Sustained-Release Naltrexone For Opioid Dependence (Review)

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TABLE OF CONTENTS

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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 Study authors and drug companies were contacted to obtain any unpublished material or missing data.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
Foe 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 68% 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 skeptical 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 polylactic 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.

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 intervention

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

Retrieved from literature search, but not predefined in protocol:

- Low-dose versus high-dose sustained-release naltrexone

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

See: Cochrane Drugs and Alcohol Group methods used in reviews.

To identify studies for this review detailed electronic searches for each data base 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. MEDLINE (January 1966 to November 2007)
2. Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2006) which includes the Cochrane Drugs and Alcohol Group Trials Register
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)

Search strategy for MEDLINE (OVID - 1950 to November week 1 2007):

1 naltrexone/
2 naltrexon$.tw.
3 or / 1-2
4 exp Delayed-Action Preparations/
5 implant$.tw.
6 depot$.tw.
7 ((sustain$ or time$ or controlle$ or delay$ or slow or prolonge$ or extend$) adj2 release$).tw.
8 ((prolonge$ or delay$) adj2 action$).tw.
9 or / 4-8
10 3 and 9
11 animals/ not humans/
12 10 not 11

Detailed search strategies for the other databases are described in additional Table 03.

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. Triallists and pharmaceutical companies were approached to obtain unpublished results, but contact proved difficult to establish.

METHODS OF THE REVIEW

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
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.

DESCRIPTION OF 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 01.

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 table 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 table 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 02*)*

- **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 (Gölz 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.

METHODOLOGICAL QUALITY

(See additional Table 01*)*

Study of effectiveness
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).

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 without parallel control group: 9 reports
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).

RESULTS

- **Effectiveness of sustained-release naltrexone for opioid dependence**

For the 1 report (Comer 2006) that met inclusion criteria for effectiveness studies, the following primary treatment outcomes allowed calculations of effect estimates:
(1) Retention in treatment (number of participants in each group completing the 8-week study period)
(2) Time to drop out (number of days in treatment)
All confidence intervals are 95%, effect estimates are based on intention-to-treat analyses.
(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* comparison 01, outcome 01; and low dose, onestudy, 38 participants, RR 1.54 (CI 0.78 to 3.05), *see* comparison 01outcome 02. 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* comparison 01, outcome 03.
(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* comparison 01 outcome 04, and between high and low dose depot, one study, 42 participants, WMD 12.0 (CI 1.69 to 22.31), *see* comparison 01, outcome 05. There was no statistically significant difference between low dose depot and placebo, one study, 38 participants, WMD 9.0 (CI -3.40 to 21.40), *see* comparison 01, outcome 06.

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 (Turncliff 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 seperately 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* comparison 02, outcome 01, sub-category 01 and for number of participants discontinuing the trial due to adverse effects, 38 participants, RR 0.28, (CI 0.01 to 6.38), *see* comparison 02, outcome 01, 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* comparison 02, outcome 02, sub-category 01. In Garbutt 2005, no significant differences for reporting 1 or more severe adverse event , 414 participants, RR 0.68 (CI 0.31 to 1.48), *see* comparison 02, outcome 02, subcategory 02 and for reporting injection site pain ,414 participants, RR 1.29 (CI 0.73 to 2.28), *see* comparison 02, outcome 02, sub-category 03., while de difference was statistically significant in favour of control group for number of participants discontinuing the trial due to adverse effects, 414 participants, RR 2.11 (CI 1.15 to 3.88), *see* comparison 02, outcome 02, sub-category 04.

Low-dose naltrexone depot compared to placebo injection:

- **Opioid dependence**, 1 RCT by Comer 2006:

No significant differnces between the groups for reporting 1 or more adverse effects, 38 participants, RR 1.30 (CI 0.74 to 2.28), *see* comparison 02, outcome 03, sub-category 01, number of participants discontinuing the trial due to adverse effects, 38 participants, RR 1.80 (CI 0.18 to 18.21), *see* comparison 02, outcome 03, sub-category 02 and reporting injection site induration RR 0.90 (CI 0.60 to 5.60), *see* comparison 02, outcome 03, 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* comparison 02, outcome 04, 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* comparison 02, outcome 04, 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* comparison 02, outcome 04, sub-category 03. No statistically significant difference in Kranzler 1998 and Kranzler 2004 for reporting injection site induration , 353 participants, RR 1.17 (CI 0.76 to 1.80), *see* comparison 02, outcome 04, 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* comparison 02, outcome 04, 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* comparison 02, outcome 04, 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* comparison 02, outcome 04, 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, contusion and one or more reaction) was significant with pooled RR 1.18 (CI 1.02 to 1.36), *see* comparison 02, outcome 04, 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* comparison 02, outcome 05, sub-category 01) and for reporting one or more injection site reaction, 42 participants, RR 1.32 (CI 0.08 to 22.92), *see* comparison 02, outcome 05, 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* comparison 02, outcome 06, 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 02, outcome 06, 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* comparison 02, outcome 07, sub-category 01. No significant differences for reporting injection site pain, 415 participants, RR 1.37 (CI 0.76 to 2.44), *see* comparison 02, outcome 07, 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* comparison 02, outcome 07, 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* comparison 02, outcome 08.

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* comparison 02, outcome 09).

(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 urin samples provided per participant, these data were omitted from our analyes 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 formula-

tions 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 01). 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.

POTENTIAL CONFLICT OF INTEREST

None

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Carreno 2003**
Methods	non-RCT: uncontrolled, prospective trial, 1 year observation period
Participants	opioid dependent outpatients, n=156, treatment seeking
Interventions	Wedgewood naltrexone implant 1000 mg, rapid opioid detoxification with induction onto naltrexone: sequential treatment periods possible
Outcomes	retention in treatment, relapse to opioid use, adverse effects, Addiction Severity Index outcomes
Notes	included for safety analyses only: no comparison group
Allocation concealment	D – Not used

Study	**Comer 2002**
Methods	non-RCT: dose-finding trial (phase II), 2 sequential treatment groups, 6 weeks observation period
Participants	opioid dependent inpatients, n=12, non treatment seeking
Interventions	Biotek naltrexone depot 192 or 384 mg, detoxification followed by depot injections, heroin challenge protocol
Outcomes	heroin effects during blockade, opioid withdrawal symptoms, naltrexone plasma levels, adverse effects
Notes	included for safety analyses only: non treatment seeking sample
Allocation concealment	D – Not used

Characteristics of included studies (*Continued*)

Study	**Comer 2006**
Methods	RCT: 2 centers, 3 parallel treatment groups, placebo-controlled randomized trial, 8 weeks observation period
Participants	opioid dependent outpatients, n=60, treatment seeking
Interventions	Biotek naltrexone depot 192 or 384 mg, or placebo, detoxification followed by depot injections, all 3 treatment groups with manualised relapse prevention therapy
Outcomes	retention in treatment / time to drop out, illicit drug use by urinalysis, heroin craving, depression, adverse effects
Notes	only study included for analyses of effectiveness
Allocation concealment	B – Unclear

