Naltrexone implant treatment for opioid dependence

Literature Review

NALTREXONE IMPLANTS FOR OPIOID DEPENDENCE
Literature review- 2010

INTRODUCTION

There has been substantial media interest and controversy over the use of naltrexone implants for the treatment of opioid dependence. Naltrexone implants have not been approved for human use in Australia due to a lack of results from clinical trials demonstrating their pharmaceutical quality, safety and efficacy.

The National Health and Medical Research Council (NHMRC) has funded five research projects relating to naltrexone to a total of $1,507,714. A grant awarded to Professor Hulse (ID: 303106) supported a randomised controlled trial (RCT) comparing naltrexone implants with naltrexone tablets as a treatment for heroin dependence. As there is only one other published RCT on naltrexone implants (Kunøe 2009), the release of Hulse's paper prompted an assessment of the available evidence on the safety and efficacy of naltrexone implants for opioid dependence.

The only naltrexone product approved for widespread use in Australia is oral naltrexone, which is registered for both opioid detoxification and maintenance treatment, though not listed on the Pharmaceutical Benefits Scheme (PBS) for this indication (oral naltrexone is licensed and PBS listed for treating alcohol dependence). While naltrexone implants may currently be legally manufactured by an appropriately licensed facility meeting the requirements of the Australian Code of Good Manufacturing Practice for Medicinal Products, until such time as they are evaluated and approved for registration by the Therapeutic Goods Administration (TGA), naltrexone implants may only be used under certain exemptions within the *Therapeutic Goods Act 1989* applying to clinical trials and to the provision of unapproved products under the Special Access Scheme. In order for the TGA to approve naltrexone implants a sponsor must first apply to the TGA for registration. At the time of writing no application for registration has yet been made to the TGA.

The Royal Australasian College of Physicians (RACP) Chapter of Addiction Medicine is developing a *Position Statement regarding use of unregistered long-acting naltrexone products for the treatment of opioid dependence* (RACP unpublished). The Draft RACP Statement states that: treatment with unlicensed long-acting naltrexone products should only be considered as a second-line treatment approach in patients who are not responding to conventional treatment, and who continue to actively use unsanctioned opioids in a high-risk manner. The Draft RACP Statement discusses several safeguards for experimental treatment with long-acting naltrexone products:
1. informed consent;
2. treatment in a clinical trial setting or as 'second line' where conventional treatment has failed;
3. specialist patient assessment;
4. continuing research on safety, efficacy and cost effectiveness; and
5. robust mechanisms for monitoring appropriateness, safety and efficacy.

BACKGROUND

Opioids are a class of drugs that relieve pain and can create a sense of well-being. Opioids are depressants, slowing the functions of the brain and body (O'Brien 2004).While heroin is the most well known opioid in relation to dependence, other opioids include methadone, buprenorphine, opium, codeine and morphine (O'Brien 2004). Evidence-based guidelines exist to guide safe and legitimate use of these drugs in medical settings for the treatment of conditions associated with severe acute and chronic pain (Macintyre et al 2010). For the

purpose of this review, opioid dependence is defined as a maladaptive pattern of substance abuse leading to clinically significant impairment or distress as manifested by a number of symptoms, including tolerance (American Psychiatric Association 2000). Tolerance is defined as either 1) a need for markedly increased amount of the opioid to achieve intoxication or the desired effect; or 2) markedly diminished effect with continued use of the same amount of the opioid (American Psychiatric Association 2000) and relates to illicit opioid use and dependence.

Opioid dependence is a chronic lifelong condition, which requires substantial therapeutic intervention as relapse is common (O'Brien 2004). Recent data (AIHW 2009) indicate that treatment seeking heroin users in Australia in 2007-2008 were:
- mean age of 31
- 66% male
- 67% using ≥ one drug in addition to heroin (25% cannabis, 19% amphetamines)
- 91% injecting drug users.

Three pharmacotherapies are registered in Australia for treatment of opioid dependence: methadone, buprenorphine or buprenorphine/naloxone, and naltrexone. These are only registered in oral forms and may be used in detoxification or long term maintenance (with the exception of naltrexone tablets which are only registered for maintenance, not detoxification). The main goal of treatment for opioid dependence is "to reduce the health, social and economic harms to individuals and the community arising from illicit opioid use" (DoHA 2007). It is recommended that pharmacotherapies only be part of a more comprehensive treatment program involving medical, social and psychological support (DoHA 2007; O'Brien 2004).

At present, the most effective and researched treatment for opioid dependence is agonist replacement therapy with methadone (Amato 2005, O'Brien 2004). MMT is a substitution based treatment in that it replaces the illicit opioid with a legal opioid which is considered to be safer than heroin which is illicit, and therefore unregulated. Methadone maintenance treatment (MMT) has been shown to reduce illicit opioid use and substantially increase retention in treatment (Lobmaier 2008). MMT can give people a chance to improve their health and social situation without having to cope with withdrawal. During treatment, clients are physically dependent on opioids and have to attend a clinic/pharmacy daily or several times a week for their dose (O'Brien 2004).

On 30 June 2008, it was estimated that 41,347 people in Australia were receiving methadone, buprenorphine or buprenorphine/naloxone for treatment of opioid dependence, an increase of about 2,500 from each of the previous three years. Naltrexone is not included in these data as there is no legislative requirement to report its prescription to government authorities (AIHW 2008).

Naltrexone may be more suitable than MMT for people seeking abstinence-based treatment as it is long acting and has few side effects (DoHA 2007). Abstinence based treatments can be clinically indicated, and/or are sometimes sought by patients. Oral naltrexone has been approved for this indication. Naltrexone blocks the effects of opioids by blocking opioid receptors. The rationale for using naltrexone is that if a person does not experience any positive effect, they will stop using opioids (O'Brien 2004). However, this is considered to be a simplistic notion. Opioid dependence is a complex syndrome involving a number of genetic, physiological, neurobiological and psychological factors. People who use naltrexone do not develop a tolerance or dependence on it (Navaratnam 1994; Rawson 2000; both cited in

Lobmaier 2008). While naltrexone implant treatment could be considered as an option where conventional treatment has failed, it is **not** a first line treatment.

Russia is the only country in the world that has approved the use of naltrexone implants in routine clinical practice. Naltrexone is the only treatment approved for treating addiction in Russia. People working with addicts in Russia have reported that naltrexone implants are problematic as they are too expensive for most addicts to afford, are primarily delivered in isolation (ie without other treatment or support), do not reduce cravings, do not help addicts psychologically to stop and are therefore seeing a poor success rate (Holt 2010). They have also reported that long acting naltrexone implants may increase suicide rates during treatment and fatal overdose post treatment (Holt 2010).

Systematic reviews of the literature have found that oral naltrexone maintenance therapy, alone or in association with psychosocial therapy, is more effective than non-active placebo, alone or with psychosocial therapy, in limiting heroin use during treatment, but this effect declined over time (Minozzi 2006; Adi 2007). No clear benefit was shown in terms of retention in treatment, side effects or relapse at follow up. Australian research also raises concern over poor retention; and noted that people taking naltrexone tablets reduced their heroin use dramatically but most stopped naltrexone treatment in the first few months, with significantly more ceasing these treatments than those on methadone or buprenorphine treatment (O'Brien 2004).

The low rate of retention in treatment is of particular concern as high retention rates increase the likelihood of achieving longer term objectives such as reduced illicit opioid use, and improved general health and social functioning (Simpson 1979; DoHA 2007). The Australian *Clinical Guidelines and Procedures for the Use of* [oral] *Naltrexone in the Management of Opioid Dependence* (National Drug Strategy 2003) recognise naltrexone's limitations in relapse prevention and only recommend it for opioid users committed to long-term abstinence. Similarly, Waal (2006) states that except for highly motivated patients, the benefits of oral naltrexone may be short term. The short term nature of adherence poses a problem as the person's opioid tolerance will have reduced, potentially increasing the possibility of overdose. An increased overdose risk has been reported after cessation of oral naltrexone (Digiusto et al 2004) and this risk may extend to naltrexone implants.

Another factor that is important to consider is the risks associated with commencement of treatment with naltrexone. Naltrexone is an abstinence based treatment and as such requires patients to undergo detoxification prior to commencement. Risks in this period relate to acute opioid withdrawal and include agitation, anxiety, muscle aches, insomnia, sweating, abdominal cramping, diarrhea, nausea and vomiting (Doyon 2004).

The advantage of sustained release naltrexone, either by an implant inserted under the skin or depot injection, is that doses are required less frequently, potentially reducing rates of non compliance, between-dosage withdrawal and relapse, and providing the patient an opportunity to affect significant life changes (Kunøe 2009; Lobmaier 2008). To date, no sustained release formulation is approved for treating opioid dependence in Australia, Europe or the United States of America (Lobmaier 2008). The available evidence for use of naltrexone implants comes from clinical trials of patients who have been granted access through schemes like the SAS.

A Cochrane systematic review by Lobmaier (2008) found insufficient evidence to evaluate the efficacy of sustained-release naltrexone. In the one RCT that met inclusion criteria, depot injections of naltrexone showed promise in increasing time in treatment compared to a placebo,

but by eight weeks this increase was ambiguous. The most prominent adverse effects were general symptoms of fatigue and pain at the injection site. No studies met the inclusion criteria (RCT), for assessing the efficacy of naltrexone implants for treating opioid dependent patients. Seven met inclusion criteria for assessing adverse effects. The adverse effects reported were local tissue reaction, wound infection, implant removal, headaches and nausea. The majority of these trials did not have a control group and systematic assessment of adverse effects was lacking (Lobmaier 2008).

Recognising that Lobmaier (2008) did not find any RCTs evaluating the efficacy and adverse effects of naltrexone implants for opioid dependence, the aim of this review is to identify and evaluate studies published after Lobmaier's review, as well as to assess those that were excluded by Lobmaier (2008) because they were of lower level design.

OBJECTIVES

1. To assess the clinical effectiveness of naltrexone implants for long term maintenance from opioid dependence compared to placebo or alternative treatments.
2. To assess adverse effects of naltrexone implants in opioid dependent patients.

It is not the purpose of this review to consider:
a. the use of naltrexone for detoxification (rapid or ultrarapid detoxification) as oral naltrexone is only registered for long term maintenance
b. the use of naltrexone for other conditions (e.g. alcohol or tobacco dependence)
c. other preparations of naltrexone (e.g. oral or depot preparations)
d. the regulatory environment.

METHOD

Search Strategy
Electronic searches were performed to identify all clinical trials investigating the effectiveness, side effects and adverse events of sustained-release naltrexone.

All references obtained in full text by Lobmaier (2008), included and excluded were considered. The search strategy used by Lobmaier (2008) is detailed at Appendix A and included studies up to November 2007.

To identify studies published since Lobmaier (2008), the search strategy was duplicated as close as possible for studies published between November 2007 and June 2009. The search was restricted to the following databases: 1. Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2009); 2. MEDLINE (November 2007 to 2009 June Week 4); 3. EMBASE (November 2007 to 2009 Week 27); and 4. PsycINFO (November 2007 to 2009 June Week 1). Detailed search strategies for each database are at Appendix A.

A basic search of the NHS Evidence Portal (http://www.evidence.nhs.uk/), the clinical trial register (http://clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (www.who.int/ictrp) using the keywords 'naltrexone' and 'implant' was also conducted. As this review is of published scientific literature, no attempt was made to identify grey literature. It should be noted that results of unpublished studies usually favour a lack of efficacy and may affect the conclusions reached.

Inclusion and Exclusion Criteria

Inclusion criteria were:
- population - opioid-dependent patients
- adverse effects - clinical trials of any design
- effectiveness - comparative clinical trials, either within or between subject design, of naltrexone implants compared to any other treatment (e.g. oral naltrexone, agonist replacement therapy, psychosocial intervention, placebo) or no treatment.

