence

Another main symptom of opioid dependence is the loss of control over opioid use, e.g. by failing to reduce intake despite genuinely trying or failing to stay abstinent following detoxification. The latter is the case with the majority of users who achieve abstinence in inpatient settings. Repeated studies have shown that most patients in this situation relapse to regular heroin use within the first year following discharge - the majority doing so within the first 1-3 months following discharge (Gossop et al. 2002; Darke et al. 2005). Such a
return to heroin use represents a setback in each patient’s recovery, but more importantly greatly increases the risk of dying from overdose (Darke et al. 2006; Ravndal & Amundsen, 2009). Terminating maintenance treatment is also associated with return to pre-treatment mortality levels (Zanis & Woody, 1998; Clausen et al. 2008). Understanding the mechanisms behind relapse to opioid use is thus central to further prevent deaths among patients with opioid dependence.

3.1.1. Biological mechanisms of relapse

When regular use of opioids has commenced, the reward experienced through DA release in the NAcc are counteracted by homeostatic processes in the brain (Koob & Le Moal, 2008). Once intake of opioids ceases, patients experience withdrawal symptoms. The precise mechanisms behind withdrawal are not understood, but avoiding withdrawal may nonetheless become an incentive for the patient to continue using opioids. The unbalancing of the reward system caused by opioid intake is also thought to precipitate a more widespread CNS stress reaction that may continue for some time following the achievement of abstinence (Koob & LeMoal, 2008).

Regular opioid use may prime frontal regions of the brain towards focusing on opioids- and opioid-related behaviours (Kalivas & Volkow, 2005; Robinson & Berridge, 2008). Stimulation of the reward/punishment system with other means - other drugs, substances, stressful events, sensation-seeking - may reinvoke the craving for opioids (Koob & Le Moal, 2008). Individuals suffering from post-traumatic stress may be especially at risk for drug use and relapse, as one of their core symptoms include problems with emotional regulation. On a cellular level, the use of opioids and other drugs increases the expression of a protein from CNS cells, ΔFosB, which gradually accumulates over the course of several weeks. Studies suggest ΔFosB increases sensitivity to opioids, thereby increasing the risk of relapse even after detoxification (Chao & Nestler, 2004).
3.1.2. Behavioral mechanisms of relapse

Morphine and heroin can act as reinforcers of behaviour in an operant sense of the term (Wikler, 1948). Operant conditioning is based on the ‘law of effect’: the reward or ‘reinforcement’ of an action will greatly increase the likelihood that the individual repeats the action (Thorndike, 1911; Skinner, 1938). In addition to pleasant experiences, a reward can also come in the form of relief of pain or stress, known as ‘negative reinforcement.’ Should tolerance or other mechanisms prevent drug intake from resulting in ‘high’ on intake, the addictive behaviour is likely to take even longer to eliminate by removal of reward (Ferster & Skinner, 1957). Once other objects or actions are perceived as associated with the primary reward, these will themselves be perceived as rewarding - a phenomenon called secondary conditioning. Objects present during drug-taking can also become associated with the drug reward through classical conditioning (Pavlov, 1927), something which has been shown to be strong enough to elicit withdrawal symptoms in former opioid dependent persons (O’Brien, 1991).

3.1.3. Cognitive and motivational relapse mechanisms

Coping skills are central to the cognitive psychology understanding of addiction. These theories emphasize the patient’s agency and possibilities despite external and internal pressures to continue drug use. There are numerous cognitive theories on motivation and relapse, but one of the more widely referenced the Relapse Prevention approach has been chosen here as an example of such approaches. The Relapse Prevention approach sees relapse to drug use as occurring as a result of high-risk situations and inadequate coping (Witkiewitz & Marlatt, 2004). For patients dependent on drugs, situations with a high risk of relapse often appear suddenly and unexpectedly (Hawkins & Hawkins, 1998). In order to maintain abstinence in these situations, the patient can relate to the situation in a number of ways: focusing on the short-lived nature of drug urges and cravings (Gossop et al. 2002), focusing on the negative outcomes of relapse, using relaxation techniques, etc. Motivation is seen as a result of the person’s perception of self-efficacy and the value she or he currently assigns to drug use.

The concept of mindfulness has become increasingly important in cognitive psychotherapy for a range of disorders. Mindfulness emphasizes the importance of attention to oneself and
one’s surroundings in uncovering individual mechanisms behind drug use and relapse (Witkiewitz et al. 2005). Awareness and reflection is seen as key to break automatic cycles of thought and action related to drug use, and this approach is beginning to show promising results in the treatment of substance abuse (Bowen et al. 2009).

3.1.4. Social mechanisms of relapse

A common identity as opioid users is established through opioid users’ shared interest in - and experience with opioid use, in the numerous ways of obtaining drugs or money, in sharing traumatic experiences and sometimes in the shared resentment for the ‘non-using society’ in general and public servants in particular (Becker, 1963; Cohen, 1990; Bourgois et al, 1997; Smith-Solbakken & Tungland, 1997; Johansen, 2002; Best et al. 2003). Interacting with the non-using majority often involves the activation of awareness and embarrassment of the contrast between the opioid-users’ life and that of others, as well as lack of trust and outright discrimination from family and other non-using members of society (Cohen, 1990). Using more drugs is a common strategy for coping with such experiences, as is re-narrating one’s history towards that of a conflicted hero in constant struggle with a cruel and inhumane society of non-users (Becker, 1963; Flynn, 2005). Although overdose is always a risk for opioid users, a number of users despair and overdose with suicidal intent (Biong, 2008). Other drugs or alcohol can also be used to (temporarily) influence emotional states or sleep/hunger patterns; thus poly-drug use is the norm among treatment-seeking heroin users (Ross et al. 2005). This tends to further deteriorate mental and physical health (Regier et al. 1990). Opioid users’ attribution of withdrawal symptoms to opioid use is an important element in patients’ experience of themselves as dependent; some users will then quit, while others will continue using and increasingly construct themselves as dependent (Lindesmith, 1968; DeGrandpre, 2006). Thus, according to social theory, maintaining abstinence from opioids following detoxification or residential treatment is thus made difficult by having previously adapted to life as a drug user in social cognition and - networks. This position has gradually diminished the skills and resources necessary to lead a comfortable life without having drugs as an important ingredient in one’s personal and social life.
3.2. Naltrexone and its role in the prevention of relapse

Naltrexone is a medication with a potential to assist opioid users in maintaining abstinence from opioids. This potential derives from the pharmacological effects of naltrexone as well as the secondary effects.

As an opioid antagonist, naltrexone has the ability to block (or ‘antagonize’) opioid agonists like heroin and morphine from activating opioid receptors (Blumberg et al. 1967). Its lack of agonist properties makes it seem like an ideal pharmacotherapy for opioid dependence: it produces no discernible drug ‘high’ or no sedative effect and therefore has little to no potential for overdose or abuse (Martin et al. 1973; Resnick et al. 1974; Verebey et al. 1976; Tai & Blaine, 1997). The dosage of naltrexone necessary to block regular dosages of opioids is thought to lie at plasma concentrations of 1-2 ng/ml or above (Verebey et al. 1976; Sullivan et al. 2006a).

The blockade of opioid receptors by naltrexone must be assumed to prevent and sometimes reverse the biological changes associated with active opioid use; e.g. the reward system in the midbrain would not have to adjust to the dopamine release in the NAcc caused by relapse; levels of ΔFosB proteins should gradually stop accumulating and eventually decrease. Sensitivity of opioid receptors would return to normal levels (or perhaps higher) (Zukin et al. 1982; Yoburn et al. 1989, 1990).

On a behavioral level, the lack of ‘high’ following opioid use in a naltrexone patient should lead to a decrease or even complete ‘extinguishing’ of the association between intake behaviour and ‘high’ (Wikler, 1965; 1976).

On a cognitive and motivational level, knowledge about the presence of naltrexone blockade can mean less intrusive and distractive thoughts about relapse, and free mental resources to focus on recovery-related tasks. The fear (or anticipation) of relapsing is gone or postponed. The presence of naltrexone means opioid-related social interactions should be reduced and eventually stop.
In addition to its ability to block opioids, naltrexone intake has also been known to reduce craving for heroin, alcohol, and other drugs (Sideroff et al. 1978; Ooteman et al. 2007; Jayaram-Lindström et al. 2008). The precise mechanism for this has not been determined, and its significance in the treatment of opioid dependent persons may be hard to distinguish from effects resulting from the awareness of opioid blockade.

Although the 1-2 ng/ml level is thought to block opioids in most circumstances, difficulties in ascertaining the exact blocking level arise from the competitive nature of receptor activation. This means the naltrexone blockade could be overcome in special circumstances: e.g. if the opioid agonist used had a high affinity for opioid receptors, like fentanyl; or if extreme dosages of normal opioids are used in combination with the plasma level of naltrexone approaching sub-therapeutic levels (Toll et al. 1998; Nestler et al. 2008). Another limitation also comes from its opioid-specific nature: Naltrexone does not block the effects of non-opioid drugs or alcohol. As most heroin users are combination drug users (Ross et al. 2005), it is conceivable that a former heroin user could undergo naltrexone treatment but still continue combination drug use.

3.3. Naltrexone formulations for clinical treatment

The minimum target of administration of naltrexone in clinical settings, then, is to achieve a reliable plasma concentration of naltrexone above 1 ng/ml until the person no longer has a need for the pharmacological assistance naltrexone provides. Two main methods of administration have been developed for this purpose.

3.3.1. Oral naltrexone treatment

Oral formulations of naltrexone hydrochloride were the first types of naltrexone treatment for opioid dependence. Studies have found that 50 mg per day or 100 mg every other day of oral naltrexone is sufficient to block street quantities of heroin (Resnick et al. 1974; Judson et al. 1981). However, the effectiveness of oral naltrexone in treating opioid dependent patients is usually limited by compliance problems (O’Brien et al. 1975; Greenstein et al. 1981; Minozzi et al. 2006). The proportion of the originally recruited sample of patients that remain in oral naltrexone treatment at six months is usually small - from 5% to about 30% (e.g. San et al. 1991; Nunes et al. 2006). Retention can be increased when family,
supervisors, or parole officers administer the tablets (Krupitsky et al. 2004; Washton et al. 1984; Cornish et al. 1997) or comprehensive approaches like Contingency Management or Behavioral Naltrexone Therapy are used (Carroll et al. 2001; Rothenberg et al. 2002; Sullivan et al. 2007). However, some are skeptical that these approaches will be able to retain more than 20-40% of patients in clinical settings (Nunes et al. 2006). In addition, one study using urine verification of naltrexone intake found that fewer than 50% of oral naltrexone tablets were actually ingested by opioid dependent patients (Sullivan et al. 2006b).

### 3.3.2. Sustained release naltrexone

As some investigators had anticipated the problems with compliance in oral naltrexone treatment (Resnick et al. 1974), research on the development of sustained release naltrexone formulations was started only a few years after the discovery of naltrexone itself (Leafe et al. 1973; Martin & Sandquist, 1974; Yolles et al. 1975). The National Institute on Drug Abuse (NIDA) devoted several research monographs exclusively to sustained release naltrexone (NIDA, 1978; 1981) and gave them mention in many other monographs. None of these efforts resulted in a product that was suitable for use in clinical treatment. One naltrexone implant prototype was tested by Chiang and colleagues in pilot studies on healthy volunteers (Chiang, 1984; Chiang, 1985). The implant released naltrexone, but only at an estimated half of blocking levels (0.4-0.5 ng/ml). Although this was sometimes sufficient to block the administered opioid challenges, the implants also caused tissue reactions in three out of the five patients, and were not reliable in their release of naltrexone (range: 2-4 weeks).

In the early 1990’s, innovations in polylactide polymers were utilized in the development of depot injectables for antipsychotics. Pilot studies found it was also feasible to administer naltrexone in this manner (Heishman et al 1994; Alim et al 1995). With NIDA support, the technology for depot injectables was further refined to enable the release of naltrexone at 1 ng/ml or more for 4 weeks. One such formulation was recently approved for use in the treatment of alcohol dependence (Kranzler, 1998; Garbutt et al. 2005) and depot injectables seem promising in the treatment of opioid dependence (Comer et al. 2002).
The 1990’s also saw developments in capsules that could release naltrexone after surgical insertion. Several small-scale entrepreneurs began development of such naltrexone implants without regulatory supervision or approval, and they were soon marketed for use in private addiction clinics. The insertion of naltrexone implants was often done during the sedation of patients when combined with a rapid detoxification (ROD) or ultra-rapid detoxification (UROD).

In Norway, a group of addiction professionals at the University of Oslo and the Norwegian Institute of Public Health took interest in naltrexone after being contacted by patients who had received naltrexone implants in countries like Spain, Portugal, and the UK. The initiative was taken to summarize existing knowledge about naltrexone in Norwegian (Bachs & Waal, 2002) and to conduct pilot studies on the safety and kinetics of the available implant formulations.

The first Norwegian study of a sustained release naltrexone formulation took place in 2002/2003, and investigated a Wedgwood (‘compound pharmacy’) type implant. The investigation showed that the naltrexone release of this implant was unreliable and ranged from three weeks to three months. The implants caused several tissue reactions and needed to be surgically removed in three of 12 patients (Waal et al. 2003; Olsen et al. 2004).

Another type of naltrexone implant was developed in Western Australia by George O’Neil (Hulse & O’Neil, 2002). Twenty pellets were said to release naltrexone at therapeutic levels for five to six months. The Norwegian naltrexone group conducted a pilot study in which 12 patients received either 10 or 20-pellet implants. These implants were found to have a satisfactory naltrexone release, high patient satisfaction, and produced considerable reductions in self-reported opioid use 12 months post implant (Waal et al. 2006).

The latter pilot study and the publication of other promising findings in Australia (Arnold-Reed et al. 2003; Hulse et al. 2004; Hulse et al. 2004b) supported the potential of using this type of implant in larger clinical studies. Two trials were planned: One would compare opioid use among patients who completed inpatient treatment for opioid dependence and then received their usual abstinence-oriented aftercare with or without naltrexone implants.
The other would recruit opioid dependent inmates to be randomised to either methadone maintenance or naltrexone implants shortly before release from prison (Lobmaier et al. 2010; in press).

Material from both of these trials and a literature review were used in this thesis to investigate research questions on the aims (chapter 2) related to the effectiveness, adverse events, and clinical feasibility of sustained release naltrexone treatment for opioid dependence.
4. Research questions

The effectiveness and safety of using sustained release naltrexone to treat opioid dependence were investigated in two studies that addressed three main questions:

1) What is the evidence base on the safety of sustained release naltrexone and its effectiveness in the treatment of opioid dependence? (Paper 1)

2) How effective are naltrexone implants in reducing relapse to opioid use following completion of inpatient treatment? (Papers 1 & 2)

3) What kind of adverse events are associated with clinical use of naltrexone implants, and how frequently do they occur? (Papers 1 & 2)

Two aspects of the feasibility of treating opioid dependence with sustained release naltrexone in clinical settings were investigated:

4) How many opioid dependent patients engage in the use of opioid agonists during naltrexone implant treatment? To what extent do they experience a drug ‘high’ following such use? Which factors are associated with opioid use during naltrexone implant treatment? (Paper 3)

5) How many naltrexone implant patients are retained beyond the first course of treatment? Which pre- and in-treatment factors are associated with being retained in naltrexone implant treatment for opioid dependence? (Paper 4)
5. Methods and materials

Two different methodologies were used to address the above research questions:

• A systematic review of the existing knowledge in the field of sustained release naltrexone.
• Clinical studies of naltrexone implants.

5.1. Systematic review of the literature

Systematic searches of the literature were conducted in 20 databases in accordance with the Cochrane Collaboration and Systematic Review guidelines before the quality of studies were assessed and those satisfying evaluation criteria were included in analyses. In the review of efficacy, only randomised controlled trials with opioid dependent patients were accepted for inclusion. For adverse events, non-randomised studies were included and descriptive analyses were conducted. A complete list of outcomes, search databases, and search terms can be found in the paper (Paper 1). The number of screened and included studies can be seen in Figure 1 (below).

Meta-analyses were performed where appropriate for all outcomes. Individual and pooled relative risks (RR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes using the fixed-effects model unless studies were heterogeneous, in which case the random-effects model was used. Statistical heterogeneity was assessed by the Chi-squared test, with P < 0.05 indicating heterogeneity. Additionally, I-squared (values from 0 to 100 %, with 0 % indicating no observed heterogeneity) were calculated to assess inconsistency. Weighted mean differences (WMD) with 95% CI were calculated for continuous outcomes.
Figure 1. Overview of articles included or excluded in the literature review.

520 potentially relevant references screened title and abstract

444 references excluded on basis of title and abstract

76 reports obtained in full text

57 reports excluded after reading

2 secondary reports excluded

17 reports included in the review

1 RCT included in the effectiveness analyses
17 reports included in the safety analyses

6 RCTs

11 non-RCTs
5.2. Clinical studies

The data in papers 2-4 came from samples recruited for three different studies, as shown in figure 2. The treatment RCT addressed questions on effectiveness and adverse events, while two studies of larger samples of naltrexone implant patients each addressed separate aspects of clinical feasibility: the extent to which patients used - and experienced ‘high’ from opioids (paper 3) and the extent to which patients were retained in naltrexone implant treatment (paper 4). The Design section (below) provides more information on the trials to which the patients in these studies were recruited.

Figure 2. Overview of naltrexone implant patients in three recent Norwegian trials and the criteria and number of such patients admitted to studies across trials (papers 3 & 4).
5.2.1. Demographics

The inpatient RCT patients had the following characteristics in mean years (sd):

- Age: 34 (9); heroin use: 7 (5); morphine/codeine use: 2 (4); benzodiazepine use: 5 (6);
- Heavy alcohol use: 3 (6); Amphetamine use: 4 (5); Polydrug use: 10 (7); years in prison: 1 (2). Twenty patients (33%) were women, 47 (84%) were injecting users, and the mean (s.d.) lifetime number of overdoses was 5 (7).

Naltrexone implant patients participating in clinical studies of opioid use and retention (n=63) had the following characteristics in mean (s.d.) years:

- Age: 34 (8); heroin use: 7 (4); morphine/codeine use: 2 (5); benzodiazepine use: 5 (5);
- Heavy alcohol use: 4 (6); Amphetamine use: 5 (6); Polydrug use: 10 (7); years in prison: 2 (3). Sixteen (25%) were women, 55 (87%) were injecting users, and the mean (s.d.) lifetime number of overdoses was 5 (7).

Three patients included in the paper 3 study did not satisfy criteria for inclusion in the paper 4 study and vice versa. Slight variations may therefore occur in the demographic data reported in the two papers.
5.2.2. Instruments and outcomes

All three clinical studies of naltrexone implants used identical instruments and outcomes as listed below. The exceptions to this were the use of visual analogue scales (VAS) and MINI dependence symptoms, which were only used in the treatment RCT.

The European Addiction Severity Index (Europ-ASI) 5th edition

The European version of the Addiction Severity Index (McLellan et al. 1992; Kotkevi & Hargers, 1995) is a 40-minute structured interview focusing on assessing the patients’ lifetime experiences and current situation in seven domains: physiological health; education and employment; substance use, overdose history and treatment; criminal activity and legal history; family history of substance use; family relationships and history; mental health.

The Addiction Severity Index has satisfactory levels of reliability and validity (McLellan et al. 1980; Kosten et al. 1985; McLellan et al. 1985; McLellan et al. 1992). These properties have largely been characteristic of the ASI in other languages (e.g. Hendricks et al. 1989; Liang et al. 2008) as well as in automated phone- or internet versions (Brodey et al. 2004). The Europ-ASI is designed for both clinical and research use. Patients’ progress can be monitored by calculating severity ratings and composite scores from key items in each domain, and these can be combined for an overall score.

The reliability of the instrument in the hands of non-professionals has sometimes been questioned (e.g. Grissom & Bragg, 1991), especially the composite scores for their potential for bias and lack of reliability (Mäkelä, 2004). Severity ratings and composite scores were, however, not used as outcomes in this thesis. All interviewers used in our naltrexone implant studies were trained during a 3-day course and licensed to use the Europ-ASI by the Norwegian Europ-ASI secretariat.
The Europ-ASI measures substance use in two ways:

- Days used of the last 30 days (range: 0-30).

- 6-month self-estimate of use on a 0-3 scale. ‘0’ designated ‘no use’, ‘1’ use at a frequency of 1-3 times per month; ‘2’ use at 1-3 times per week; ‘3’ daily or almost daily.

Both of these measures were preserved from earlier versions of the ASI (McLellan et al. 1980) as they were shown to have acceptable levels of reliability and validity (McLellan et al. 1985; McLellan et al. 1992; Alterman et al. 1998). Nonetheless, some aspects of substance use are not measured by the Europ-ASI outcome measures, including daily substance dosage and frequency of use. In addition, potential confounders can be introduced during this period - e.g. spending time in a controlled environment where drugs are not easily accessible, or in maintenance treatment, where opioids are given to stabilise the opioid dependence. This would be recorded in the Europ-ASI as non-using days or as days using maintenance opioids, respectively (McLellan et al. 1992).

**Timeline follow-back**

Timeline follow-back (TLFB) was used to assess opioid use during each six month study period. TLFB is an interviewing technique based on cueing the patient’s memory for drug use one week at a time during a given period (Sobell & Sobell, 1992; 1995). Although the 0-3 estimation of frequency of use is used in the Europ-ASI due to doubts about the accuracy of patients’ memory beyond 30 days (McLellan et al. 1992), these doubts have not been verified in samples of sustained release naltrexone patients who use opioids. TLFB also has the advantage of providing an approximation of when in a given time period use of a substance occurred, started, or subsided. This was of special interest to us, as we could relate such data on opioid use to the five-six month release period of the naltrexone implants. Opioid-reported TLFB has previously shown 81% concordance with immunoassay urine analyses of opioid use in a 365-day time window (Fals-Stewart et al. 2000).
Mini Neuropsychiatric Interview - drug abuse and dependence sections

The Mini Neuropsychiatric Interview (MINI) was developed as a short screening instrument for current psychiatric diagnoses incorporating most major symptomatic (axis I) disorders from the DSM-IIIR and ICD-10 diagnostic classification system (Sheehan et al. 1997). The substance use sections consist of simple yes/no items on the DSM criteria for drug dependence and - abuse. If the patient has qualified for three or more of the seven dependence criteria or one or more of the four abuse criteria during the last 12 months, the patient fulfills criteria for these diagnoses. These two parts of the MINI were used in the paper 2 study to measure whether patients fulfilled diagnostic criteria for opioid dependence and/or abuse at follow-up. In order to enable the monitoring of symptoms during the six-month study period, the original 12-month criterion for diagnosis was replaced with a ‘within the study period’ criterion in the follow-up interview. This means that patients who were abstinent for 6 months and not designated as ‘fulfilling criteria for opioid dependence’ would nonetheless have fulfilled these criteria if the original 12-month criterion had been used.

Hair analysis

Hair samples were collected and analyzed at inclusion and at each six-month follow-up. Samples were analyzed using liquid chromatograph gas spectrometry (LC-MS-MS) for the most commonly used drugs and their metabolites, with the exception of cannabis and alcohol/glucoronides. An exact description of the measurement technique and the complete list of drugs screened for can be found in a previous paper (Hegstad et al. 2008). Although our chromatographic method of analysis was likely to be more precise than previous techniques based on immunoassay, a number of practical problems such as varying hair length (Shearer et al. 2006) were deemed likely to influence hair results. Hair results were therefore only used for confirmation of self-reported drug use, rather than as a stand-alone result.
Visual analogue scales

Visual analogue scales (VAS) consist of a question and two extremes (e.g. ‘good’ - ‘bad’) at the opposite ends of a drawn line. The patient rates his or her subjective opinion of the topic or question by placing a mark on the line; e.g. placing it exactly between the two extremes signifies indifference or an unremarkable rating. The literature has found the wording of the VAS question and design of lines to be crucial for a reliable and valid response: This includes the design of instructions for responding, the placement and wording of questions and of descriptive anchor phrases, the line design, and the importance of unidirectional formulation of lines (see Wewers & Lowe, 1990). The VAS used in the investigations included in this thesis complied with these guidelines.

The Beck Depression Inventory

The Beck Depression Inventory (BDI; Beck et al. 1961) was used in our studies as a measure of depressive symptoms. This self-response inventory consists of 21 items with four different statements that constitute a 0-3 rating (total range: 0-63). A more recent version brought questions more up to date with DSM-III criteria for depression (Beck et al. 1988). Nonetheless, the validity and reliability of the BDI-1a we used is high, with Cronbach’s Alpha (internal consistency) of 0.85 (Beck et al. 1988; Ambrosini et al. 1991; Richter et al. 1998). In samples of drug dependent patients, concurrent validity has been satisfactory with an r of 0.60 - 0.70 (Rounsaville et al. 1979; Reynolds and Gould, 1981; Schaefer et al. 1985).

The Hopkins Symptom Checklist 25

The Hopkins Symptom Checklist 25 (SCL-25) consists of ten anxiety items and 15 depression items taken from the longer, 90-item SCL-90R (Derogatis, 1974). The 25 items are scored on a 1-4 likert scale (range: 25-100), and then divided by 25. Clinical cutoff has been found to be between 1.5 and 1.8 in most investigations (Winokur et al. 1984; Nettelbladt et al. 1993; Sandanger et al. 1998). Although the SCL-25 lacks the diagnostic precision of larger diagnostic interviews like the CIDI (e.g. Sandanger et al. 1998) it can nonetheless be used as a screening instrument for general psychiatric distress (Nettelbladt et al. 1993).
**The Satisfaction With Life Scale**

The Satisfaction With Life Scale (SWLS) is a five-item instrument designed to measure subjective well-being (Diener et al. 1985; Pavot et al. 1998). The patient responds on a 1-7 likert scale (range: 5-35). Although its three-factor structure has not always been substantiated (Hultell & Gustavsson, 2008), this will have few consequences when used as a general, one-factor measure. The SWLS has been translated to a wide variety of languages and displays satisfactory internal consistency (Cronbach’s alpha >.80) and construct validity versus positive and negative affect (Pavot et al. 1991; Pavot & Diener, 1993; Lucas et al. 1996; Pavot et al. 1998; Vittersø & Nilsen, 2002; Pavot & Diener, 2008; Hultell & Gustavsson, 2008).