Study	**Dunbar 2006**
Methods	RCT: dose-finding trial (phase I), 2 sequential panels of 5 treatment groups, 2 (panel A) or 5 (panel B) months observation period
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
Allocation concealment	B – Unclear

Study	**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-i.v. sedation) rapid detoxification followed by implant
Outcomes	opioid use, naltrexone plasma levels, adverse effects
Notes	included for safety analyses only: no comparison group
Allocation concealment	D – Not used

Study	**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
Allocation concealment	D – Not used

Study	**Garbutt 2005**
Methods	RCT: 24 centers, 3 parallel treatment groups, placebo-controlled randomised trial,24 weeks observation period

Characteristics of included studies (*Continued*)

Participants	alcohol dependent outpatients, n=624, treatment seeking
Interventions	Alkermes naltrexone depot 190 or 380mg, or placebo, sequentially administered monthly during 6 months, 12 sessions of manual based supportive therapy
Outcomes	alcohol consumption, time to drop out, changes in liver enzyme levels adverse events, side effects
Notes	included for safety analyses only: alcohol dependent sample
Allocation concealment	B – Unclear

Study	**Gölz 2000**
Methods	non-RCT: 2 sequential treatment groups, prospective trial, 2 year observation period
Participants	opioid dependent outpatients, n=108, treatment seeking
Interventions	Wedgewood naltrexone implant 1000 mg or thrice weekly oral naltrexone, rapid opioid detoxification under anesthesia followed by induction onto naltrexone, unclear if repeated implantations possible, free to choose groups
Outcomes	relapse to opioid use, abstinence, duration of receptor blockade, additional safety data provided by Partecke
Notes	included for safety analyses only: no adequate comparison group
Allocation concealment	D – Not used

Study	**Hulse 2005**
Methods	non-RCT: uncontrolled, retrospective record-linkage study, pre-post design, 18 months observation period
Participants	opioid dependent outpatients, n=361 treatment seeking
Interventions	GoMedical naltrexone implant 3400mg, rapid opioid detoxiofication with induction onto naltrexone
Outcomes	hospital presentations due to opioid or other drug poisonings implants removed
Notes	included for safety analyses only: uncontrolled, retrospective record-linkage study
Allocation concealment	D – Not used

Study	**Johnson 2004**
Methods	RCT: 4 centers, 2 parallel treatment groups, placebo-controlled randomised trial, 4 months observation period
Participants	alcohol dependent outpatients, n=30, treatment seeking
Interventions	Alkermes naltrexone depot 400mg or placebo, psychosocial support once monthly, manual based at the two US centers
Outcomes	alcohol consumption, pharmacokinetics, changes in liver enzymes, adverse effects
Notes	included for safety analyses only: alcohol dependent sample
Allocation concealment	B – Unclear

Study	**Kranzler 1998**
Methods	RCT: 2 parallel treatment groups, placebo-controlled randomised trial, 12 weeks observation period
Participants	alcohol dependent outpatients, n=20, treatment seeking
Interventions	Biotek naltrexone depot 206mg or placebo, two weeks with oral naltrexone lead-in, weekly psychotherapy sessions
Outcomes	alcohol consumption, pharmcokinetics, changes in gamma GT levels,

Characteristics of included studies (*Continued*)

	adverse effects
Notes	included for safety analyses only: alcohol dependent sample
Allocation concealment	B – Unclear

Study	**Kranzler 2004**
Methods	RCT: 30 centers, 2 parallel treatment groups, placebo-controlled randomised trial, 3 months observation period
Participants	alcohol dependent outpatients, n=333, treatment seeking
Interventions	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
Outcomes	alcohol consumption, adverse effects
Notes	included for safety analyses only: alcohol dependent sample
Allocation concealment	A – Adequate

Study	**Sullivan 2006**
Methods	non-RCT: uncontrolled, dose-finding trial (phase II), 6 weeks observation period
Participants	opioid dependent inpatients, n=5, non treatment seeking
Interventions	Biotek naltrexone depot 384 mg, detox and oral naltrexone lead-in followed by depot injection, heroin challenge protocol
Outcomes	heroin dose effects, adverse events
Notes	included for safety analyses only: non treatment seeking sample
Allocation concealment	D – Not used

Study	**Tait 2007**
Methods	two parallel treatment groups, record linkage, 5 and a half years observation period
Participants	opioid dependent outpatients, n=341 treatment seeking
Interventions	GoMedical naltrexone implant 2200 mg, methadone maintenance treatment, possibility of sequential treatment episodes not stated
Outcomes	mortality
Notes	included for safety analyses
Allocation concealment	D – Not used

Study	**Turncliff 2005**
Methods	non-RCT: 2 parallel treatment groups, matched case-control trial, 3 months observation peroid
Participants	alcohol dependent outpatients (currently abstinent, liver impaired) and healthy controls, n=25, treatment seeking
Interventions	Alkermes naltrexone depot 190 mg
Outcomes	pharmacokinetics, adverse effects
Notes	included for safety analyses only: alcohol dependent sample
Allocation concealment	D – Not used

Study	Waal 2003
Methods	non-RCT: uncontrolled, prospective trial, 2 months observation period
Participants	opioid dependent outpatients, n=10, treatment seeking
Interventions	Wedgewood naltrexone implant 1000 mg, sequential treatment periods possible, counselling sessions
Outcomes	pharmcokinetics, drug use, adverse effects
Notes	included for safety analyses only: no comparison group
Allocation concealment	D – Not used

Study	Waal 2006
Methods	non-RCT: uncontrolled, prospective trial, 1 year observation period (after last implant)
Participants	opioid dependent outpatients, n=13, treatment seeking
Interventions	GoMedical naltrexone implant 1800 or 3600 mg, sequential treatment periods possible
Outcomes	pharmacokinetics, drug use, quality of life, adverse effects
Notes	included for safety analyses only: no comparison group
Allocation concealment	D – Not used

Characteristics of excluded studies

Study	Reason for exclusion
Albanese 2000	oral naltrexone
Brewer 2001	no clinical trial (comment)
Brewer 2002	case study, adverse effect data not reported
Brewer 2004	case report, adverse effect data not reported
Carreno 2002	oral naltrexone
Chiang 1984	pilot study on healthy volunteers with focus on pharmacokinetics
Chiang 1985a	pilot study on healthy volunteers with focus on pharmacokinetics
Chiang 1985b	pilot study on healthy volunteers: concludes with recommending no further investigations on this particular product
Collins 2005	oral naltrexone
Colquhoun 2005	non-RCT, adverse effect data not reported
Dean 2005	no clinical trial (review)
Dean 2006	oral naltrexone
Garcia-Alonso 1989	oral naltrexone
Gooberman 1998	abstract from conference presentation only
Grusser 2006	non-RCT, adverse effect data not reported
Hamilton 2002	non-RCT, adverse effect data not reported
Harrison 2006	no clinical trial (review)
Heading 2006	no clinical trial (review)
Hulse 2002a	non-RCT, adverse effect data not reported
Hulse 2002b	case report, adverse effect data not provided
Hulse 2003a	non-RCT, adverse effect data not reported