Exclusion criteria were:
- not published in English language
- published prior to 2000 (Lobmaier 2008 included studies pre 2000)
- intervention was oral or depot preparations of naltrexone
- non clinical trial (e.g. reviews, editorials, comments)
- the use of naltrexone implants for detoxification from opioids (including rapid or ultrarapid detoxification)
- the use of naltrexone for other conditions (e.g. in alcohol or tobacco dependence)
- outcome measures outside of the protocol below (e.g. pharmacokinetic properties, memory ability)
- sample size less than ten.

Outcomes to be Examined

The outcomes assessed were selected based on those identified by Lobmaier (2008). Primary outcomes were:
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/percentage of days met/not met for scheduled visits
3) Retention in treatment: time to drop out
4) Adverse effects.

Secondary outcomes were:
5) Use of 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; hospital admissions
9) Duration of achieved therapeutic naltrexone blood levels: ng/ml as a function of time
10) Heroin craving.

Data Extraction Strategy

One author assessed potentially relevant studies for inclusion and extracted data onto a pre designed data extraction table. Results were extracted, where possible for intention-to-treat (ITT) populations, as raw numbers, plus any summary measures with standard deviations, confidence intervals and *p*-values. Both steps were checked by a second reviewer.

Quality Assessment Strategy

Studies were assessed for measures to avoid selection, performance, attrition and detection biases. Overall there was a low risk of selection and attrition bias, a low to medium risk of detection bias and a high risk of performance bias. The high risk of performance bias stemmed primarily from the lack of control for possible confounding factors such as pre-existing illness, level of motivation, situational influences and socioeconomic factors.

Methodological quality is reported in the data extraction tables but was not used as a threshold for inclusion of trials. The study design and level of evidence was assessed using the NHMRC *How to use the evidence: assessment and application of scientific evidence* (2000).

Data Analysis

The main results can be found in the data extraction tables. Studies are grouped according to the outcome measured. It was not appropriate to do a meta-analysis due to differences in the outcomes and substantial differences in length of follow-up (Cochrane Collaboration 2002).

RESULTS

Quantity of Evidence

The searches produced one hundred and ninety three citations, of which nineteen were excluded on the basis of the year of publication. One hundred and forty three were excluded on the basis of title/abstract/keywords as they did not fulfil one or more of the inclusion criteria, i.e. only abstract available in English, intervention other than naltrexone implants, non clinical trial, non opioid dependent patients, outcome measures outside of the protocol or sample size less than ten.

Thirty citations were obtained in full text for further assessment. Of these, fifteen studies did not meet the inclusion criteria for this review: one examined an intervention other than naltrexone implants (oral naltrexone), four were non clinical trials (e.g. reviews, comments), four examined outcome measures outside of the protocol (e.g. pharmacodynamic results or memory ability), and six had sample sizes less than ten.

Characteristics of included studies are at Appendix B and characteristics of excluded studies (excluded at the full text assessment stage) are at Appendix C.

Fifteen studies met the inclusion criteria for this review: fourteen were included for evaluation of effectiveness and nine for evaluation of adverse effects. Eight studies were included in both the safety and effectiveness analyses. *Figure 1* shows a flowchart of the study inclusion process.

It should be noted that in six reports (Hulse 2005a, Ngo 2008a, Ngo 2008b, Ngo 2007, Tait 2008a; Tait 2008b) the same population was investigated. Essentially, the same cohort is reported on six times rather than six different cohorts being reported on. Results have only been reported once against each outcome under investigation. If the same outcomes were reported in more than one report, those with tests of significance were given preference over those with only narrative results.

For adverse effects evaluation, missing information from two studies (Gölz 2000, Olsen 2004) were obtained from Lobmaier (2008) review.

Quality of Evidence

Two RCTs, providing level II evidence, were included in the review. Eleven comparative non-randomised studies were included in the review providing level III-2 to IV evidence. Two studies without control groups, providing level IV evidence, were included in the analysis. Loss to follow-up was variable across studies, with high loss to follow-up common in this field of research. Some studies employed strategies to follow-up patients through carers, while others conducted analyses on an 'Intention To Treat' basis.
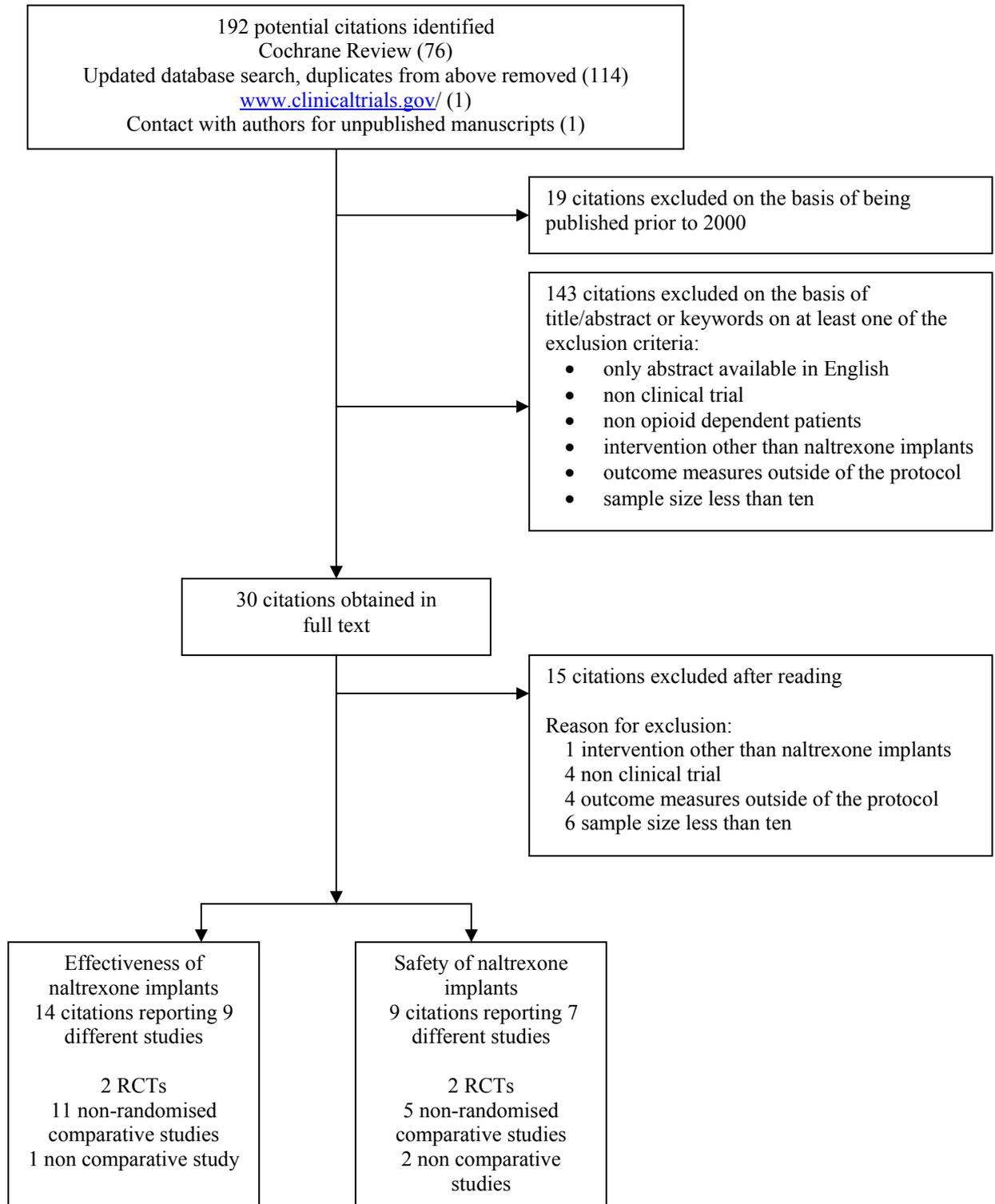
Confounding factors identified included:
- Demographic variables – age, gender
- Social variables – occupation, social support, education, financial status, situational influences, level of motivation i.e. those who chose oral naltrexone may have been less motivated, selecting a treatment option that seems easier to opt out of
- Drug history – age at first use, duration of use, comorbidity with other drugs, previous treatment for substance abuse
- Health status – pre-existing illness, psychiatric symptoms
- Cost – patients undergoing MMT in Australia may pay a co-payment equal to approximately one third of the total cost of treatment (Rowe 2008), while naltrexone implants are privately funded and are therefore more expensive. Three years of MMT costs patients about the same as one naltrexone implant. This is a potential confounding factor that was not controlled for where participants selected their own treatment group.

Adjustment for confounding factors in analyses varied between studies. Caution should be exercised in interpreting the results of these studies as:
- The sample sizes were small – ideally they should be in line with well developed RCTs of similar treatments.
- Duration of treatment and follow up was inadequate – should be longer than the duration of treatment and given the chronic relapsing nature of the condition, follow up should be for at least 12 months in line with trials of other depot medications.
- The comparators are inappropriate – comparator should be current best practice (currently this is considered to be MMT with psychosocial support) and details of this treatment should be well documented. The evidence surrounding oral naltrexone is not strong and so its role as a comparator must be questioned at this time.
- Many studies are not independent, with several papers being published describing the same cohort.
- The number of implant manufacturers is also small and as a result problems with implants may be associated with particular formulations.

A full summary of the quality of the included studies is given in Appendix D.

Figure 1: *Flow chart of study inclusion process*

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┌─────────────────────────────────────────────────────┐
│        192 potential citations identified             │
│              Cochrane Review (76)                     │
│  Updated database search, duplicates from above       │
│              removed (114)                            │
│            www.clinicaltrials.gov/ (1)                │
│  Contact with authors for unpublished manuscripts (1) │
└─────────────────────────────────────────────────────┘
            │
            │         ┌──────────────────────────────────────┐
            ├────────▶│ 19 citations excluded on the basis of │
            │         │ being published prior to 2000          │
            │         └──────────────────────────────────────┘
            │
            │         ┌──────────────────────────────────────┐
            │         │ 143 citations excluded on the basis of │
            │         │ title/abstract or keywords on at least │
            │         │ one of the exclusion criteria:         │
            ├────────▶│   • only abstract available in English │
            │         │   • non clinical trial                 │
            │         │   • non opioid dependent patients      │
            │         │   • intervention other than naltrexone │
            │         │     implants                           │
            │         │   • outcome measures outside of the    │
            │         │     protocol                           │
            │         │   • sample size less than ten          │
            │         └──────────────────────────────────────┘
            ▼
┌──────────────────────────┐
│ 30 citations obtained in  │
│        full text          │
└──────────────────────────┘
            │
            │         ┌──────────────────────────────────────┐
            │         │ 15 citations excluded after reading    │
            │         │                                        │
            ├────────▶│ Reason for exclusion:                  │
            │         │   1 intervention other than naltrexone │
            │         │     implants                           │
            │         │   4 non clinical trial                 │
            │         │   4 outcome measures outside of the    │
            │         │     protocol                           │
            │         │   6 sample size less than ten          │
            │         └──────────────────────────────────────┘
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| Effectiveness of naltrexone implants 14 citations reporting 9 different studies 2 RCTs 11 non-randomised comparative studies 1 non comparative study | Safety of naltrexone implants 9 citations reporting 7 different studies 2 RCTs 5 non-randomised comparative studies 2 non comparative studies |

Results Reported in the Studies

Full results of the studies on effectiveness and safety are at Appendix E and Appendix F, respectively. Detailed quality assessment of all included studies is at Appendix D.