**Scoring of opioid ‘high’**

Naltrexone implant patients who used opioids were asked about the resultant euphoric experience or ‘high’ from such use. These were noted in the Europ-ASI’s ‘notes’ field in the substance use section. These statements were then listed on a sheet and rated by Dr. Lobmaier and myself on a 0-3 scale; a score of ‘0’ was given to statements signifying no ‘high’ was felt; a score of ‘1’ was given to statements that expressed uncertainty regarding the experience of ‘high’; a score of ‘2’ was given to statements telling of partial ‘high’ experiences (e.g. ‘not like before naltrexone but definitely something’); while a score of ‘3’ was reserved for statements that described ‘full high’. To avoid bias supporting the blocking effect of naltrexone, disagreements between raters were resolved by choosing the higher rating.
5.2.3. Design

a) Inpatient aftercare study

Matched pilot study

This study was designed as a case-control study, matching volunteer implant patients to voluntary control patients on type of opioid used, age +/- 5 years, and gender before commencing treatment. After 9 months of recruitment with these criteria in 2005, only 12 patients (or 6 matched pairs) had been recruited, as the interest for naltrexone implant treatment was far greater than the number of patients volunteering to be non-implant controls. In addition, no female pairs could be recruited. Due to these problems, no further patients were admitted to the study after nine months of recruitment. The 12 patients recruited in this design continued as a pilot study with follow-up and cross-over opportunity every 6 months for 18 months.

Treatment RCT

The new inpatient treatment trial compared the rate of relapse to opioid use among opioid dependent patients who were randomly allocated to receive or not receive a naltrexone implant in addition to their usual follow-up after completion of inpatient treatment. Inpatient treatment included detoxification and long-term residential services. Patients were recruited by staff at their in- or outpatient clinic, and sometimes following direct contact between the patient and the principal investigator (NK) before they entered inpatient treatment. A stratified permuted block protocol made by an independent statistician was used by study-independent staff to make two equally sized sets of sealed envelopes. Following the signing of the informed consent and completion of study instruments, the envelope was opened in the presence of the patient. No placebo, concealment or masking was used. Target recruitment was 50 patients for each group in 12 months of recruitment. However, upon recruiting only 30 patients after 12 months, the recruitment period was increased to 18 months (from January 2006 to June 2007).

This randomized investigation was a two-centre study, with the Addiction Unit, Sørlandet Hospital Kristiansand recruiting, allocating, implanting, and conducting follow-up in the Agder municipalities; the remainder of South-Eastern Norway was covered by the
b) Prison study

This study was designed to compare relapse to opioid use among former inmates receiving either methadone maintenance or naltrexone implants every 6 months until 18 months following release (Lobmaier et al. 2010; in press). Of the 46 inmates recruited in this study, half were randomly allocated to naltrexone implants, of which n=16 received a naltrexone implant before release. Cross-over was offered from 6-months follow-up, and two inmates from the control group were successfully implanted. The total number of implanted patients in the prison study was thus n=18.

5.2.4. Ethical and regulatory aspects

The three clinical trials were approved by the Regional Ethical Committee for Medicine and Health Research, and registered in the public database http://www.clinicaltrials.gov under the designators NCT00269607, NCT00521157, and NCT00204243. Written informed consents were used and informed patients of the right to withdraw from the study and have implants removed without questions asked. Information about the naltrexone implants and their status as an experimental treatment was given in a separate product folder. Naltrexone implants were given as supplements to standard aftercare, meaning patients’ GP or other regular treatment staff remained responsible for the participants’ healthcare. Implant ‘carrier cards’ were given to implanted patients in order to inform health personnel about the implant, study staff contact details, and options in case of serious injury and medical pain relief was needed. None of the authors had any conflicts of interest in any of the trials.

5.2.5. Statistical analyses and power analyses

Power analyses in treatment RCT

Opioid use among non-implant patients was pre-estimated to occur on a mean of 6 (s.d.: 10) of the last 30 days of the study, whereas naltrexone implant patients were estimated to use on a mean of 1 (s.d.: 3) day of the last 30. Adopting a significance level of .05 in an ordinary student’s t-test, results were calculated to reach significance with a minimum group size of
n=25 in the control group and n=8 in the implant group. The reliability of the outcome measure (found in the Europ-ASI) was estimated at 0.70. As attrition from recruitment to six-month follow-up was a regarded as a potential threat to statistical power, target recruitment was set at n=50 in each group, or n=100 total.

**Power analyses in other clinical studies**

These exploratory studies adhered to the principles of exploratory data analysis (EDA - Tukey, 1977), which does not condone power estimates at an early stage of investigation - e.g. before the number of groups, their sizes, the variance of outcome measures and strength of associations are known (Behrens, 1997). Thus, no power analyses were conducted in these studies.

**Statistical analyses**

Analysis of variance (ANOVA) was used for analyses of any difference in opioid use in the treatment RCT between the naltrexone implant group and the non-implant group. The analyses controlled for gender, study centre, and any significant pre-study differences between implant and non-implant groups.

To assess the effectiveness of naltrexone implants in preventing a return to opioid dependence, the 'Number Needed to Treat' (NTT) statistic was used. NNT quantifies the effectiveness of an intervention in terms of the number of patients one needs to treat in order to prevent a bad outcome - in this case, fulfilling MINI criteria for opioid dependence. The ideal outcome in an NNT statistic is 1, which signifies that everyone improves in the intervention group and no-one in the control group shows any improvement. A high NNT (e.g. ‘13’) translates to little detectable benefit of implementing the treatment.

For analyses of efficacy, an intention-to-treat approach (ITT) was used. In order to provide a conservative estimate of the effect of the intervention, data on all patients who are allocated to treatment or control at study start are also included in the analysis of follow-up data - including patients who were diseased or otherwise missing at follow-up. Data on missing patients can be substituted for in various ways, the most common of which is 'last response carried forward' (LRCF). In LRCF, the patients’ relevant data are assumed to have remained
unchanged since the last observation before the patient went missing; these data are therefore included in the ITT analysis. As our study collected data only at inclusion and follow-up, adopting the ITT approach with LRCF meant presuming that patients who were missing from follow-up had returned to pre-study levels of substance use. In order to also provide results on the performance of groups without imputed data, separate analyses were conducted that included data only from patients who remained in treatment and attended follow-up, called ‘completer analyses’.

Further group comparisons were conducted as t-tests with independent groups. If visual inspection of the scatterplot indicated failure of the normality assumption or Levene’s test indicated differences in distribution, results were double-checked using a non-parametric test. These included the Mann-Whitney U-test for continuous variables and Chi Square for dichotomous variables.

For predictor variables, t-tests of the factors significantly different between outcome groups (e.g. ‘retained’/’not retained’) were used for an initial selection of potential outcome predictors. The factors who were significantly (<.05) related to outcomes were entered into a non-parametric intercorrelation matrix with the outcome variable using Spearman’s Rho. If variables showed an R of 0.7 or above, the variable that correlated highest with the outcome variable was selected for inclusion in regression analysis. For the final analyses of predictors, binomial analysis of regression was used with backwards inclusion of variables at a .05 significance level.
6. Main findings

6.1. Efficacy and adverse events in the literature

The literature review of efficacy studies found only one randomized controlled trial (Comer et al. 2006) that satisfied criteria for inclusion. As Cochrane guidelines do not permit conducting a meta-analysis with less than four studies, the results of the review on this point was inconclusive due to a lack of research.

In the review of adverse events, seventeen studies satisfied inclusion criteria. Ten of these studies were on opioid users, one on healthy volunteers, five on alcohol dependent patients, and one compared healthy volunteers to alcohol dependent patients. Adverse events differed with diagnosis and the type of sustained release technology. Alcohol dependent patients tended to report nausea, fatigue, vomiting, decreased appetite and upper abdominal pain.

Opioid dependent patients reported fatigue, headache and other general complaints. Injection-site reactions were frequently reported with depot naltrexone, but were generally short-lived. Implantation of naltrexone caused infection and allergic reactions that sometimes resulted in surgical removal. Other adverse events seemed dose-related, and were more frequent in naltrexone than placebo groups; however, a statistically significant effect could only be detected in data on alcohol dependent patients.

6.2. Effectiveness and adverse events in a randomized comparison

Fifty-six patients were included in the randomized controlled trial of naltrexone implants, of which 52 (93%) attended six-month follow-up. Of the 29 patients allocated to naltrexone implants, three discharged themselves from the clinic before receiving the implant, one of whom died of an overdose after a few days. Three implant patients had the implant removed, one due to site infection. Two patients reported implantation site rupturing that required antibiotics. Although patients reported their implant sites to have spontaneously opened, a pathologist alerted us to the possibility that these were attempted self-removals. One patient in the control group died of an overdose.
In addition, adverse events occurred after the six-month study period of this trial that are outside the scope of the current investigations but should nonetheless be mentioned here: Three weeks after declining the offer of implantation at follow-up, one control patient died of an overdose. A patient who started in the implant group declined further implantations due to his high level of recovery but died of unknown causes about 18 months after receiving the first implant. A naltrexone implant patient on his second implant required hospital treatment after an accident and suffered a non-lethal stroke during his stay. One control patient in the pilot treatment study relapsed about ten months into the study and died of an overdose around month 13. These cases will be reported as part of an upcoming paper on the 6-12 month outcomes of naltrexone implant treatment.

Intention-to-treat analyses showed opioid use was significantly reduced in the naltrexone implant group, who reported using any opioid on an average of 37 (s.d.: 64) of the 180 days compared to 64 days (s.d.: 71) for the control group. When only completer data was considered, mean use for the implant group was 20 days (s.d.: 43) and 94 days (s.d.: 81) for control participants, respectively. During the 30-days preceding follow-up as measured with the Europ-ASI, implant patients had used opioids on a mean (s.d.) of 6.3 (1.5) days compared to control patients’ 11.4 (13.9) days. Completer data on the same variable found that implant patients had used opioids on 6.3 (11.5) days compared to control patients’ 17.5 (14.3) days.

The differences between implant patients and control patients on opioid use outcomes are listed in Table 1.
Table 1. Opioid outcomes for implant- and control participants in the treatment RCT.

<table>
<thead>
<tr>
<th></th>
<th>Intention-to-treat sample (n=56)</th>
<th>Treatment completer sample (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean diff F 95% C.I.</td>
<td>Mean diff F 95% C.I.</td>
</tr>
<tr>
<td>Heroin timeline follow-back; Days used of last 180 days</td>
<td>45.6* 7.0 14.1 – 77.3</td>
<td>57.8** 13.3 28.2 – 87.4</td>
</tr>
<tr>
<td>Heroin (Europ-ASI); Days used of last 30 days</td>
<td>8* 5.8 1.8 – 14</td>
<td>9* 6.9 2.8 – 15.3</td>
</tr>
<tr>
<td>All opioids timeline follow-back; Days used of last 180 days</td>
<td>60.2** 8.1 20.9 – 99.5</td>
<td>73.5** 14.8 37.3 – 109.8</td>
</tr>
<tr>
<td>All opioids (Europ-ASI); Days used of last 30 days</td>
<td>9* 5.4 1.6 - 16.4 11.2** 9.2 4 – 18.5</td>
<td></td>
</tr>
</tbody>
</table>

Note: Range was 0-180 days for timeline followback variables and 0-30 days for Europ-ASI.

Other opioid-related variables, like the 0-3 six-month frequency of use, 30-day injecting drug use, and 30-day poly-drug use, showed similar improvement as shown in table 2. The naltrexone group also experienced significantly higher quality of life and lower heroin craving compared to control patients. Satisfaction with the naltrexone implant was a mean of 78 (s.d.: 22) on a 0-100 scale among all implant patients, including those who had implants removed.
Table 2. Other significant differences between implant- and control patients in the treatment RCT.

<table>
<thead>
<tr>
<th>Outcome (range)</th>
<th>Intention-to-treat sample (n=56)</th>
<th>Treatment completer sample (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean diff</td>
<td>F</td>
</tr>
<tr>
<td>Poly-drug use last 30 days (0-30)</td>
<td>6.4* 4.2 0.6 – 12.3</td>
<td>6.5* 4.5 .89 – 13.2</td>
</tr>
<tr>
<td>Heroin craving (0-100)</td>
<td>27** 7.2 9.4 – 44.2</td>
<td>38.5** 18.9 21.6 – 55.5</td>
</tr>
<tr>
<td>Life Satisfaction (5-35)</td>
<td>5.4* 5.3 0.68 – 10.1</td>
<td>6* 6.5 1.2 – 10.7</td>
</tr>
<tr>
<td>Recommend implant to friend (0-100)</td>
<td>28.5* 9.1 10.8 – 46.2</td>
<td>22.5* 7.1 12.6 – 47.6</td>
</tr>
<tr>
<td>Satisfaction (allocation) (0-100)</td>
<td>42** 25 25.9 – 58.5</td>
<td>44.7** 11.6 24.8 – 58</td>
</tr>
</tbody>
</table>

Note: Visual analogue scales (VAS) were used to assess craving, allocation satisfaction, and strength of recommendation, while the Satisfaction with Life Scale was used for life satisfaction. The EuropASI was used in the measuring of poly-drug use.

There were no significant differences between the treatment RCT groups on other variables of interest; e.g. non-opioid substance use, criminal activity, or mental health.

The Number Needed to Treat (NNT) for every patient that would no longer fulfill criteria for opioid dependence was found to be 2.8 in intention to treat analyses and 2.4 in completer analyses.
6.3. Feasibility in clinical settings - opioid use and retention

Plasma analyses showed the naltrexone implants released naltrexone above the therapeutic limit of 1 ng/ml for at least 5 months, and above 2 ng/ml for about 4 months.

Opioid use was reported by a slight majority of the sixty naltrexone implant patients, with (n=34) of the 60 naltrexone implant patients reporting having used opioids at some point during the six-month study period. Mean days of opioid use was 24 days (s.d.: 49) in the 180-day time period. Sixteen patients (27% of the total) used opioids on six or more occasions, of which nine patients (15% of the sample) used on 90 days or more (see Figure 2).

Figure 1. Number of days on which illicit opioids were used by sustained-release naltrexone patients in the 180-day study period (abstainers excluded).
Exploratory analyses showed high-frequency users (6+ days of opioid use or more) had a steady increase in use during the six-month period on naltrexone, while low-frequency users (1-5 days of opioid use) mostly engaged in occasional experimentation (see Figure 3). A number of cases were included in the paper to better illustrate clinical diversity behind these descriptions.

**Figure 3. Opioid use development among high- and low-frequency opioid-using naltrexone implant patients.**

Note: ‘Low use’ = 1-5 days of use; ‘high’ use = 6-180 days of use. All differences from month 2 onwards were significant.

Opioid use among naltrexone implant patients was significantly correlated with more use of all non-opioid drugs.
Nine patients reported feeling 'high' following the use of opioids, of which three were 'full high' and six were reduced experiences of 'high.' Patients who reported a greater extent of 'high' following opioid use had significantly higher intake of benzodiazepines, opioids, and buprenorphine than patients who used opioids without feeling any 'high.'

Of the 61 implant patients who were offered a second implant, 17 declined and 44 accepted. Of these 44 patients, 31 (51% of the original sample of n=61) were eventually re-implanted. Five of those who declined reimplantation did so on reasons of feeling recovered from opioid dependence. Of those who were not reimplemented, only three started maintenance treatment with buprenorphine and three entered long-term residential treatment. Nineteen patients discontinued or dropped out from naltrexone implant treatment without plans for entering other treatments and without considering themselves recovered from opioid dependence.

Retention was predicted by having a history of longer employments, as well as less needle use and more family engagement in the month preceding inclusion (Table 3).

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>B</th>
<th>S.E.</th>
<th>sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longest employment, years</td>
<td>0.57</td>
<td>0.23</td>
<td>.014</td>
</tr>
<tr>
<td>Needle use, days of last 30 days</td>
<td>-0.12</td>
<td>0.04</td>
<td>.003</td>
</tr>
<tr>
<td>Family problems days of last 30 days</td>
<td>0.75</td>
<td>.64</td>
<td>.019</td>
</tr>
</tbody>
</table>

Note: Result of binary logistic regression with backward conditional (.05) inclusion of variables.

Patients who later received a second implant had used significantly less opioids and amphetamines and had been less criminally involved during the first treatment period than non-retained naltrexone patients.
Main findings
7. Discussion

7.1. Summary of findings

**Aim 1:** Investigate the effectiveness of sustained release naltrexone in preventing relapse among opioid dependent patients who complete inpatient treatment.

The review of the sustained release naltrexone literature confirmed our impression that there was a lack of prospective, controlled studies of the effect of sustained release naltrexone on relapse to opioid use. Only one study satisfied criteria for inclusion in the review of efficacy, which was insufficient for conducting a meta-analysis and for drawing conclusions about efficacy in the systematic review.

Our randomised clinical trial showed that naltrexone implants significantly reduced opioid use after completion of inpatient treatment compared to similarly motivated control patients receiving usual-treatment aftercare.

**Aim 2:** Assess the safety of naltrexone implant treatment for opioid dependence.

The literature did not allow for quantified analyses of the safety of naltrexone implant treatment for opioid dependence. Descriptive analyses nonetheless suggested more side-effects or site-related events in active naltrexone groups compared to placebo.

In the treatment RCT, one site-related infection occurred and two patients requested removal before completing a medical examination. One of these complaints, diarrhea, re-appeared when the patient on a later date requested to try implantation again and was put on 25 mg of oral naltrexone following detoxification. Most patients also experienced some site pain a few days following insertion of the implant. In addition, many patients experienced less severe symptoms associated with naltrexone like headache, gastrointestinal complaints, restlessness, and muscle aches. These resolved once naltrexone levels stabilised - usually 1-3 weeks following implantation.
The three cases of pre-naltrexone discharges and the two possible attempts at implant self-removal shows that patients’ fluctuations in motivation for long-term abstinence from heroin and other opioids is a potentially important source of adverse events in this type of treatment - leading to the tragic death of one patient overdosing following discharge. The consequences of ambivalence towards abstinence was apparent from the results despite our best efforts to explain the consequences of entering sustained release naltrexone treatment to every potential study participant. Still, the beneficial effects of sustained release naltrexone treatment on opioid use in the remaining patients means the overall level of safety nonetheless seems acceptable.

**Aim 3:** Evaluate the feasibility of using naltrexone implants as a treatment for opioid dependence in clinical settings.

Two important aspects of feasibility were evaluated as part of this thesis in separate explorative studies on naltrexone implant patients: Opioid use among patients was investigated in order to ascertain whether the levels of naltrexone released by the implant seemed sufficient to block the effects of heroin. Had a majority used opioids with a reported ‘high’, it would have been appropriate to question the feasibility of using these naltrexone implants in clinical treatment. Results showed that naltrexone blocked opioids in most cases, but that a minority of patients experienced a drug ‘high’ and used opioids and other drugs frequently. The size of this group (about 15% of naltrexone implant patients) was not large enough to threaten the overall clinical feasibility of the treatment.

Retention among patients has severely limited the clinical feasibility of oral naltrexone treatment, and our study therefore investigated how large a proportion of naltrexone implant patients would discontinue treatment once presented with the first (non-surgical) opportunity to do so.

We found that about half of patients were retained from the first six months of treatment to the second six months of treatment. The low number of implant removals during treatment means that most of this group can be assumed to achieve 10-12 months of continuous
antagonist protection. Retention thus seems much less of a problem to the clinical feasibility of naltrexone implant treatment than it is in oral naltrexone treatment.

7.2. Contribution

The papers included in this thesis have made several contributions to research on sustained release naltrexone for opioid dependence. As usable sustained release formulations have only recently been developed, this thesis is among the first to investigate clinical topics related to this type of treatment in opioid dependent patients.

• The review of the literature was the first article to systematically collect, categorize and evaluate the literature on the safety and efficacy of sustained release naltrexone in the treatment of opioid dependence.

• The randomised controlled trial was the first prospective, controlled comparison published on naltrexone implants for opioid dependence. It was also the first RCT of sustained release naltrexone with 5-6 months’ naltrexone release, and is as of January 2010 the second of only three controlled studies of sustained release naltrexone for opioid dependence that have reached publication. Our RCT is the only of these trials to have used treatment-as-usual controls, thus providing data on the prognosis of patients with a high level of abstinence motivation within the existing treatment system.

• The opioid use study was the first explorative group-based study of opioid use among sustained release naltrexone patients. It is therefore the first study to address questions of how many users engage in how much opioid use with what consequences. As previous studies on this topic have been predominantly based on case material (e.g. Gibson et al. 2007), this group-based study advanced the level of knowledge on this behaviour that should inform future debate on the safety of naltrexone treatment.

• The retention study was the first prospective study of retention in naltrexone implant treatment. It is the second study of retention in sustained release naltrexone treatment and has three times as many patients as the first study to bring data on this topic. It is also the
first study to bring data on pre- and in-treatment factors associated with retention in sustained release naltrexone treatment for opioid dependence.
7.3. Strengths

The above section highlights many of the strengths of this research relative to other studies and general developments in the field (e.g. preceding and having a larger sample size than many previous studies). Further advantages of the specific studies are outlined below.

7.3.1. Strengths of the systematic literature review

• The systematic and detailed procedures of the Cochrane guidelines for systematic reviews were adhered to in this review. This decreases the risk of overestimating the significance of the literature on this topic on the basis of a few studies or of studies not designed to address the research questions.

7.3.2. Strengths of clinical studies

• The use of a randomised controlled design rather than a cohort design in the treatment RCT enabled a valid comparison with similarly motivated patients.

• The open (or ‘non-masked’) design of the treatment RCT may have increased recruitment relative to a masked design.

• The external validity of the clinical studies was strengthened by them being designed to interfere as little as possible with ordinary aftercare following discharge from controlled settings: patients knew whether they were in the naltrexone implant or the usual treatment group, and were only required to attend follow-up six months after the first interview.

• Sample demographics indicate that the studies succeeded in recruiting opioid users with a reasonably long experience with injecting use of opioids and other drugs. This increases the likelihood that the findings can be generalized to clinical settings.

• Basing participation upon the continuation of existing aftercare also meant that study participation was unlikely to be experienced as an interruption of existing treatment services.
• The high six-month retention rate for research follow-up in the treatment RCT (93%) meant fewer data had to be imputed in a ‘last response carried forward’ procedure, and fewer uncertainties regarding the extent to which data reflects patient performance.

• The opportunity for control patients in the treatment RCT to cross over to naltrexone implants at six months likely prevented dropout in this group. The offer of two naltrexone implant periods to all participants regardless of their initial, randomly assigned condition is also likely to have allowed control patients to feel they too gained something from participating - even if they did not receive an implant during the first period. This also allowed us to discard other schemes for compensating patients for participation, e.g. money or vouchers, which could have complicated the ability to generalize of findings to clinical settings.

• The use of timeline followback for the 180-day study period produced data on the timing of opioid use for comparison with naltrexone levels. Such temporal continuity of data proved of high interest to the investigation on opioid use among naltrexone implant patients (paper 3).

• The retention study collected and provided data on on the alternative treatments sought by patients who discontinued naltrexone implant treatment. This provides more information on the treatment preferences of former naltrexone implant patients and the risks associated with discontinuation of treatment.
7.4. Limitations

7.4.1. Limitations of the systematic literature review

The Cochrane guidelines for systematic reviews have been criticized for putting too much emphasis on internal validity, focusing on short-term interventions of limited relevance or interest to the addiction field (e.g. Tucker & Roth, 2006; Pearson & Coomber, 2009). Widening the criteria to include non-randomised or cohort studies of sustained release naltrexone in the evaluation of effectiveness could thus have yielded a broader basis of articles from which to evaluate its safety and effectiveness in the treatment of opioid dependence.

7.4.2. Limitations of clinical studies

Material

- The samples’ representativeness of opioid users in Norway or elsewhere is not determined, even though knowledge about this is one of the main purposes of clinical research standards for reporting of recruitment and attrition (e.g. CONSORT).

Estimation of representativeness in our clinical studies is made difficult by several aspects of study design and current scientific reporting standards, as well as aspects of opioid dependence disorder and the treatment offered for this disorder. For example, the recruitment process was prolonged and involved a large number of clinics or prisons, of which only some contributed patients to the studies. Instances of patient-to-patient (or ‘snowball’) recruitment occurred as the treatment RCT progressed. It is estimated that many opioid dependent patients do not seek treatment (WHO, 2009). Outside hospital settings, it has been shown that information on new products or treatments take time to reach all potential members of a relevant community (Rogers, 1964). This contrasts with medical problems for which the CONSORT was designed - e.g. the vast majority of patients suffering complicated fractures of the tibia will seek treatment in well-organised clinics that are often clearly defined within a geographical area and are generally positively inclined towards research participation.
Despite these limitations it is plausible that the majority of opioid users at any given time will not feel ready for a long-term pharmacologically induced abstinence from opioids. The clinically relevant population thus consists of the subset of patients who would be willing to undergo this kind of treatment, rather than all patients with opioid dependence. In a clinical setting, this criterion is likely to be of greater significance to sample composition than many of the factors normally thought to affect representativeness.

The main concern with representativeness in clinical trials is usually that patients enter the trial who are much better functioning than those who will eventually be offered the treatment in the community. Such a sample could benefit more from treatment than would be the case in ordinary clinical settings. Patient demographics in our studies showed that patients on average were experienced opioid users with a history of poly-drug use, were approaching their mid-thirties, and consisted of $1/4$ to $1/3$ females. Most had tried and failed existing treatments (inpatient - and/or maintenance treatment) at least once. These characteristics are similar to other opioid dependent patients in clinical settings.

- The number of patients recruited for all clinical studies was insufficient for several research purposes, including subsample analysis / analyses of outcome-related factors, estimation of mortality, and decreasing the risk of type I and type II errors.

A larger sample could have reduced uncertainties in all of the above areas, and we would have liked to see larger number of patients recruited, especially to reduce the risk of type I and type II errors. While it would have been of great interest to estimate mortality in our investigations, this was not our main objective.

The additional importance of increased accuracy in the analyses of factors / subgroups is uncertain; e.g. it is likely that the precise kind and number of outcome-related factors will show some variation across cultural and clinical settings. Most such factors would nonetheless have a high probability of being related to a return to opioid-dominated poly-drug use. Although it is possible that larger studies will bring data on isolated but important factors influencing effectiveness and / or retention, our sample size has been sufficient to support the more general tendency in the findings.
• Reliance on self-report measures left the opioid outcomes vulnerable to the under-reporting of drug use. Analyses of drug compounds and metabolites in urine would have reduced this risk and provided a better biological basis for outcome analysis than did hair analyses.

Self-reported data on drug use have repeatedly been found to have satisfactory reliability and validity compared to biomarkers (Darke, 1998; Fals-Stewart et al. 2000). Although there is always potential for some underestimation in self-reporting of data, our findings and experiences indicate that drug use was generally reported. Collection of urine or other frequent biomarkers would have significantly increased the amount of effort required to participate in the study, and could potentially have deterred some users from volunteering.