Hulse 2003b	non-RCT, adverse effect data not reported
Hulse 2003c	case report, adverse effect data not provided
Hulse 2004a	no clinical trial
Hulse 2004b	no clinical trial
Hulse 2004c	non-RCT, adverse effect data not reported
Hulse 2004d	non-RCT, adverse effect data not reported
Iversen 2005	no clinical trial
Jasinski 2006	no clinical trial
Jeffrey 2007	non-RCT, hepatitis C treatment-related outcomes only, adverse effect data not reported
Johnson 2006	no clinical trial
Lerner 1992	oral naltrexone
Marlowe 2006	no clinical trial
Martin 1974	no clinical trial (dogs)
Modesto-Lowe 2002	no clinical trial (review)
NRCC report 1978	oral naltrexone
Ngo 2007	non-RCT, adverse effect data not reported
O'Brien 2005	no clinical trial (comment)
O'Brien 2006	no clinical trial (comment)
O'Malley 1992	oral naltrexone
Oliver 2005	no clinical trial (letter)
Pekta 1998	abstract available only
Pitt 1981	no clinical trial (animals) and duplicate of NIDA research monograph 28
Poser 1996	no clinical trial (review)
Rabinowitz 1998	oral naltrexone
Ramenskaya 2005	no clinical trial (pharmacokinetic results)
Rawson 2000	no clinical trial (review)
Reece 2007	non-RCT, adverse effect data not reported
Resnick 1977	no clinical trial (review)
Reuning 1976	no clinical trial (animals)
Riddle 2001	no clinical trial (review)
Schwope 1975	no clinical trial (mice)
Sobel 2001	abstract available only
Suhaida 2004	no clinical trial (in vitro study)
Teagle 2007	no clinical trial (press release)
Warhaft 2003	no clinical trial (letter)
Wesson 2003	abstract available only, 9 and 12 months follow-up data from same sample as included report Kranzler 2004
Willette 1978	no clinical trial
Willette 1981	no clinical trial (review and animal studies)
Wodak 2001	no clinical trial (review)

Characteristics of excluded studies (*Continued*)

Characteristics of ongoing studies

Study	**Hulse**
Trial name or title	A randomised, double-blind, placebo-controlled clinical trial of naltrexone implants for the treatment of heroin addiction
Participants	opioid dependent outpatients (DSM IV)
Interventions	2 groups: naltrexone implant + oral placebo compared to placebo implant + oral naltrexone
Outcomes	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
Starting date	recruitment and follow-up is completed
Contact information	Gary Hulse: hulseg@meddent.uwa.edu.au
Notes	Country: Australia

Study	**Kunøe**
Trial name or title	Naltrexone Implants - a Randomised Study http://clinicaltrials.gov reference: NCT00521157
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

Study	**Lobmaier**
Trial name or title	Naltrexone Implants - a Treatment Alternative for Heroin Dependent Prisoners? http://clinicaltrials.gov reference: NCT00520793
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

Study	**Nunes 2002**
Trial name or title	Behavioral Naltrexone Therapy: A Novel Treatment for Heroin Dependence Clinicaltrial.gov reference: NCT00332228
Participants	opioid dependent outpatients

Characteristics of ongoing studies (*Continued*)

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

Study	**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
Participants	opioid dependent outpatients
Interventions	6 months observation, 2 groups: behavioral naltrexone therapy for depot naltrexone (depot-BNT) compared to BNT plus oral naltrexone
Outcomes	opioid use, retention in treatment, medication compliance
Starting date	Recruitment started September 2007
Contact information	Yaacov Elkus: elkusya@pi.cpmc.columbia.edu and Elizabeth Martinez: martine@pi.cpmc.columbia.edu
Notes	Country: USA

Study	**Tiihonen**
Trial name or title	Naltrexone depot implant in the treatment of co-morbid amphetamine and opioid dependence: a double-blind, randomised, placebo-controlled trial
Participants	Amphetamine and opioid dependent outpatients
Interventions	10 weeks observation, two groups: naltrexone implant compared to placebo implant
Outcomes	amphetamine use, opioid dependence, use of benzodiazepines and cannabis
Starting date	recruitment started November 2007, anticipated completed by December 2009
Contact information	Jari Tiihonen: jari.tiihonen@niuva.fi
Notes	Country: Russia

Study	**Woody**
Trial name or title	Effectiveness of Oral and Depot Naltrexone in Treating Heroin Dependent Individuals Seeking Treatment for Heroin Addiction clinicaltrials.gov reference NCT00218426
Participants	opioid dependent outpatients
Interventions	6 months observation, 3 groups: 1) oral naltrexone + placebo injection, 2) oral placebo + depot naltrexone 3) oral placebo + placebo injection
Outcomes	opioid use, time to drop out, other drug use, psychiatric symptoms, HIV risk
Starting date	recruitment started July 2006
Contact information	George Woody: woody@tresearch.org and

Characteristics of ongoing studies (*Continued*)

	Evgeny Krupitsky: kru@ek3506.spb.edu
Notes	Country: Russia

ADDITIONAL TABLES

Table 01. Reports and potential sources of bias

report	selection bias	performance bias	attrition bias	detection bias
Kranzler 2004	A	A	A	B
Garbutt 2005	B	A	A	A
Comer 2006	B	A	A	B
Johnson 2004	B	A	A	B
Kranzler 1998	B	A	A	B
Dunbar 2006	B	A	B	B
Comer 2002	non-RCT, 2 sequential treatment groups	not applicable (N/A)	loss to follow-up completely recorded	N/A
Turncliff 2005	non-RCT, 2 matched-controlled treatment groups	N/A	loss to follow-up completely recorded	N/A
Galloway 2005	non-RCT, uncontrolled	N/A	loss to follow-up completely recorded	N/A
Gölz 2000	non-RCT, 2 sequential treatment groups	N/A	loss to follow-up completely recorded	N/A
Foster 2003	non-RCT, uncontrolled	N/A	loss to follow-up completely recorded	N/A
Hulse 2005	non-RCT, record-linkage data	N/A	N/A	prospectively collected data: blind to treatment allocation at outcome assessment
Tait 2007	non-RCT, record-linkage data	N/A	N/A	prospectively collected data: blind to treatment allocation at outcome assessment
Sullivan 2006	non-RCT, uncontrolled	N/A	loss to follow-up completely recorded	N/A
Waal 2003	non-RCT, uncontrolled	N/A	loss to follow-up completely recorded	N/A
Waal 2006	non-RCT, uncontrolled	N/A	loss to follow-up completely recorded	N/A
Carreno 2003	non-RCT, uncontrolled	N/A	unclear or not done	N/A