<u>Findings on effectiveness</u>

1) Opioid use during and after treatment

Two RCTs (Kunøe 2009, Hulse 2009) examining opioid use during and after treatment (level II evidence) found significantly lower opioid use at six month follow-up in the implant group compared to the control group.

Five of the included comparative studies (Colquhoun 2005, Hulse 2005a, Ngo 2008b, Reece 2007, Tait 2008a) examined opioid use during and after treatment (level III-2 to IV evidence). Colquhoun (2005) found that, at six and twelve month follow-up, relapse to opioids in the implant group was lower in formerly abstinent participants compared to participants who had previously relapsed. Interestingly, relapse rates were higher in the implant group than the control group where participants had been abstinent and lower where participants had previously relapsed (Colquhoun 2005).

Hulse (2005a) (also reported by Ngo 2008b) found no significant change in risk of opioid overdose from six months pre treatment to six months post treatment for implant or control groups. However, Tait (2008a) found a significant decline in opioid overdoses in the implant group from six months pre treatment to six months post treatment. Ngo (2008b) reported a significant reduction in opioid overdoses and hospital admissions for other opioid conditions in the implant group when follow-up was extended to three and a half years. Reece (2007) found that work prior to treatment and the presence of cannabis in the urine were significantly related to opiate free success.

2) Treatment adherence

The one included RCT (Kunøe 2009) examining treatment adherence (level II evidence) found no significant difference in outpatient treatment attendance between the implant group and controls at six month follow-up.

Two comparative studies (Grusser 2006, Reece 2007) examined treatment adherence (level III-2 to IV evidence). Grusser (2006) reported one relapse at six weeks post treatment and two relapses at twelve weeks post treatment in the implant group. In the control group ten participants had relapsed and three switched to long term Levomethadone at six week follow-up. By twelve week follow-up the remaining participants of the control group could not be located. Reece (2007) reported that 70%, 52% and 39% of implant, oral and historic oral participants, respectively, tested positive for naltrexone indicating treatment adherence.

3) Retention in treatment: time to drop out

Two of the included comparative studies (Carreńo 2003, Colquhoun 2005) examined retention in treatment (level III-2 evidence). Carreńo (2003) found a significantly higher treatment retention rate in the implant group at six and twelve month follow-up compared to the control group. Within the implant group Colquhoun (2005) found greater treatment retention at six and

twelve months follow-up in abstinent participants than those who had relapsed. Treatment retention was higher in the implant group than controls at six and twelve month follow-up in both abstinent and relapsed participants.

5) Use of drugs other than opioids during and after treatment

Two RCTs (Kunøe 2009, Hulse 2009) examining the use of drugs other than opioids during and after treatment (level II evidence) found no significant difference between the implant group and controls in self reported use of non-opioid drugs at six month follow-up.

Three of the included comparative studies (Hulse 2005a, Ngo 2008b, Reece 2007) examined use of drugs other than opioids during and after treatment (level III-2 to IV evidence). Hulse (2005a) reported fourteen sedative overdoses in the six months post treatment compared to eight in the six months pre treatment, six of which occurred in the first ten days after treatment. These results should be interpreted with caution as significance was not reported. Ngo (2008b) found no significant change in risk of non-opioid overdose from six months pre treatment to three and a half years post treatment. However, Ngo (2008b) also reported a significantly increased risk of non-opioid hospital admissions at six month and three and a half years follow-up in the implant group. Reece (2007) reported a significantly greater use of amphetamines in the implant group compared to control groups.

6) Criminal activity and incarceration

The one RCT (Kunøe 2009) examining criminal activity and incarceration (level II evidence) found no significant difference in self reported criminal activity between the implant group and control group at six month follow-up.

7) Quality of life

The one included RCT (Kunøe 2009) examining quality of life (level II evidence) found higher overall quality of life in the implant group compared to the control group at six month follow up. The quality of life outcome comprised measures of life satisfaction, satisfaction with treatment allocation and recommendation of the treatment to a friend (Kunøe 2009).

Three of the included comparative studies (Carreńo 2003, Colquhoun 2005, Reece 2007) examined quality of life outcomes (level III-2 to IV evidence). Carreńo (2003) reported no significant difference between the implant and control groups on quality of life measures at six month follow up, with the exception of a significant improvement in family/ social relationships in the implant group. Within the implant group Colquhoun (2005) found a significant increase in self esteem and quality relationships in successfully abstinent participants at six and twelve month follow-up. There was not a significant difference in these measures between abstinent participants of the implant and control groups at six and twelve month follow-up. Reece (2007) found a significant improvement in work status post treatment in both implant and control groups.

8) Mental health

The one included RCT (Kunøe 2009) examining mental health outcomes (level II evidence) found no significant difference in self reported depression between the implant group and controls.

Four of the included comparative studies (Ngo 2008a, Ngo 2007, Tait 2008a, Waal 2006) examined mental health outcomes (level IV evidence). Ngo (2008a, 2007) found a significant reduction in mental health related hospital admissions across mental disorders in the implant group post treatment. Ngo (2008a, 2007) also reported a higher risk of hospitalisation in participants with a history of mental disorder, participants with more than five years of heroin dependence and females (when compared to males). There was a decrease in hospital admissions pre and post treatment for mood disorders though this was not statistically significant (Ngo 2008a, 2007). There was no significant difference in risk of hospitalisation pre and post treatment across the mental disorders examined (Ngo 2008a, 2007).

Tait (2008a) reported a significant decrease in opioid related admissions six months post implant treatment. The trend in mental health admissions was not significant over the periods six months pre and post: first heroin use; oral naltrexone treatment; and implant treatment. Waal (2006) reported that anxiety/stress levels remained stable pre and post treatment and that depression levels decreased at eight weeks but increased at twelve weeks post follow up. The results of the Waal (2006) study should be interpreted with caution as significance was not reported.

9) Duration of achieved therapeutic naltrexone blood levels

Two RCTs (Kunøe 2009, Hulse 2009) examined therapeutic naltrexone blood levels (level II evidence). The usefulness of the target therapeutic naltrexone blood levels (1 and 2ng/ml) is yet to be supported by strong evidence. Kunøe (2009) found that naltrexone and 6-ß-naltrexone levels stayed above 1ng/ml for six months and above 2ng/ml for five months. This result should be interpreted with caution as only 48% of participants presented for plasma testing (Kunøe 2009). Hulse (2009) estimated, based on monthly blood samples, that naltrexone levels were maintained above 2ng/ml for 56 and 43 days, and above 1ng/ml for 101 and 124 days in men and women respectively.

The one included comparative study (Waal 2006) examining therapeutic naltrexone blood levels (level IV evidence) found plasma naltrexone levels were maintained above 1 to 2ng/ml for one to three months after a single implant and three to five months after a double implant.

10) Heroin craving

The one RCT (Kunøe 2009) examining heroin craving (level II evidence) found that heroin cravings were significantly lower at six month follow-up in the implant group compared to controls.

The one included comparative study (Waal 2006) examining heroin craving (level IV evidence) found a reduction in craving for eight weeks post treatment, and an increase at week 12, increasing the possibility of relapse. The results of the Waal (2006) study should be interpreted with caution as statistical significance was not reported.

Findings on safety

4) Adverse effects

Reporting on mortality in some naltrexone implant trials has been inconsistent (Byrne 2000). As naltrexone is an antagonist treatment, patients undergo detoxification prior to implantation.

This process has been associated with significant morbidity and mortality though is often not reported as related to the naltrexone treatment. Adverse effects of detoxification should be reported on in naltrexone trials as it is a component of the treatment context.

Further research on adverse effects is required before a statement on safety can be confidently made. Adverse effects in this review were classified as site related, possibly naltrexone related and mortality. Adverse effects results should be interpreted with caution as the majority of these studies did not have a control group or perform a systematic assessment of adverse effects.

a) site related
Two RCTs (Kunøe 2009, Hulse 2009) examining adverse effects (level II evidence) found site related effects. Kunøe (2009) found site related adverse effects in eight participants including allergic reactions, local tissue reaction and wound opening. Of these, three participants had implants removed. In the Hulse (2009) study one participant experienced a wound hematoma, which did not require removal of the implant.

Five of the included comparative studies (Carreńo 2003, Hulse 2005a, Ngo 2008b, Tait 2008b, Waal 2006) examined adverse effects (level III-2 to IV evidence). Carreńo (2003) reported local allergic tissue reactions in 4.5% of participants and local wound infection in 1.9% of participants. None of the adverse effects required implant removal. Hulse (2005a) (also reported by Ngo 2008b and Tait 2008b) reported three implant removals in the first week, two for psychological reasons and one for infection at the wound site. Another implant was removed at 169 days as a result of an allergic reaction. Waal (2006) reported two local tissue reactions, one which was mild and one which developed necrosis and required removal. At twelve week follow-up six participants reported some anxiety or discomfort at being able to feel the implant (Waal 2006).

Two studies without control groups (Olsen 2004, Foster 2003) examining adverse effects (level IV evidence) reported site related effects. Olsen (2004) reported three implant removals, one each due to necrosis, local tissue reaction and psychological reason. Foster (2003) reported mild local tissue reactions in 15% of participants.

Site related adverse effects were, for the most part, mild and resolved without removal of the implant.

b) possibly naltrexone related
Two RCTs (Kunøe 2009, Hulse 2009) examining adverse effects potentially related to naltrexone treatment (level II evidence) observed typical opiate withdrawal symptoms of diarrhoea, headaches, nausea and vomiting. In the Kunøe (2009) study, one participant in the implant group and four in the control group overdosed on a combination of opioids, amphetamines and/or benzodiazepines. Hulse (2009) reported no overdoses requiring hospital treatment or admission at six month follow-up.

Four included comparative studies (Waal 2006, Hulse 2005a, Ngo 2008b, Tait 2008a) examined adverse effects potentially related to naltrexone treatment (level III-2 to IV evidence). Waal (2006) reported adverse effects including diarrhoea, muscle pain, irritability and anxiety in all participants, though they were considered to be few and mild with the exception of one participant who had received four previous implants. Hulse (2005a) (also reported by Ngo 2008b) found no significant change in risk of opioid overdose from six months pre treatment to six months post treatment for implant or control groups. However,

Tait (2008a) found a significant decline in opioid overdoses in the implant group from six months pre treatment to six months post treatment. Ngo (2008b) reported a significant reduction in opioid overdoses and hospital admissions for other opioid conditions in the implant group when follow-up was extended to three and a half years.

One study without a control group (Olsen 2004) examining adverse effects potentially related to naltrexone treatment (level IV evidence) reported irritability, dysphoria, cephalagia, nausea and muscular discomfort. It should be noted that many of these reported symptoms are likely due to opioid withdrawal.

c) mortality

One included RCT (Kunøe 2009) examining adverse effects (level II evidence) had two participants die from overdose, one allocated to the treatment group prior to implantation and one in the control group three months into the study. As neither participant was implanted with a naltrexone implant, their deaths are not related to naltrexone implant treatment.

Three comparative studies (Hulse 2005a, Ngo 2008b, Tait 2008b) examining adverse effects (level III-2 to IV evidence) reported mortality. Hulse (2005a) reported one death due to head trauma. Ngo (2008b) reported one drug related death in the implant group and five drug related deaths in the MMT group. Tait (2008b) reported two drug related deaths and one suicide in the implant group and five drug related deaths and two suicides in the control group. It should be noted that the Ngo (2008b) and Tait (2008b) studies reported on the same base cohort.

One study without a control group (Foster 2003) examining adverse effects (level IV evidence) reported one death from pulmonary embolism and one death from suicide. Both were deemed unrelated to the implant.

DISCUSSION

Caution should be exercised in interpreting the results of these studies as the sample sizes were small, duration of treatment and follow-up was inadequate, the comparators are inappropriate and many studies report on the same base cohort.