Methods
• The absence of a placebo control group in the treatment RCT leaves the findings vulnerable to placebo effects.

The possible influence of the placebo effect is a threat to internal validity in all clinical trials of naltrexone. The difficulties of controlling for placebo effects in naltrexone treatment were experienced by Keegan and colleagues (1976):

1) “The patients tested their medication and, hence, were often the only ones to know what they received.”
2) “Patients who found they were not receiving naltrexone saw no point in continuing the program.”

(Keegan et al. 1976; pp. 76).

These experiences, and the ethical problems of implementing a design that might lead patients to engage in self-testing, discouraged us from doing a double-blind placebo study. Placebo effects nonetheless remain a potential threat to internal validity in both open and masked studies of treatment with opioid antagonists. The significance of this
methodological threat to the adoption of a new treatment should be weighed against other important aspects of a study in the context of clinical treatment; e.g. external validity and its potential for saving lives (Tucker & Roth, 2006; Pearson & Coomber, 2010).

• The risk of bias in the treatment RCT is increased by the lack of independence / masking in e.g. data analyses, using the same persons for data collection at recruitment and follow-up, and by the lack of independent monitoring.

Although minimizing risk of bias is important in any research study, it is uncertain that such design elements would have influenced conclusions of this RCT. The risk of bias was reduced by our lack of interests in the producer of the naltrexone implant and the policy of emphasizing the importance of negative results to science when talking to patients about the study. Some of the proposed precautions could also weaken other aspects of the study; e.g. a good relationship with one member of study staff throughout the study can increase patients’ confidence in the research and prevent dropout.

• The use of treatment-as-usual as the control intervention in the treatment RCT risked helping fewer patients than e.g. the use of manualized relapse prevention therapy or medical interventions like oral naltrexone or buprenorphine. Little is known about what treatment the control group actually received in a treatment-as-usual design.

Additional intervention to implants/no implants could have had a positive influence on general outcomes, but could also have reduced the clinically interesting results produced by the treatment-as-usual design. A comparison with methadone or buprenorphine was caused many patients to withdraw from our prison study when the group assignment did not match their initial treatment preference (Lobmaier et al. 2010). The use of treatment-as-usual also had the advantage of involving each participant’s existing treatment network in the study; structured psychotherapy could have risked less involvement from these professionals both during and after the study. In addition, the treatment RCT measured treatment variables like utilization of counseling, psychotherapy, maintenance treatment, and inpatient treatment and reported all statistically significant outcomes in the paper.
Results may have been affected by the non-parametric distribution of outcomes on opioid use (e.g. Chapter 6, Fig 1), as the most common statistical procedures usually suppose a normal distribution in calculations of significance. The lack of a parametric distribution also affects the value of the mean, which could have been replaced by a different measure of central tendency (median/mode).

The statistical analyses most familiar to a scientific readership (e.g. ANOVA, t-tests) generally presuppose normal distribution in their calculation of statistical significance. We used such tests in the reporting of results mainly for presentational purposes. All findings were checked using non-parametric tests (e.g. rank tests; Mann-Whitney U-test; Spearman’s Rho; binomial logistic regression). Although these sometimes have limitations of their own (e.g. 'ties' for rank tests; not providing means-based outcomes), we believe this left the overall integrity of the findings intact. A common approach to this type of problem - converting continuous data to dichotomous outcomes - was not adopted as we found the continuous data on opioid use to be of too great interest to split them in this manner. Other measures of central tendency imply simplifications of their own and are not as readily understood by readers as the mean.
Discussion
7.5. Comparison with similar research

Two other groups have conducted prospective studies on the effectiveness of sustained release naltrexone in reducing opioid use since the start of the naltrexone research projects in 2005: The Columbia group (Comer, Sullivan et al. 2006) and the University of Western Australia (UWA) group (Hulse et al. 2009). Despite the differences in study design and cultural setting, all studies find that the level of adverse events resulting from treatment is acceptable, and that there is a considerable reduction in opioid use following detoxification on a magnitude of 45% (Hulse et al 2009) to 62% (our study) over the different control groups. Our data and those of the Columbia study both show that sustained release naltrexone produces reduced craving for heroin and has satisfactory levels of retention from first to second naltrexone administration.

The findings of the three controlled studies on sustained release naltrexone occasionally display slight discrepancies in findings. The Columbia study found an improvement in opioid-positive urines of 51% in the naltrexone group relative to placebo controls. This is slightly lower than our study (about 62% improvement), but comparable to the UWA study’s 45% advantage of naltrexone implants over oral naltrexone in the proportion of patients returning to daily use. The retention rate in the Columbia study was also somewhat greater - 68% compared to our 51%. On opioid use, 38% (or 6 of 16) urine samples in the Columbia study were positive for opioids in the naltrexone group. This is higher than the self-reported means of 37 of 180 days (about 20% of days) in our treatment RCT (paper 2) and the 24 of 180 days (13%) in the opioid use study (paper 3).

The above differences may be due to methodological differences as well as differences in cultural setting. The UWA study encountered problems with naltrexone release that potentially confounds their findings and makes comparison with more reliable formulations difficult. The following comparisons will therefore be limited to the Columbia study and our own studies, which both had naltrexone release profiles that conformed to expectations.

The differences in material and methods between our studies and the Columbia study could contribute to the lower relative advantage of naltrexone and the higher retention rate in that study:
Discussion

The more frequent follow-up and manualized therapy of the Columbia study could have benefitted control patients more than naltrexone patients, thereby reducing the relative advantage of the naltrexone group. It could also provide increased support for patients who were considering discontinuing naltrexone treatment.

The Columbia study’s use of placebo and masking could have lead patients to unmask their condition by self-testing with opioids (Keegan et al. 1976). In a single-dosage comparison (one naltrexone dosage or placebo), such self-testing might be confined to an initial phase following administration. The Columbia study nonetheless employed a two-dosage (192 mg/384 mg) active medication vs. placebo design, in which some patients might continue testing occasionally in order to ascertain whether they were in the low-dosage group and the antagonist effect was wearing off. If we assume that the placebo design worked and was not unblinded, this too might explain a slightly lower advantage of naltrexone: a placebo effect could increase the performance of the control group, thus reducing the gap to the naltrexone group. A mixed scenario of some patients engaging in self-testing and others not is also possible.

As the Columbia study lasted 60 days, a few number of days spent self-testing would constitute a larger proportion of the total study length than it would in our 180-day study period. The use of twice weekly urines as outcomes also meant that a single episode of use could cause a 1/16 (6%) increase in outcomes for that user, whereas it would lead to an increase of only 1/180 (0,006%) in our timeline follow-back measurements. This difference in outcome sensitivity means patients in the two studies could have had highly similar patterns of use despite the small differences in results.

The Columbia study’s exclusion of patients with recent regular poly-drug use could also increase the performance of the sample as a whole, including the control group. Such patients would be less at risk of relapsing to poly-drug use during treatment, and could be more likely to be retained in a second course of sustained release naltrexone treatment.
Ambivalent patients could also be less reluctant to remain in the Columbia study’s 4-week injectable naltrexone treatment than in our 24-28 week surgically implanted naltrexone treatment.

Our results on effectiveness have a higher risk of being influenced by bias among investigators and patients, as the Columbia study used only biomarker outcome, was monitored by an independent monitoring agency, and had analyses and data collection done by investigator-independent staff.

Finally, the sample sizes of the groups range from small (n=20 in the 384 mg Columbia naltrexone group) to medium (n=61 in our retention study). This puts outcomes in both studies more at risk of measurement and statistical errors than with larger sample sizes.

This comparison of studies has confirmed the results of the systematic review that there are few controlled studies currently published on the efficacy and safety of sustained release naltrexone in opioid dependent patients. In the few studies that have been conducted, there is nonetheless a high degree of consistency in findings: sustained release naltrexone seems effective, sufficiently safe, and feasible for continued clinical study.
Discussion
7.6. Implications

Implications for research

Theories on relapse and naltrexone effects

Contrary to Abraham Wikler’s (1965) hypotheses, use of opioids did not seem to benefit naltrexone patients’ prognoses in our studies. On the contrary, such use seemed to precipitate more rather than less opioid use, and increase the risk of patients’ exit from treatment. Similar results have been found in oral naltrexone patients (Sullivan et al. 2006b; 2007). This suggests that naltrexone research based on laboratory studies of animals oversimplifies the situation relative to opioid dependent, poly-drug using human outpatients. Wikler seems to have been open for this possibility in the 1970’s (Wikler, 1976), and suggested the lack of therapeutic effect of blocked self-injection in humans was due to the influence of other conditioned responses - e.g. classical conditioning to heroin-related cues (O’Brien et al. 1991). We should also be open to the possibility that factors like the sense of identity as a drug user or insufficient coping skills could exert an influence on relapse in these patients. Continued non-opioid drug use would maintain many of the same biological and social factors related to relapse as opioid use would.

Basic research

The finding that a minority of naltrexone patients relapse to pre-treatment levels of opioid use should be further explored by investigating the biological foundations of naltrexone’s effects: the antagonism of the opioid receptor. Data on the extent of opioid receptor blockade given different blood levels of naltrexone could inform us on whether the 1 ng/ml concentration is too low for producing antagonism of normal heroin dosages. This would be an advance over previous PET studies of naltrexone blockade (e.g. Lee et al. 1988). It would also be important to gain knowledge about the consequences of individual differences related to receptor numbers or types, metabolism of naltrexone, and receptor adaptation to the effectiveness of long-term naltrexone treatment.

Another meaningful area of basic research would be the continued development of sustained release formulations. The ideal sustained release formulation would be minimally invasive to administer, release naltrexone at 2 ng/ml or more for several months at a time, and could be removed in the event of an accident or injury requiring anesthesia. While the current
formulations are satisfactory given the benefits of treatment, there is still room for improvement in all of these areas.

**Clinical studies**

Our early findings justify the implementation of more and larger studies. This would address uncertainties pertaining to low statistical power. In addition, longitudinal studies should be undertaken in order to get more data on the potential role of sustained release naltrexone in recovery from opioid dependence - which usually takes several years (Woody et al. 1978). More research is also needed to determine the chances of dropout given different treatment conditions and patient populations: e.g. comparing shorter-acting formulations and more invasive, longer-acting ones on recruitment figures and long-term retention. Qualitative research could identify the specific issues related to recovery with sustained release naltrexone, and the findings could be incorporated into a psychosocial treatment tailored to support these patients.

It will be important for a safe implementation of the treatment that various approaches to avoiding pre-naltrexone dropout and overdose are investigated. For example, instruments on abstinence motivation or ambivalence might be able to indicate which patients should not be allowed to enter sustained release naltrexone treatment for safety reasons. Another approach is the adoption of rapid detoxification techniques (ROD). The advantages and disadvantages of adopting this procedure (see Collins et al. 2005) with sustained release naltrexone treatment should be compared to traditional detoxification techniques; although more ambivalent patients might be more easily inducted onto naltrexone using ROD, our findings suggest they could later be at increased risk of attempting self-removal and/or discontinuing treatment.

A perhaps unsurprising finding in this thesis was the replication of something often seen in addiction treatment: worse patients do worse in treatment, those better off do better. This suggests sustained release naltrexone treatment can be delivered as part of two treatment philosophies: as a part of recovery and as harm reduction among patients who e.g. may wish to continue non-opioid drug use. Both of these options should be explored further in clinical investigations. Although most will favor a recovery-oriented approach to sustained release
naltrexone treatment, its potential for protecting against overdose means its harm-reduction potential should not be dismissed.

**Implications for clinical practice**

The main implication for clinical treatment of opioid use comes from the finding that sustained release naltrexone continues to show promise as an effective and clinically feasible treatment for opioid dependence with high patient satisfaction and an acceptable rate of adverse events. With more such evidence, opioid dependent patients entering treatment may soon have sustained release naltrexone as an option in addition to opioid maintenance treatment and medication-free methods. Pre-treatment screening of patients for sufficient abstinence motivation and in-treatment monitoring of drug use should be considered in order to minimize the adverse events associated with ambivalence.

The findings in this thesis also support the use of supplemental approaches that see opioid dependence as a comprehensive disorder with multiple problems of conduct and substance abuse. The findings of the clinical studies of this thesis are open to the interpretation that most patients had sufficient naltrexone release to block heroin, but that some still sought opioids for social and psychological reasons. These patients had a greater chance of discontinuing treatment. Following this line of thought, more comprehensive treatment approaches like contingency management (Carroll et al. 2001) would seem to have greater chances of succeeding than approaches focusing on single issues (e.g. opioid dependence). In addition, sustained release naltrexone is a potential treatment of choice for better-functioning patients dependent on opioids; e.g. those dependent on prescription opioids. Sustained release naltrexone would be more compatible with normal vocational and family functioning, as it does not involve continued dependence on opioids and the daily pick-ups inherent in maintenance treatment with opioid agonists. These patients might benefit from less comprehensive supplemental treatments, e.g. psychotherapy (Woody et al. 1983).
Implications for policy

The effects of naltrexone implants on relapse to heroin use provides further impetus for considering the approval of sustained release naltrexone in the treatment of opioid dependence. The effectiveness of sustained release naltrexone on opioid use means the introduction of sustained release naltrexone treatment would likely reduce the amount of funds currently assigned to coping with the consequences of heroin dependence (McLellan et al 1996; Mark et al. 2001; Darke et al. 2007). Naltrexone’s lack of abuse potential and its ability to support abstinence means it may be more popular among parts of the electorate than e.g. maintenance treatment. However, such a priority currently lacks a scientific basis and may be unfortunate for patients who are not ready for abstinence (Hall et al. 2008). Our findings suggest that these patients have an elevated risk for pre-naltrexone overdose and in-treatment self-harm. Several decades of research indicates that these more ambivalent patients would greatly benefit from receiving maintenance treatment with methadone or buprenorphine.

Rather than replacing existing treatments, sustained release naltrexone seems well suited to ease the transition between today’s main treatment options for opioid dependence: maintenance treatment and non-pharmacological approaches. The first maintains patients in opioid dependence, and is the logical step up from illicit heroin use. Ending maintenance treatment, however, is currently associated with relapse and return to pre-maintenance levels of overdose risk (Clausen et al. 2008). This overdose risk seems likely to decrease if sustained release naltrexone is commenced during discharge (Tait et al. 2008; Reece, 2009). Non-pharmacological treatments currently involve outpatient phases that offer more freedom to relapse than the majority of former opioid users can manage; however, the odds of remaining abstinent will improve if sustained release naltrexone is used. The true potential of sustained release naltrexone on a policy level may thus lie in helping to realize the potential of existing treatments - rather than signaling their demise.
7.7. Conclusions

The research in this thesis investigated the effectiveness, safety, and feasibility of sustained release naltrexone for opioid dependence.

A systematic review of the literature published until 2007 found that too little research had been published to conclude about the effectiveness and adverse events.

We conducted a randomised clinical trial among opioid dependent patients who completed inpatient treatment in order to investigate whether naltrexone implants would be a useful, safe, and feasible supplement to usual aftercare after discharge. Naltrexone implants produced considerable reductions in opioid use in the following 180 days compared to controls. Adverse events were acceptable and satisfaction with the treatment was high. Naltrexone patients also reported reduced craving for opioid and improved quality of life compared to controls.

Two aspects of feasibility were investigated: the extent to which patients engage in opioid use despite undergoing naltrexone treatment, and the extent to which patients discontinued treatment once the first implant period was at an end. About half of patients were found to use opioids while undergoing naltrexone treatment, most of whom only tried a few times. Frequent opioid users tended to use more stimulants and benzodiazepines and tended to report ‘high’ following use.

Substance use and criminal activity during treatment was similarly associated with not continuing in naltrexone implant treatment. Nonetheless, about 50% of patients were retained after six months, which is sufficient for clinical implementation of the treatment.
References


References


References


Witkiewitz, K., Marlatt, G.A., 2004. Relapse prevention for alcohol and drug problems: that was Zen, this is Tao. Am Psychol. 59, 224-35.


Sustained-Release Naltrexone For Opioid Dependence
(Review)

Lobmaier P, Kornor H, Kunoe N, Bjørndal A

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 4

http://www.thecochranelibrary.com

Sustained-Release Naltrexone For Opioid Dependence (Review)
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
TABLE OF CONTENTS

HEADER ......................................................................................................................... 1
ABSTRACT ..................................................................................................................... 1
PLAIN LANGUAGE SUMMARY ..................................................................................... 2
BACKGROUND ........................................................................................................... 2
OBJECTIVES ............................................................................................................. 3
METHODS .................................................................................................................. 3
RESULTS ................................................................................................................... 5
DISCUSSION .............................................................................................................. 12
AUTHORS’ CONCLUSIONS ..................................................................................... 14
ACKNOWLEDGEMENTS ............................................................................................ 14
REFERENCES ............................................................................................................ 14
CHARACTERISTICS OF STUDIES ........................................................................... 19
DATA AND ANALYSES ............................................................................................. 35
  Analysis 1.1. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 1 treatment retention in high-dose depot vs. placebo. .......................................................... 36
  Analysis 1.2. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 2 treatment retention in low-dose depot vs. placebo. .......................................................... 37
  Analysis 1.3. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 3 treatment retention in high-dose vs. low-dose depot. .................................................. 37
  Analysis 1.4. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 4 time to drop out in high-dose depot vs. placebo. ......................................................... 38
  Analysis 1.5. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 5 time to drop out in high-dose vs. low-dose depot. ......................................................... 38
  Analysis 1.6. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 6 time to drop out in low-dose depot vs. placebo. ......................................................... 39
  Analysis 2.1. Comparison 2 safety outcomes treatment vs. control, Outcome 1 high-dose depot vs. placebo in opioid dependence. ......................................................... 39
  Analysis 2.2. Comparison 2 safety outcomes treatment vs. control, Outcome 2 high-dose depot vs. placebo in alcohol dependence. ......................................................... 40
  Analysis 2.3. Comparison 2 safety outcomes treatment vs. control, Outcome 3 low-dose depot vs. placebo in opioid dependence. ......................................................... 41
  Analysis 2.4. Comparison 2 safety outcomes treatment vs. control, Outcome 4 low-dose depot vs. placebo in alcohol dependence. ......................................................... 42
  Analysis 2.5. Comparison 2 safety outcomes treatment vs. control, Outcome 5 low-dose depot vs. placebo in healthy volunteers. ......................................................... 44
  Analysis 2.6. Comparison 2 safety outcomes treatment vs. control, Outcome 6 high-dose vs. low-dose depot in opioid dependence. ......................................................... 45
  Analysis 2.7. Comparison 2 safety outcomes treatment vs. control, Outcome 7 high-dose vs. low-dose depot in alcohol dependence. ......................................................... 46
  Analysis 2.8. Comparison 2 safety outcomes treatment vs. control, Outcome 8 one or more adverse effects in liver impaired vs. healthy controls. ................................... 47
  Analysis 2.9. Comparison 2 safety outcomes treatment vs. control, Outcome 9 mortality in naltrexone implant vs. methadone maintenance. ............................................. 47
APPENDICES ............................................................................................................... 47
WHAT’S NEW ............................................................................................................. 49
HISTORY .................................................................................................................... 50
CONTRIBUTIONS OF AUTHORS .......................................................................... 50
DECLARATIONS OF INTEREST ............................................................................. 50
SOURCES OF SUPPORT ......................................................................................... 50
INDEX TERMS ........................................................................................................... 51

Sustained-Release Naltrexone For Opioid Dependence (Review)
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**Sustained-Release Naltrexone For Opioid Dependence**

Philipp Lobmaier1, Hege Kornør2, Nikolaj Kunoe3, Arild Bjørndal4

1Norwegian Centre for Addiction Research, University of Oslo, Oslo, Norway. 2Norwegian Knowledge Centre, Health Services, Oslo, Norway. 3Unit of Addiction Medicine, University of Oslo, Oslo, Norway. 4Norwegian Health Services Research Centre, Oslo, Norway

Contact address: Philipp Lobmaier, Norwegian Centre for Addiction Research, University of Oslo, Kirkeveien 166, Oslo, 0407, Norway. p.p.lobmaier@medisin.uio.no. (Editorial group: Cochrane Drugs and Alcohol Group.)

_Cochrane Database of Systematic Reviews_, Issue 4, 2009 (Status in this issue: Unchanged)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DOI: 10.1002/14651858.CD006140.pub2

This version first published online: 23 April 2008 in Issue 2, 2008.

Last assessed as up-to-date: 24 January 2008. (Help document - Dates and Statuses explained)


**ABSTRACT**

**Background**

Naltrexone is an opioid antagonist which effectively blocks heroin effects. Since opioid dependence treatment with naltrexone tablets suffers from high dropout rates, several depot injections and implants are under investigation. Sustained-release formulations are claimed to be effective, but a systematic review of the literature is lacking.

**Objectives**

To evaluate the effectiveness of sustained-release naltrexone for opioid dependence and its adverse effects in different study populations.

**Search strategy**

The following databases were searched from their inception to November 2007: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, LILACS, PsycINFO, ISI Web of Science, trial database at http://clinicaltrials.gov, available NIDA monographs, CPDD and AAAP conference proceedings. The reference lists of identified studies, published reviews and relevant web sides were searched manually. Study authors and drug companies were contacted to obtain any unpublished material or missing data.

**Selection criteria**

To evaluate effectiveness only RCTs were included. To evaluate safety, any clinical trial reporting adverse effects was assessed. Treatment condition was extended to include alcohol dependent subjects and healthy volunteers.

**Data collection and analysis**

Reviewers independently evaluated the reports, rated methodological quality and extracted data. Analyses were performed separately for opioid dependent, alcohol dependent and healthy participants.

**Main results**

For effectiveness, one report met inclusion criteria. Two dosages of naltrexone depot injections (192 and 384 mg) were compared to placebo. High-dose significantly increased days in treatment compared to placebo (WMD 21.00, 95% CI 10.68 to 31.32, p<0.0001). High-dose compared to low-dose significantly increased days in treatment (WMD 12.00, 95% CI 1.69 to 22.31, p=0.02). Number of patients retained in treatment did not show significant differences between groups.

For adverse effects, seventeen reports met inclusion criteria analyses, six were RCTs. Side effects were significantly more frequent in naltrexone depot groups compared to placebo. In alcohol dependent samples only, adverse effects appeared to be significantly more
frequent in the low-dose naltrexone depot groups compared to placebo (RR 1.18, 95% CI 1.02 to 1.36, p=0.02). In the opioid dependent sample, group differences were not statistically significant. Reports on systematic assessment of side effects and adverse events were scarce.

Authors’ conclusions

There is insufficient evidence to evaluate the effectiveness of sustained-release naltrexone for treatment of opioid dependence.

For naltrexone injections, administration site-related adverse effects appear to be frequent, but of moderate intensity and time limited. For a harm-benefit evaluation of naltrexone implants, more data on side effects and adverse events are needed.

PLAIN LANGUAGE SUMMARY

People with opioid dependence require substantial therapeutic effort to keep them drug free. Their use of illicit opioids can be reduced and retention in treatment improved with supervised agonist replacement therapy with methadone, which is a highly addictive drug. Naltrexone is a long-acting, opioid-antagonist that blocks heroin effects. It is used to prevent relapse of both opioid and alcohol dependence. Highly motivated people do best with naltrexone. Most opioid users are sceptical about treatment with naltrexone tablets and many drop out early on. Dropouts can be reduced with supervised tablet taking, offering incentives and using sustained-release naltrexone such as subcutaneous implants or depot injections.

There is insufficient evidence from randomised controlled trials to evaluate the effectiveness of sustained-release naltrexone. In the one controlled study that met inclusion criteria, 60 outpatients were randomised to one of three groups that received two sequential depot injections of naltrexone (192 or 384 mg) or placebo injections. The mean dropout time was 48 days with high dose naltrexone compared with 27 days on placebo; an increase in treatment of 21 days (range 11 to 31 days). The lower depot dose gave a lesser benefit. The number retained in treatment at eight weeks did not show a clear difference and ranged from a mean of 66% to 39% of participants in the different groups. ‘Wanting heroin’ did not differ on naltrexone but ‘needing heroin’ scored significantly lower with depot naltrexone compared to placebo. The most prominent adverse effects were general symptoms of fatigue and pain at the injection site. Seventeen reports met inclusion criteria for assessing adverse effects. Seven looked specifically at naltrexone implants for treatment of opioid dependence and wound infection, allergic reaction to the implant and number of implants removed. The majority of the trials did not have a control group and systematic assessment of adverse effects was lacking.

BACKGROUND

Opioid dependence is considered a chronic lifelong relapsing disorder, which requires substantial therapeutic efforts to keep patients drug free (McLellan 2000). The prevalence of opioid dependence is rather low and varies from 0.1 to 1.0 % among adult populations in Europe and the US, but reliable estimates are difficult to obtain (EMCDDA 2006; OAS 2005).

The currently most effective and well-investigated treatment for opioid dependence is agonist replacement therapy with methadone (Amato 2005; Mattick 2003; van den Brink 2006). Methadone Maintenance Treatment (MMT) implies supervised intake of a long-acting opioid receptor agonist. MMT reduces illicit opioid use and increases retention in treatment substantially. Despite evidence of its effectiveness, clinicians as well as users may be critical towards long-term prescription of a highly addictive drug. Hence, non-addictive alternatives have been in the focus of research for several decades.

Naltrexone is a long-acting, non-selective opioid-antagonist with highest affinity to mu-opioid receptors (Gonzalez 1988). A daily ingested dose of 50 mg sufficiently blocks the effect of opioids to prevent relapse. Tolerance to and dependence on naltrexone does not develop (Navaratnam 1994; Rawson 2000). Oral naltrexone is approved for relapse prevention of alcohol and opioid dependence in several countries. Some trials showed promising results
of oral naltrexone maintenance compared to placebo (Guo 2001), whereas others failed to detect an effect (San 1991). A Cochrane review did not find enough evidence to unequivocally support the clinical effectiveness of oral naltrexone in the treatment of opioid dependence (Minozzi 2006).

An important factor predicting treatment outcome of opioid dependence is treatment retention. Compared to agonist replacement therapy, the majority of opioid users are rather sceptical towards treatment with naltrexone tablets. Hence, maintenance therapy with oral naltrexone suffers from high early dropout rates, which has been counteracted by supervised ingestion of the tablets. Systematic use of incentives in order to externally strengthen patient motivation has been evaluated (Preston 1999). Another important variable to predict treatment outcome is vocational and social stability. Systematically selected and supposedly highly motivated patients seem to do better in oral naltrexone maintenance therapy than unbiased samples (Ginzburg 1984; Cornish 1997).