Table 02. Reports according to study medication used

NTX formulation	Dose (mg)	Condition	Report
Alkermes depot (Vivitrol)	190	alcohol dependence	Turncliff 2005
	190 and 380	healthy volunteers	Dunbar 2006
	190 and 380	alcohol dependence	Garbutt 2005
	400	alcohol dependence	Johnson 2004
Biotek depot (Depotrex)	192 and 384	opioid dependence	Comer 2002
	192 and 384	opioid dependence	Comer 2006
	206	alcohol dependence	Kranzler 1998
	384	opioid dependence	Sullivan 2006
DrugAbuse Sciences depot (Naltrel)	150 and 300	alcohol dependence	Kranzler 2004
	300	alcohol dependence	Galloway 2005
GoMedical implant	1800 and 3600 (corrected by Tait 2007: 1100 mg and 2200 mg)	opioid dependence	Waal 2006
	3600 (corrected by Tait 2007: 2200 mg)	opioid dependence	Hulse 2005
	2200	opioid dependence	Tait 2007
Wedgewood implant	1000	opioid dependence	Foster 2003
	1000	opioid dependence	Waal 2003
	1000	opioid dependence	Gölz 2000
	1000	opioid dependence	Carreno 2003

Table 03. Electronic search strategies

Search strategy

Cochrane Central Register of Controlled Trials
1. Substance-related disorders*:ME
2. ((opioid) next (addict* or dependen* or abuse*)).ti,ab
3. #1 or #2
4. Heroin:MESH
5. (opioid* or opiate*)
6. Methadone:MESH
7. #4 or #5 or #6
8. NARCOTIC ANTAGONISTS:ME
9. Naltrexone:MESH
10. Naltrexone:ti,ab,kw
11. (sustain* next naltrexone):TI,AB,KW
12. delayed-action preparations
13. #8 or #9 or #10 or #11 or #12
14. #3 and #7 and #13

EMBASE

Table 03. Electronic search strategies (*Continued*)

Search strategy

1. Naltrexone/
2. naltrexone.tw.
3. or / 1-2
4. exp controlled release formulation/
5. exp controlled drug release/
6. exp sustained release preparation/
7. implant$.tw.
8. depot$.tw.
9. ((sustain$ or time$ or controlle$ or delay$ or slow or prolonge$ or extend$) adj2 release$).tw.
10. ((prolonge$ or delay$) adj2 action$).tw.
11. or/4-10
12. 3 and 11
13. (animals/ or animal experiment/) not humans/
14. 12 not 13

CINAHL - Cumulative Index to Nursing & Allied Health Literature
1. Naltrexone/
2. naltrexone.tw.
3. or / 1-2
4. Delayed-Action Preparations/
5. Drug Implants/
6. implant$.tw.
7. depot$.tw.
8. ((sustain$ or time$ or controlle$ or delay$ or slow or prolonge$ or extend$) adj2 release$).tw.
9. ((prolonge$ or delay$) adj2 action$).tw.
10. or / 4-9
11. 3 and 10

LILACS
basic search form: naltrexone

PsycINFO (1806 to November week 1 2007)
1. naltrexone/
2. naltrexone.tw.
3. or / 1-2
4. implant$.tw.
5. depot$.tw.
6. ((sustain$ or time$ or controlle$ or delay$ or slow or prolonge$ or extend$) adj2 release$).tw.
7. ((prolonge$ or delay$) adj2 action$).tw.
8. or / 4-7
9. 3 and 8
10. animals/
11. 9 not 10

ISI Web of Science (1975 to November 2007)
#6 #5 AND #1
DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2007
#5 #4 OR #3 OR #2
DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2007
#4 TS=((depot* or implant*))
DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2007

Table 03. Electronic search strategies (*Continued*)

Search strategy
#3 TS=((prolonge* or delay*) SAME action*) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2007
#2 TS=((sustain* or time* or controlle* or delay* or slow or prolonge* or extend*) SAME release*) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2007
#1 TS=(naltrexone*) DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI, A&HCI; Timespan=1975-2007

ANALYSES

Comparison 01. effectiveness outcomes treatment vs. control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 treatment retention in high-dose depot vs. placebo	1	40	Relative Risk (Fixed) 95% CI	1.75 [0.92, 3.34]
02 treatment retention in low-dose depot vs. placebo	1	38	Relative Risk (Fixed) 95% CI	1.54 [0.78, 3.05]
03 treatment retention in high-dose vs. low-dose depot	1	42	Relative Risk (Fixed) 95% CI	1.14 [0.72, 1.80]
04 time to drop out in high-dose depot vs. placebo	1	40	Weighted Mean Difference (Fixed) 95% CI	21.00 [10.68, 31.32]
05 time to drop out in high-dose vs. low-dose depot	1	42	Weighted Mean Difference (Fixed) 95% CI	12.00 [1.69, 22.31]
06 time to drop out in low-dose depot vs. placebo	1	38	Weighted Mean Difference (Fixed) 95% CI	9.00 [-3.40, 21.40]

Comparison 02. safety outcomes treatment vs. control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 high-dose depot vs. placebo in opioid dependence			Relative Risk (Fixed) 95% CI	Subtotals only
02 high-dose depot vs. placebo in alcohol dependence			Relative Risk (Fixed) 95% CI	Subtotals only
03 low-dose depot vs. placebo in opioid dependence			Relative Risk (Fixed) 95% CI	Subtotals only
04 low-dose depot vs. placebo in alcohol dependence			Relative Risk (Fixed) 95% CI	Subtotals only
05 low-dose depot vs. placebo in healthy volunteers			Relative Risk (Fixed) 95% CI	Subtotals only
06 high-dose vs. low-dose depot in opioid dependence			Relative Risk (Fixed) 95% CI	Subtotals only
07 high-dose vs. low-dose depot in alcohol dependence			Relative Risk (Fixed) 95% CI	Subtotals only
08 one or more adverse effects in liver impaired vs. healthy controls	1	25	Relative Risk (Fixed) 95% CI	3.25 [1.14, 9.24]

09 mortality in naltrexone implant vs. methadone maintenance	1	894	Relative Risk (Fixed) 95% CI	0.65 [0.25, 1.66]