Effectiveness
Significant reductions in opioid use and hospital admissions (mental health and opioid related) were reported in the implant groups as well as a significantly higher treatment retention rate and improved quality of life (selected measures – work, satisfaction, family/social relationships).

The review found mixed results in relation to adherence to treatment, maintenance of therapeutic blood naltrexone levels, and heroin craving. The usefulness of the target therapeutic naltrexone blood levels (1 and 2ng/ml) is yet to be supported by strong evidence. The variable nature of heroin craving could indicate high risk periods where participants should have increased support to prevent relapse. Interestingly, there was lower opioid use and higher treatment retention rate and quality of life scores when participants were abstinent prior to commencing implant or control treatments. These results potentially indicate an effect of motivation to remain drug free. Naltrexone implants should form part of an integrated treatment program addressing broader social support and individual issues associated with drug use.

The review found no significant difference between implant and control groups in relation to criminal activity or use of non-opioid drugs, though there was some indication of an increase in the use of sedatives and amphetamines in the implant group.

Safety

Reporting on mortality in some naltrexone implant trials has been inconsistent (Byrne 2000). Further research on adverse effects is required before a statement on safety can be confidently made. As naltrexone is an antagonist treatment, patients undergo detoxification prior to implantation. This process has been associated with significant morbidity and mortality though is often not reported as related to the naltrexone treatment. Adverse effects of detoxification should be reported on in naltrexone trials as it is a component of the treatment context.

Adverse effects in this review were classified as site related, possibly naltrexone related and mortality. Adverse effects results should be interpreted with caution as the majority of these studies did not have a control group or perform a systematic assessment of adverse effects. As reported above, site related adverse effects were mostly mild and symptoms reported as possibly naltrexone related may also be symptoms of opiate withdrawal. However, adverse effects results should be interpreted with caution as the majority of these studies did not have a control group or perform a systematic assessment of adverse effects.

Concern about a possible increased risk from opioid overdose due to loss of tolerance in patients who return to opioid use after being treated with naltrexone remains to be assessed by longer term follow up studies of larger numbers of patients treated using implants.

Further research

Research into the efficacy and safety, as well as cost effectiveness, of naltrexone implants is needed. Any research conducted should be voluntary, rigorous and overseen by research ethics committees meeting NHMRC standards.

The evidence reviewed also suggests a need for further research to better understand:
 – risk factors for relapse - in order to strengthen relapse prevention strategies
 – effect of motivation, social support and supplementary treatments (individual, family or group therapy) on patient outcomes ie. abstinence or relapse
 – the therapeutic blood level of naltrexone and how long the implant maintains therapeutic naltrexone levels
 – optimal dosing and minimal effective dose
 – safety over longer duration of treatment and post treatment
 – efficacy of naltrexone implants in relation to best practice treatments.

CONCLUSION

While naltrexone implant treatment may show some efficacy as part of an integrated program, more research is needed. Naltrexone implants are an experimental product and as such should only be used in the context of a well conducted RCT with sufficient sample size, appropriate duration of treatment and follow up, regular robust monitoring, provision of a comprehensive psychosocial treatment program, and with comparison to current best practice. Until these trials have occurred and the relevant data are available and validated, the efficacy of the treatment, alone or in comparison to conventional first line treatments, cannot be determined.

Opioid dependent populations are often vulnerable, desperate and stigmatised and can be subject to extreme pressure from family, friends and the authorities to seek treatment. As required for all medical research on human subjects, informed consent should be sought, and signed, for all participants in naltrexone implant trials. Participants should be informed of, and understand, the experimental nature of the implant and potential adverse effects. Information should be presented in a way that can be understood by people with low levels of literacy. Participation in naltrexone implant trials should be assessed on a case by case basis by a suitably qualified specialist in addiction medicine (RACP, unpublished) and balanced against availability, evidence for, and cost of conventional first line treatments.

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APPENDIX A: SEARCH STRATEGIES

A)   Search Strategy Used in the Cochrane Review:
    'Sustained-Release Naltrexone for Opioid Dependence' (Lobmaier 2008)

CENTRAL search strategy
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

MEDLINE search strategy
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

EMBASE 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 (Cochrane Central Register of Controlled Trials) search strategy
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 search strategy
basic search form: naltrexone

PsycINFO search strategy
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

ISIWeb of Science search strategy
#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
#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

B) Search Strategy Used to Extend Lobmaier (2008) to 7 June 2009

CENTRAL search strategy
Note: Searched for the terms across all fields
Note: Searched 2007+, as appears difficult to limit to items added since a particular month.
1.   Substance-related disorders
2.   ((opioid) next (addict* or dependen* or abuse*
3.   1 or 2
4.   heroin
5.   opioid* or opiate*
6.   methadone
7.   4 or 5 or 6
8.   narcotic antagonists
9.   naltrexone
10. sustain* next naltrexone
11. delayed action preparations or delayed-action preparations
12. 8 or 9 or 10 or 11
13. 3 and 7 and 12
Limited to 2007-2009

MEDLINE search strategy
Note: Changed the strategy to exclude studies on animals only, but include studies on both animals AND humans
1.   Naltrexone/
2.   naltrexon$.tw.
3.   1 or 2
4.   exp Delayed-Action Preparations/
5.   implant$.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.   4 or 5 or 6 or 7 or 8
10. 3 and 9
11. animals/ not (humans/ and animals/)
12. 10 not 11
Limited to Entry date = 200711$ or 200712$ or 2008$ or 2009$

EMBASE search strategy
Note: Changed the strategy to exclude studies on animals only, but include studies on both animals AND humans. Included nonhumans as this heading used more frequently than animals in Embase.
1.   naltrexone/
2.   naltrexone.tw.

3. 1 or 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. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 3 and 11
13. (animals/ or nonhuman/ or animal experiment/) not (human/ and (animals/ or nonhuman/ or animal experiment/))
14. 12 not 13
Limited to Entry month = 2008 or 2009
Limited to Delivery date = 200711$ or 200712$ (Entry month not divided into months for 2007, so used delivery date instead)

PsycINFO search strategy
1. naltrexone/
2. naltrexone.tw.
3. 1 or 2 (786)
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. 4 or 5 or 6 or 7
9. 3 and 8
10. animals/
11. 9 not 10
Limited to Update code = 200711$ or 200712$ or 2008$ or 2009$

APPENDIX B: CHARACTERISTICS OF INCLUDED STUDIES

Study	Design (level of evidence)	Population	Sample size (n/group)	Intervention	Comparator	Period of follow-up	Outcomes measured
RCTs							
Kunøe 2009	Randomised controlled trial (II)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	56 (29/27)	Go Medical naltrexone implant (2200mg)	Usual care- encouraged to contact relevant aftercare such as out-patient counselling, application for entry to the Norwegian maintenance treatment program, re-admission to detoxification, or residential treatment	6 months	1,2,4,5,6,7,8,9,10
Hulse 2009	Randomised controlled trial (II)	Opioid dependant outpatients who had completed preclinical screening	70 (35/34▪)	All participants underwent detoxification followed by (double placebo controlled): Go Medical naltrexone implant (2300mg) or placebo implant and oral naltrexone tablets (50mg/d) or placebo tablets	Usual care- encouraged to attend weekly individual, group or family therapy	6 months	1,4,5,9
Comparative studies							
Carreño 2003	Concurrent control (III-2) Prospective design	Opioid dependent outpatients	440 (156/284)	ROD using a combination of antagonists followed by long term maintenance with Wedgewood naltrexone implant (1000mg) and CBT	Classic detoxification followed by maintenance with oral naltrexone (dose not reported) and CBT	12 months	3,4,7
Colquhoun 2005	Concurrent control (III-2)	Opioid dependent outpatients	83 (41/42)	Go Medical naltrexone implant (1700mg single or double) plus counselling and regular phone support	Oral naltrexone (dose not reported) plus counselling and regular phone support	12 months (plus 8 months during treatment)	1,3,7
Grusser 2006	Concurrent control (III-2)	Opioid dependent patients	68 (17 in each group)	UROD with oral naltrexone, followed by one week of oral naltrexone treatment (50mg/d), followed by naltrexone implant (1000mg brand not stated)	1) Detoxified and treated with oral Levomethadone (dose not reported) 2) Actively consuming opioid addicts 3) Healthy volunteers	12 weeks (compared to data collected 4 days after UROD, and 6 weeks into treatment)	2,8**,10**

Study	Design (level of evidence)	Population	Sample size (n/group)	Intervention	Comparator	Period of follow-up	Outcomes measured
*Hulse 2005a^*	Cohort-pre/post test (IV). Record linkage	Opioid dependent outpatients	361	Go Medical naltrexone implant (2200mg corrected by Ngo 2007) simultaneously with ROD	6 months pre treatment	6 months	1,4,5
*Ngo 2008a^*	Cohort-pre/post test (IV). Record linkage	Opioid dependant outpatients	359	Go Medical naltrexone implant (2200mg) simultaneously with ROD	Pre treatment period truncated to match post treatment follow-up	1.78 years post-treatment	8
*Ngo 2008b^*	Concurrent cohort (III-2) Retrospective record linkage	Opioid dependent outpatients	836 (314/ 522)	Go Medical naltrexone implant (2200mg) simultaneously with ROD	MMT (methadone syrup prescribed by medical practitioners and dispensed by pharmacists), no information on dosage	3.5 years (plus 6 months pre treatment)	1,4,5
*Ngo 2007^*	Case series-pre/post test (IV). Record linkage	Opioid dependent outpatients	359	Go Medical naltrexone implant (2200mg) simultaneously with ROD	Pre treatment period truncated to match post treatment follow-up	1.78 years post-treatment	8
Reece 2007	Concurrent and historical control study, within group comparisons pre/post test on outcomes of interest (IV). Record linkage	Opioid dependent outpatients	376 (102/113/ 161)	Go Medical and Wedgewood naltrexone implants (1100mg and 1000mg respectively). 25 patients (24.5%) had multiple implants	Revia naltrexone tablets (50mg/d) a) concurrent control b) historical control (12 months prior to NIG and above)	12 months	2,5,7
*Tait 2008a^*	Cohort-pre/post test (IV). Record linkage	Opioid dependent outpatients who had received oral naltrexone prior to implant	130	Go Medical naltrexone implant (2200mg) simultaneously with ROD	6 months pre and post first self-reported heroin use 6 months pre and post oral naltrexone 6 months pre and post implant	6 months	1,8
*Tait 2008b^*	Concurrent cohort (III-2) Record linkage	Opioid dependent outpatients	894 (341/ 553)	Go Medical naltrexone implant (2200mg) simultaneously ROD	MMT	3.5 to 5.5 years	4

Study	Design (level of evidence)	Population	Sample size (n/group)	Intervention	Comparator	Period of follow-up	Outcomes measured
Waal 2006	Case series- pre/post test (IV)	Opioid dependent outpatients	13	Go Medical naltrexone implant (1800mg single, double or single + double)	1 week pre treatment	11.3 months	1*,4, 5*,7*,8, 9,10
Studies with no control group							
Foster 2003	Consecutive cohorts - post test (IV)	Opioid dependent patients	101 (55/46)	Wedgewood implant (1000mg single, double or single + double) 1st cohort: ROD under general anaesthesia followed by implant 2nd cohort: ROD (non-iv sedation) followed by implant	N/A No comparison made between cohorts	12 weeks	1,4,10
Olsen 2004	Case series- post test (IV)	Opioid dependent outpatients enrolled in professional treatment or counselling programmes	10	Wedgewood naltrexone implant (1000mg single, 3 or 4 implants)	N/A	80 days	4,9*
ROD, Rapid Opioid Detoxification; UROD, Ultrarapid Opioid Detoxification; CBT, Cognitive Behavioural Psychotherapy							

Notes 1) Opioid use; 2) Treatment adherence; 3) Retention in treatment: time to drop out; 4) Adverse effects; 5) Use of drugs other than opioids; 6) Criminal activity and incarceration; 7) Quality of life; 8) Mental health; 9) Duration of achieved therapeutic naltrexone blood levels; 10) Heroin craving

* Not included in analysis of this outcome as there was no control group

** Not included in analysis of this outcome because measurements were taken four days after detoxification to assess its effectiveness for opioid detoxification

^ Same base cohort

▪1 participant indicated that they were not heroin dependant so were excluded from analysis.