From a pharmacological point of view, efforts have been made to improve retention in treatment by administering naltrexone as a subcutaneous implant or depot injection. Development of sustained-release formulations commenced three decades ago (Chiang 1985; Reuning 1976). Only recently has sustained-release naltrexone become available for evaluation in larger human samples (Comer 2007). The objective of using sustained-release naltrexone is to secure medication compliance for weeks or even months, thus removing the onus from patients to take naltrexone tablets daily. At least 9 different sustained-release formulations are available. To date, none is approved for opioid dependence treatment in Australia, the EU or the US. Three depot injection formulations are under investigation, providing therapeutic naltrexone blood levels between 1 and 2 ng/ml for approximately 4 weeks: Vivitrol by Alkermes Inc., Depotrex by Biotek Inc. and Naltrel by Elbion. Another approach to provide therapeutic blood levels for several months is to load a biodegradable polyactic based polymer with naltrexone in implant formulations. Several implants are available commercially or through clinical trials: Sherman, Wedgewood, GoMedical (http://www.naltrexane.com/), Cravex (Partecke 2007), Prodetoxone, which is approved for treatment of opioid dependence in Russia (Krupitsky 2007) and a Chinese implant formulation (Moran 2007, see also http://www.1212.hk/). Since treatment with sustained-release naltrexone is hardly or even not reversible for a limited period of time, carefully assessing patients’ motivation must be considered essential before treatment start. While results from clinical trials involving several hundred patients have been published, a systematic review of the literature is lacking.

The aim of this review is to evaluate the effectiveness and adverse effects of sustained-release naltrexone formulations used in humans.

OBJECTIVES

To evaluate the effect of sustained-release naltrexone for opioid dependence compared to placebo or alternative treatment.

To evaluate adverse effects of sustained-release naltrexone formulations currently under investigation in different study populations.

METHODS

Criteria for considering studies for this review

Types of studies

For assessment of effectiveness only randomised-controlled clinical trials on sustained-release naltrexone for treatment of opioid dependence were considered. For evaluation of safety and adverse effects prospective controlled and uncontrolled trials, case series and record-linkage studies were considered.

Types of participants

Adults or adolescents with opioid dependence. Studies investigating naltrexone treatment for other conditions were excluded for effectiveness evaluation. For adverse effects evaluation only, any research on healthy participants and any research on treatment for other conditions than opioid dependence was included.

Types of interventions

Any use of sustained-release formulations (i.e. depot or implant) of naltrexone compared to any other pharmacological or psychosocial or no treatment.

- Sustained-release naltrexone versus oral naltrexone
- Sustained-release naltrexone versus placebo
- Sustained-release naltrexone versus agonist replacement therapy
- Sustained-release naltrexone versus psychosocial interventions
- Sustained-release naltrexone versus no treatment

Types of outcome measures

Predefined primary outcomes:

1. Opioid use during and after treatment: use/no use; number of days with use, self-report; number of positive urine samples per participant
2. Treatment adherence:
a) Induction: started/not started
b) Compliance with protocol: days met for scheduled visits/not met; percentage met/not met; number of implants voluntarily removed.
(3) Retention in treatment: time to drop out.
(4) Adverse effects and severe AEs: percentage with/without; time to AE.
Predefined secondary outcomes
(5) Use of illicit drugs other than opioids during and after treatment: use/no use; number of days with use, self-report; number of positive urine samples per patient
(6) Criminal activity and incarceration: yes/no; number of days with criminal activity; number of offences; number of incarcerations; time spent in prison.
(7) Quality of life: as measured by validated and self-developed questionnaires, e.g. satisfaction with treatment on visual analogue scale (VAS).
(8) Mental health: any appropriate questionnaires; number of diagnoses.
(9) Duration of achieved therapeutic naltrexone blood levels: ng/ml as a function of time.
Outcome measures not considered in protocol but retrieved from literature search:
(10) Heroin craving

Search methods for identification of studies
To identify studies for this review detailed electronic searches for each database were performed.
Electronic searches:
Electronic searches were performed to identify any RCTs investigating the effect of sustained-release naltrexone and any type of study on side effects and adverse events. The detailed search strategy was developed for MEDLINE but revised appropriately for each database to match vocabulary and syntax rules. No language restrictions were made.
The following databases were searched to identify reports on the effectiveness and adverse effects of sustained-release naltrexone:
1. Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2006) which includes the Cochrane Drugs and Alcohol Group Trials Register; 2. MEDLINE (January 1966 to November 2007); 3. EMBASE (1980 to 2007 week 45); 4. CINAHL - Cumulative Index to Nursing & Allied Health Literature (1982 to November, week 2 2007); 5. LILACS (November 2007); 6. PsycINFO (1806 to November 2007); 7. ISI Web of Science (1975 to November 2007). Detailed search strategies for each database are described in Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7
Additional searches
Manual searches in reference lists, relevant web sites, the trial registers at http://www.clinicaltrials.gov and http://www.controlled-trials.com, conference abstracts (Annual Meetings of the College on Problems of Drug Dependence (CPDD), Annual Meetings of the American Academy of Addiction Psychiatry (AAAP)) were performed. Trialists and pharmaceutical companies were approached to obtain unpublished results, but contact proved difficult to establish.

Data collection and analysis
Study selection
Two authors independently assessed potentially relevant studies for inclusion. Any disagreement between the authors was resolved by discussion. If consensus was not achieved, the senior author was consulted. Missing information was sought by contacting study authors.
Assessment of methodological quality
Two authors independently assessed methodological quality of eligible studies. Any disagreement was resolved by consulting the senior author. Methodological quality assessment of all included studies was used to systematically describe possible bias and did not present a threshold for inclusion of trials.
Study quality of RCTs was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions criteria (Higgins 2006):

(1) Measures to avoid selection bias
Allocation concealment in RCTs:
A) Adequate allocation concealment: central randomisation (e.g. allocation by a central office unaware of participant characteristics), pre-numbered or coded identical bottles or containers which are administered serially to participants, drug prepared by the pharmacy, serially numbered, opaque, sealed envelopes, on-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered, or other description that contained elements convincing of concealment.
B) Unclear allocation concealment: when the authors either did not report an allocation concealment approach at all or report an approach that did not fall in the category A or C.
C) Inadequate allocation concealment: alternation or reference to case numbers, dates of birth, day of the week. Any procedure that is entirely transparent before allocation, such as an open list of random numbers or other description that contained elements convincing of not concealment.
D) no allocation concealment used
(2) Measures to avoid performance bias
Blinding of those providing and receiving the intervention in RCTs:
A) double blind
B) single blind (blinding of participants)
C) unclear
D) no blinding
(3) Measures to avoid attrition bias

Sustained-Release Naltrexone For Opioid Dependence (Review)
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Description of drop outs in RCTs:
A) Loss to follow up completely recorded (for each group)
B) Loss to follow up incompletely recorded (data reported only for one group or for the overall sample)
C) Unclear or not done

(4) Measures to avoid detection bias
Blinding of the outcome assessor in RCTs:
A) Blind to treatment allocation at outcome assessment
B) Unclear
C) Not blind to treatment allocation at outcome assessment

Data collection
Two review authors independently extracted data using predefined data extraction forms. Any disagreement was resolved by consensus, if necessary by discussion with a third reviewer.

Data synthesis
Meta-analyses were performed were appropriate for all pre-specified outcomes. Individual and pooled relative risks (RR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes, using the fixed-effects model unless studies were heterogeneous, in which case the random-effects model was used. Statistical heterogeneity was assessed by the Chi-squared test, with P < 0.05 indicating heterogeneity. Additionally, I-squared (values from 0 to 100%, with 0% indicating no observed heterogeneity) were calculated to assess inconsistency. Weighted mean differences (WMD) with 95% CI were calculated for continuous outcomes. From a clinical perspective, it seemed reasonable to analyse safety outcomes from reports on opioid dependent, alcohol dependent and healthy volunteers separately.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
Sixty eight reports of potential interest were identified and assessed, only 1 (Comer 2006) met criteria for inclusion into effectiveness analyses.
Seventeen of 68 identified reports were included to evaluate adverse effects of sustained-release naltrexone treatment (including Comer 2006). In 2 reports the same population was investigated and only the primary publication (Waal 2003) was included. For adverse effects evaluation, unpublished data from 2 reports was retrieved and used (Gölz 2000, Waal 2003). A flow chart of the study inclusion process is provided in additional Figure 1.
Flow chart of study inclusion process

Potentially relevant references identified total: N=911
from source:
MEDLINE N=146
EMBASE N=516
CINAHL N=39
the Cochrane Library N=26
PsycINFO N=102
LILACS N=31
ISI Web of Knowledge N=673
http://clinicaltrials.gov N=6
manual search N=13

duplicates excluded N=391

Potentially relevant references screened title and abstract N=520

References excluded on basis of title and abstract N=444

References obtained in full text N=76

References excluded after reading N=57

Secondary references excluded N=2

Primary references included in the review N=17

RCT included in the effectiveness analyses N=1
Reports of adverse effects included in the safety analyses N=17

RCTs included in the safety analyses N=6
non-RCTs included in the safety analyses N=11
Studies excluded from effectiveness and safety analyses
Reasons for exclusion of the remaining 50 reports were: publication was no clinical trial (25 reports), adverse effect data not provided (11 reports), intervention was oral naltrexone (9 reports), publication on pharmacokinetics of a non-recommendable formulation (3 reports), abstract available only (1 report), two references to same publication (1 report). (See Characteristics of excluded studies)

Included studies
(a) Study of effectiveness of sustained-release naltrexone for opioid dependence
One RCT, conducted in the USA, met inclusion criteria (Comer 2006). A depot formulation of sustained-release naltrexone (Depotrex) was investigated among 60 outpatients. Three parallel groups received 2 sequential naltrexone injections of 192 mg or 384 mg, the control group received 2 placebo injections. In addition, all participants were offered manualised relapse prevention therapy. Clinic visits were scheduled twice weekly during the 8 weeks observation period. Primary outcome measures were treatment retention and opioid use assessed by urinalysis. Other illicit drug use, heroin craving, adverse effects, depression and severity of opioid and cocaine use were considered secondary outcomes. All outcome analyses were conducted on the intention-to-treat (ITT) population.

(b) Studies of adverse effects of sustained-release NTX
Seventeen reports were included in the adverse effect analyses, 6 were RCTs. (See Characteristics of included studies)

- Populations
In 10 reports participants were opioid dependent. Two of these reports were restricted to a non-treatment seeking population (Comer 2002; Sullivan 2006). Sample sizes ranged from 5 (Sullivan 2006) to 894 participants (Tait 2007) with a mean size of 168 participants (median=64.5). In 1 report (Dunbar 2006) the effects of sustained-release naltrexone on 42 healthy volunteers were investigated. Six reports on alcohol dependent subjects were included, with sample sizes ranging from 16 (Galloway 2005) to 624 participants (Garbutt 2005) and a mean size of 174.7 participants (median=27.5).

- Country
2 trials were conducted in Australia, 1 in Germany, 2 in Norway, 1 in Spain, 1 in the UK and 10 in the USA.

- Interventions
The investigated drugs included 3 depot formulations (Alkermes, Biotek, DrugAbuse Sciences) containing 150 to 400 mg of naltrexone and 2 implant formulations (GoMedical, Wedgewood) containing 1000 to approximately 2200 mg of naltrexone. In 10 of 17 reports depot formulations of sustained-release naltrexone were used. The study samples were healthy volunteers, alcohol or opioid dependent patients in 1, 6 and 3 reports, respectively. In the remaining 7 reports on naltrexone implants, all participants were opioid dependent. (See additional Table 1)

Table 1. Reports according to study medication used

<table>
<thead>
<tr>
<th>NTX formulation</th>
<th>Dose (mg)</th>
<th>Condition</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkermes depot (Vivitrol)</td>
<td>190</td>
<td>alcohol dependence</td>
<td>Turncliff 2005</td>
</tr>
<tr>
<td></td>
<td>190 and 380</td>
<td>healthy volunteers</td>
<td>Dunbar 2006</td>
</tr>
<tr>
<td></td>
<td>190 and 380</td>
<td>alcohol dependence</td>
<td>Garbutt 2005</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>alcohol dependence</td>
<td>Johnson 2004</td>
</tr>
<tr>
<td>Biotek depot (Depotrex)</td>
<td>192 and 384</td>
<td>opioid dependence</td>
<td>Comer 2002</td>
</tr>
<tr>
<td></td>
<td>192 and 384</td>
<td>opioid dependence</td>
<td>Comer 2006</td>
</tr>
<tr>
<td></td>
<td>206</td>
<td>alcohol dependence</td>
<td>Kranzler 1998</td>
</tr>
</tbody>
</table>
Table 1. Reports according to study medication used (Continued)

<table>
<thead>
<tr>
<th>Drug/Abuse Sciences depot (Naltrel)</th>
<th>Opioid dependence</th>
<th>Sullivan 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 and 300</td>
<td>Alcohol dependence</td>
<td>Kranzler 2004</td>
</tr>
<tr>
<td>300</td>
<td>Alcohol dependence</td>
<td>Galloway 2005</td>
</tr>
<tr>
<td>GoMedical implant</td>
<td>Opioid dependence</td>
<td>Waal 2006</td>
</tr>
<tr>
<td>1800 and 3600 (corrected by Tait 2007: 1100 mg and 2200 mg)</td>
<td>Opioid dependence</td>
<td>Hulse 2005</td>
</tr>
<tr>
<td>3600 (corrected by Tait 2007: 2200 mg)</td>
<td>Opioid dependence</td>
<td>Tait 2007</td>
</tr>
<tr>
<td>Wedgewood implant</td>
<td>Opioid dependence</td>
<td>Foster 2003</td>
</tr>
<tr>
<td>1000</td>
<td>Opioid dependence</td>
<td>Waal 2003</td>
</tr>
<tr>
<td>1000</td>
<td>Opioid dependence</td>
<td>Götz 2000</td>
</tr>
<tr>
<td>1000</td>
<td>Opioid dependence</td>
<td>Carreno 2003</td>
</tr>
</tbody>
</table>

- **Groups of comparison**

**Opioid dependent samples**

Six of the 10 reports with opioid dependent samples were uncontrolled studies, 5 investigating naltrexone implants ([Carreno 2003; Foster 2003; Hulse 2005; Waal 2003; Waal 2006] and 1 naltrexone depot (Sullivan 2006). Of the 4 reports with groups of comparison, the only RCT was conducted by [Comer 2006], comparing naltrexone depot to placebo injections. Two studies were designed with 2 sequential treatment groups, comparing low- and high-dose naltrexone depot ([Comer 2002] or implants and oral naltrexone ([Götz 2000]). One report compared naltrexone implants to methadone maintenance based on record-linkage data ([Tait 2007]).

**Alcohol dependent samples**

In all 6 reports with alcohol dependent samples naltrexone depot injections were investigated. Four reports were RCTs ([Garbutt 2005; Johnson 2004; Kranzler 1998; Kranzler 2004]). In 1 report liver impaired patients were compared to matched, healthy controls ([Turncliff 2005]) and in 1 report a single treatment group was investigated (Galloway 2005).

**Healthy volunteers**

In 1 dose-finding, phase I RCT naltrexone depot was investigated among healthy volunteers ([Dunbar 2006]).

**Outcome measures**

Two categories of adverse effects were assessed in 9 of the 17 reports: possibly naltrexone-related AEs (e.g. headache, nausea) and administration site-related AEs, such as itching, pain, tissue reactions or surgical site revision. In the majority of studies involving opioid dependent populations only administration site-related AEs were reported, however, in the record-linkage study by [Tait 2007] mortality during course of treatment was investigated. Most reports on alcohol dependent subjects included assessment of AEs possibly related to both categories: the drug naltrexone and its particular formulation used. The predefined outcome measure time to AE was not assessed in any report.

**Studies ongoing**

We found six studies ongoing, as soon as results will be available, we will update the results.
Risk of bias in included studies
(See additional Table 2)

<table>
<thead>
<tr>
<th>report</th>
<th>selection bias</th>
<th>performance bias</th>
<th>attrition bias</th>
<th>detection bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kranzler 2004</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Garbutt 2005</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Comer 2006</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Johnson 2004</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Kranzler 1998</td>
<td>B</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Dunbar 2006</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Comer 2002</td>
<td>non-RCT, 2 sequential treatment groups</td>
<td>not applicable (N/A)</td>
<td>loss to follow-up completely recorded</td>
<td>N/A</td>
</tr>
<tr>
<td>Turncliff 2005</td>
<td>non-RCT, 2 matched-controlled treatment groups</td>
<td>N/A</td>
<td>loss to follow-up completely recorded</td>
<td>N/A</td>
</tr>
<tr>
<td>Galloway 2005</td>
<td>non-RCT, uncontrolled</td>
<td>N/A</td>
<td>loss to follow-up completely recorded</td>
<td>N/A</td>
</tr>
<tr>
<td>Golz 2000</td>
<td>non-RCT, 2 sequential treatment groups</td>
<td>N/A</td>
<td>loss to follow-up completely recorded</td>
<td>N/A</td>
</tr>
<tr>
<td>Foster 2003</td>
<td>non-RCT, uncontrolled</td>
<td>N/A</td>
<td>loss to follow-up completely recorded</td>
<td>N/A</td>
</tr>
<tr>
<td>Hulse 2005</td>
<td>non-RCT, record-linkage data</td>
<td>N/A</td>
<td>N/A</td>
<td>prospectively collected data: blind to treatment allocation at outcome assessment</td>
</tr>
<tr>
<td>Tait 2007</td>
<td>non-RCT, record-linkage data</td>
<td>N/A</td>
<td>N/A</td>
<td>prospectively collected data: blind to treatment allocation at outcome assessment</td>
</tr>
<tr>
<td>Sullivan 2006</td>
<td>non-RCT, uncontrolled</td>
<td>N/A</td>
<td>loss to follow-up completely recorded</td>
<td>N/A</td>
</tr>
<tr>
<td>Waal 2003</td>
<td>non-RCT, uncontrolled</td>
<td>N/A</td>
<td>loss to follow-up completely recorded</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Table 2. Reports and potential sources of bias (Continued)

<table>
<thead>
<tr>
<th>Study of effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the 1 report included for analyses of effectiveness, the method of allocation concealment was not clearly described (category B). The trial was conducted in a double-blind fashion (category A) and loss to follow up was recorded completely for each treatment arm (category A). It remains unclear whether or not the outcome assessors were blind to which intervention participants had received (category B).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Studies of adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs: 6 reports</td>
</tr>
<tr>
<td>1) Comparison and allocation concealment:</td>
</tr>
<tr>
<td>In 1 of 6 RCTs an opioid dependent sample was investigated, this report was also included for analyses of effectiveness (Comer 2006). A detailed description of an adequate method for allocation concealment (category A) was provided by 1 study group (Kranzler 2004), the other 5 descriptions were rated category B: unclear allocation concealment.</td>
</tr>
<tr>
<td>2) Blinding of participant / provider:</td>
</tr>
<tr>
<td>All 6 RCTs were considered double-blind (category A), i.e. those receiving and providing treatment were blind to the intervention used.</td>
</tr>
<tr>
<td>3) Drop out:</td>
</tr>
<tr>
<td>In 5 RCTs loss to follow up was completely recorded for each treatment group (category A). The RCT by Dunbar 2006 was rated category B: loss to follow up incompletely recorded.</td>
</tr>
<tr>
<td>4) Blinding of the outcome assessor:</td>
</tr>
<tr>
<td>One of 6 RCTs was considered triple blind: besides participants and treatment staff, researchers assessing outcomes were blind to treatment allocation (Garbutt 2005). The remaining 5 RCTs were rated category B: unclear if outcome assessor was blind to treatment allocation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects of interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the 1 report (Comer 2006) that met inclusion criteria for effectiveness studies, the following primary treatment outcomes allowed calculations of effect estimates:</td>
</tr>
<tr>
<td>(1) Retention in treatment (number of participants in each group completing the 8-week study period)</td>
</tr>
<tr>
<td>(2) Time to drop out (number of days in treatment)</td>
</tr>
<tr>
<td>All confidence intervals are 95%, effect estimates are based on intention-to-treat analyses.</td>
</tr>
<tr>
<td>(1) Retention in treatment at week 8 was 68.2%, 60.0% and 38.9% of participants in the high dose, low dose and placebo group. There was no statistically significant difference between either dosage of depot naltrexone and placebo with high dose, one study, 40 participants, RR 1.75 (CI 0.92 to 3.34), see Analysis 1.1; and low dose, one study, 38 participants, RR 1.54 (CI 0.78 to 3.05), see Analysis 1.2. No statistically significant difference was found between groups receiving naltrexone depot, one study, 42 participants, RR 1.14 (CI 0.72 to 1.80), see Analysis 1.3.</td>
</tr>
<tr>
<td>(2) Time to drop out was 48, 36 and 27 days in the high dose, low dose and placebo group. Group comparisons were statistically significant between high dose naltrexone depot and placebo, one study, 40 participants, WMD 21.0 (CI 10.68 to 31.32), see Analysis 1.4, and between high and low dose depot, one study, 42 participants, WMD 12.0 (CI 1.69 to 22.31), see Analysis 1.5.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects of interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Effectiveness of sustained-release naltrexone for opioid dependence</td>
</tr>
<tr>
<td>Eight of the 9 reports were investigations on opioid dependent samples, only Galloway 2005 investigated an alcohol dependent sample. In 7 reports loss to follow up was completely recorded for treatment groups. In the remaining 2 reports the description of drop-outs was either not done (Carreno 2003) or not feasible due to record-linkage study design (Hulse 2005).</td>
</tr>
</tbody>
</table>

| non-RCTs without parallel control group: 9 reports |
| Data of opioid dependent patients receiving naltrexone implant to patients entering methadone maintenance. Patient data was recorded prospectively by health care staff who was considered blind to treatment condition. Reporting drop-out was not feasible due to record-linkage study design. |

| non-RCTs without parallel control group: 2 reports |
| Turncliff 2005 used a matched case-control design to compare liver impaired alcohol dependent patients and healthy controls. This trial was open-lable, loss to follow up was completely recorded for each group. Tait 2007 retrospectively compared record-linkage data of opioid dependent patients receiving naltrexone implant to patients entering methadone maintenance. Patient data was recorded prospectively by health care staff who was considered blind to treatment condition. Reporting drop-out was not feasible due to record-linkage study design. |

| non-RCTs without parallel control group: 8 reports |
| Studies of adverse effects (see table characteristics of included studies) |
| RCTs: 6 reports |
| 1) Comparison and allocation concealment: |
| In 1 of 6 RCTs an opioid dependent sample was investigated, this report was also included for analyses of effectiveness (Comer 2006). A detailed description of an adequate method for allocation concealment (category A) was provided by 1 study group (Kranzler 2004), the other 5 descriptions were rated category B: unclear allocation concealment. |
| 2) Blinding of participant / provider: |
| All 6 RCTs were considered double-blind (category A), i.e. those receiving and providing treatment were blind to the intervention used. |
| 3) Drop out: |
| In 5 RCTs loss to follow up was completely recorded for each treatment group (category A). The RCT by Dunbar 2006 was rated category B: loss to follow up incompletely recorded. |
| 4) Blinding of the outcome assessor: |
| One of 6 RCTs was considered triple blind: besides participants and treatment staff, researchers assessing outcomes were blind to treatment allocation (Garbutt 2005). The remaining 5 RCTs were rated category B: unclear if outcome assessor was blind to treatment allocation. |

| non-RCTs with parallel control group: 2 reports |
| Turncliff 2005 used a matched case-control design to compare liver impaired alcohol dependent patients and healthy controls. This trial was open-lable, loss to follow up was completely recorded for each group. Tait 2007 retrospectively compared record-linkage data of opioid dependent patients receiving naltrexone implant to patients entering methadone maintenance. Patient data was recorded prospectively by health care staff who was considered blind to treatment condition. Reporting drop-out was not feasible due to record-linkage study design. |

| non-RCTs with parallel control group: 8 reports |
| Studies of adverse effects (see table characteristics of included studies) |
| RCTs: 6 reports |
| 1) Comparison and allocation concealment: |
| In 1 of 6 RCTs an opioid dependent sample was investigated, this report was also included for analyses of effectiveness (Comer 2006). A detailed description of an adequate method for allocation concealment (category A) was provided by 1 study group (Kranzler 2004), the other 5 descriptions were rated category B: unclear allocation concealment. |
| 2) Blinding of participant / provider: |
| All 6 RCTs were considered double-blind (category A), i.e. those receiving and providing treatment were blind to the intervention used. |
| 3) Drop out: |
| In 5 RCTs loss to follow up was completely recorded for each treatment group (category A). The RCT by Dunbar 2006 was rated category B: loss to follow up incompletely recorded. |
| 4) Blinding of the outcome assessor: |
| One of 6 RCTs was considered triple blind: besides participants and treatment staff, researchers assessing outcomes were blind to treatment allocation (Garbutt 2005). The remaining 5 RCTs were rated category B: unclear if outcome assessor was blind to treatment allocation. |

| non-RCTs with parallel control group: 2 reports |
| Turncliff 2005 used a matched case-control design to compare liver impaired alcohol dependent patients and healthy controls. This trial was open-lable, loss to follow up was completely recorded for each group. Tait 2007 retrospectively compared record-linkage data of opioid dependent patients receiving naltrexone implant to patients entering methadone maintenance. Patient data was recorded prospectively by health care staff who was considered blind to treatment condition. Reporting drop-out was not feasible due to record-linkage study design. |
depos and placebo, one study, 38 participants, WMD 9.0 (CI -3.40 to 21.40), see Analysis 1.6.
The comparisons described below were regarded secondary outcomes by Comer 2006. Calculation of effect estimates was not possible with the data provided.
(3) heroin craving assessed on visual analogue scales
(4) depression / severity of drug use
(5) naltrexone blood levels
(3) Heroin craving, on visual analogue scales:
“Wanting heroin” did not show significant group differences throughout the study. “Needing heroin” was scored significantly lower by the high and low dose naltrexone depot group compared to the placebo group (p<0.001).
(4) Depression (HAM-D scale); severity of opioid and cocaine use (CGIS):
No significant difference between treatment groups was reported on depression or severity of drug use scores. In regard to depression, all groups scored lower on HAM-D at follow-up than at baseline.
(5) Mean plasma levels of naltrexone during the 8 weeks study period ranged from 1.3 to 3.2 ng/ml in the high dose group. In the low dose group mean plasma levels were measured between 0.4 and 1.9 ng/ml 4 weeks after the first injection plasma trough levels were reached and the naltrexone depot re-administered. The following outcomes were predefined in the review’s protocol, but not reported in Comer 2006:
Opioid use per participant
Other drug use per participant
Treatment adherence
Criminal activity / incarceration

• Adverse effects of sustained-release naltrexone treatment in RCTs

In 8 of the 17 reports included for assessment of adverse effects parallel comparison groups were used. Six of the 8 reports were RCTs (Comer 2006; Dunbar 2006; Garbutt 2005; Johnson 2004; Kranzler 1998; Kranzler 2004) and 2 were non-RCTs (Turner 2005; Tait 2007). In 7 of the 8 reports naltrexone depot injections were investigated and possibly drug-related adverse effects were assessed. Only Tait 2007 investigated naltrexone implants in comparison to methadone maintenance and assessed mortality. Effect analyses for non-RCTs were performed separately from the RCTs. Subgroup analyses were performed separately for the different populations, i.e. opioid dependent, alcohol dependent and healthy controls.