COVER SHEET

Title	Sustained-Release Naltrexone For Opioid Dependence
Authors	Lobmaier P, Kornør H, Kunøe N, Bjørndal A
Contribution of author(s)	Three review authors (PL, HK, NK) independently assessed potentially relevant studies for inclusion. If consensus was not achieved, the senior reviewer (AB) was consulted. Two review authors (PL, HK) independently extracted data and independently assessed methodological quality of eligible studies. A third review author resolved any disagreements. All four review authors read, discussed and approved this review.
Issue protocol first published	2006/3
Review first published	2008/2
Date of most recent amendment	25 January 2008
Date of most recent SUBSTANTIVE amendment	25 January 2008
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Philipp Lobmaier Research Fellow Norvegian Centre for Addiction Research University of Oslo, Kirkeveien 166 Oslo 0407 NORWAY E-mail: p.p.lobmaier@medisin.uio.no Tel: +47 - 23 36 89 38 Fax: +47 23368901
DOI	10.1002/14651858.CD006140.pub2
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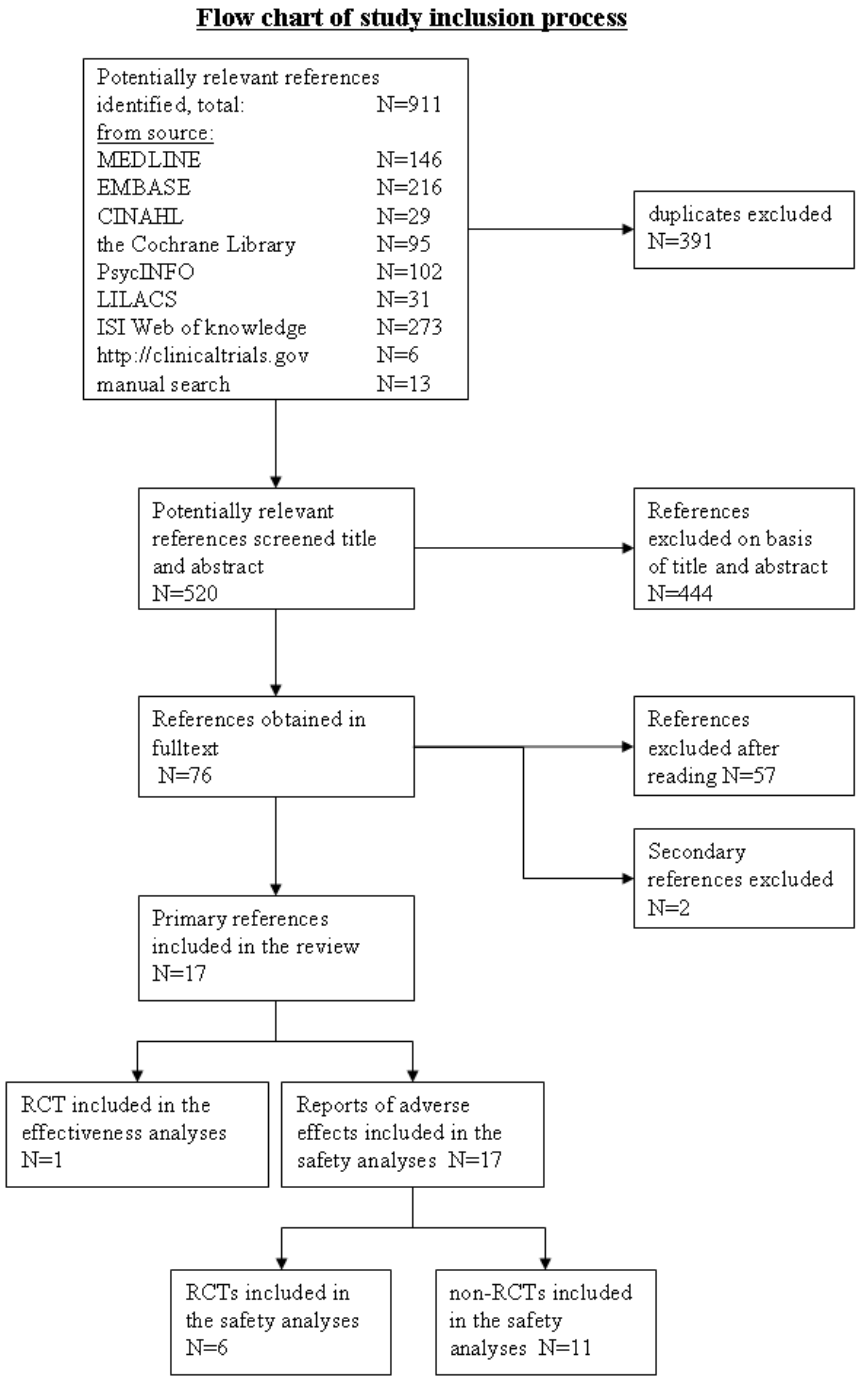
GRAPHS AND OTHER TABLES

Figure 01.



Analysis 01.01. Comparison 01 effectiveness outcomes treatment vs. control, Outcome 01 treatment retention in high-dose depot vs. placebo

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 01 effectiveness outcomes treatment vs. control

Outcome: 01 treatment retention in high-dose depot vs. placebo

Study	high-dose naltrexone n/N	placebo injection n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Comer 2006	15/22	7/18		100.0	1.75 [0.92, 3.34]
Total (95% CI)	22	18		100.0	1.75 [0.92, 3.34]
Total events: 15 (high-dose naltrexone), 7 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.70 p=0.09					

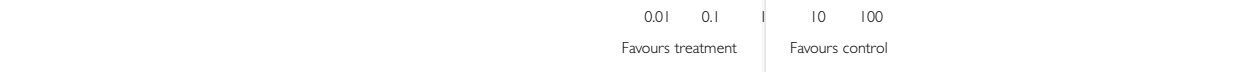
Analysis 01.02. Comparison 01 effectiveness outcomes treatment vs. control, Outcome 02 treatment retention in low-dose depot vs. placebo

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 01 effectiveness outcomes treatment vs. control

Outcome: 02 treatment retention in low-dose depot vs. placebo

Study	low-dose naltrexone n/N	placebo injection n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Comer 2006	12/20	7/18		100.0	1.54 [0.78, 3.05]
Total (95% CI)	20	18		100.0	1.54 [0.78, 3.05]
Total events: 12 (low-dose naltrexone), 7 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.25 p=0.2					



Analysis 01.03. Comparison 01 effectiveness outcomes treatment vs. control, Outcome 03 treatment retention in high-dose vs. low-dose depot

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 01 effectiveness outcomes treatment vs. control

Outcome: 03 treatment retention in high-dose vs. low-dose depot

Study	high-dose naltrexone n/N	low-dose naltrexone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Comer 2006	15/22	12/20		100.0	1.14 [0.72, 1.80]
Total (95% CI)	22	20		100.0	1.14 [0.72, 1.80]

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

Test for heterogeneity: not applicable

Test for overall effect z=0.55 p=0.6

Analysis 01.04. Comparison 01 effectiveness outcomes treatment vs. control, Outcome 04 time to drop out in high-dose depot vs. placebo