APPENDIX C: CHARACTERISTICS OF EXCLUDED STUDIES

Study	Reason for exclusion
Farid 2008	Not a clinical trial (review)
Gibson 2007	Sample size less than 10
Hall 2008a	Not a clinical trial (review)
Hall 2008b	Not a clinical trial (comment)
He 2009	Outcome measures outside of protocol (memory ability). No adverse effect data reported
Hulse 2008	Outcome measures outside of protocol (biodegradability). No adverse effect data reported
Hulse 2005b	Outcome measures outside of protocol (pharmacodynamic results on tissue biopsies)
Hulse 2004a	Sample size less than 10. No adverse effect data reported
Hulse 2004b	Outcome measures outside of protocol (maternal and neonatal outcomes). No adverse effect data reported
Hulse 2003	Sample size less than 10. No adverse effect data reported
Hulse 2002a	Sample size less than 10. No adverse effect data reported
Hulse 2002b	Sample size less than 10. No adverse effect data reported
Lintzeris 2008	Sample size less than 10 (total sample size was 12, but <10 participants reported as opioid dependent)
Montoya 2008	Not a clinical trial (review)
Sullivan 2007	Intervention other than naltrexone implants (oral naltrexone)

APPENDIX D: QUALITY ASSESSMENT OF INCLUDED STUDIES

RCTs

Study	Random assignment to treatment groups	Blinding at treatment allocation	Method of blinding adequately described	Eligibility criteria described	Groups comparable at baseline	Groups treated identically apart from intervention	Reasons for withdrawal described and ITT used	Outcome assessors blind to allocation	Outcomes measured consistently	Outcomes measured in a reliable way	Power calculation reported
Kunøe 2009	Y Computer generated randomisation list	N Open allocation of participants	Y Open label envelopes sealed and numbered by staff independent of the study and provided to participants as per randomised list	Y Implantation and participation free to all participants. Reasons for ineligibility: not completing in-patient treatment, awaiting transfer to other clinics and starting maintenance treatment. High degree of motivation	Y Group differences analysed using two-way ANOVA with Bonferroni correction. The only significant pre-treatment difference between groups was benzodiazepine use, which was controlled for	N Usual care uncontrolled, statistical analysis used to control for possible confounding factors (except the influence of treatment centre on measures of mental health and quality of life)	Y 93% follow-up at 6 months. ITT analysis performed. The worst recorded score in the group was used for missing responses that lacked an equivalent item at inclusion	U	Y	Y Self reports: Addiction Severity Index, timeline follow-back interview technique, DSM-IV diagnoses using the Mini International Neuropsychiatric Interview (MINI), Euro-ASI, Beck Depression Inventory, Hopkins Symptom Checklist, Temporal Satisfaction With Life Scale. Heroin use verified against hair samples	N
Hulse 2009	Y Computer generated randomisation codes	Y Packs were labelled with randomisation codes. Personnel generating codes and handling medications	Y Study research officers undertaking assessment, recruitment and follow up did not have access	Y Opioid dependant, residing in Perth, 18+, willingness to be randomised. Self reported screening questionnaire and	Y Baseline characteristics not significantly different. Data were collected on age, gender, body weight, and opiate	Y All participants underwent detoxification prior to treatment allocation. Both groups received an	Y 6 (2 ONG, 4 NIG) withdrew without heroin use. 4 stayed in contact, 2 unavailable to follow up.	Y	Y	Y Self reported data on opioid and other drug use and adverse events, opioid or other drug overdose, any other treatments. Blood naltrexone levels measured using liquid chromatography-mass	Y

Study	Random assignment to treatment groups	Blinding at treatment allocation	Method of blinding adequately described	Eligibility criteria described	Groups comparable at baseline	Groups treated identically apart from intervention	Reasons for withdrawal described and ITT used	Outcome assessors blind to allocation	Outcomes measured consistently	Outcomes measured in a reliable way	Power calculation reported
		did not have contact with participants	to the codes	medical examination. Exclusion criteria ≥3 opioid overdoses in past month, oral naltrexone treatment > 3 times in past 4 months, previous sustained release naltrexone treatment, enrolled in other opioid dependence research, pregnancy, active infection, contraindications to naltrexone, inability to complete study protocol	treatment Index Social Functioning and General Health Questionnaire	implant (active naltrexone or placebo) and tablets (active naltrexone or placebo). Both groups were encouraged to attend weekly individual, group or family therapy	Overall 5 ONG and 4 NIG unavailable for follow up. 1 participant contracted active MRSA and was switched from NIG to ONG on medical advice. ITT analysis performed-missing blood naltrexone levels were classified as 0			spectrometry. Unsupervised urine drug screening	

Y, yes; N, no; U, unclear; MMT, methadone maintenance treatment; ITT, intention to treat analysis; ONG, oral naltrexone group; NIG , naltrexone implant group; ^ Same base cohort

Comparative studies

Study	Sample representative of the population	Recruitment/ eligibility criteria reported	Consideration and strategies to control, possible confounding factors	Losses to follow up reported and included in analysis	Other interventions received differentially during follow-up	Outcome assessors blind to treatment allocation	Outcomes measured in a reliable way	Missing data (group or time-point data) accounted for
Carreño 2003	Y First 156 patients treated under the NIMROD program (ROD using a combination of antagonists, followed by naltrexone implant plus individual motivational orientation and CBT. NIG: 98% males, mean age 28.8 years, 75% had a partner, 83.3% stable work, 79.1% middle to technical education level. 80.58% used heroin, 6.08% used methadone, and 13.33% used heroin and methadone, 14.6% injected	Y Outpatients with criteria of opioid dependence (ICD-10), compliance with the centres admission criteria, no concomitant disease, contraindications or conditions making follow-up difficult, willing to consent and started program between September 1998 and October 2000	N Pre treatment, the NIG scored higher than the oral group on occupation/ support (p<0.05), no adjustments reported	U U if included in analysis Y Reported: 101/156 (65%) completed the program. Of these, only 56% returned for 6 month follow up and 21% for 12 month follow up	U	U	Y EuropASI and retention index (assessed objectively). EuroASI assesses psychiatric status, family/social relationships, legal status, drug use, alcohol use, occupation/ support and medical status	N
Colquhoun 2005	Y Opioid dependent outpatients. NIG: 25 (61%) males, 16 (39%) females. Mean age 26.2 years, mean years using opiates 7.2 (sd 5.0), mean years of education 10.6 years. A large number of participants in both groups were moderately to highly depressed	Y Clients had to be motivated to be opiate free, have suitable social support and no psychiatric diagnoses or medical issues that would make detoxification dangerous	N No significant difference (p<0.05) between groups in age, years using opioids, years of education, daily opioid dose, psychiatric symptoms, and depression. Patients self selected treatment group	Y	N Number of counselling sessions was not significantly different between the groups	N	N Self-esteem and quality of relationships using a 10 point Likert scale. Both administered via telephone survey of participants and their support person	U

Study	Sample representative of the population	Recruitment/ eligibility criteria reported	Consideration and strategies to control, possible confounding factors	Losses to follow up reported and included in analysis	Other interventions received differentially during follow-up	Outcome assessors blind to treatment allocation	Outcomes measured in a reliable way	Missing data (group or time-point data) accounted for
Grusser 2006	N Small sample. NIG: 3 females and 14 males, mean age 34.76 years (sd 9.63). The mean duration of heroin use across all four groups was 7.02 years (sd 5.82)	N	N In part. Age, duration of heroin use and gender were considered but patients in groups one and two chose their treatment	N Reported but not included in analysis at 6 and 12 weeks	U	U	U Unclear how relapse rates were assessed. Drug dependence: DSM-IV-TR Craving and current mood: Questionnaire on Differentiated Assessment of Addiction Depression: General Depression Scale	U
*Hulse 2005a^*	Y Opioid dependent persons who had not previously been treated with a naltrexone implant. 218 (60%) male, 143 (40%) female. Mean duration of heroin use 5.7 years (sd 5.3). 174 (48%) prior oral naltrexone maintenance, with 17% having entered into oral naltrexone maintenance >3 times. Males were significantly older than the females [mean 28.5, sd 7.2 vs mean 26.6 sd 7.9; t 2.4, p <0.017]	Y Opioid users treated for the first time with a naltrexone implant at a not for profit community based clinic in Perth between Jan 2001 and Dec 2002. 361 (94%) of 384 possible participants considered eligible, i.e. could be followed up via the WALD. Exclusion: no consent given (5), implants removed in the first week (3), and incarceration prior to implant (15)	N In part. Age, age of first heroin use, duration of heroin use, gender, previous use of oral naltrexone considered. Mentioned confounder of age and sex in relation to mortality	Y 1 participant died and 1 had an early removal, both were included in the analysis. 326 (90%) were in the WALD, 257 (71%) were in the EDIS and 335 (93%) were in both	U	Y Prospectively collected data: assessor blind to treatment allocation at outcome assessment	Y Prospectively collected hospital admission and mortality data from the WALD and the EDIS. Overdoses were identified using ICD10 codes	N/A due to record linkage design

Study	Sample representative of the population	Recruitment/ eligibility criteria reported	Consideration and strategies to control, possible confounding factors	Losses to follow up reported and included in analysis	Other interventions received differentially during follow-up	Outcome assessors blind to treatment allocation	Outcomes measured in a reliable way	Missing data (group or time-point data) accounted for
*Ngo 2008a^*	Y As per Hulse 2005a	Y As per Hulse 2005a	Y Potential confounders such as age, gender, pre-existing history of mental illness and length of heroin use were considered	Y 1 participant died	U	Y Prospectively collected data: assessor blind to treatment allocation at outcome assessment	Y Prospectively collected hospital admission and mortality data from the WALD cases identified using ICD-9-CM diagnosis codes	Y 2 cases with missing data were removed from analysis
*Ngo 2008b^*	Y Base cohort as per Hulse 2005a NIG: 314; 129 (41%) females [mean age 27.1 years sd 8.1], 185 (59%) male [mean age 29.0 years sd 7.5] MMT: 522; 198 (37.9%) females [mean age 30.4 years sd 9.1 years], 324 (62.1%) males [mean age 32.1 years sd 8.9 years]	Y As per Hulse 2005a MMT cohort ineligible if taking methadone for pain management, treatment crossover, or incarcerated	N Age and sex and their modifying interactions were examined but other factors, e.g. level of motivation, situational influences, socioeconomic background, and pre existing illness were not	N 82.6% MMT, 92.2% NIG lost to follow up, not included in analysis	U The MMT cohort was only included as a reference group, so between group comparisons must be viewed with great caution	Y Hospital morbidity and mortality collected prospectively and independent of research team	Y Prospectively collected hospital morbidity data from the WALD. Physician coded mental health hospital admission using ICD 9 or 10. Inconsistencies in coding between different ICD codes are inevitable	N/A due to record linkage design