(1) RCTs

High-dose naltrexone depot compared to placebo injection:

• Opioid dependence, one RCT (Comer 2006):

No significant differences for reporting 1 or more adverse effects, 38 participants, RR 1.36 (CI 0.79 to 2.35), see Analysis 2.1, sub-category 01 and for number of participants discontinuing the trial due to adverse effects, 38 participants, RR 0.28, (CI 0.01 to 0.38), see Analysis 2.1, sub-category 02.

• Alcohol dependence, two RCTs (Garbutt 2005 and Johnson 2004):

Group differences of reporting 1 or more adverse effects were not significant in Johnson 2004, 30 participants, RR 1.15 (CI 0.73 to 1.81), see Analysis 2.2, sub-category 01. In Garbutt 2005, no significant differences for reporting 1 or more severe adverse events, 414 participants, RR 0.68 (CI 0.31 to 1.48 ), see Analysis 2.2, sub-category 02 and for reporting injection site pain, 414 participants, RR 1.29 (CI 0.73 to 2.28), see Analysis 2.2, sub-category 03., while de difference was statistically significant in favour of control group for number of participants discontinuing the trial due to adverse events, 414 participants, RR 2.11 (CI 1.15 to 3.88), see Analysis 2.2, sub-category 04.

Low-dose naltrexone depot compared to placebo injection:

• Opioid dependence, 1 RCT by Comer 2006:

No significant differences between the groups for reporting 1 or more adverse effects, 38 participants, RR 1.30 (CI 0.74 to 2.28), see Analysis 2.3, sub-category 01, number of participants discontinuing the trial due to adverse events, 38 participants, RR 1.80 (CI 0.18 to 18.21), see Analysis 2.3, sub-category 02 and reporting injection site induration RR 0.90 (CI 0.60 to 5.60), see Analysis 2.3, sub-category 03.

• Alcohol dependence, 3 RCTs by Garbutt 2005; Kranzler 1998; Kranzler 2004

In the trials by Kranzler 1998 and Kranzler 2004 group differences of reporting 1 or more adverse effects were not significant , 353 participants. RR 1.06 (CI 0.95 to 1.179, see Analysis 2.4, sub-category 01. In the trial by Garbutt 2005 no differences for number of participants discontinuing the trial due to adverse effects, 419 participants. RR 1.00 (CI 0.49 to 2.04), see Analysis 2.4, sub-category 02. In all 3 trials group no statistically significant differences for reporting injection site pain, 772 participants, RR 1.17 (95% CI 0.92 to 1.47), see Analysis 2.4, sub-category 03. No statistically significant difference in Kranzler 1998 and Kranzler 2004 for reporting injection site induration , 535 participants, RR 1.71 (CI 0.76 to 1.80), see Analysis 2.4, sub-category 04. In Kranzler 2004 no differences for reporting injection site contusion , 499 participants, RR 1.24, 95% (CI 0.60 to 2.57), see Analysis 2.4, sub-category 05, while the difference between groups was significantly in favour of control for reporting 1 or more injection site reaction, 333 participants, RR 1.19 (CI 1.02 to 1.38), see Analysis 2.4, sub-category 06. In Garbutt 2005 severe adverse events were described as most commonly hospital admissions for alcohol detoxification. Two cases of pneumonia were judged possibly naltrexone depot-related. Group differences of reporting an severe adverse events were not significant, 419 participants, RR 0.73 (CI 0.34 to 1.55), see Analysis 2.4, sub-category 07. In all 3 trials group differences of reporting any type of injection site related adverse effect (i.e. injection site pain, induration, con-
tusion and one or more reaction) was significant with pooled RR 1.18 (CI 1.02 to 1.36), see Analysis 2.4, sub-category 08.

- Healthy volunteers, 1 RCT by Dunbar 2006:

No difference between the groups for reporting 1 or more AE were not significant, 42 participants, RR 2.46 (CI 0.16 to 38.89), see Analysis 2.5, sub-category 01 and for reporting one or more injection site reaction, 42 participants, RR 1.32 (CI 0.08 to 22.92), see Analysis 2.5, sub-category 02.

High-dose compared to low-dose naltrexone depot:

- Opioid dependence, 1 RCT by Comer 2006:

No difference for reporting 1 or more adverse effects, 42 participants, RR 1.05 (CI 0.68 to 1.6), see Analysis 2.6, sub-category 01 and for number of participants discontinuing the trial due to adverse effects, 42 participants, RR 0.18 (CI 0.01 to 3.59), see comparison Analysis 2.6, sub-category 02.

- Alcohol dependence, 1 RCT by Garbutt 2005:

Group differences for number of participants discontinuing the trial due to adverse effects were significant in favour of control, 415 participants, RR 2.12 (CI 1.02 to 3.22), see Analysis 2.7, sub-category 01. No significant differences for reporting injection site pain, 415 participants, RR 1.37 (CI 0.76 to 2.44), see Analysis 2.7, sub-category 02 and for reporting an severe adverse effect (as described above), 415 participants, RR 0.93 (CI 0.40 to 2.15), see Analysis 2.7, sub-category 03.

(2) non-RCTs with parallel control group

Liver impaired compared to healthy controls:

In the report by Turncliff 2005 the same dose of naltrexone depot (Alkermes Inc. 190 mg) was administered in two non-randomized groups: cases consisting of liver impaired, currently abstinent alcohol dependent patients matched to a control group of healthy volunteers. The relative risk of reporting 1 or more AE was statistically significant in favour of control, 25 participants, RR 3.25 (CI 1.14 to 9.24), see Analysis 2.8.

Naltrexone implant compared to methadone maintenance:

In Tait 2007 mortality of two non-randomised cohorts of opioid dependent patients treated with naltrexone implants (GoMedical Inc.) or methadone maintenance is described. Of the 341 patients in the naltrexone group, 6 died in the study period between 2001 and 2006, whereas 15 of 553 patients in MMT died during those years. Group differences were not statistically significant with RR 0.65, CI 0.25 to 1.66 (see Analysis 2.9).

(3) Adverse effects of sustained-release naltrexone treatment reported in non-RCTs without control group

(a) Naltrexone implant (GoMedical Inc., Australia) for treatment of opioid dependence

In the report by Waal 2006 a local tissue reaction was evident in 2 of 13 participants, in both cases the sites were surgically revised and the implants removed. According to unpublished data from this trial, possibly naltrexone-related adverse effects were decreasing during the course of the study, for example: irritability was reported by 6 of 12 patients 1 week after treatment start; at week 8 only 2 of 6 subjects reported irritability. Headache and nausea were experienced by 5, respectively 2 of 12 participants 1 week after treatment start. At week 8 none of the 6 patients still in treatment complained about headache or nausea. In the report by Hulse 2005 3 implant removals in 361 treated patients were registered: 1 due to wound infection and 2 on patients’ request. No statement on possibly drug-related AEs or number of treatment responsive wound infections was made.

(b) Naltrexone implant (Wedgewood pharmacy, USA) for treatment of opioid dependence

Local tissue reactions occurred 7 times among 156 patients (Carreno 2003). Furthermore 3 incidents of wound infection and no implant removal were reported in this sample. According to reports by Foster 2003; Gölz 2000 and Waal 2003 the numbers of local tissue reactions were 15 of 101, 25 of 104 and 2 of 10 patients, respectively. Unpublished data from Gölz 2000 indicates wound infection in 6 of 104 patients (Partecke 2007). In the first cohort of 55 patients from Foster 2003, 2 patients died during treatment. Both deaths were deemed unrelated to implant treatment. No death was reported during treatment in the second cohort of 46 patients. Waal 2003 reports 3 implant removals, 2 due to adverse effects and 1 on patient’s request. 6 of 10 patients complained about dysphoria during the course of the study.

(c) Naltrexone depot injection (Biotek Inc., USA) for treatment of opioid dependence

In the report by Comer 2002, 11 out of 12 participants experienced pain at the injection site, no incidence of induration, erythema or irritation was observed. According to Sullivan 2006, 3 out of 5 subjects complained about pain, a burning sensation or induration.

(d) Naltrexone depot injection (Elbion NV Belgium, formerly DrugAbuse Sciences Inc., USA) for treatment of alcohol dependence

All 16 participants in the report by Galloway 2005 experienced 1 or more possibly naltrexone-related adverse effect, 15 out of 16 reported administration site-related adverse effects. None of the adverse effects were rated serious (i.e. having significant medical consequences) by research staff.

DISCUSSION

The main result of this review is a negative one: evidence to evaluate effectiveness of sustained-release naltrexone for treatment of opioid dependence is scarce. Only one report met inclusion criteria for analyses of effectiveness (Comer 2006). The naltrexone depot injection appeared dose-dependently beneficial: more subjects in the high-dose group spent longer time in treatment than subjects in the low-dose or placebo group. Time to drop-out was significantly longer in the high-dose group compared to the 2 other
groups. Craving scores also seemed to support the effectiveness of sustained-release naltrexone, as scorings on "needing heroin", but not on "wanting heroin", were significantly lower in the groups receiving naltrexone depot. Urinalysis findings on heroin use were reported and indicated a considerable reduction in the high-dose group compared to the low-dose or placebo group. Since urinalysis findings could not be related to number of urine samples provided per participant, these data were omitted from our analyses and calculation of overall effect estimates was considered inappropriate. Despite consistent findings, we find it premature to conclude with the effectiveness of sustained-release naltrexone for treatment of opioid dependence on the basis of only one report. Any conclusion from a systematic literature review should be based on findings from several (at least two) clinical trials using satisfactory measures to limit possible bias.

One of the major challenges in oral naltrexone treatment has been high drop out rates, which are also reflected by the findings from the Cochrane review on oral naltrexone (Minozzi 2006). When comparing oral naltrexone with or without psychosocial support to placebo, two months retention rates did not exceed 60% (Lerner 1992). The mean retention rate from the five included trials was as low as 33.3%. The two months retention rate of 68.2% achieved in the high-dose depot group investigated by Comer 2006, indicates a considerable advantage of sustained-release naltrexone, which needs to be confirmed by further investigations.

For treatment of opioid dependence, only the Russian Federation has recently approved the naltrexone implant Prodetoxone (Krupitsky 2007). However, our literature search did not retrieve any clinical trials on that formulation. Although to date evidence on effectiveness of sustained-release naltrexone for treatment of opioid dependence is clearly lacking, we would like to point out that several thousand opioid dependent patients are treated with naltrexone depots, and more frequently, implants. In Australia (Hulse 2005; Tait 2007) China (Moran 2007), Egypt (Maksoud 2006), Germany (Partecke 2007), England (Brewer 2002) and Russia (Ramenskaya 2005), naltrexone implants are used in clinical studies and, probably more widely, in private clinic settings. Independent of the circumstances of treatment, randomised-controlled trials seem to be the exception rather than the rule. Analysing reasons for the imbalance between number of opioid dependent patients in naltrexone implant treatment and number of good quality reports goes beyond the scope of this review.

The second objective of this systematic review was to assess the safety of sustained-release naltrexone when used in opioid and alcohol dependent samples and healthy volunteers. Safety outcomes were assessed separately for the three different populations. From a clinical perspective, qualitatively similar adverse effects would be expected regardless of treatment condition, but frequency of reporting may differ considerably due to different treatment goals in opioid (blocking the effect) and alcohol (reducing craving) dependence. Therefore, performing meta-analyses was regarded inappropriate. Nevertheless, alcohol dependent samples may contribute substantially to safety evaluation by illustrating trends applicable to opioid dependent samples.

Possibly naltrexone-related adverse effects

Findings on supposedly naltrexone-related adverse effects revealed significant group differences for nausea, fatigue, vomiting, decreased appetite, dizziness and upper abdominal pain in alcohol dependent patients (Garbutt 2005; Kranzler 2004, data not shown). These adverse effects seemed to occur in a dose-related fashion and most infrequently in the placebo group. Findings are consistent with side effects of oral naltrexone treatment described earlier (Martin 1973).

For an opioid dependent sample, Comer 2006 reports adverse effects with the most prominent symptoms being general disorders such as fatigue and administration site-related conditions. The composite outcome one or more adverse effect did not reach statistical significance, but was less frequently reported in the placebo group. These findings are in line with the Cochrane review on oral naltrexone (Minozzi 2006).

Although the number of possibly naltrexone-related adverse effects was not significantly different between groups in any RCT, the placebo groups reported adverse effects less frequently, independent of the condition studied. Severe adverse events, as reported by Garbutt 2005, were mostly hospital admissions for alcohol detoxification and favoured the naltrexone depot group. Six of ten opioid dependent participants in Waal 2003 complained about dysphoria, but this trial lacks a control group. In another trial without a control group (Waal 2006), complaints about adverse effects possibly caused by naltrexone (e.g. irritability, headache, nausea) were decreasing during the course of the study.

Administration site-related adverse effects and mortality

Findings for administration site-related adverse effects showed no significant group differences for injection site pain, -induration, or -contusion. In the report by Kranzler 2004 the naltrexone depot group reported more frequently than the placebo group one or more injection site reaction. Moreover, the composite outcome any injection site-related adverse effect showed a statistically significant advantage of the placebo group compared to low-dose naltrexone in alcohol dependent samples (Garbutt 2005; Kranzler 1998; Kranzler 2004).

In the seven reports on naltrexone implant for treatment of opioid dependence, adverse effect assessment consisted of wound infection, allergic reaction to foreign body and number of implants removed. However, findings should be interpreted with caution, as the majority of the trials did not have a control group. Besides, systematic assessment of adverse effects was mostly lacking and...
loss to follow-up was not always reported completely. We therefore find it inappropriate to calculate prevalence of allergic reactions or wound infections. Nevertheless, it should be kept in mind that these adverse effects do occur with any of the implant formulations investigated and that they may lead to surgical revision of the implant site.

The non-randomised trial which investigated mortality had several limitations and causality to interpret group differences cannot be imputed (Tait 2007). Data is based on retrospective record-linkage and information on number and duration of treatment episodes was unavailable for both groups.

When gathering data on adverse effects, substantial differences in methodological quality became obvious (Table 2). Four of the six reports on alcohol dependent patients were double-blind, placebo-controlled, randomised trials providing complete information on participants lost to follow-up. Only one out of ten reports on opioid dependent patients met a similar standard. Systematic assessment of drug- and administration site-related adverse effects was more prevalent in research involving alcohol dependent subjects compared to opioid dependent subjects. Regardless of the condition studied, any trial on experimental treatment such as sustained-release naltrexone, should be subject to the same quality requirements, i.e. active assessment and log of adverse effects, events and severe adverse events.

AUTHORS’ CONCLUSIONS

Implications for practice

To date, there is insufficient evidence to evaluate effectiveness of sustained-release naltrexone for treatment of opioid dependence. Sustained-release naltrexone formulations should still be considered investigational drugs, however, naltrexone depot injections available today seem promising in the treatment of opioid dependence.

Findings of possibly sustained-release naltrexone-related side effects are in line with research on naltrexone tablets. For naltrexone depot injections, administration site-related adverse effects such as pain appear to be frequent, but usually of moderate intensity and time limited. Data on administration site-related adverse effects of naltrexone implants is scarce. Hence, commercial use of any implant formulation still needs to be evaluated thoroughly.

Implications for research

Future studies of sustained-release naltrexone involving opioid dependent patients should provide a complete description of drop-out and be conducted with a control group, preferably in a randomised-controlled fashion. RCTs evaluating effectiveness for treatment of opioid dependence should compare sustained-release naltrexone to oral naltrexone or agonist replacement treatment with methadone or buprenorphine. Besides effectiveness, any research on naltrexone implants should also focus on safety to make an analysis of harm-benefit possible.

ACKNOWLEDGEMENTS

We would like to thank Karianne Hammerstrøm, Anne Ekanger and Ingeild Kirkhelei from the Norwegian Knowledge Centre for the Health Services and Simona Vecchi from the Department of Epidemiology ASL RME, Rome, Italy for conducting literature searches for this review. We are also grateful to Dres. Hulse, Krupitsky, Partridge, Wäal and Woody for supporting our work by providing unpublished data and additional information. Finally, we would like to thank our contact editor from the Cochrane Drugs and Alcohol Group Dr Silvia Minozzi.

REFERENCES

References to studies included in this review

Carreno 2003 [published data only]

Comer 2002 [published data only]

Comer 2006 [published data only]

Dunbar 2006 [published data only]

Foster 2003 [published data only]

Galloway 2005 [published data only]
* Galloway GP, Koch M, Cello R, Smith DE. Pharmacokinetics,

Garbutt 2005 *published data only*


Götz 2000 *published and unpublished data*


Hulse 2005 *published data only (unpublished sought but not used)*


Johnston 2004 *published data only*


Kranzler 1998 *published data only*


Kranzler 2004 *published data only*


Sullivan 2006 *published data only*


Tait 2007 *published data only*

* Tait RJ, Ngo HT, Hulse GK. Mortality in heroin users 3 years after naltrexone implant or methadone maintenance treatment. *Journal of Substance Abuse Treatment* in press.

Turncliff 2005 *published data only*


Waal 2003 *published and unpublished data*


Waal 2006 *published data only*


References to studies excluded from this review

Albanese 2000 *published data only*


Brewer 2001 *published data only*


Brewer 2002 *published data only*


Brewer 2004 *published data only*


Carreno 2002 *published data only*


Chiang 1984 *published data only*


Chiang 1985a *published data only*


Chiang 1985b *published data only*


Collins 2005 *published data only*

Colquhoun 2005  

Dean 2005  

Dean 2006  

Garcia-Alonso 1989  

Gooberman 1998  

Grusser 2006  

Hamilton 2002  

Harrison 2006  

Heading 2006  

Hulse 2002a  

HULSE 2002b  

Hulse 2003a  

Hulse 2003b  

Hulse 2003c  

Hulse 2004a  

Hulse 2004b  

Hulse 2004c  

Hulse 2004d  

Iversen 2005  

Jainski 2006  

Jeffrey 2007  

Johnson 2006  

Lerner 1992  

Marlowe 2006  

Martin 1974  

Modesto-Lowe 2002  

Ngo 2007  
Ngo HT, Tair RJ, Arnold-Reed DE, Hulse GK. Mental health outcomes following naltrexone implant treatment for heroin-depen-
References to ongoing studies
Hulse  [published data only]  
Hulse GK, Arnold-Reed D, Bulsara M. A randomised, double-blind, placebo-controlled clinical trial of naltrexone implants for the treatment of heroin addiction. Personal communication.

Kunøe  [published data only]  

Lobmaier  [published data only]  

Nunes 2002  [published data only]  

Nunes 2008  [published data only]  
Nunes E. Behavioral Naltrexone Therapy (BNT) for Promoting Adherence to Oral Naltrexone (BNT-Oral) vs Extended Release Injectable Depot Naltrexone (Depot-BNT); a Randomized Trial. Clinicaltrials.gov reference: NCT00577408.

Tiihonen  [published data only]  

Woody  [published data only]  

Additional references

Amato 2005  

Chiang 1985  

Comer 2007  

Cornish 1997  

EMCDDA 2006  

Ginzburg 1984  

Gonzalez 1988  

Guo 2001  

Higgins 2006  

Krupitsky 2007  

Maksoud 2006  
Maksoud NA. Evolution of Techniques over 10 years and 10000 cases. 3rd Berlin Stapleford International Addiction Conference. 2006.

Martin 1973  

Mattick 2003  

McLellan 2000  

Minozzi 2006  

Moran 2007  

Navaratnam 1994  
Navaratnam V, Jamaludin A, Raman N, Mohamed M, Mansor SM. Determination of naltrexone dosage for narcotic agonist blockade in...

**OAS 2005**


**Partecke 2007**


**Preston 1999**


**San 1991**


**van den Brink 2006**


* Indicates the major publication for the study
**Characteristics of included studies  [ordered by study ID]**

**Carreno 2003**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>non-RCT: uncontrolled, prospective trial, 1 year observation period</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>opioid dependent outpatients, n=156, treatment seeking</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Wedgewood naltrexone implant 1000 mg, rapid opioid detoxification with induction onto naltrexone: sequential treatment periods possible</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>retention in treatment, relapse to opioid use, adverse effects, Addiction Severity Index outcomes</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses only: no comparison group</td>
<td></td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

**Comer 2002**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>non-RCT: dose-finding trial (phase II), 2 sequential treatment groups, 6 weeks observation period</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>opioid dependent inpatients, n=12, non treatment seeking</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Biotek naltrexone depot 192 or 384 mg, detoxification followed by depot injections, heroin challenge protocol</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>heroin effects during blockade, opioid withdrawal symptoms, naltrexone plasma levels, adverse effects</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses only: non treatment seeking sample</td>
<td></td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>
### Comer 2006

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT: 2 centres, 3 parallel treatment groups, placebo-controlled randomised trial, 8 weeks observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>opioid dependent outpatients, n=60, treatment seeking</td>
</tr>
<tr>
<td>Interventions</td>
<td>Biotek naltrexone depot 192 or 384 mg, or placebo, detoxification followed by depot injections, all 3 treatment groups with manualised relapse prevention therapy</td>
</tr>
<tr>
<td>Outcomes</td>
<td>retention in treatment / time to drop out, illicit drug use by urinalysis, heroin craving, depression, adverse effects</td>
</tr>
<tr>
<td>Notes</td>
<td>only study included for analyses of effectiveness</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Dunbar 2006

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT: dose-finding trial (phase I), 2 sequential panels of 5 treatment groups, 2 (panel A) or 5 (panel B) months observation period</th>
</tr>
</thead>
</table>
| Participants     | healthy volunteers, outpatients  
- Panel A consisted of n=28 participants in 3 treatment groups: low dose, high dose, placebo  
- Panel B consisted of n=14 participants in 2 treatment groups: high dose or placebo |
| Interventions    | Alkermes naltrexone depot 190 or 380 mg, or placebo, oral naltrexone lead-in followed by single (panel A) or multiple (panel B) depot injections. |
| Outcomes         | pharmacokinetics, adverse effects                                                                                  |
| Notes            | included for safety analyses only: healthy volunteers                                                               |

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
### Foster 2003

**Methods**
non-RCT: uncontrolled, prospective trial, 12 weeks observation period

**Participants**
opioid dependent outpatients, seeking treatment in private clinic, first cohort n=55, second cohort n=46

**Interventions**
Wedgewood naltrexone implant 1000 mg, sequential treatment periods possible
- first cohort: rapid detoxification under general anaesthesia (RODA) followed by implant
- second cohort: domiciliary (i.e. non-iv sedation) rapid detoxification followed by implant

**Outcomes**
opioid use, naltrexone plasma levels, adverse effects

**Notes**
included for safety analyses only: no comparison group

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

### Galloway 2005

**Methods**
non-RCT: uncontrolled, prospective trial, 6 weeks observation period

**Participants**
alcohol dependent outpatients, n=16, treatment seeking

**Interventions**
DrugAbuse Sciences naltrexone depot (300mg), oral naltrexone lead-in followed by depot injection, weekly individual counselling sessions

**Outcomes**
alcohol use, alcohol craving, pharmacokinetics, adverse effects

**Notes**
included for safety analyses only: alcohol dependent sample

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>
### Garbutt 2005

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>RCT: 24 centres, 3 parallel treatment groups, placebo-controlled randomised trial, 24 weeks observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Alcohol dependent outpatients, n=624, treatment seeking</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Alkermes naltrexone depot 190 or 380mg, or placebo, sequentially administered monthly during 6 months, 12 sessions of manual based supportive therapy</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Alcohol consumption, time to drop out, changes in liver enzyme levels, adverse events, side effects</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Included for safety analyses only; alcohol dependent sample</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Gölz 2000

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Non-RCT: 2 sequential treatment groups, prospective trial, 2 year observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Opioid dependent outpatients, n=108, treatment seeking</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Wedgewood naltrexone implant 1000 mg or thrice weekly oral naltrexone, rapid opioid detoxification under anaesthesia followed by induction onto naltrexone, unclear if repeated implantations possible, free to choose groups</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Relapse to opioid use, abstinence, duration of receptor blockade, additional safety data provided by Partecke</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Included for safety analyses only; no adequate comparison group</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>
### Hulse 2005

<table>
<thead>
<tr>
<th>Methods</th>
<th>non-RCT: uncontrolled, retrospective record-linkage study, pre-post design, 18 months observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>opioid dependent outpatients, n=361 treatment seeking</td>
</tr>
<tr>
<td>Interventions</td>
<td>GoMedical naltrexone implant 3400mg, rapid opioid detoxification with induction onto naltrexone</td>
</tr>
<tr>
<td>Outcomes</td>
<td>hospital presentations due to opioid or other drug poisonings implants removed</td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses only: uncontrolled, retrospective record-linkage study</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

### Johnson 2004

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT: 4 centres, 2 parallel treatment groups, placebo-controlled randomised trial, 4 months observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>alcohol dependent outpatients, n=30, treatment seeking</td>
</tr>
<tr>
<td>Interventions</td>
<td>Alkermes naltrexone depot 400mg or placebo, psychosocial support once monthly, manual based at the two US centres</td>
</tr>
<tr>
<td>Outcomes</td>
<td>alcohol consumption, pharmacokinetics, changes in liver enzymes, adverse effects</td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses only: alcohol dependent sample</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Kranzler 1998

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT: 2 parallel treatment groups, placebo-controlled randomised trial, 12 weeks observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>alcohol dependent outpatients, n=20, treatment seeking</td>
</tr>
</tbody>
</table>
**Kranzler 1998** (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Biotek naltrexone depot 206mg or placebo, two weeks with oral naltrexone lead-in, weekly psychotherapy sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>alcohol consumption, pharmacokinetics, changes in gamma GT levels, adverse effects</td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses only: alcohol dependent sample</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