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 01 effectiveness outcomes treatment vs. control

Outcome: 04 time to drop out in high-dose depot vs. placebo

Study	high-dose naltrexone N	Mean(SD)	placebo injection N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Comer 2006	22	48.00 (13.00)	18	27.00 (19.00)		100.0	21.00 [10.68, 31.32]
Total (95% CI)	22		18			100.0	21.00 [10.68, 31.32]

Test for heterogeneity: not applicable

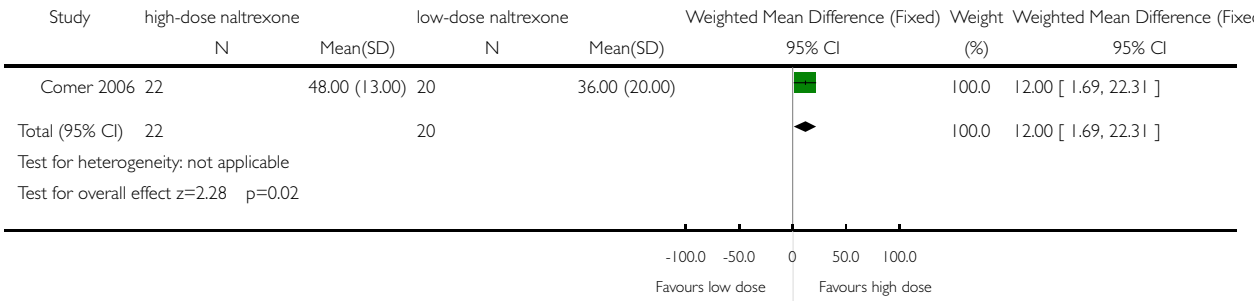
Test for overall effect z=3.99 p=0.00007

Analysis 01.05. Comparison 01 effectiveness outcomes treatment vs. control, Outcome 05 time to drop out in high-dose vs. low-dose depot

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 01 effectiveness outcomes treatment vs. control

Outcome: 05 time to drop out in high-dose vs. low-dose depot

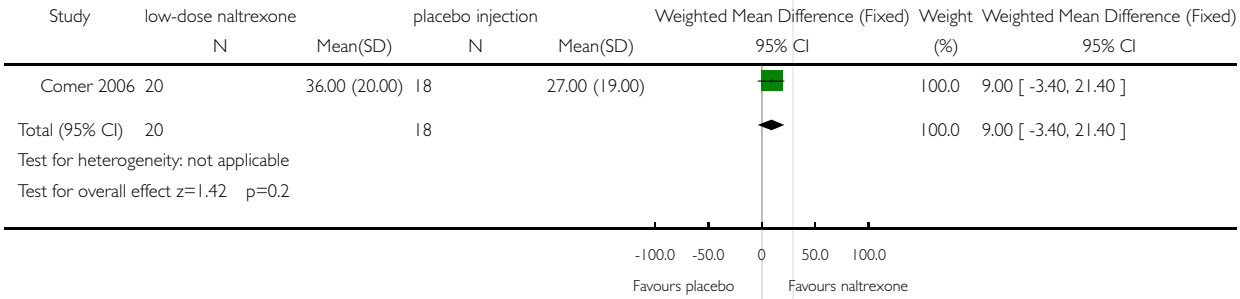


Analysis 01.06. Comparison 01 effectiveness outcomes treatment vs. control, Outcome 06 time to drop out in low-dose depot vs. placebo

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 01 effectiveness outcomes treatment vs. control

Outcome: 06 time to drop out in low-dose depot vs. placebo



Analysis 02.01. Comparison 02 safety outcomes treatment vs. control, Outcome 01 high-dose depot vs. placebo in opioid dependence

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 02 safety outcomes treatment vs. control

Outcome: 01 high-dose depot vs. placebo in opioid dependence

Study	high-dose naltrexone n/N	placebo injection n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 one or more adverse effects					
Comer 2006	15/22	9/18		100.0	1.36 [0.79, 2.35]
Subtotal (95% CI)	22	18		100.0	1.36 [0.79, 2.35]
Total events: 15 (high-dose naltrexone), 9 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.12 p=0.3					
02 discontinued due to adverse effects					
Comer 2006	0/22	1/18		100.0	0.28 [0.01, 6.38]
Subtotal (95% CI)	22	18		100.0	0.28 [0.01, 6.38]
Total events: 0 (high-dose naltrexone), 1 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.80 p=0.4					

Analysis 02.02. Comparison 02 safety outcomes treatment vs. control, Outcome 02 high-dose depot vs. placebo in alcohol dependence

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 02 safety outcomes treatment vs. control

Outcome: 02 high-dose depot vs. placebo in alcohol dependence

Study	high-dose naltrexone n/N	placebo injection n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 one or more adverse effects					
Johnson 2004	23/25	4/5		100.0	1.15 [0.73, 1.81]
Subtotal (95% CI)	25	5		100.0	1.15 [0.73, 1.81]
Total events: 23 (high-dose naltrexone), 4 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.60 p=0.5					
02 severe adverse effects					
Garbutt 2005	10/205	15/209		100.0	0.68 [0.31, 1.48]
Subtotal (95% CI)	205	209		100.0	0.68 [0.31, 1.48]
Total events: 10 (high-dose naltrexone), 15 (placebo injection)					

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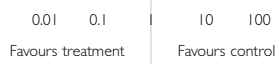
Study	high-dose naltrexone n/N	placebo injection n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					
03 injection site pain					
Garbutt 2005	24/205	19/209		100.0	1.29 [0.73, 2.28]
Subtotal (95% CI)	205	209		100.0	1.29 [0.73, 2.28]
Total events: 24 (high-dose naltrexone), 19 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.87 p=0.4					
04 discontinued due to adverse effects					
Garbutt 2005	29/205	14/209		100.0	2.11 [1.15, 3.88]
Subtotal (95% CI)	205	209		100.0	2.11 [1.15, 3.88]
Total events: 29 (high-dose naltrexone), 14 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.41 p=0.02					



Analysis 02.03. Comparison 02 safety outcomes treatment vs. control, Outcome 03 low-dose depot vs. placebo in opioid dependence

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 02 safety outcomes treatment vs. control

Outcome: 03 low-dose depot vs. placebo in opioid dependence

Study	low-dose naltrexone n/N	placebo injection n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 one or more adverse effects					
Comer 2006	13/20	9/18		100.0	1.30 [0.74, 2.28]
Subtotal (95% CI)	20	18		100.0	1.30 [0.74, 2.28]
Total events: 13 (low-dose naltrexone), 9 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.91 p=0.4					
02 discontinued due to adverse effects					
Comer 2006	2/20	1/18		100.0	1.80 [0.18, 18.21]
Subtotal (95% CI)	20	18		100.0	1.80 [0.18, 18.21]
Total events: 2 (low-dose naltrexone), 1 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.50 p=0.6					