Study	Sample representative of the population	Recruitment/ eligibility criteria reported	Consideration and strategies to control, possible confounding factors	Losses to follow up reported and included in analysis	Other interventions received differentially during follow-up	Outcome assessors blind to treatment allocation	Outcomes measured in a reliable way	Missing data (group or time-point data) accounted for
*Ngo 2007^*	Y As per Hulse 2005a	Y As per Hulse 2005a	Y Investigated influence of gender, age, prior history of hospital admission, and duration of heroin use. Pre treatment truncated to match post treatment	U Not reported. Likely to be as per Hulse 2005a	U	Y Hospital morbidity and mortality collected prospectively and independent of research team	Y Physician coded mental health hospital admission using ICD-9 and 10, but use of diagnostic codes from different versions means coding inconsistencies are inevitable	N/A due to record linkage design
Reece 2007	Y Patients presenting to a low cost private naltrexone clinic in Brisbane. NIG: 69 (68%) male, 33(32%) female. mean age 26.1 years, mean duration of opiate use 5.5 years. 9% on social security alone, 64% in socioeconomic class III-V and 27% in socioeconomic class I-II. 25% had 'weak' social support, 51% 'average' and 25% 'strong'	N No information on types of participants eligible for programs offered by the clinic	N Matched for age, sex, duration of opioid use and dose used. Participants selected treatment. Financial status and social support better in the NIG, differences not controlled for	Y Overall follow-up was 82%. Urine drug screen follow-up was 76%. ITT analysis performed	U	U	N Primary outcome was 'opiate free success', defined as a composite measure including self report, having a urine drug screen negative for opiates or having a carer report satisfactory progress	U
*Tait 2008a^*	Y Base cohort as per Hulse 2005a, but restricted to treatment resistant group. Mean history of heroin dependency 7.5 years (sd 4.9),	Y As per Hulse 2005a had to have received oral naltrexone 12 months prior to their implant, leaving	U	Y As per Hulse 2005a 1 participant died	Y 24 (19%) received an agonist therapy post implant,	Y Mortality data collected prospectively and independent	Y ICD-9 or 10	N/A due to record linkage design

Study	Sample representative of the population	Recruitment/ eligibility criteria reported	Consideration and strategies to control, possible confounding factors	Losses to follow up reported and included in analysis	Other interventions received differentially during follow-up	Outcome assessors blind to treatment allocation	Outcomes measured in a reliable way	Missing data (group or time-point data) accounted for
	which is higher than average. 59% male, 41% female. 45% had only ever received oral and implantable naltrexone, 34% reported use of agonist treatment prior to implant treatment	130/139 (93.5%)			mainly MMT, dates are unavailable	of research team		
*Tait 2008b^*	Y Base cohort as per Hulse 2005a NIG: 40% female [mean age 27.0 years sd 7.9], 60% male [mean age 28.8 years; sd 7.4]	Y As per Hulse 2005a	Y Only for age and gender	Y As per Hulse 2005a	U Additional treatment episodes possible but not reported	Y Mortality data collected prospectively and independent of research team	Y WALD which compiles extensive health information for individuals	N/A due to record linkage design
Waal 2006	Y Actively seeking this type of treatment. Small sample, 11 male, 2 female [mean age 26.9 sd 4.9]. Mean history of heroin dependency 4.8 years (sd 3.3). Most had extensive experience with several other psychoactive substances. Participants had received a range of previous treatments	Y Participants were actively interested in naltrexone implants	U	Y 2 participants interviewed with retrospective data	U	N/A due to pre/ post test deign	Y Liquid chromatography/ mass spectrometry operated in electrospray ionisation, Hopkins symptom checklist, Beck depression rating scale, side effects checklist, Likert scales	N Compliance with monthly evaluation procedures varied. Only 7/13 participants accounted for on mental health and craving outcomes at week 12

Y, yes; N, no; U, unclear; MMT, methadone maintenance treatment; NIG naltrexone implant group; ^ Same base cohort; ROD, rapid opioid detoxification; WALD, West Australian Health Services Research Linked Database

Studies with no control group

Study	Was the sample representative of patients in the population as a whole?	Were recruitment/ eligibility criteria reported?	Were losses to follow-up reported and included in analysis?	Were losses to follow up> 20%?	Were outcomes measured in a reliable way?	Were missing data (group or time-point data) accounted for?
Olsen 2004	Y Small sample. 5 male, 5 female [median age 30.5 (23-29)]. Median heroin use of 7.5 years (4-15). All HCV positive. Under no obligation to abstain from drug use	Y Participants had to be taking part in a professional treatment or counselling program	Y	N 3 participants were lost to follow up. Adverse effect results reported for all participants	U	N/A No missing data
Foster 2003	Y Opioid dependent outpatients, seeking treatment in private clinic. Cohort one: 76% male, 24% female [mean age 29.8 years sd 5.57]. 51% unemployed, 33% current and 67% previous injectors, mean opiate habit 6.7 years Cohort two: 83% male, 17% female [mean age 27.4 years]. Comprehensive demographic data not collected	N	Y	N	N Self report (semi structured interview be telephone) with corroboration by family members/carers where possible. Craving on a 10 point visual analogue scale. Blood concentrations measured in several patients not in these cohorts	N/A
Y, yes; N, No; U, unclear; HCV, hepatitis C virus						

APPENDIX E: RESULTS OF STUDIES ON EFFECTIVENESS

1) Opioid use during and after treatment

RCTs

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Kunøe 2009 Norway	56 (29/27)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	Go Medical naltrexone implant 2200mg	Usual care, i.e. encouraged to contact relevant aftercare: out-patient counselling, Norwegian maintenance treatment program, re admission to detoxification, or residential treatment	6 months	*Between group comparison* a) 6 month follow up: heroin use significantly lower in NIG (mean 17.9 days) vs controls (mean 63.6 days) difference 45.6 p<0.05, F 7.0 [95% CI 14.1, 77.3] ASI 30 day variable, NIG mean 3.5 days of heroin use vs 11.4 days in controls, difference 8, p<0.05, F 5.8 [95% CI 1.8, 14], and ASI frequency scale, difference 0.73, p<0.05 [95% CI 0.11, 1.34] b) 6 month follow up for all opioid use, NIG scored significantly lower (mean 37 days) than controls (mean 97.1 days) difference 60.2 p<0.01, F 8.1 [95% CI 20.9, 99.5] ASI 30 day variable, NIG mean 6.3 days of opioid use vs 17.4 days in controls, difference 9, p<0.01, F 5.4 [95% CI 1.6, 16.4], and ASI frequency scale, difference p<0.001 [95% CI 0.45, 1.7]. c) Abstinence from all opioids for the whole period was not significant, 11/29 in the implant group vs 5/27 in controls. d) At the 6 month follow-up assessment opioid dependence as per DSM-IV diagnoses using MINI was significantly lower in the implant group (9/29) vs controls (18/27), OR= 0.225, p=0.015 [95% CI 0.07, 0.69] Note: The results of hair analysis matched self-reported opioid use in patients available for testing (86%).
Hulse 2009 Australia	70 (35/34)	Opioid dependant outpatients who had completed preclinical screening, exclusion criteria detailed	Go Medical naltrexone implant (2.3g) Oral naltrexone tablets (50mg/d)	All underwent detoxification and were implanted with active or placebo implant. All were encouraged to attend weekly individual, group or family therapy	6 months	*Between group comparison* At 6 month follow-up, heroin use was significantly lower in the implant group [hazard ratio 4.49; 95%CI 1.85,10.90] Return to regular heroin use occurred significantly earlier in the oral group (median 115 days SE 12.0) compared to the implant group (median 158 days SE 9.4) p=0.001. 12% and 6% of oral and NIG, respectively, returned to heroin 1 to 3 days per week. 0% and 14% of oral and NIG, respectively, returned to heroin 1 to 3 days per month. Self reported complete abstinence in 27% and 63% of the oral and implant groups respectively.

Comparative studies

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Colquhoun 2005 Australia	83 (41/42)	Opioid dependent outpatients	Go Medical naltrexone implant (1700mg single or double) plus counselling and regular phone support	Oral naltrexone plus counselling and regular phone support	12 months (plus 8 months during treatment)	*Between group comparison* Abstinent participants were those who had used opioids only a few times since detoxification. In patients who had remained abstinent from opioids, relapse in the NIG was higher than control at 6 months post treatment, 33/41 (80%) vs 23/42 (55%) respectively. This trend continued at 12 months post treatment, where rates were 25/41 (61%), vs 17/42 (40%) respectively. No ratio or CI reported. In patients who had relapsed from opioids (including those non contactable) relapse in the NIG was lower than controls at 6 months post treatment, 8/41(20%) vs 19/42(45%) respectively. This trend continued at 12 months post treatment, where rates were 16/41 (39%), vs 25/42 (60%) respectively. No ratio or CI reported
*Hulse 2005a^* Australia	361	Opioid dependent outpatients	Go Medical naltrexone implant (2200mg) simultaneously with ROD	6 months pre treatment	6 months	*Within group comparison* For emergency department presentations and hospital admissions and when data from emergency department presentations and hospital admissions were combined, there were more opioid overdoses 6 months pre treatment vs 6 months post treatment but the significance was not reported. Refer to Ngo 2008b
*Ngo 2008b^* Australia	836 (314/ 522)	Opioid dependent outpatients	Go Medical naltrexone implant (2200mg) simultaneously with ROD	MMT (methadone syrup prescribed by medical practitioners and dispensed by pharmacists)	3.5 years (plus 6 months pre treatment)	*Between group comparison* There was no significant change in risk for other opioid hospitalisations from 6 months pre treatment to 6 months post treatment for either cohort. In the MMT cohort there was no significant change in risk of other opioid hospitalisations pre treatment to 3.5 years post treatment whereas for the implant cohort it was significantly reduced, 181 events vs 332 events respectively, OR 0.64 [95% CI 0.46, 0.89], α = 0.05 There was a significant decline in hospital admission rates from opioid overdose from 6 months pre treatment to 3.5 years post treatment in the NIG, RR 0.29 [95% CI 0.15, 0.55], α = 0.05 whereas the change was not significant in the MMT cohort. There was a significant increase in hospital admission rates for other opioid conditions from 6 months pre treatment to 3.5 years post treatment in the MMT cohort, RR 1.35 [95% CI 1.14-1.61], α = 0.05 vs a significant decline in the NIG RR 0.55 [95% CI 0.46-0.65], α = 0.05. In the NIG female patients 30 years and older incurred fewer other opioid hospital admissions than their younger counterparts, RR 0.32 [95% CI 0.16-0.65], α = 0.05

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Reece 2007 Australia	376 (102/ 113/ 161)	Opioid dependent outpatients	Go Medical and Wedgewood naltrexone implants (1.1g and 1g respectively) Many had multiple implants	Revia naltrexone tablets (50mg/d) a) concurrent control b) historical control (12 months prior to NIG)	12 months	*Within group comparison* Within the NIG social support, work prior to treatment and the presence of cannabis in the urine were significantly related to opiate free success.
*Tait 2008a^* Australia	130	Opioid dependent outpatients who had received oral naltrexone prior to implant	Go Medical naltrexone implant (2200mg)	6 months pre and post: first heroin use, oral naltrexone treatment, implant	6 months	*Within group comparison* There was a significant decline in opioid overdoses from 6 months before oral naltrexone to 6 months post implant treatment (Wilcoxon Z= 2.3, p=0.02). Opioid overdoses increased from 0 in both the 6 months before and after first heroin use, to 7 in the both the 6 months before and after oral naltrexone to 2 in the 6 months before implant and 0 in the 6 months post implant (Friedman χ^2 15.2 (5), p =0.01).

MMT, methadone maintenance treatment; NIG, naltrexone implant group; ROD, rapid opioid detoxification; ^ same base cohort

2) Treatment adherence

RCT

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Kunøe 2009 Norway	56 (29/27)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	Go Medical naltrexone implant (2200mg)	Usual care, i.e. encouraged to contact relevant aftercare: out-patient counselling, Norwegian maintenance treatment program, re admission to detoxification, or residential treatment	6 months	*Between group comparison* At 6 months follow up there was no significant difference in outpatient treatment attendance between the implant group and controls, p>0.05.