**Kranzler 2004**

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT: 30 centres, 2 parallel treatment groups, placebo-controlled randomised trial, 3 months observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>alcohol dependent outpatients, n=333, treatment seeking</td>
</tr>
<tr>
<td>Interventions</td>
<td>DrugAbuse Sciences naltrexone depot 300 or 150 mg, or placebo, oral naltrexone lead-in followed by sequentially administered depot injections during 3 months, 4 manual based counselling sessions</td>
</tr>
<tr>
<td>Outcomes</td>
<td>alcohol consumption, adverse effects</td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses only: alcohol dependent sample</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

**Sullivan 2006**

<table>
<thead>
<tr>
<th>Methods</th>
<th>non-RCT: uncontrolled, dose-finding trial (phase II), 6 weeks observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>opioid dependent inpatients, n=5, non treatment seeking</td>
</tr>
<tr>
<td>Interventions</td>
<td>Biotek naltrexone depot 384 mg, detox and oral naltrexone lead-in followed by depot injection, heroin challenge protocol</td>
</tr>
</tbody>
</table>
Sullivan 2006  *(Continued)*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>heroin dose effects, adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes</td>
<td>included for safety analyses only: non treatment seeking sample</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

Tait 2007

<table>
<thead>
<tr>
<th>Methods</th>
<th>two parallel treatment groups, record linkage, 5 and a half years observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>opioid dependent outpatients, n=341 treatment seeking</td>
</tr>
<tr>
<td>Interventions</td>
<td>GoMedical naltrexone implant 2200 mg, methadone maintenance treatment, possibility of sequential treatment episodes not stated</td>
</tr>
<tr>
<td>Outcomes</td>
<td>mortality</td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

Turncliff 2005

<table>
<thead>
<tr>
<th>Methods</th>
<th>non-RCT: 2 parallel treatment groups, matched case-control trial, 3 months observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>alcohol dependent outpatients (currently abstinent, liver impaired) and healthy controls, n=25, treatment seeking</td>
</tr>
<tr>
<td>Interventions</td>
<td>Alkermes naltrexone depot 190 mg</td>
</tr>
<tr>
<td>Outcomes</td>
<td>pharmacokinetics, adverse effects</td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses only: alcohol dependent sample</td>
</tr>
</tbody>
</table>

**Risk of bias**
Turncliff 2005  *(Continued)*

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

**Waal 2003**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>non-RCT: uncontrolled, prospective trial, 2 months observation period</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>opioid dependent outpatients, n=10, treatment seeking</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Wedgewood naltrexone implant 1000 mg, sequential treatment periods possible, counselling sessions</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>pharmacokinetics, drug use, adverse effects</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses only: no comparison group</td>
<td></td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>

**Waal 2006**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>non-RCT: uncontrolled, prospective trial, 1 year observation period (after last implant)</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>opioid dependent outpatients, n=13, treatment seeking</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>GoMedical naltrexone implant 1800 or 3600 mg, sequential treatment periods possible</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>pharmacokinetics, drug use, quality of life, adverse effects</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>included for safety analyses only: no comparison group</td>
<td></td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>D - Not used</td>
</tr>
</tbody>
</table>
### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albanese 2000</td>
<td>oral naltrexone</td>
</tr>
<tr>
<td>Brewer 2001</td>
<td>no clinical trial (comment)</td>
</tr>
<tr>
<td>Brewer 2002</td>
<td>case study, adverse effect data not reported</td>
</tr>
<tr>
<td>Brewer 2004</td>
<td>case report, adverse effect data not reported</td>
</tr>
<tr>
<td>Carreno 2002</td>
<td>oral naltrexone</td>
</tr>
<tr>
<td>Chiang 1984</td>
<td>pilot study on healthy volunteers with focus on pharmacokinetics</td>
</tr>
<tr>
<td>Chiang 1985a</td>
<td>pilot study on healthy volunteers with focus on pharmacokinetics</td>
</tr>
<tr>
<td>Chiang 1985b</td>
<td>pilot study on healthy volunteers: concludes with recommending no further investigations on this particular product</td>
</tr>
<tr>
<td>Collins 2005</td>
<td>oral naltrexone</td>
</tr>
<tr>
<td>Colquhoun 2005</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>Dean 2005</td>
<td>no clinical trial (review)</td>
</tr>
<tr>
<td>Dean 2006</td>
<td>oral naltrexone</td>
</tr>
<tr>
<td>Garcia-Alonso 1989</td>
<td>oral naltrexone</td>
</tr>
<tr>
<td>Gooberman 1998</td>
<td>abstract from conference presentation only</td>
</tr>
<tr>
<td>Grusser 2006</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>Hamilton 2002</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>Harrison 2006</td>
<td>no clinical trial (review)</td>
</tr>
<tr>
<td>Heading 2006</td>
<td>no clinical trial (review)</td>
</tr>
<tr>
<td>Hulse 2002a</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>Hulse 2002b</td>
<td>case report, adverse effect data not provided</td>
</tr>
<tr>
<td>Hulse 2003a</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>Hulse 2003b</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Hulse 2003c</td>
<td>case report, adverse effect data not provided</td>
</tr>
<tr>
<td>Hulse 2004a</td>
<td>no clinical trial</td>
</tr>
<tr>
<td>Hulse 2004b</td>
<td>no clinical trial</td>
</tr>
<tr>
<td>Hulse 2004c</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>Hulse 2004d</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>Iversen 2005</td>
<td>no clinical trial</td>
</tr>
<tr>
<td>Jasinski 2006</td>
<td>no clinical trial</td>
</tr>
<tr>
<td>Jeffrey 2007</td>
<td>non-RCT, hepatitis C treatment-related outcomes only, adverse effect data not reported</td>
</tr>
<tr>
<td>Johnson 2006</td>
<td>no clinical trial</td>
</tr>
<tr>
<td>Lerner 1992</td>
<td>oral naltrexone</td>
</tr>
<tr>
<td>Marlowe 2006</td>
<td>no clinical trial</td>
</tr>
<tr>
<td>Martin 1974</td>
<td>no clinical trial (dogs)</td>
</tr>
<tr>
<td>Modesto-Lowe 2002</td>
<td>no clinical trial (review)</td>
</tr>
<tr>
<td>Ngo 2007</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>NRCC report 1978</td>
<td>oral naltrexone</td>
</tr>
<tr>
<td>O’Brien 2005</td>
<td>no clinical trial (comment)</td>
</tr>
<tr>
<td>O’Brien 2006</td>
<td>no clinical trial (comment)</td>
</tr>
<tr>
<td>O’Malley 1992</td>
<td>oral naltrexone</td>
</tr>
<tr>
<td>Oliver 2005</td>
<td>no clinical trial (letter)</td>
</tr>
<tr>
<td>Pekta 1998</td>
<td>abstract available only</td>
</tr>
<tr>
<td>Pitt 1981</td>
<td>no clinical trial (animals) and duplicate of NIDA research monograph 28</td>
</tr>
<tr>
<td>Poser 1996</td>
<td>no clinical trial (review)</td>
</tr>
<tr>
<td>Rabinowitz 1998</td>
<td>oral naltrexone</td>
</tr>
</tbody>
</table>
(Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramenskaya 2005</td>
<td>no clinical trial (pharmacokinetic results)</td>
</tr>
<tr>
<td>Rawson 2000</td>
<td>no clinical trial (review)</td>
</tr>
<tr>
<td>Reece 2007</td>
<td>non-RCT, adverse effect data not reported</td>
</tr>
<tr>
<td>Resnick 1977</td>
<td>no clinical trial (review)</td>
</tr>
<tr>
<td>Reuning 1976</td>
<td>no clinical trial (animals)</td>
</tr>
<tr>
<td>Riddle 2001</td>
<td>no clinical trial (review)</td>
</tr>
<tr>
<td>Schwoppe 1975</td>
<td>no clinical trial (mice)</td>
</tr>
<tr>
<td>Sobel 2001</td>
<td>abstract available only</td>
</tr>
<tr>
<td>Suhaida 2004</td>
<td>no clinical trial (in vitro study)</td>
</tr>
<tr>
<td>Teagle 2007</td>
<td>no clinical trial (press release)</td>
</tr>
<tr>
<td>Warhaft 2003</td>
<td>no clinical trial (letter)</td>
</tr>
<tr>
<td>Wesson 2003</td>
<td>abstract available only, 9 and 12 months follow-up data from same sample as included report Kranzler 2004</td>
</tr>
<tr>
<td>Willette 1978</td>
<td>no clinical trial</td>
</tr>
<tr>
<td>Willette 1981</td>
<td>no clinical trial (review and animal studies)</td>
</tr>
<tr>
<td>Wodak 2001</td>
<td>no clinical trial (review)</td>
</tr>
</tbody>
</table>

**Characteristics of ongoing studies [ordered by study ID]**

**Hulse**

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A randomised, double-blind, placebo-controlled clinical trial of naltrexone implants for the treatment of heroin addiction</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>opioid dependent outpatients (DSM IV)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 groups: naltrexone implant + oral placebo compared to placebo implant + oral naltrexone</td>
</tr>
</tbody>
</table>
### Hulse (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>naltrexone blood levels, retention in treatment, opiate use, opiate overdose, opiate related morbidity and mortality, craving for heroin, other drug use, other drug overdose, other drug-related morbidity or mortality, social functioning, general health, implant insertion site healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting date</td>
<td>recruitment and follow-up is completed</td>
</tr>
<tr>
<td>Contact information</td>
<td>Gary Hulse: <a href="mailto:hulseg@meddent.uwa.edu.au">hulseg@meddent.uwa.edu.au</a></td>
</tr>
<tr>
<td>Notes</td>
<td>Country: Australia</td>
</tr>
</tbody>
</table>

### Kunøe

| Trial name or title       | Naltrexone Implants - a Randomised Study  
| Methods                  |                                                                                                                                                                                                       |
| Participants             | opioid dependent outpatients opting for relapse prevention with naltrexone implants compared to treatment-as-usual controls                                                                         |
| Interventions            | 12 months, observation 2 groups: treatment start with naltrexone implants before institutional discharge, group cross over optional after 6 months |
| Outcomes                 | drug use, quality of life, depression, adverse effects                                                                                                                                             |
| Starting date            | recruitment started January 2006, completed in June 2007                                                                                                                                             |
| Contact information      | Nikolaj Kunøe: nikolaj.kunoe@medisin.uio.no                                                                                                                                                    |
| Notes                    | Country: Norway                                                                                                                                                                                         |

### Lobmaier

| Trial name or title       | Naltrexone Implants - a Treatment Alternative for Heroin Dependent Prisoners?  
| Methods                  |                                                                                                                                                                                                       |
| Participants             | opioid dependent inmates                                                                                                                                                                               |
Interventions 18 months observation 2 groups: treatment start with naltrexone implants or methadone maintenance before prison release, cross over optional after 6 and 12 months

Outcomes drug use, criminal activity, quality of life, depression, adverse effects

Starting date recruitment started May 2005, completed July 2007

Contact information Philipp Lobmaier: p.p.lobmaier@medisin.uio.no

Notes Country: Norway

Nunes 2002

Trial name or title Behavioral Naltrexone Therapy: A Novel Treatment for Heroin Dependence Clinicaltrial.gov reference: NCT00332228

Methods

Participants opioid dependent outpatients

Interventions 6 months observation, 4 groups: 1) behavioral therapy plus depot naltrexone 2) behavioral therapy plus placebo injections 3) Compliance Enhancement (CE), simulating standard treatment with oral naltrexone plus depot naltrexone 4) CE plus placebo injections

Outcomes heroin use, retention in treatment, naltrexone blood levels,

Starting date recruitment started June 2002

Contact information Stephen Anen: anenste@pi.cpmc.columbia.edu

Notes Country: USA

Nunes 2008

Trial name or title Behavioral Naltrexone Therapy (BNT) for Promoting Adherence to Oral Naltrexone (BNT-Oral) vs Extended Release Injectable Depot Naltrexone (Depot-BNT); a Randomized Trial

Methods

Participants opioid dependent outpatients
<table>
<thead>
<tr>
<th><strong>Nunes 2008</strong> (Continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
</tr>
<tr>
<td><strong>Contact information</strong></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Tiihonen</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial name or title</strong></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
</tr>
<tr>
<td><strong>Contact information</strong></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Woody</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial name or title</strong></td>
</tr>
<tr>
<td><strong>Methods</strong></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
</tr>
<tr>
<td>Interventions</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>Starting date</td>
</tr>
<tr>
<td>Contact information</td>
</tr>
<tr>
<td>Notes</td>
</tr>
</tbody>
</table>
### DATA AND ANALYSES

#### Comparison 1. effectiveness outcomes treatment vs. control

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 treatment retention in high-dose depot vs. placebo</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.75 [0.92, 3.34]</td>
</tr>
<tr>
<td>2 treatment retention in low-dose depot vs. placebo</td>
<td>1</td>
<td>38</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.54 [0.78, 3.05]</td>
</tr>
<tr>
<td>3 treatment retention in high-dose vs. low-dose depot</td>
<td>1</td>
<td>42</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.14 [0.72, 1.80]</td>
</tr>
<tr>
<td>4 time to drop out in high-dose depot vs. placebo</td>
<td>1</td>
<td>40</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>21.0 [10.68, 31.32]</td>
</tr>
<tr>
<td>5 time to drop out in high-dose vs. low-dose depot</td>
<td>1</td>
<td>42</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>12.0 [1.69, 22.31]</td>
</tr>
<tr>
<td>6 time to drop out in low-dose depot vs. placebo</td>
<td>1</td>
<td>38</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>9.0 [-3.40, 21.40]</td>
</tr>
</tbody>
</table>

#### Comparison 2. safety outcomes treatment vs. control

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 high-dose depot vs. placebo in opioid dependence</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 one or more adverse effects</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.36 [0.79, 2.35]</td>
</tr>
<tr>
<td>1.2 discontinued due to adverse effects</td>
<td>1</td>
<td>40</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.28 [0.01, 6.38]</td>
</tr>
<tr>
<td>2 high-dose depot vs. placebo in alcohol dependence</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 one or more adverse effects</td>
<td>1</td>
<td>30</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.15 [0.73, 1.81]</td>
</tr>
<tr>
<td>2.2 severe adverse effects</td>
<td>1</td>
<td>414</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.68 [0.31, 1.48]</td>
</tr>
<tr>
<td>2.3 injection site pain</td>
<td>1</td>
<td>414</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.29 [0.73, 2.28]</td>
</tr>
<tr>
<td>2.4 discontinued due to adverse effects</td>
<td>1</td>
<td>414</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.11 [1.15, 3.88]</td>
</tr>
<tr>
<td>3 low-dose depot vs. placebo in opioid dependence</td>
<td>1</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 one or more adverse effects</td>
<td>1</td>
<td>38</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.3 [0.74, 2.28]</td>
</tr>
<tr>
<td>3.2 discontinued due to adverse effects</td>
<td>1</td>
<td>38</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.8 [0.18, 18.21]</td>
</tr>
<tr>
<td>3.3 injection site induration</td>
<td>1</td>
<td>38</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.9 [0.06, 13.36]</td>
</tr>
<tr>
<td>4 low-dose depot vs. placebo in alcohol dependence</td>
<td>3</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>4.1 one or more adverse effect</td>
<td>2</td>
<td>353</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.06 [0.95, 1.17]</td>
</tr>
</tbody>
</table>
4.2 discontinued due to adverse effects 1 419 Risk Ratio (M-H, Fixed, 95% CI) 1.00 [0.49, 2.04]
4.3 injection site pain 3 772 Risk Ratio (M-H, Fixed, 95% CI) 1.17 [0.92, 1.47]
4.4 injection site induration 2 353 Risk Ratio (M-H, Fixed, 95% CI) 1.17 [0.76, 1.80]
4.5 injection site contusion 1 333 Risk Ratio (M-H, Fixed, 95% CI) 1.24 [0.60, 2.57]
4.6 one or more injection site reaction 1 333 Risk Ratio (M-H, Fixed, 95% CI) 1.19 [1.02, 1.38]
4.7 severe adverse effect 1 419 Risk Ratio (M-H, Fixed, 95% CI) 0.73 [0.34, 1.55]
4.8 injection site related to adverse effects, pooled 3 1791 Risk Ratio (M-H, Fixed, 95% CI) 1.18 [1.02, 1.36]
5 low-dose depot vs. placebo in healthy volunteers
5.1 one or more adverse effects 1 42 Risk Ratio (M-H, Fixed, 95% CI) 2.46 [0.16, 38.89]
5.2 one or more injection site reaction 1 42 Risk Ratio (M-H, Fixed, 95% CI) 1.32 [0.08, 22.92]
6 high-dose vs. low-dose depot in opioid dependence
6.1 one or more adverse effects 1 42 Risk Ratio (M-H, Fixed, 95% CI) 1.05 [0.68, 1.61]
6.2 discontinued due to adverse effects 1 42 Risk Ratio (M-H, Fixed, 95% CI) 0.18 [0.01, 3.59]
7 high-dose vs. low-dose depot in alcohol dependence
7.1 discontinued due to adverse effects 1 415 Risk Ratio (M-H, Fixed, 95% CI) 2.12 [1.16, 3.90]
7.2 injection site pain 1 415 Risk Ratio (M-H, Fixed, 95% CI) 1.37 [0.76, 2.44]
7.3 severe adverse effects 1 415 Risk Ratio (M-H, Fixed, 95% CI) 0.93 [0.40, 2.15]
8 one or more adverse effects in liver impaired vs. healthy controls
8.1 one or more injection site reaction 1 25 Risk Ratio (M-H, Fixed, 95% CI) 3.25 [1.14, 9.24]
9 mortality in naltrexone implant vs. methadone maintenance 1 894 Risk Ratio (M-H, Fixed, 95% CI) 0.65 [0.25, 1.66]

Analysis 1.1. Comparison I effectiveness outcomes treatment vs. control, Outcome I treatment retention in high-dose depot vs. placebo.

Review: Sustained-Release Naltrexone For Opioid Dependence
Comparison: I effectiveness outcomes treatment vs. control
Outcome: I treatment retention in high-dose depot vs. placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>high-dose naltrexone n/N</th>
<th>placebo injection n/N</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comer 2006</td>
<td>15/22</td>
<td>7/18</td>
<td>1.75 [0.92, 3.34]</td>
<td>100.0%</td>
<td>1.75 [0.92, 3.34]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>22</td>
<td>18</td>
<td>100.0%</td>
<td>1.75 [0.92, 3.34]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 15 (high-dose naltrexone), 7 (placebo injection)
Heterogeneity: not applicable
Test for overall effect: Z = 1.70 (P = 0.088)
Analysis 1.2. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 2 treatment retention in low-dose depot vs. placebo.

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 1 effectiveness outcomes treatment vs. control

Outcome: 2 treatment retention in low-dose depot vs. placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>low-dose naltrexone n/N</th>
<th>placebo injection n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comer 2006</td>
<td>12/20</td>
<td>7/18</td>
<td>1.54 [0.78, 3.05]</td>
<td>100.0%</td>
<td>1.54 [0.78, 3.05]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>20</td>
<td>18</td>
<td>1.54 [0.78, 3.05]</td>
<td>100.0%</td>
<td>1.54 [0.78, 3.05]</td>
</tr>
</tbody>
</table>

Total events: 12 (low-dose naltrexone), 7 (placebo injection)

Heterogeneity: not applicable

Test for overall effect: Z = 1.25 (P = 0.21)

Analysis 1.3. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 3 treatment retention in high-dose vs. low-dose depot.

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 1 effectiveness outcomes treatment vs. control

Outcome: 3 treatment retention in high-dose vs. low-dose depot

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>high-dose naltrexone n/N</th>
<th>low-dose naltrexone n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comer 2006</td>
<td>15/22</td>
<td>12/20</td>
<td>1.14 [0.72, 1.80]</td>
<td>100.0%</td>
<td>1.14 [0.72, 1.80]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>22</td>
<td>20</td>
<td>1.14 [0.72, 1.80]</td>
<td>100.0%</td>
<td>1.14 [0.72, 1.80]</td>
</tr>
</tbody>
</table>

Total events: 15 (high-dose naltrexone), 12 (low-dose naltrexone)

Heterogeneity: not applicable

Test for overall effect: Z = 0.55 (P = 0.58)
Analysis 1.4. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 4 time to drop out in high-dose depot vs. placebo.

Review: Sustained-Release Naltrexone For Opioid Dependence
Comparison: 1 effectiveness outcomes treatment vs. control
Outcome: 4 time to drop out in high-dose depot vs. placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>high-dose naltrexone</th>
<th>placebo injection</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Comer 2006</td>
<td>22 48 (13)</td>
<td>18 27 (19)</td>
<td>100.0 %</td>
<td>21.00</td>
<td>[ 10.68, 31.32 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>22</td>
<td>18</td>
<td>100.0 %</td>
<td>21.00</td>
<td>[ 10.68, 31.32 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 3.99 (P = 0.000067)

Analysis 1.5. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 5 time to drop out in high-dose vs. low-dose depot.

Review: Sustained-Release Naltrexone For Opioid Dependence
Comparison: 1 effectiveness outcomes treatment vs. control
Outcome: 5 time to drop out in high-dose vs. low-dose depot

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>high-dose naltrexone</th>
<th>low-dose naltrexone</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Comer 2006</td>
<td>22 48 (13)</td>
<td>20 36 (20)</td>
<td>100.0 %</td>
<td>12.00</td>
<td>[ 1.69, 22.31 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>22</td>
<td>20</td>
<td>100.0 %</td>
<td>12.00</td>
<td>[ 1.69, 22.31 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 2.28 (P = 0.023)
Analysis 1.6. Comparison 1 effectiveness outcomes treatment vs. control, Outcome 6 time to drop out in low-dose depot vs. placebo.

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 1 effectiveness outcomes treatment vs. control

Outcome: 6 time to drop out in low-dose depot vs. placebo

Study or subgroup | low-dose naltrexone | placebo injection | Mean Difference | Weight | Mean Difference |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>N(N) Fixed 95% CI</td>
<td>N(N) Fixed 95% CI</td>
<td></td>
</tr>
<tr>
<td>Comer 2006</td>
<td>20 (36)</td>
<td>18 (27)</td>
<td>100.0 %</td>
<td>9.00 [ -3.40, 21.40 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>20</td>
<td>18</td>
<td>100.0 %</td>
<td>9.00 [ -3.40, 21.40 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 1.42 (P = 0.16)

Analysis 2.1. Comparison 2 safety outcomes treatment vs. control, Outcome 1 high-dose depot vs. placebo in opioid dependence.

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 2 safety outcomes treatment vs. control

Outcome: 1 high-dose depot vs. placebo in opioid dependence

Study or subgroup | high-dose naltrexone | placebo injection | Risk Ratio | Weight | Risk Ratio |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N n/N</td>
<td>M-H,Fixed,95% CI</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>one or more adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comer 2006</td>
<td>15/22</td>
<td>9/18</td>
<td>1.36 [ 0.79, 2.35 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>22</td>
<td>18</td>
<td>100.0 %</td>
<td>1.36 [ 0.79, 2.35 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 15 (high-dose naltrexone), 9 (placebo injection)

Heterogeneity: not applicable

Test for overall effect: Z = 1.12 (P = 0.26)

2 discontinued due to adverse effects

| Subtotal (95% CI) | 22 | 18 | 100.0 % | 0.28 [ 0.01, 6.38 ] |

Total events: 0 (high-dose naltrexone), 1 (placebo injection)

Heterogeneity: not applicable

Test for overall effect: Z = 0.80 (P = 0.42)
### Analysis 2.2. Comparison 2 safety outcomes treatment vs. control, Outcome 2 high-dose depot vs. placebo in alcohol dependence.

**Review:** Sustained-Release Naltrexone For Opioid Dependence  
**Comparison:** 2 safety outcomes treatment vs. control  
**Outcome:** 2 high-dose depot vs. placebo in alcohol dependence

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>high-dose naltrexone</th>
<th>placebo injection</th>
<th>Risk Ratio M-H,Fixed(95% CI)</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 one or more adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson 2004</td>
<td>23/25</td>
<td>4/5</td>
<td>1.15 [ 0.73, 1.81 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>25</td>
<td>5</td>
<td>1.15 [ 0.73, 1.81 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Total events: 23 (high-dose naltrexone), 4 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.60 (P = 0.55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 severe adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garbutt 2005</td>
<td>10/205</td>
<td>15/209</td>
<td>0.68 [ 0.31, 1.48 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>205</td>
<td>209</td>
<td>0.68 [ 0.31, 1.48 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Total events: 10 (high-dose naltrexone), 15 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.97 (P = 0.33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 injection site pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garbutt 2005</td>
<td>24/205</td>
<td>19/209</td>
<td>1.29 [ 0.73, 2.28 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>205</td>
<td>209</td>
<td>1.29 [ 0.73, 2.28 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Total events: 24 (high-dose naltrexone), 19 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.87 (P = 0.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 discontinued due to adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garbutt 2005</td>
<td>29/205</td>
<td>14/209</td>
<td>2.11 [ 1.15, 3.88 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>205</td>
<td>209</td>
<td>2.11 [ 1.15, 3.88 ]</td>
<td>100.0 %</td>
<td></td>
</tr>
<tr>
<td>Total events: 29 (high-dose naltrexone), 14 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.41 (P = 0.016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Analysis 2.3. Comparison 2 safety outcomes treatment vs. control, Outcome 3 low-dose depot vs. placebo in opioid dependence.

**Review:** Sustained-Release Naltrexone For Opioid Dependence

**Comparison:** 2 safety outcomes treatment vs. control

**Outcome:** 3 low-dose depot vs. placebo in opioid dependence

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>low-dose naltrexone</th>
<th>placebo injection</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I one or more adverse effects</td>
<td>13/20 9/18</td>
<td></td>
<td>100.0 %</td>
<td>1.30 [ 0.74, 2.28 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>20 18</td>
<td></td>
<td>100.0 %</td>
<td>1.30 [ 0.74, 2.28 ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 discontinued due to adverse effects</td>
<td>2/20 1/18</td>
<td>100.0 %</td>
<td>1.80 [ 0.18, 18.21 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>20 18</td>
<td></td>
<td>100.0 %</td>
<td>1.80 [ 0.18, 18.21 ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 injection site induration</td>
<td>1/20 1/18</td>
<td>100.0 %</td>
<td>0.90 [ 0.06, 13.36 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>20 18</td>
<td></td>
<td>100.0 %</td>
<td>0.90 [ 0.06, 13.36 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 13 (low-dose naltrexone), 9 (placebo injection)

Heterogeneity: not applicable

Test for overall effect: Z = 0.91 (P = 0.36)

Total events: 2 (low-dose naltrexone), 1 (placebo injection)

Heterogeneity: not applicable

Test for overall effect: Z = 0.50 (P = 0.62)

Total events: 1 (low-dose naltrexone), 1 (placebo injection)

Heterogeneity: not applicable

Test for overall effect: Z = 0.08 (P = 0.94)
### Analysis 2.4. Comparison 2 safety outcomes treatment vs. control, Outcome 4 low-dose depot vs. placebo in alcohol dependence.