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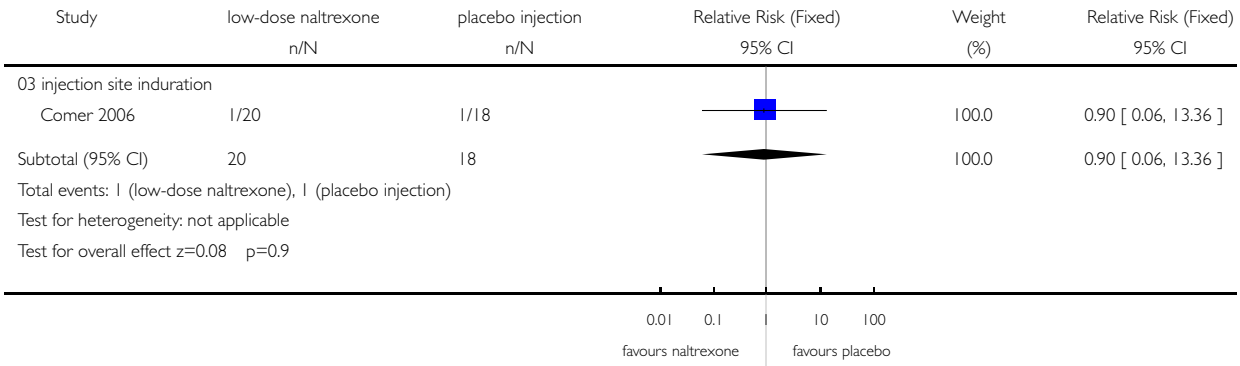
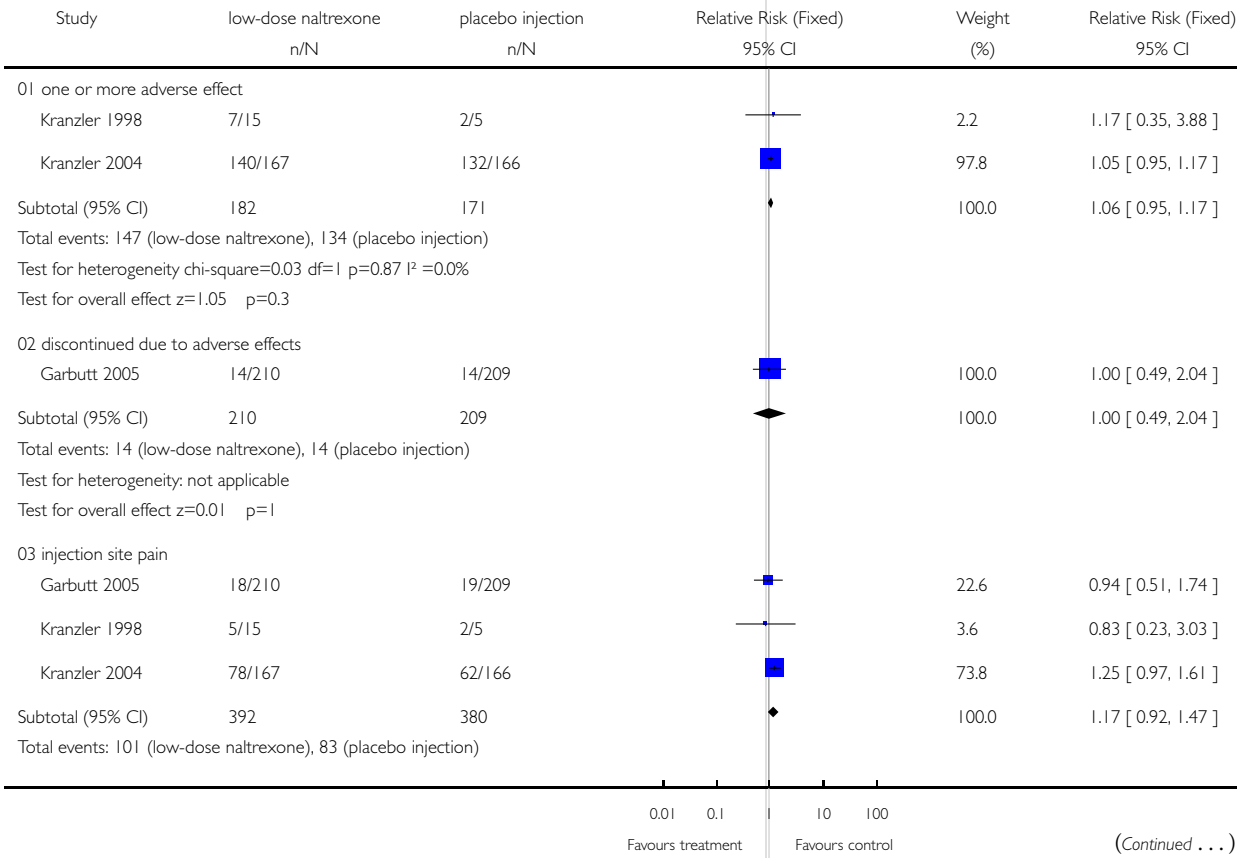


Analysis 02.04. Comparison 02 safety outcomes treatment vs. control, Outcome 04 low-dose depot vs. placebo in alcohol dependence

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 02 safety outcomes treatment vs. control