Comparative studies

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Grusser 2006 Germany	68 (17/17)	Opioid dependent patients	UROD with oral naltrexone, followed by one week of oral naltrexone treatment (50mg/d), followed by naltrexone implant (1000mg)	2) Detoxified and treated with oral Levomethadone 3) Actively consuming opioid addicts 4) Healthy volunteers	12 weeks compared with data collected 4 days after detoxification, and 6 weeks into treatment	*Within group comparison* a) 6 weeks after treatment: There was one relapse in the NIG. Only 4 participants remained in group 2; 10 had relapsed and 3 had switched to long-term Levomethadone without any intention of becoming drug free. No significance reported. b) 12 weeks after treatment 2 participants in the NIG had relapsed. None of the remaining 4 subjects in group 2 could be located. No significance reported.
Reece 2007 Australia	376 (102/ 113/ 161)	Opioid dependent outpatients	Go Medical and Wedgewood naltrexone implants (1.1g and 1g respectively), many had multiple implants	Revia naltrexone tablets (50mg/d) a) concurrent control b) historical control (12 months prior to NIG and above)	12 months	*Between group comparison* The proportion of patients in each group whose urine tested positive for naltrexone were 70%, 52% and 39% respectively.
NIG, naltrexone implant group; UROD, ultrarapid opioid detoxification; ^ same base cohort						

3) Retention in treatment: time to drop out

Comparative studies

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Carreño 2003 Spain	440 (156/ 284)	Opioid dependent outpatients	UROD combination of antagonists followed by Wedgewood naltrexone implant (1000mg) and CBT	Classic detoxification followed by maintenance with oral naltrexone and CBT	12 months	*Between group comparison* At 6 and 12 months post treatment the treatment retention index was significantly greater in the implant group (80% at 6 months, 65% at 12 months) than the oral group (42% at 6 months, 17% at 12 months), p<0.05. No CI reported.
Colquhoun 2005 Australia	83 (41/ 42)	Opioid dependent outpatients	Go Medical naltrexone implant (1700mg single or double) plus counselling and regular phone support	Oral naltrexone plus counselling and regular phone support	12 months (plus 8 months during treatment)	Abstinent participants were those who had used opioids only a few times since detoxification. *Within group comparisons* In the NIG the time compliant to naltrexone was greater in the abstinent group than those who had relapsed at 6 and 12 months, p<0.05. NIG participants abstinent at 6 and 12 months estimated the implant was effective for 6 months. Those NIG participants who relapsed estimated the implant was effective for 4 months, p<0.05. *Between group comparisons* In patients who had remained abstinent from opioids, time spent in treatment was higher in the NIG than the ONG at 6 months post treatment, mean 176.6 days (sd 68.1) vs mean 120 days (sd 104.8) respectively. No p value or CI reported. This trend remained at 12 months post treatment [mean 187.3 days (sd 69.1) vs 123.21 days (sd 105.5) respectively]. No p value or CI reported. In patients who had relapsed to opioid use, time spent in treatment was higher in the NIG than the ONG at 6 months post treatment, [mean 112.5 days (sd 50) vs mean 19.7 days (sd 31.7) respectively]. No p value or CI reported. This trend remained at 12 months post treatment [mean 120 days (sd 45.6) vs 30.1 days (sd 54.25) respectively]. No p value or CI reported.
NIG, naltrexone implant group; ONG, oral naltrexone group; UROD, ultrarapid opioid detoxification						

5) Use of drugs other than opioids during and after treatment

RCTs

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Kunøe 2009 Norway	56 (29/27)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	Go Medical naltrexone implant (2200mg)	Usual care, i.e. encouraged to contact relevant aftercare such as out-patient counselling, application for entry to the Norwegian maintenance treatment program, re admission to detoxification, or residential treatment	6 months	*Between group comparison* At 6 month follow up there was no significant difference in self reported use of alcohol or non opioid drugs between the NIG and controls, p>0.05.
Hulse 2009 Australia	70 (35/34)	Opioid dependant outpatients who had completed preclinical screening, exclusion criteria detailed	Go Medical naltrexone implant (2.3g) Oral naltrexone tablets (50mg/d)	All underwent detoxification and were implanted with an active or placebo implant. All participants were encouraged to attend weekly individual, group or family therapy.	6 months	*Between group comparison* Overall use of non opioid drugs was similar between groups [hazard ratio 0.58 95% CI 0.32, 1.05] Most frequently reported category of non opioid drug was cannabis, followed by stimulants.

Comparative studies

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
*Hulse 2005a^* Australia	361	Opioid dependent outpatients	Go Medical naltrexone implant (2200mg) simultaneously with ROD	6 months pre treatment	6 months	*Within group comparison* There were more sedative overdoses in the 6 months post treatment than the 6 months pre treatment as measured by emergency department presentations and hospital admissions, significance not reported. Refer to Ngo 2008b The number of other drug overdoses was the same in the 6 months pre treatment as the 6 months post treatment, as measured by emergency department presentations. There were more other drug overdoses in the 6 months post treatment than the 6 months pre treatment as measured by hospital admissions, significance not reported. When hospital admissions and emergency department presentations were combined, there were less sedative overdoses in the 6 months pre treatment (8, 1.9%) than the 6 months post treatment (16, 4.4%) p <0.01. Nine overdoses were in the first 10 days after treatment and if excluded the trend is neutral or reversed. Other drug overdoses increased from the 6 months pre treatment (2, 0.6%) to post treatment (5, 1.4%), significance not reported.
*Ngo 2008b^* Australia	836 (314/ 522)	Opioid dependent outpatients	Go Medical naltrexone implant (2200mg) simultaneously with ROD	MMT (methadone syrup prescribed by medical practitioners and dispensed by pharmacists)	3.5 years (plus 6 months pre treatment)	*Between group comparison* Comparing non opioid overdose admissions from 6 months pre treatment to 6 months post treatment, no significant change in either cohort for patients aged 25 years, significantly increased risk in patients aged 35 years. MMT: OR 5.03 [95 % CI 1.18, 21.54], α = 0.05 NIG: OR 16.31 [95% CI 3.07, 86.53], α = 0.05 There was no significant change in risk of non opioid oversdose admissions from 6 months pre treatment to 3.5 years post treatment for either cohort. *Within group comparison* MMT: no significant change in risk of other non opioid admissions 6 months pre treatment to 6 months or 3.5 years post treatment NIG: significantly increased risk at both follow-up periods, RR 1.33 [95% CI 1.01, 1.73], α = 0.05. 12 vs 31 events at 6 months OR 2.54 [95% CI 1.19, 5.43], α = 0.05 and 105 vs 138 events at 3.5 years, OR 1.52 [95% CI 1.04, 2.23], α = 0.05 In the NIG reduced risk for each one year age increment, at 3.5 years the OR was 0.96 [95% CI 0.94, 0.98].

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Reece 2007 Australia	376 (102/ 113/ 161)	Opioid dependent outpatients	Go Medical and Wedgewood naltrexone implants (1.1g and 1g respectively), many had multiple implants	Revia naltrexone tablets (50mg/d) a) concurrent control b) historical control (12 months prior to NIG and above)	12 months	*Between group comparison* Urinary analysis was performed to test use of amphetamines, morphine, Tetrahydrocannabinol (THC), cocaine and methadone. The rate of obtaining a urine drug screen for each of the groups was 98%, 70% and 76% respectively. Amphetamine use was significantly greater in the NIG than either the concurrent or historical ONG or compared to both controls combined, Chi Square 7.13, df 1, OR 2.78 [95% CI 1.22, 6.42], p=0.0075 Chi Square 11.14, df 1, OR 3.28 [95% CI 1.52, 7.18], p<0.001 Chi Square 13.83, df 1, OR 3.05 [95% CI 1.60, 5.83], p=0.0002 respectively

MMT, methadone maintenance treatment; NIG, naltrexone implant group; ONG, oral naltrexone group; ROD, rapid opioid detoxification; ^ same base cohort

6) Criminal activity and incarceration

RCT

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Kunøe 2009 Norway	56 (29/27)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	Go Medical naltrexone implant (2200mg)	Usual care, i.e. encouraged to contact relevant aftercare such as out-patient counselling, application for entry to the Norwegian maintenance treatment program, re admission to detoxification, or residential treatment	6 months	*Between group comparison* At 6 months follow up there was no significant difference in self reported criminal activity between the implant group and controls, p>0.05.

7)   Quality of life

RCT

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Kunøe 2009 Norway	56 (29/27)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	Go Medical naltrexone implant (2200mg)	Usual care, i.e. encouraged to contact relevant aftercare such as out-patient counselling, application for entry to the Norwegian maintenance treatment program, re admission to detoxification, or residential treatment	6 months	*Between group comparison* a) Life satisfaction: at 6 month follow up NIG scored higher than controls on the Temporal Satisfaction With Life Scale, mean difference 5.4, $p < 0.05$, F 5.3 [95% CI 0.68, 10.1] b) Recommend treatment to a friend: at 6 month follow up NIG scored higher than controls, mean 85 vs 56.5 respectively, on a visual analogue scale of treatment satisfaction, mean difference 28.5, $p < 0.05$, F 9.1 [95% CI 10.8, 46.2]. c) Satisfaction with treatment allocation: at 6 month follow up NIG scored higher than controls, mean 78 vs 36 respectively, mean difference 42, $p < 0.01$, F 25 [95% CI 25.9, 58.5]

Comparative studies

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Carreño 2003 Spain	440 (156/ 284)	Opioid dependent outpatients	ROD using a combination of antagonists followed by long term maintenance Wedgewood naltrexone implant (1000mg) and CBT	Classic detoxification followed by maintenance with oral naltrexone and CBT	12 months	*Between group comparison* No significant differences were found between the two groups at either follow-up, except at 6 months post treatment the NIG scored better than the ONG on family/social relationships, $p = 0.05$, no CI reported

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Colquhoun 2005 Australia	83 (41/ 42)	Opioid dependent outpatients	Go Medical naltrexone implant (1700mg single or double) plus counselling and regular phone support	Oral naltrexone plus counselling and regular phone support	12 months (plus 8 months during treatment)	Abstinent participants were those who had used opioids only a few times since detoxification. *Within group comparisons*: in participants who were successful in abstaining from opioid use there was a significant increase in self esteem and quality relationships between pre treatment and 6 and 12 months post treatment, p<0.01, in both groups. No CI reported. *Between group comparisons*: in participants successful in abstaining from opioid use, the differences between the NIG and the ONG on measures of self esteem and relationship quality at pre treatment were not significant, p=0.86 and 0.81 respectively. In this same group at 6 months post treatment, the NIG had lower self esteem ratings than the ONG (mean difference 1.2), p=0.018. No CI reported. The ONG also tended to score better on relationships at 6 months post treatment compared to the NIG, but the difference was not significant, p=0.055. Among abstinent participants, there was no significant difference in self esteem or relationship quality at 12 months post treatment, p>0.05
Reece 2007 Australia	376 (102/ 113/ 161)	Opioid dependent outpatients	Go Medical and Wedgewood naltrexone implants (1g and 1.1g respectively), many had multiple implants	Revia naltrexone tablets, (50mg/d) c) concurrent control d) historical control (12 months prior to NIG and above)	1 month for this aspect of the study (plus 1 month before ROD)	*Within group comparison* Within the NIG and concurrent ONG work status improved from before to after treatment, NIG: 18% pre treatment vs 50% after treatment, weighted OR 4.67 [95% CI 2.35, 9.33], p<0.001 Concurrent ONG: 25% pre treatment vs 48% post treatment weighted OR 2.78 [95% CI 1.52, 5.09], p<0.001. The improvement in the historic ONG was not significant, p=0.178

NIG, naltrexone implant group; ONG, oral naltrexone group; ROD, rapid opioid detoxification; CBT, cognitive behavioural psychotherapy; ^ same base cohort

8) Mental health

RCT

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Kunøe 2009 Norway	56 (29/27)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	Go Medical naltrexone implant (2200mg)	Usual care, i.e. encouraged to contact relevant aftercare such as out-patient counselling, application for entry to the Norwegian maintenance treatment program, re admission to detoxification, or residential treatment	6 months	*Between group comparisons* At 6 month follow up there was no significant difference in self reported depression (Beck Depression Inventory and subscale of the 25-item Hopkins Symptom Checklist) between the implant group and controls, p>0.05.