**Review:** Sustained-Release Naltrexone For Opioid Dependence

**Comparison:** 2 safety outcomes treatment vs. control

**Outcome:** 4 low-dose depot vs. placebo in alcohol dependence

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>low-dose naltrexone</th>
<th>placebo injection</th>
<th>Risk Ratio M-H,Fixed</th>
<th>95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 one or more adverse effect</td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed</td>
<td>95% CI</td>
<td></td>
<td>M-H,Fixed</td>
<td>95% CI</td>
</tr>
<tr>
<td>Kranzler 1998</td>
<td>7/15</td>
<td>2/5</td>
<td></td>
<td>2.2</td>
<td>1.17 [0.35, 3.88]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranzler 2004</td>
<td>140/167</td>
<td>132/166</td>
<td></td>
<td>97.8</td>
<td>1.05 [0.95, 1.17]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>182</td>
<td>171</td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.06 [0.95, 1.17]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 147 (low-dose naltrexone), 134 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.03$, df = 1 ($P = 0.87$); $I^2 = 0.0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.05$ ($P = 0.30$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 discontinued due to adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garbutt 2005</td>
<td>142/10</td>
<td>142/209</td>
<td></td>
<td>100.0</td>
<td>1.00 [0.49, 2.04]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>210</td>
<td>209</td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.00 [0.49, 2.04]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 14 (low-dose naltrexone), 14 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.01$ ($P = 0.09$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 injection site pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garbutt 2005</td>
<td>18/210</td>
<td>19/209</td>
<td></td>
<td>22.6</td>
<td>0.94 [0.51, 1.74]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranzler 1998</td>
<td>5/15</td>
<td>2/5</td>
<td></td>
<td>3.6</td>
<td>0.83 [0.23, 3.03]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranzler 2004</td>
<td>78/167</td>
<td>62/166</td>
<td></td>
<td>73.8</td>
<td>1.25 [0.97, 1.61]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>392</td>
<td>380</td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.17 [0.92, 1.47]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 101 (low-dose naltrexone), 93 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 1.01$, df = 2 ($P = 0.60$); $I^2 = 0.0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.28$ ($P = 0.20$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 injection site induration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranzler 1998</td>
<td>11/15</td>
<td>2/5</td>
<td></td>
<td>9.7</td>
<td>1.83 [0.60, 5.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranzler 2004</td>
<td>11/167</td>
<td>28/166</td>
<td></td>
<td>90.3</td>
<td>1.10 [0.69, 1.75]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>171</td>
<td>167</td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.17 [0.76, 1.80]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 42 (low-dose naltrexone), 30 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.69$, df = 1 ($P = 0.41$); $I^2 = 0.0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.72$ ($P = 0.47$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 injection site contusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranzler 2004</td>
<td>15/167</td>
<td>12/166</td>
<td></td>
<td>100.0</td>
<td>1.24 [0.60, 2.57]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>167</td>
<td>166</td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.24 [0.60, 2.57]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued...)
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>low-dose naltrexone</th>
<th>placebo injection</th>
<th>Risk Ratio Weight</th>
<th>Risk Ratio M-H,Fixed(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total events:</strong></td>
<td>15 (low-dose naltrexone), 12 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 0.58 (P = 0.56)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 one or more injection site reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kranzler 2004</td>
<td>123/167</td>
<td>103/166</td>
<td>100.0 %</td>
<td>1.19 [ 1.02, 1.38 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI):</strong></td>
<td>167</td>
<td>166</td>
<td>100.0 %</td>
<td>1.19 [ 1.02, 1.38 ]</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>123 (low-dose naltrexone), 103 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 2.25 (P = 0.025)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 severe adverse effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garbutt 2005</td>
<td>11/210</td>
<td>15/209</td>
<td>100.0 %</td>
<td>0.73 [ 0.34, 1.55 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI):</strong></td>
<td>210</td>
<td>209</td>
<td>100.0 %</td>
<td>0.73 [ 0.34, 1.55 ]</td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>11 (low-dose naltrexone), 15 (placebo injection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 0.82 (P = 0.41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 injection site related to adverse effects, pooled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garbutt 2005</td>
<td>18/210</td>
<td>19/209</td>
<td>8.3 %</td>
<td>0.94 [ 0.51, 1.74 ]</td>
</tr>
<tr>
<td>Kranzler 1998</td>
<td>16/30</td>
<td>4/10</td>
<td>2.6 %</td>
<td>1.33 [ 0.58, 3.06 ]</td>
</tr>
<tr>
<td>Kranzler 2004</td>
<td>247/668</td>
<td>205/664</td>
<td>89.1 %</td>
<td>1.20 [ 1.03, 1.39 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI):</strong></td>
<td>908</td>
<td>883</td>
<td>100.0 %</td>
<td>1.18 [ 1.02, 1.36 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.63$, df = 2 ($P = 0.73$); $I^2 = 0.0\%$

Test for overall effect: Z = 2.24 ($P = 0.025$)
### Analysis 2.5. Comparison 2 safety outcomes treatment vs. control, Outcome 5 low-dose depot vs. placebo in healthy volunteers.

#### Review: Sustained-Release Naltrexone For Opioid Dependence

#### Comparison: 2 safety outcomes treatment vs. control

#### Outcome: 5 low-dose depot vs. placebo in healthy volunteers

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>low-dose naltrexone</th>
<th>placebo injection</th>
<th>Risk Ratio (M-H,Fixed 95% CI)</th>
<th>Weight</th>
<th>Risk Ratio (M-H,Fixed 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 one or more adverse effects</td>
<td>Dunbar 2006</td>
<td>6/36</td>
<td>0/6</td>
<td>100.0 %</td>
<td>2.46 [0.16, 38.89]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td><strong>36</strong></td>
<td><strong>6</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>2.46 [0.16, 38.89]</strong></td>
</tr>
<tr>
<td>2 one or more injection site reactions</td>
<td>Dunbar 2006</td>
<td>3/36</td>
<td>0/6</td>
<td>100.0 %</td>
<td>1.32 [0.08, 22.92]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td><strong>36</strong></td>
<td><strong>6</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.32 [0.08, 22.92]</strong></td>
</tr>
</tbody>
</table>

Total events: 6 (low-dose naltrexone), 0 (placebo injection)

Heterogeneity: not applicable

Test for overall effect: Z = 0.64 (P = 0.52)

Test for overall effect: Z = 0.19 (P = 0.85)
Analysis 2.6. Comparison 2 safety outcomes treatment vs. control, Outcome 6 high-dose vs. low-dose depot in opioid dependence.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>high-dose naltrexone</th>
<th>low-dose naltrexone</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 one or more adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comer 2006</td>
<td>15/22</td>
<td>13/20</td>
<td>100.0 %</td>
<td>1.05</td>
<td>[0.68, 1.61]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>22</td>
<td>20</td>
<td>100.0 %</td>
<td>1.05</td>
<td>[0.68, 1.61]</td>
</tr>
<tr>
<td>Total events: 15 (high-dose naltrexone), 13 (low-dose naltrexone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.22 (P = 0.83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 discontinued due to adverse effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comer 2006</td>
<td>0/22</td>
<td>2/20</td>
<td>100.0 %</td>
<td>0.18</td>
<td>[0.01, 3.59]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>22</td>
<td>20</td>
<td>100.0 %</td>
<td>0.18</td>
<td>[0.01, 3.59]</td>
</tr>
<tr>
<td>Total events: 0 (high-dose naltrexone), 2 (low-dose naltrexone)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.12 (P = 0.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.01 0.1 1 10 100
favour high-dose
favour low-dose
Paper 2
Challenges to antagonist blockade during sustained-release naltrexone treatment

Addiction (accepted for publication)


Background
Naltrexone is a competitive opioid antagonist that effectively blocks the action of heroin and other opioid agonists. Sustained-release naltrexone formulations are now available that provide long-acting opioid blockade. This study investigates the use of heroin and other opioids among opioid dependent patients receiving treatment with long-acting naltrexone implants, their subjective experience of drug ‘high’ after opioid use, and factors associated with opioid use.

Methods
Participants (n=60) were opioid dependent patients receiving treatment with naltrexone implants. Outcome data were collected over a 6 month period on substance use, drug ‘high’, depression, and criminal activity. Blood samples were taken to monitor naltrexone plasma levels, and hair samples to verify self-reported opioid use.

Results
More than half (57%, n=34) of the patients challenged the blockade with illicit opioids during the 6 month treatment period; 43% (n=26) were abstinent from opioids. Mean opioid use was reduced from 18 (s.d.:13) days during the month preceding treatment to 6 (s.d.: 11) after 6 months. Sixteen patients (27%) used opioids on six or more days, and these accounted for 1409 (97%) of the total 1446 days of opioid use. Nine patients reported partial drug ‘high’ following illicit opioid use, and three reported full ‘high’. Opioid use was associated with use of non-opioid drugs and criminal behaviour.

Conclusions
Challenging naltrexone blockade with heroin on at least one occasion is common among sustained-release naltrexone patients, but only a minority of patients use opioids regularly. Challenges represent a warning sign for poor outcomes and often occur in the context of poly-drug use and social adjustment problems.

Naltrexone is a competitive opioid antagonist that is known to block the action of heroin and other opioids [1-4]. However, some opioid use persists [5-10], even in patients confirmed as having taken naltrexone [10] and in patients on sustained-release formulations of naltrexone [9, 11]. Different models of addiction take different perspectives regarding possible harms associated with opioid use during naltrexone treatment. From a pharmacological perspective, naltrexone’s blockade of agonists leads to a substantial reduction in the risk of respiratory arrest resulting from opioid intake. Taking a behavioural perspective, Abraham Wikler’s [12] theory on antagonist pharmacotherapy for opioid addiction proposes that blocked heroin use should be harmless or even therapeutic: repeated administrations followed by the lack of reinforcement provided by the heroin ‘high’ should lead to extinction and gradually eliminate the user’s desire for heroin. However, empirical data from clinical studies of oral naltrexone treatment suggest that blocked heroin use among oral naltrexone patients may be harmful in that it often leads to dropout and relapse to unblocked use [10, 13].
Despite the capacity of naltrexone to block the effects of heroin, studies on oral naltrexone have reported experiences of drug 'high' among naltrexone patients after heroin use [5-8, 14, 15]. While some such experiences may have occurred among patients who were not compliant with their oral naltrexone regimen [16], two single-case reports have recently reported of similar experiences occurring in sustained-release naltrexone patients [17, 18]. In addition, an autopsy search found two naltrexone implant patients who died of drug-related causes [19]. This has caused concerns about the extent to which sustained-release naltrexone blocks the effect of heroin and other opioids [18, 19]. The possible role of poly-drug use on the experience of drug 'high' [20, 21] or mortality [22] was, however, not discussed in these papers. The self-challenges that occur in clinical samples can be expected to include high opioid dosages as well as other drugs in combination with opioids. It is not known to what extent this produces different results from laboratory-based challenge studies.

Sustained-release preparations of naltrexone have recently shown promise in reducing relapse to heroin use [9, 11, 23, 24]. It is important that better information be collected about the benefits and drawbacks of this type of treatment. In particular, research is required which investigates the extent to which patients on sustained-release naltrexone challenge this treatment by using opioids, including how often they use opioids, and with what sorts of risk. This study investigates the use of heroin and other opioids among opioid dependent patients treated with sustained-release naltrexone implants; in addition, the extent to which these patients experience 'high' from such use is investigated, as well as the behaviours and problems associated with opioid use.

**Methods**

Patients were included in clinical trials of 20-pellet naltrexone implants from GoMedical Industries, Australia, previously shown to provide naltrexone blockade for five to six months [25-27]. Two of the trials have been described elsewhere [24, 28] while the third was a pilot study (n=6) using identical implants and materials. Trials included patients who were opioid dependent adults (18 or above), not psychotic or pregnant, and who volunteered for participation in naltrexone implant research. Patients or inmates who had been coerced into treatment were not eligible for participation. The trials were approved by the regional ethical board, funded by public grants from the South Eastern Norway Regional Health Authority and the Norwegian Research Council, and registered in clinicaltrials.gov as NCT00269607, NCT00521157, and NCT00204243. The naltrexone implants were imported for research purposes in 2005-2006 with the approval of both the Australian and Norwegian medicinal agencies. The experimental nature of the treatment was emphasized in all communication with the patients, including the product information folder and the written informed consent.

The main outcome variables were opioid use and subjectively reported drug ‘high’. The use of opioids and other substances were measured using the European version of the fifth Addiction Severity Index (ASI) [29]. Outcome variables were days used during the previous 30 days, and a frequency scale describing the whole 6-month period on a 0-3 scale (0 = no use; 1 = 1-3 times per month; 2 = 1-3 times per week; 3 = daily or almost daily). Data on different opioid drugs in the ASI were analyzed separately (including heroin, morphine, methadone, buprenorphine, codeine), and these data were also summed into a composite (all opioids) outcome.
variable. Time-line follow-back was used to assess days' opioid use in each of the six study months. Based on previous findings that some patients would be expected to “test” the blockade no more than a few times [30], we created a dichotomous variable based on whether patients used opioids on one to five days versus six days or more during the six-month study period. All patients were asked about opioid dosage. Non-opioid substance use, criminal activity, and employment situation were assessed using the ASI. The Beck Depression Inventory [31] was used to assess depression. The Temporal Satisfaction with Life Scale’s ‘present’ items [32] was used to assess life satisfaction, and the Hamilton Symptom Checklist 25 (SCL-25) [33] used to assess general mental health.

Heroin 'high' was assessed by means of patients' verbal reports of subjective opioid euphoria or 'high' during the follow-up interview: these were recorded and later rated by the 1st and 2nd authors on a 0-3 scale using 0 for "No high"; 1 = "Not certain"; 2 = "Some high"; and 3 = "Full high." Cases of non-agreement between raters or multiple narratives by the same patient were resolved by selecting the higher rating.

Blood samples were taken at convenience during the study period to verify naltrexone plasma levels [33] released by the implants [25-27]. Hair samples were taken during follow-up and analyzed for the presence of opioids using liquid chromatography mass spectrometry (LC-MS-MS) as described elsewhere [35]. Additional hair- and blood samples were requested for patients who reported opioid effects.

Analyses were done with SPSS 16 for Mac OS X using ANOVA controlling for gender and age. If Levene's test or plots indicated that the normality assumption was violated, the rank-test procedure (e.g. Spearman’s R) was used instead. For all tests, a .05 significance level was used. Chi-square with Fischer’s exact test was used for binomial variables.

**Results**

Sixty implant patients met inclusion criteria and were recruited to the study. Mean age was 33.7 (s.d. 8) years (range: 21-55). Mean years of heroin use was 6.7 (s.d. 4.5; range: 0-20), poly-drug use 10.4 (s.d. 7.4; range: 0-34), injecting drug use 9 (s.d. 8; range: 0-31) years, while years in prison was 2 (s.d. 3.1; range: 0-14) and completed education 11 (s.d. 2; range: 0-15) years. Fourteen were women. Of the sixty participants, 42 came from treatment settings and 18 from criminal justice settings. Five participants did not attend the 6 month follow-up interview: for these patients, data were collected from secondary sources such as family members or treatment staff.

**Opioid use**

More than half of the naltrexone patients (57%, n=34) used illicit opioids on one or more occasions during the 6 month treatment period: 43% (n=26) reported having been abstinent from opioids throughout this period. The distribution of opioid-use among naltrexone patients is shown in Figure 1 (Fig 1). Fourteen naltrexone patients reported using opioids on one or two days, 16 (27%) used opioids on 6 days or more, of which nine (15%) reported using opioids on 90 days or more. The mean frequency of opioid use for the 34 opioid-using patients was 24 (s.d. 49) days during the 180-day study period (range: 0-180 days). Median was 4 days, while mode was 2 days.

Frequency of opioid use was reduced from a mean of 2.4 (s.d. 1) on the 0-3 frequency scale before implantation to 0.9 (s.d. 1) after six months (difference: 1.5; 95% C.I.: 1.1-1.7; p<.001). Illicit opioids were used
on a mean of 18 (s.d. 13) out of 30 days (range: 0-30 days) in the month preceding implantation: this fell to a mean of 6 days (s.d. 11) in the last treatment month (difference: 12; 95% C.I.: 8.1-15.5; p<.001). There was a tendency for opioid use to increase during the 6 month period, with a mean of 1 (s.d. 4) day’s opioid use was reported for the first treatment month increasing to 6 (s.d. 11) in the last treatment month (range: 0-30; difference: 5 days; 95% C.I.: 2.2-7.6; p<.01). Using opioids in month 1 was associated with a moderately increased risk of using illicit opioids again later in the study (Chi square risk estimate = 2.7; 95% C.I.: 1.7-4.4; p=.029).

Subgroup analysis of the 34 opioid users showed the low-frequency (1-5 days) group (n=18) used illicit opioids on a mean of 2 (s.d. 1) days during the study period (range: 0-10 days), while the high-frequency use (6 or more days) group (n=16) averaged 50 (s.d. 13) days of opioid use (difference: 86 days; 95% C.I.: 57-115; p<.001). The high-frequency use group accumulated 1409 (97%) of the total of 1446 reported days of illicit opioid use. The high-use group on average returned to pre-treatment levels of use, with 20 (s.d. 13) days of use in the last 30 days of naltrexone treatment compared to a mean of 25 (s.d. 9) days in the month preceding treatment (range: 0-30 days; difference: 4.5 days; 95% C.I.: -2.5-11.7; p=.19). For the low-frequency group, illicit opioids were used on a mean of 1 (s.d. 1) days in the last study month: this was significantly reduced from the 16 (s.d.13) days before implantation (difference: 15; 95% C.I.: 8-22; p<.001).

Development of illicit opioid use differed between the two groups when assessed using time-line follow-back (see Figure 2). The extent of opioid use by the low-use patients remained unchanged throughout the 6 month treatment period, while the high-use group steadily increased opioid use after an initial reduction of use at the start of treatment. Month-by-month differences between groups were significant (p<.01) from month 2 onwards.

The main types of opioid used by naltrexone patients were heroin (n=19) in dosages of 0.1-0.5 grams, illicit buprenorphine (n=9) in doses of 2-16 mg, injected morphine (n=5) tablets in doses of 150-500 mg, and one patient (n=1) who obtained daily methadone doses of 20-40 mg from his partner. Two patients deliberately sought to challenge the blockade with higher than usual amounts of opioids at 1.5 grams of heroin and 700 mg

---

**Figure 1. Number of days on which illicit opioids were used by sustained-release naltrexone patients in the 180-day study period**

![Bar chart showing days of opioid use](image)

**Figure note:**
Frequency of illicit opioid use among naltrexone implant patients in the 180-day treatment period. Many naltrexone implant patients (n=26 of 60; not shown) stayed abstinent from opioids, but the majority engaged in self-challenge behaviour of the naltrexone blockade.
Hair analyses indicated that underreporting of opioid use was rare. Analyses of the 46 collected hair samples showed 33 to be concordant with self-reported opioid use. Of the 13 discordant sets, 2 were positive results for patients not reporting opioid use: 11 patients had no trace of opioids in hair but reported opioid use.

Naltrexone patients who used opioids during treatment were more frequent poly-drug users during the entire six-month implant treatment period (R=.32; p=.017), and during the last 30 days of treatment (R=.32; p=.018). They were more frequent users of benzodiazepines in the previous six-months (R=.33; p=.014) and 30 days (R=.27; p=.044); more frequent users of cocaine in the six-month period (R=.32; p=.028); more frequent users of amphetamines in the previous six months (R=.29; p=.028) and the last study month (R=.35; p=.008); opioid users were also more frequent users of cannabis in the last study month (R=.32; p=.017). They reported having spent more money buying illicit drugs during the six-month period (R=.36; p=.008).

Patients who used opioids during treatment were more likely to have used drugs by injection during the six-month naltrexone treatment period (R=.45; p<.001); they had injected more frequently than those abstinent from opioids (R=.33; p=.013), and reported more frequent sharing of injecting equipment (R=.34; p=.011).

Naltrexone patients who used opioids during treatment were more likely to have been charged with acquisitive crimes during the study period (R=.28; p=.040), more likely to have been convicted of a crime (R=.36; p=.007), spent more months in custody or prison (R=.36; p=.007), had more days of the previous month in prison or custody (R=.28; p=.036), and were more likely to be awaiting further criminal charges or sentences (R=.40; p=.002).

Patients who abstained from opioids during treatment were more satisfied with their quality of life at the end of the six-month study period (R=.38; p=.004), more satisfied with their housing situation (R=.33; p=.016), more likely to be in skilled work (R=.27; p=.045), worked more days during the last study month (R=.31; p=.029), and reported lower levels of anxiety in the six-month study period (R=.32; p=.026) compared to naltrexone patients who had used opioids. There was also a tendency for opioid abstinent naltrexone patients to be less depressed than opioid users on the Beck Depression Inventory (p=.055). Patients who used opioids on only one or two occasions during the six...
month naltrexone period had more problems with non-opioid drug use and crime than abstinent patients, although these differences rarely reached statistical significance.

**Opioid ‘high’**

Statements on subjective experience of ‘high’ following opioid use were recorded from 31 of the 34 opioid-using patients: 19 reported they had felt no euphoria or "high", and three were not sure if they had felt anything. Nine patients who had used opioids reported having felt some degree of subjective drug ‘high’: of these, six described having an effect that was categorized as a "partial high", and three patients reported having felt a "full" euphoric effect or "high" on at least one occasion. Mean rating of patients’ statements on the 0-3 drug effect rating scale was 0.77 (s.d 1.1) for the whole study period. The mean scores for the subgroups were 0.14 (s.d 0.4) for the ‘no high’ group, and 2.33 (s.d. 0.5) for the ‘high’ subgroup (range: 0-3; p<.001).

Those who reported more drug ‘high’ were more frequent users of all opioids than the ‘no high’ group during the last 30 days of the study (R=.40; p=.027). Patients feeling more ‘high’ were more frequent users of buprenorphine during the six month study period (R=.60; p<.001) and during the previous 30 days (R=.44; p=.016). Patients who experienced drug ‘high’ were more frequent users of benzodiazepines during the previous six months (R=.41; p=.025) and in the previous 30 days (R=.50; p=.005).

No deaths occurred during the study period. Of the non-fatal overdoses that were reported, two overdoses were reported by a patient who had used opioids and who reported having experienced full opioid ‘high’ (described below). Another patient reported two non-fatal overdoses following the use of non-opioid drugs only.

The three patients who at some point reported full ‘high’ were: A man in his 20’s

<table>
<thead>
<tr>
<th>Case 1: M45</th>
<th>Case 2: F38</th>
<th>Case 3: F36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I: Persistent blocked use</strong></td>
<td><strong>II: Alleviating withdrawal</strong></td>
<td><strong>III: Blockade challenge</strong></td>
</tr>
<tr>
<td>This male of forty-five injected heroin during the first two weeks following implantation. He described the effect as “a disappointment” but after a further four weeks of amphetamine use he began adding heroin to his “mix” every day. Daily use continued for two months until rearest. At six months follow-up, he was encouraged to speak freely about any heroin ‘high’ but repeated that he had felt no discernible effect from his opioid use. This man had been a street drug user all of his adult life, only interrupted by periods of imprisonment. Although naltrexone seems to have been effective in blocking his experience of heroin ‘high’, other factors (e.g. social and conditioning types) appears to have supported regular use.</td>
<td>Prior to implantation, this woman of 38 had experienced severe withdrawal distress during a two-week detoxification. The morning after receiving the implant, she discharged herself from the clinic and soon proceeded to inject heroin. She felt this relieved her withdrawal distress, but never felt any opioid high and suffered no overdoses during the six-month period. As it seems unlikely that heroin intake would exert an isolated effect on some dependence symptoms but not others, it is possible that her withdrawal symptoms were not directly caused by the absence of opioids. The patients’ experience could instead be influenced by other plausible mechanisms like non-opioid drug use and - dependence, anxiety, and negative reinforcement effects.</td>
<td>Daily use of amphetamines and benzodiazepines started within days of receiving the naltrexone implant. After about two months, she tried heroin and started daily use, feeling “a partial high.” When admitted to detoxification at five and a half months, she reported withdrawal symptoms. Unexpectedly, withdrawal was not alleviated by the standard tapering of up to 8 mg buprenorphine. As this suggests that the patient’s naltrexone blockade was still intact, her partial experience of ‘high’, any dependence symptoms as well as subsequent withdrawal symptoms may have related to the use of non-opioid drugs.</td>
</tr>
</tbody>
</table>

**Table 1 note:** Case examples of naltrexone implant patients using opioid agonists. Benzodiazepines and/or stimulant use before and/or alongside the intake of opioids made it difficult for both patients and investigators to make firm conclusions about the influence of opioid intake on patients’ symptoms and experiences.
diagnosed with bipolar disorder who used buprenorphine twice during month 6 together with benzodiazepines and amphetamines. He said this buprenorphine use had ‘produced similar high to before starting on naltrexone.’ Another man reported having used heroin on a daily basis following implantation, and reported a consistent and full ‘high’ before being lost to follow-up after three months. The third patient was a man in his late forties who injected morphine in 200 and 500 mg quantities two weeks after implantation without feeling any effect. After a 4-week relapse to amphetamine and benzodiazepine use and experiencing hallucinations, he started injecting again and now reported ‘full high.’ After a week’s recuperation and detoxification on a psychiatric ward, he injected 300 mg of morphine but found it now had no effect. After relapsing to amphetamines again, he once more reported “full high.” At follow-up two months later he also said he had had two non-lethal overdoses (see above). Table 1 presents three typical examples of patients who used opioids despite having a functioning naltrexone blockade.

**Antagonist plasma levels**

Plasma analyses showed that all samples taken at the end of month 5 were above the therapeutic level of 1 ng/ml of naltrexone, indicating a reliable naltrexone release for about five months (see Figure 3). Of the samples taken during month 6, three had dropped below this protective level. During this last month of treatment, all participants were reminded that naltrexone levels would soon be depleted and encouraged to seek treatment in existing treatment services.