Outcome: 04 low-dose depot vs. placebo in alcohol dependence



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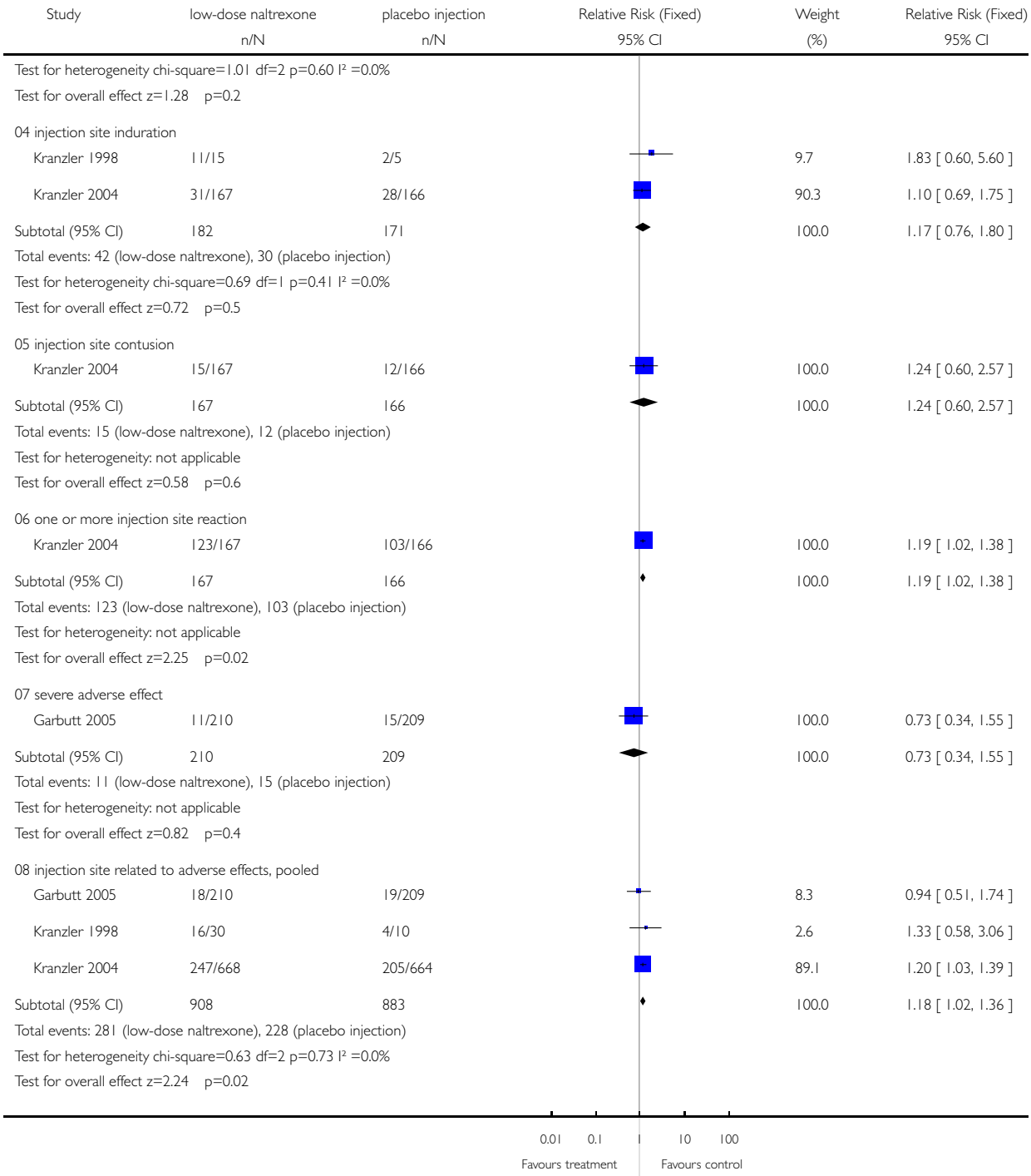

Analysis 02.05. Comparison 02 safety outcomes treatment vs. control, Outcome 05 low-dose depot vs. placebo in healthy volunteers

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 02 safety outcomes treatment vs. control

Outcome: 05 low-dose depot vs. placebo in healthy volunteers

Study	low-dose naltrexone n/N	placebo injection n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 one or more adverse effects					
Dunbar 2006	6/36	0/6		100.0	2.46 [0.16, 38.89]
Subtotal (95% CI)	36	6		100.0	2.46 [0.16, 38.89]
Total events: 6 (low-dose naltrexone), 0 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.64 p=0.5					
02 one or more injection site reaction					
Dunbar 2006	3/36	0/6		100.0	1.32 [0.08, 22.92]
Subtotal (95% CI)	36	6		100.0	1.32 [0.08, 22.92]
Total events: 3 (low-dose naltrexone), 0 (placebo injection)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.19 p=0.8					

Analysis 02.06. Comparison 02 safety outcomes treatment vs. control, Outcome 06 high-dose vs. low-dose depot in opioid dependence

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 02 safety outcomes treatment vs. control

Outcome: 06 high-dose vs. low-dose depot in opioid dependence

Study	high-dose naltrexone n/N	low-dose naltrexone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 one or more adverse effects					
Comer 2006	15/22	13/20		100.0	1.05 [0.68, 1.61]
Subtotal (95% CI)	22	20		100.0	1.05 [0.68, 1.61]
Total events: 15 (high-dose naltrexone), 13 (low-dose naltrexone)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.22 p=0.8					
02 discontinued due to adverse effects					
Comer 2006	0/22	2/20		100.0	0.18 [0.01, 3.59]
Subtotal (95% CI)	22	20		100.0	0.18 [0.01, 3.59]
Total events: 0 (high-dose naltrexone), 2 (low-dose naltrexone)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.12 p=0.3					

Analysis 02.07. Comparison 02 safety outcomes treatment vs. control, Outcome 07 high-dose vs. low-dose depot in alcohol dependence

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 02 safety outcomes treatment vs. control

Outcome: 07 high-dose vs. low-dose depot in alcohol dependence

Study	high-dose naltrexone n/N	low-dose naltrexone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 discontinued due to adverse effects					
Garbutt 2005	29/205	14/210		100.0	2.12 [1.16, 3.90]
Subtotal (95% CI)	205	210		100.0	2.12 [1.16, 3.90]
Total events: 29 (high-dose naltrexone), 14 (low-dose naltrexone)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.42 p=0.02					
02 injection site pain					
Garbutt 2005	24/205	18/210		100.0	1.37 [0.76, 2.44]
Subtotal (95% CI)	205	210		100.0	1.37 [0.76, 2.44]
Total events: 24 (high-dose naltrexone), 18 (low-dose naltrexone)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.05 p=0.3					
03 severe adverse effects					
Garbutt 2005	10/205	11/210		100.0	0.93 [0.40, 2.15]
Subtotal (95% CI)	205	210		100.0	0.93 [0.40, 2.15]
Total events: 10 (high-dose naltrexone), 11 (low-dose naltrexone)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.17 p=0.9					

Analysis 02.08. Comparison 02 safety outcomes treatment vs. control, Outcome 08 one or more adverse effects in liver impaired vs. healthy controls

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 02 safety outcomes treatment vs. control

Outcome: 08 one or more adverse effects in liver impaired vs. healthy controls

Study	liver impairment n/N	healthy n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Turncliff 2005	9/12	3/13		100.0	3.25 [1.14, 9.24]
Total (95% CI)	12	13		100.0	3.25 [1.14, 9.24]
Total events: 9 (liver impairment), 3 (healthy)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.21 p=0.03					

Analysis 02.09. Comparison 02 safety outcomes treatment vs. control, Outcome 09 mortality in naltrexone implant vs. methadone maintenance

Review: Sustained-Release Naltrexone For Opioid Dependence

Comparison: 02 safety outcomes treatment vs. control

Outcome: 09 mortality in naltrexone implant vs. methadone maintenance

Study	naltrexone implant n/N	methadone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Tait 2007	6/341	15/553		100.0	0.65 [0.25, 1.66]
Total (95% CI)	341	553		100.0	0.65 [0.25, 1.66]
Total events: 6 (naltrexone implant), 15 (methadone)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.91 p=0.4