**Discussion**

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 6 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 [3,4]. These levels of naltrexone have previously been shown to antagonize both the physiological, and reinforcing...
effects of heroin [3,4]. Even though an increase in subjective ratings of heroin intake have sometimes preceded objective signs of heroin action in laboratory studies [3,4], the increased variability of the implants’ naltrexone release during the sixth and final month of treatment was not associated with a large increase in opioid use. This suggests factors other than naltrexone depletion were important to opioid use.

Nor can repeated opioid use by naltrexone patients be readily explained in terms of the subjective ‘high’ experienced by users. Many patients confirmed the blocking properties of naltrexone by administering heroin or other illicit opioids, sometimes at high doses, to no effect. Few of the patients who repeatedly challenged the antagonist blockade reported having experienced a full drug ‘high’. Although nine of the high-frequency opioid users reported having experienced at least some drug ‘high’, this may have been due less to the effects of opioids than to the concurrent use (including injection) of other types of drugs such as benzodiazepines, amphetamines, and cocaine. The majority of drug dependent patients use multiple substances [21, 36] and naltrexone does not significantly alter the 'high' produced by the intake of non-opioid drugs. Where an opioid and one or more other types of drugs are taken at the same time, any subjective ‘high’ may be misattributed to the opioids when the effect may be due to the effects of the other substance(s). In addition, we cannot exclude the occurrence of conditioned effects [20] in these patients’ experiences of opioid ‘high’.

Whatever the reasons for using heroin or other opioids while on naltrexone, this was found to be associated with poor outcomes in a wide range of outcome domains. Patients who repeatedly challenged the naltrexone blockade showed no treatment benefit at the end of the 6 month period by which time they had returned to pre-treatment levels of opioid use. Patients who challenged the blockade showed poor outcomes in a range of other areas: they were more likely to be using non-opioid drugs (benzodiazepines, amphetamines, cocaine, and cannabis), to be injecting drugs and sharing injecting equipment, and to have social adjustment problems including a more serious involvement in crime. These findings suggest that use of opioids while receiving sustained-release antagonist treatment are likely to be associated with a number of serious problems in treatment response and as indicative of the need for urgent clinical attention. Such results do not support the suggestion [12] that blocked opioid use is insignificant or of positive therapeutic value. As has been found for oral naltrexone treatment [10], opioid use among sustained-release naltrexone patients is a risky undertaking that may compromise their involvement in treatment and increase their likelihood of involvement in a range of problem behaviours including relapse to regular heroin use [13, 37]. In the present study, even patients who used opioids only once or twice tended to report more problem behaviours relative to abstinent patients, although the sample size meant these differences did not reach statistical significance.

These findings are subject to a number of limitations. One limitation concerns the size of the sample. Our results showed that only a minority of naltrexone patients were frequent users of opioids and even fewer reported experiencing a drug “high” during treatment. Further research on these specific phenomena should, therefore, recruit larger initial samples. In addition, there are problems inherent in the use of self-report ratings or even questionnaires to assess the experience of ‘high’ after using opioids. The use of PET imaging of receptor availability under various levels of naltrexone blockade may be able to provide
better data on the nature and mechanisms involved in such experiences and on how much naltrexone is needed to block them.

Nonetheless, the findings are interesting and of clinical relevance. Despite its overall effectiveness, sustained-release naltrexone did not eliminate opioid use in all patients. Clinicians who provide this type of medication can expect that many patients may challenge the naltrexone blockade by using opioids during treatment: some patients will engage in frequent opioid use, and a minority may report opioid ‘high.’ As there can sometimes be individual variability in naltrexone release, it may be appropriate for patients reporting drug ‘high’ following opioid intake to have their naltrexone plasma levels confirmed by blood [34] or urine [36] analyses. Our results suggest that all forms of repeated challenge to the naltrexone blockade (with or without reported ‘high’) should be regarded as a warning sign for treatment providers that the patient is at risk of relapsing to a lifestyle involving poly-drug use and crime. In order to maximise each patient’s recovery potential with naltrexone, treatment services should monitor patients for injecting poly-drug use before and during sustained release naltrexone treatment. Where required, patients should be offered supplemental interventions [38] that address the wider context of substance use for the individual patient.

Acknowledgements
The authors wish to thank the South Eastern Norway Regional Health Authority and the Norwegian Research Council for funding this study. The authors also wish to thank statisticians Leif Sandvik at Oslo University Hospital and Jo Røislien at the University of Oslo.

Conflicts of interest: None.

References


26. Ngo H.T., Arnold-Reed D.E., Hansson R.C., Tait R.J., Hulse G.K. Blood naltrexone levels over time following naltrexone implant. Prog


Paper 4
Retention in naltrexone implant treatment for opioid dependence

(submitted)


Naltrexone's usefulness in the treatment of opioid dependence stems from its ability to block the action of heroin and other opioids. However, many patients are ambivalent towards naltrexone and often drop out of treatment with orally administered naltrexone. Sustained release naltrexone seems promising in reducing opioid use, but the extent to which patients remain in treatment beyond the first dosage of naltrexone is not clear.

Methods
Patients (n=61) undergoing treatment with sustained release naltrexone implants were offered a second naltrexone implant after six months. Patients who remained in treatment were compared to those who did not, on drug use, mental health, and social problems before and during naltrexone implant treatment. Information was obtained on other treatments sought by patients who discontinued naltrexone. Blood samples were used to verify naltrexone release, and hair samples to confirm opioid intake.

Results
Of the patients who received the first naltrexone implant, 51% (n=31) remained in naltrexone implant treatment. Among those who discontinued treatment, 21% expressed a wish to re-implant but failed to attend for reimplantation and 28% declined reimplantation: 6 non-retained patients initiated maintenance or residential treatment. Remaining in naltrexone treatment was related to pre-study length of employment, illicit drug use, and concern for family problems.

Higher levels of substance misuse and criminal activity during naltrexone treatment were negatively related to subsequent retention.

Conclusion
Rates of retention among opioid dependent patients receiving naltrexone implant treatment are encouraging and support this as a feasible long-term treatment option.

Naltrexone is an opioid antagonist that blocks the action of heroin and other opioids (Martin et al. 1973; Resnick et al. 1974), thereby providing protection against the reinforcing, euphoric, and sedating effects of heroin (Verebey et al. 1976; Sullivan et al. 2006) with minimal risk of medication diversion or abuse (Tai & Blaine, 1997). These characteristics also constitute a challenge when attempting to use naltrexone in clinical treatment. Naltrexone studies tend to have long recruitment times, suggesting that only a subgroup of the opioid-using population volunteer for naltrexone-assisted abstinence (Fram et al. 1989; Bell et al. 1999; Tucker, Ritter et al. 2005). More importantly, engagement in naltrexone treatment tends to falter the more often patients are presented with an opportunity to miss their naltrexone dosage and relapse to heroin (Greenstein et al. 1997). As oral naltrexone treatment presents the patient with a dropout opportunity every 24-48 hours, this mode of administering naltrexone often
sees 70-80% or more of its patients drop out by six months (San et al. 1991; Nunes et al. 2006). Retention problems can be seen as a reason why oral naltrexone may not offer an advantage over placebo in the treatment of opioid dependence (Carroll et al. 2001; Minozzi et al. 2006; Nunes et al. 2006).

Sustained release formulations of naltrexone have been developed that extend the time of medication release from a few days to one month for depot injectables (Comer et al. 2002; 2006) and for up to six months for implantable pellets (Hulse et al. 2004; Waal et al. 2006; Ngo et al. 2008). This has proven beneficial compared to placebo (Comer et al. 2006), compared to oral naltrexone (Hulse et al. 2009) and compared to 'usual treatment' controls (Kunøe et al. 2009). These findings constitute support for the hypothesis that reducing the frequency of dropout opportunities is of importance in making naltrexone treatment effective in the treatment of opioid dependence. Such opportunities are not eliminated, however, in sustained release naltrexone, but merely reduced to once every 1-6 months. In a double-blind placebo RCT of one-month injectable naltrexone 68% of active naltrexone patients were retained from the first to the second injection (Comer et al. 2006). For the longer-lasting naltrexone implants, only case series data are available (Hulse et al. 2004b). The literature is lacking prospective cohort data on retention in sustained release naltrexone treatment among opioid dependent patients who are also regular users of non-opioid drugs.

The present study prospectively investigates treatment retention among opioid dependent patients being offered a second implantation with sustained release naltrexone. The study also investigates the association between retention and pre-and in-study factors, and tracks the alternative treatments sought by patients who do not receive a second naltrexone implant.

---

**Methods**

**Participants**

Participants were opioid dependent adults (18 or above) who had voluntarily received a 20-pellet naltrexone implant from GoMedical Industries, Australia as part of their participation in one of three clinical trials. This implant has previously been shown to release naltrexone at therapeutic levels (1 ng/ml or more) for five to six months (Hulse et al. 2004; Waal et al. 2006; Ngo et al. 2008). All participants in the current study were detoxified from opioids in a residential setting before voluntary inclusion in studies on treatment-as-usual aftercare supplemented by up to two consecutive naltrexone implant periods for a total of ten to twelve months of antagonist blockade. Exclusion criteria were pregnancy, current psychotic symptoms, having been coerced into treatment, and severe or acute liver dysfunction. The trials were voluntary and open-label and were approved by the regional ethical board, funded by public grants from the South Eastern Norway Regional Health Authority and the Norwegian Research Council, and registered in clinicaltrials.gov under NCT00269607, NCT00521157, and NCT00204243.

**Procedure**

Following detoxification, signing of informed consent, baseline data collection, and initial implantation, patients were discharged from the detoxification setting. The implantation procedure and any adverse events have been described elsewhere (Kunøe et al. 2009; Lobmaier et
Four to eight weeks before six-month follow-up, patients were contacted by telephone to offer a second implant and to schedule an appointment for the follow-up data collection. Patients who declined were reminded of the dangers of overdose and encouraged to initiate some other treatment for opioid dependence (e.g. opioid maintenance treatment or long-term residential treatment). Patients who requested a second implant but failed to attend the scheduled reimplantation appointment were contacted again to inquire about their wish to reimplant. Three contact attempts were made before treatment personnel or next of kin was contacted as indicated in the original informed consent.

Assessments
The main outcome in the present study was continuation or discontinuation of naltrexone implant treatment: continuation was defined as the successful administration of a second naltrexone implant. Other variables investigated in the study were: 1) baseline (pre-study) factors related to remaining in naltrexone implant treatment. 2) follow-up (in-study) factors related to remaining in naltrexone implant treatment.

For factors relating to outcomes, the European version of the Addiction Severity Index (McLellan et al. 1992; Kotkevi & Hargers 1995) (ASI) were used to assess self-reported drug use, health - and treatment data. Substance use was recorded by the ASI in two ways: I) as days of the last 30 days and II) as a frequency scale describing the whole 6-month period on a 0-3 scale where a score of '0' means "no use", '1' is "1-3 times per month", '2' "1-3 times per week", and '3' "daily or almost daily." Injection drug use, workdays, and counseling attendance was recorded as 'days of previous month' and/or 'months of previous six months.' At follow-up only, time-line follow-back (Sobell & Sobell 1992) was used for the whole 180-day period. For mental health, the Beck Depression Inventory (Beck 1961) was used to assess depressive symptoms, while Hopkins' Symptom Checklist 25 (SCL-25) (Derogatis et al. 1974) was used to assess general mental health. The Temporal Satisfaction With Life Scale 'present' items (Pavot et al. 1998) were used to assess life satisfaction.

To investigate whether variations in naltrexone plasma levels affected outcomes, blood samples were taken of patients at follow-up and at convenience (Olsen et al. 2004). To verify opioid use, hair samples were taken during follow-up and analyzed for the presence of opioids using liquid chromatography mass spectrometry (LC-MS-MS) as described elsewhere (Hegstad et al. 2008).

Statistical analyses
The main results of this study are descriptive. T-tests were used to investigate associations between pre-treatment and in-treatment factors in relation to remaining in treatment. If inspection of the distribution indicated the normality assumption was violated, analyses were re-done using a rank-test. Significant pre-study factors were entered into a binary multiple regression with backward conditional entry of variables. For dichotomous variables, chi-square with Fisher's exact test was used. Patients who had the first implant removed or discontinued treatment due to lack of treatment need were included in descriptive analyses only. Scatterplots of main outcome variables were visually inspected to exclude outliers. All tests utilized a .05 significance level and were done with SPSS 16 for Mac OS X.
Results
Sixty-one patients were included: of these 47 (67%) were men and 14 (23%) were women. Participants had a mean age of 33.3 years (sd: 8), had spent a mean of 1.8 years (sd: 3) in prison, used heroin for a mean of 6.6 years (sd: 4.4), injected drugs for a mean of 8.7 years (sd: 7.6), and had engaged in poly-drug use for a mean of 10.4 years (sd: 7.4).

Treatment retention
More than two thirds (44, 72%) of the 61 included patients reported that they wished to accept the offer of a second implant (see Figure 1). These patients were scheduled a reimplantation appointment, and 31 (51%) received an implant. Of the 30 who did not continue with naltrexone implant treatment, 17 (28% of 61) declined the offer of a second implant while 13 patients (21%) reported wanting reimplantation but failed to attend for the second implant. Two of the three patients who had the first implant removed declined the offer to reimplant (see below). Six of those who discontinued treatment initiated other treatments for opioid dependence: three entered long-term residential treatment, and three started opioid maintenance treatment with methadone or buprenorphine.

Pre-treatment predictors of retention
In the six months before inclusion in the study, patients that would later receive a second implant used drugs by injection in a mean of 2.8 (sd: 2.5) months compared to non-retained patients' mean of 4.2 months (sd: 2.3) (mean diff: 1.4; 95%C.I.: 2.6-15.3);

Figure 1. Treatment engagement before, during six-month naltrexone implant treatment for opioid dependence.

Figure 1 note: Dropout, discontinuation, continuation, and post-naltrexone treatment alternatives among naltrexone implant patients. OMT = opioid maintenance treatment. LRT = long-term residential treatment.
In the 30 days prior to their inclusion into the study, patients that would later be retained had on average 9.4 (sd: 12) days of injection drug use compared to 19.6 (sd: 12) days for non-retained patients (mean diff: 10.2; 95% C.I.: 3.5-17; p=.004). Retained patients also had a mean of 5 days (sd: 8.7) of benzodiazepine use during the month preceding inclusion compared to a mean of 14 days (sd: 13) for those not retained (mean diff: 9; 95% C.I.: 2.6-15.3; p=.007). Patients who were later retained worried about family problems on more days than non-retained patients (mean diff: -.9; 95% C.I.: 0.1 - 1.6; p=.034). Patients who remained in naltrexone implant treatment had remained in their longest employment for a mean of 3.7 (sd: 4.3) years compared to a mean of 1.4 (sd: 1.9) for non-retained patients (mean diff: 2.4; 95% C.I.: 0.4-4.3; p=.021).

Patients who would later discontinue naltrexone implant treatment experienced more of all types of mental health problems (including hyperactivity and concentration problems) with a mean of 9.2 (sd: 12) days during the month preceding inclusion versus 3.3 days (sd: 6.5) for retained patients (mean diff: 5.9; 95% C.I.: 0.7 - 11.6; p=.044).

Injection drug use during the 6 months and 30 days prior to study entry were found to be intercorrelated above .7, and the 30-day variable was included with the other above factors in a binary logistic regression analysis with backward conditional inclusion of variables. In the final model for predictors, regression analysis included duration of longest employment period as the only lifetime predictor. In the month preceding incarceration or treatment, non-retained patients had more days of injection drug use and fewer days of concern about family problems (see Table 1).

**In-treatment factors related to retention**

Patients who received a second naltrexone implant reported less opioid use, amphetamine use, injection drug use, and days of criminal activity during the first implant period than non-retained patients. Factors from the last 30 days of the study that related to remaining in naltrexone implant treatment are shown in Table 2. Patients who relapsed to poly-drug use, blocked opioid use, and criminal activity were less likely to remain in naltrexone implant treatment.

Factors related to drug use and criminal involvement were also significant over a six-month time span. The time-line follow-back for days of opioid use in the whole 180-day period showed that reimplanted patients had used opioids on a mean of 6.4 days (sd: 27) versus a mean of 55 days (sd: 65) for non-retained patients (mean diff: 48; 95% C.I.: 18-78; p=.003). On the ASI six-month frequency scale (range: 0-3), retained patients’ opioid use averaged 0.5 (sd: 0.7) versus the discontinued patients' 1.5 (sd: 1) (mean diff: 0.7; 95% C.I.: 0.5 - 1.5; p<.001).

**Table 1. Regression coefficients of pre-treatment factors predictive of receiving a second naltrexone implant.**

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>B</th>
<th>S.E.</th>
<th>O.R.</th>
<th>95% C.I.</th>
<th>sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longest employment, years</td>
<td>0.34</td>
<td>0.14</td>
<td>1.4</td>
<td>1.1 – 1.9</td>
<td>.017</td>
</tr>
<tr>
<td>Injecting drug use, days of last</td>
<td>-0.08</td>
<td>0.03</td>
<td>0.9</td>
<td>0.9 - 1</td>
<td>.007</td>
</tr>
<tr>
<td>30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerned about family problems, days of last 30 days</td>
<td>0.52</td>
<td>0.24</td>
<td>1.7</td>
<td>1 – 2.7</td>
<td>.034</td>
</tr>
</tbody>
</table>

**Table 1 note:** Result of binary logistic regression with backward conditional (.05) inclusion of variables. The factors removed by the regression procedure were: frequency of benzodiazepine use and frequency of mental health problems in the month preceding inclusion.
Six-month heavy drinking was also higher in the non-retained group (mean 0.7 (sd: 0.9)) compared to in retained patients (mean 0.1; sd: 0.4) (mean diff: 0.6; 95% C.I.: 0.1-1.1; p=.018), as was benzodiazepine use (mean diff: 0.9; 95% C.I.: 0.3-1.4; p=.004) and amphetamine use (mean diff: 0.6; 95% C.I.: 0.01-1.3; p=.050). Non-retained patients were also more likely to report receiving income from acquisitive crime in the least 6 months (Fisher's exact test; Pearson's R=-.31; p=.049) and to have been treated by a doctor in the same period (Fisher's exact test; Pearson's R=-.34; p=.023).

Patients who remained in treatment tended to report better mental health than non-retained patients, scoring a mean of 11.2 (sd: 10) on the Beck Depression Inventory compared to 17.7 (sd: 11) for non-retained patients (mean diff: 6.5; 95% C.I.: 0.01-13; p=.050). Non retained patients also tended to answer 'yes' more often to experiencing anxiety both in the last 30 days (Fisher's exact test; Pearson's R=.31; p=.044) and in the time before that (Fisher's exact test; Pearson's R=.43; p=.005). On life satisfaction (range 5-35), retained patients scored 18 (sd: 8) and non-retained 12 (sd: 6) (mean diff: 6; 95% C.I.: 1.3-10.4; p=.013).

**Groups of special interest**

'Recovered' patients

Five patients who declined reimplantation reported they were no longer in need of any treatment for opioid dependence. Three had completed long-term residential treatment for a mean time of 12 months (sd: 12) prior to inclusion in the study. Substance use was reported by these patients for a mean of 1.2 days (sd: 1.6) for alcohol use in the last study month, with one patient reporting one day each using benzodiazepines and one using cannabis. Two of the recovered patients reported having used opioids on two occasions each. On time-line follow-back, this amounted to a mean of 0.8 (sd: 1) days of opioid use in the entire 180-day period. No hair samples taken from this group at follow-up were positive for opioids. This group was not criminally active during the study.

**Other patients declining re-implantation**

Twelve patients declined the offer of reimplantation. Among these patients, mean days of opioid use on the 180-day time-line follow-back was 58 (sd: 62). During the last 30 days of the follow-up period, these patients reported having used drugs by injection on a mean of 15.5 (sd: 14) days, reported a mean of 4 (sd: 10) heavy drinking days, reported having experienced drug-related problems on 15 days (sd: 15), and engaged in criminal activities on 2.6 (sd: 7) days. Amphetamine use was reported on nine (sd: 12) of the last 30 days. Nine

---

**Table 2. Regression coefficients of pre-treatment factors predictive of receiving a second naltrexone**

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Retained mean (sd)</th>
<th>Not retained mean (sd)</th>
<th>Mean diff.</th>
<th>95% C.I.</th>
<th>sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>All opioid use</td>
<td>1.8 (5.6)</td>
<td>12.8 (14)</td>
<td>11</td>
<td>4 - 18</td>
<td>.003</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>4.3 (9)</td>
<td>12 (13)</td>
<td>7.7</td>
<td>0.6 - 15</td>
<td>.034</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>5.3 (9.6)</td>
<td>19.3 (13)</td>
<td>14</td>
<td>6.7 - 21</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Illegal activity</td>
<td>1.8 (5.2)</td>
<td>7.2 (10)</td>
<td>5.3</td>
<td>0.01 - 11</td>
<td>.050</td>
</tr>
</tbody>
</table>

Table 2 note: All data recorded as 'days of last 30 days.' Patients who had recovered (n=5) or had their naltrexone implant removed (n=3) were not included in this analysis.
patients had no treatment plan following their discontinuation of naltrexone implant treatment (Figure 1).

Re-implantation dropout patients
Patients (n=13) who expressed a wish to reimplant but failed to do so constituted 21% of the total sample (n=61) and 30% of those expressing a wish to reimplant (n=44). In the last 30 days of the study, these patients used drugs by injection on a mean of 23 days (sd: 10), reported drug-related problems on 19 (sd: 12) days, and criminal activities on a mean of 9 (sd: 10) days. No heavy drinking days were reported in this group (mean: 0.2 s.d.: 0.6), but mean use of amphetamines were 13 (sd: 13) days of the last 30.

A comparison of opioid use during naltrexone treatment for patients who dropped out, discontinued treatment, or were reimplanted is displayed in Figure 2. The figure illustrates the influence of opioid use on treatment retention.

Cases of implant removal
Three patients had their naltrexone implant removed during the first treatment episode - one due to tissue infection with necrosis, two due to subjective complaints about gastrointestinal and site pain, respectively. At follow-up, these three had used opioids on a mean of 28 days (sd: 3) of the last study month. None of these patients received a second implant. Two declined further implant treatment. The third patient completed detoxification but abandoned her plans to have a second implant after her gastrointestinal symptoms reappeared following an initiation onto oral naltrexone. None of these patients continued to other treatments, despite staff encouragement to do so and despite all of them fulfilling the minimum criteria for agonist maintenance treatment in Norway.

Hair analyses
Of the 45 samples received, 30 were concordant for self-reported opioid use versus opioids in hair, and 15 were discordant. In 13 of these cases, patients reported low levels of use but no opioids or metabolites could be detected in hair analysis.

Naltrexone blood levels
50 patients gave a total of 73 blood samples in the first treatment period, of which three were damaged during transport and ten were excluded due to instrument calibration problems. Analyses of the remaining 60 samples showed levels of naltrexone and 6-beta naltrexol were above therapeutic levels at least five and a half months for all but three patients, who had naltrexone levels below the therapeutic limit of 1ng/ml at 157-168 days. Two of these three were successfully reimplanted.
Discussion
About half of the opioid dependent patients (51%) who completed six months of treatment with sustained-release naltrexone implants successfully received a second six month implant. About one in four (28%) turned down the offer of a second implant, and about one in five (21%) expressed a wish to receive a second implant but failed to attend for reimplantation despite repeated efforts by the clinical team to encourage their attendance. The retention of 51% of patients in this study is encouraging. Retention was more than twice as high as in six-month studies of oral naltrexone treatment. For example, San et al. (1991) found that only 17% of their sample were retained in treatment after 180 days, while the study of Nunes et al. (2006) retained 22% of patients with Behavioral Naltrexone Therapy and 9% of patients receiving ‘compliance enhancement.’

The low incidence of implant removals in the present sample suggests that most patients who remain in treatment will achieve ten to twelve months of continuous naltrexone medication. Retained patients are likely to continue the positive changes previously reported in terms of reduced relapse to regular opioid use (Hulse et al. 2004; Comer et al. 2006; Hulse et al. 2009), reduced opioid overdose (Hulse et al. 2005), and reduced overall mortality (Tait et al. 2008).

The patients who discontinued or dropped out of naltrexone implant treatment were in many ways similar to those who drop out of oral naltrexone treatment. Longer pre-treatment employment history, concern about family problems, and pre-treatment injecting drug use were associated with later retention in treatment, echoing the results of several oral naltrexone studies (Greenstein et al. 1983; Krupitsky et al. 2004; Sullivan et al. 2006b). During naltrexone implant treatment, patients who used illicit opioids despite naltrexone blockade, engaged in the use of other illicit drugs or in heavy drinking, and/or engaged in more criminal activity were less likely to continue to the second course of naltrexone. As our sample consisted of poly-substance users, we interpret all of these factors as symptoms of a return to a heroin-related lifestyle that is incompatible with a re-commitment to naltrexone-assisted abstinence.

The findings of this study are subject to several limitations. The sample size is relatively small, especially for the study of sub-groups. In addition, the novelty of naltrexone implant treatment and the clinical trial setting means the patients in this study may not be fully representative of the wider potential treatment population for naltrexone implants. However, other aspects of the present study may increase the ability to generalise results to day-to-day treatment settings; e.g. the inclusion of patients with poly-drug use and the implementation within existing addiction treatment services. This group of patients constitutes the majority of street heroin users (Ross et al. 2005), and their inclusion in the present study further strengthens the case for the clinical feasibility of sustained release naltrexone treatment for opioid dependence.

Possible options for improving retention and reducing discontinuation and dropout from sustained release naltrexone treatment might involve integrating such treatment with contingency management (Carroll et al. 2001), self-help groups (Timko and DeBenedetti 2008), or behavioral naltrexone therapy (Rothenberg et al. 2002). Outreach services may also be important in supporting and aiding any
naltrexone patients who return to the street drug scene. This could be especially valuable to the 21% who were willing to receive a second naltrexone implant but did not manage to attend for re-implantation. As family support has repeatedly proven important to retention in naltrexone treatment, abstinent family members should be mobilized before and during treatment to aid and motivate the patient to recovery. The results of this study suggest that it is feasible to treat opioid dependent patients with several administrations of long-acting sustained release naltrexone. When implemented as a treatment service alongside other proven treatments for opioid dependence, sustained release naltrexone may be used both as an enhancement of these treatments as well as a stand-alone approach.

References


naltrexone and 6-beta coverage following sequential naltrexone implants. Addict Biol. 9, 67-72.