Comparative studies

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
*Ngo 2008a^* Australia	359	Opioid dependant outpatients	Go Medical naltrexone implant (2200mg) simultaneously with ROD	Pre treatment period truncated to match post treatment follow-up	1.78 years post-treatment	*Within group comparison* Counts of patients and hospital events was categorised into non-substance related, mood related, substance related or all-cause. *1. Comparison of pre- versus post-treatment:* a) risk of patient hospitalisation for a mental condition The number of cases for patients after naltrexone treatment was consistently lower than pre-treatment. However there was not a statistically significant difference. b) rate of mental health related hospital admissions There was a reduction in mental health related hospital events post naltrexone treatment. There was a significant reduction in admissions for non-substance mental disorders IRR .630 [95% CI .478, .841 p=.0017]. This was mostly observed in male patients (p=.0002) compared to females (p=.5363). There was a significant reduction in admissions for substance-related mental disorders IRR .673 [95% CI .558, .811 p<.0001] and All-cause mental disorders IRR .641 [95%

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
						CI .536, .766 p<.0001]
						2. Evaluating contributing factors to risk of patient hospitalised due to mental illness following treatment: Higher risk: − of hospitalisation for NSRMD with history of hospitalisation for NSRMD OR 4.78 [95% CI 2.53, 9.01 p<.0001]. Females at higher risk OR 2.39 [95% CI 1.25, 4.58 p.0085]. − >5 years of heroin dependence OR 3.82 [95% CI 1.08, 13.5 p.0378]. − of hospitalisation for substance related mental disorder with history of hospitalisation for substance related mental disorder OR 1.82 [95% CI 1.10, 3.04 p.0208]. Females at higher risk OR 1.95 [95% CI 1.21, 3.15 p.0063]. *3. Length of stay* a) *median per episode* varied with different time points in the younger cohort, effect not seen in older patients. b) *total per person year* increased by 1.6 days post treatment, which is similar to the 'during use' period.
*Ngo 2007^* Australia	359	Opioid dependent outpatients	Go Medical naltrexone implant (2200mg)	Pre treatment period truncated to match post treatment follow-up	6 months	*Within group comparison* The number of hospital admissions significantly decreased pre to post treatment for NSRMD [RR 0.630 95% CI 0.472, 0.841, p = 0.0017], substance related mental disorder [RR 0.673 95% CI 0.558, 0.811, p<0.0001], and all cause mental disorder [RR 0.641 95% CI 0.536, 0.766, p<0.0001]. The number of hospital admissions decreased pre to post treatment for mood disorders, but after adjusting for confounding effects the trend was not significant (p= 0.4232), declining mainly among males [RR 0.463 95% CI 0.220- 0.974] and participants treated at a later age (26 years or older), [RR 0.356 95% CI 0.190-0.668]. There was no significant difference in risk of hospitalisation pre vs post treatment for NSRMD [OR 1.309 95% CI 0.877, 1.954], mood disorders [OR 1.283 95% CI 0.689, 2.390], substance related mental disorders [OR 1.214 95% CI 0.886, 1.664], or all cause mental disorders [OR 1.272 95% CI 0.931, 1.738]. Higher risk of non substance related hospital event post treatment with prior hospitalisation for NSRMD OR 4.78 [95% CI 2.53, 9.01]. Females were at higher risk than males, OR 2.39 [95% CI 1.25- 4.58]. Participants with >5 years of heroin use pre treatment were at higher risk from hospitalisation due to a mood disorder post treatment compared to those who had used for a shorter period, OR 3.82 [95% CI 1.08, 13.5]. Participants with a history of substance-use hospital diagnoses were at higher risk

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
						from hospitalisation due to substance use disorder post treatment OR 1.82 [95% CI 1.10, 3.04]. Females were at higher risk than males, OR 1.95 [95% CI 1.21, 3.15]. Older age at treatment was a protective factor for not developing a drug-related problem post treatment OR 0.949 (0.949- 0.958 for every one year age increment). Females were at greater risk of all cause mental disorders than males, OR 1.87 [95% CI 1.16, 3.01]. Older age at treatment was a protective factor, OR 0.951 (0.942-0.960 for every one year age increment). *Length of hospital stay* due to mental disorders was not significantly different from pre to post treatment, p=04120.
*Tait 2008a^* Australia	130	Opioid dependent outpatients who had received oral naltrexone prior to implant	Go Medical naltrexone implant (2200mg)	6 months for each: pre and post first heroin use, Pre and post oral naltrexone, pre and post implant	11.3 months	*Within group comparison* General trend for an increase in mental health admissions with an opioid related diagnoses in the 6 months post first heroin use, pre and post oral naltrexone periods, with a decline in the 6 months pre and post implant (Friedman χ^2 65.2 (5), p <0.001). There was a significant decline in mental health admissions with an opioid related diagnoses from 6 months before oral naltrexone to 6 months post implant treatment (Wilcoxon Z = 2.3, p<0.0001). The trend in mental health admissions with a drug related diagnosis other than opioids was not significant over the 6 study periods (Friedman χ^2 9.9 (5) p =0.082). In the 6 months pre implant there were two non opioid mental health admissions, 1 with stimulants and 1 with stimulants plus cannabis. In the 6 months post implant there 5 non opioid mental health admissions, 2 with unspecified multidrug use, and 1 each for sedatives, stimulants and cannabis use. The trend in mental health admissions excluding any drug related diagnoses was not significant over the 6 study periods (Friedman χ^2 3.6 (5) p =0.616).
Waal 2006 Australia	13	Opioid dependent outpatients	Go Medical naltrexone implant (1800mg single, double or single + double)	1 week pre treatment	11.3 months	*Within group comparison* Anxiety/stress levels remained relatively stable pre and post treatment, [mean 1.9 (SD 0.69) pre treatment vs 1.3 (SD 0.32) to 1.7 (SD 0.58) post treatment] P values not reported. Depression levels generally decreased from 1 week pre treatment to 8 weeks post treatment, [mean 16.8 (SD 13.8) pre treatment vs 7.6 (SD 7.2) to 12.0 (SD 12.1) in the 8 weeks post treatment]. Depression scores increased at the end of the 12 weeks post treatment[mean 14.7 (SD 10.4)] P values not reported.
NSEMD, non substance related mental disorder; ^same base cohort						

9) Duration of achieved therapeutic naltrexone blood levels

<u>RCTs</u>

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Kunøe 2009 Norway	56 (29/27)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	Go Medical naltrexone implant (2200mg)	Usual care, i.e. encouraged to contact relevant aftercare such as out-patient counselling, application for entry to the Norwegian maintenance treatment program, re admission to detoxification, or residential treatment	6 months	*Within group comparison* Plasma levels of naltrexone stayed above 1ng/ml for 6 months and above 2ng/ml for about 5 months. Levels of 6-β-naltrexone had a similar distribution. <u>Note</u>: only 14 of 29 (48%) participants presented for testing of plasma levels.
Hulse 2009 Australia	70 (35/34)	Opioid dependant outpatients who had completed preclinical screening, exclusion criteria detailed	Go Medical naltrexone implant (2.3g) Oral naltrexone tablets (50mg/d)	All underwent detoxification and were implanted with an active or placebo implant. All participants were encouraged to attend weekly individual, group or family therapy.	6 months	*Between group comparisons* Significantly more of the ONG had blood naltrexone levels <2ng/mL at months 1 (ONG 72% NIG 6%) and 2 (ONG 81% NIG 48%) and <1ng/mL at months 1 through 4 (month 1: ONG 59% NIG 0%; month 2: ONG 74% NIG 18%; month 3: ONG 80% NIG 53%; month 4: ONG 97% NIG 53%) <u>Blood naltrexone concentration estimates</u> Men (mean Body Mass Index 25.5, age 33): $\geq$ 2ng/ml 56 days [95% CI 39, 73] $\geq$ 1ng/ml 110 days [95% CI 83, 119] Women (mean BMI 25.1, age 28): $\geq$ 2ng/ml 43 days [95% CI 16, 79] $\geq$ 1ng/ml 124 days [95% CI 88, 175]

Comparative study

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Waal 2006 Australia	13	Opioid dependent outpatients	Go Medical naltrexone implant (1800mg single, double or single + double)	1week pre treatment	11.3 months	*Within group comparison* For participants without measurable naltrexone before implantation, plasma levels were maintained above 1-2ng/ml between 1 and 3 months after a single implant and 3 and 5 months after a double implant. The 6-β-naltrexone concentrations were approximately 1-2.5 times higher compared to naltrexone during the whole implant period.

10) Heroin craving

RCT

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Kunøe 2009 Norway	56 (29/27)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	Go Medical naltrexone implant (2200mg)	Usual care, i.e. encouraged to contact relevant aftercare such as out-patient counselling, application for entry to the Norwegian maintenance treatment program, re admission to detoxification, or residential treatment.	6 months	*Between group comparisons* At 6 month follow up the implant group scored lower than controls on a visual analogue scale of craving related thoughts, mean difference 27, p<0.01, F 7.2 [95% CI 9.4, 44.2]

Comparative study

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Waal 2006 Australia	13	Opioid dependent outpatients	Go Medical naltrexone implant (1800mg single, double or single + double)	1 week pre treatment	11.3 months	*Within group comparison* On a scale of 1 (not at all) to 7 (very strong). craving dropped from pre treatment to 1-8 weeks post treatment [mean 2.6 (SD 1.0) pre treatment vs 2.4 (SD 1.6) to 2.7 (SD 1.4) post treatment]. Craving increased at week 12, when the possibility of relapse came closer [mean 3.1 (SD 2.1)], p values not reported.

APPENDIX F: RESULTS OF STUDIES ON SAFETY

4) Adverse Effects

RCTs

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Kunøe 2009 Norway	56 (29/27)	Opioid dependent outpatients who had completed abstinence oriented in-patient treatment and passed an oral naltrexone challenge (25mg)	Go Medical naltrexone implant (2200mg)	Usual care, i.e. encouraged to contact relevant aftercare such as out-patient counselling, Norwegian maintenance treatment program, re admission to detoxification, or residential treatment.	6 months	a) *Site related:* 2 participants reported wound opening with leakage of fluid, 3 had allergic reactions all of which were treated. 3 participants had implants removed (1 due to necrosis, 2 on request due to discomfort- site pain or diarrhoea). b) *Possibly naltrexone related*: 1 participant in the NIG overdosed using a combination of opioids, amphetamines and benzodiazepines, 4non fatal over doses were reported in control group. c) *Mortality*: 1 in NIG prior to implant due to overdose, 1 in control group due to overdose 3 months into study.
Hulse 2009 Australia	70 (35/34)	Opioid dependant outpatients who had completed preclinical screening, exclusion criteria detailed	Go Medical naltrexone implant (2.3g) Oral naltrexone tablets (50mg/d)	All underwent detoxification and were implanted with an active or placebo implant. All participants were encouraged to attend weekly individual, group or family therapy.	6 months	a) *Site related:* 1 participant had a severe adverse event related to the surgical procedure– wound hematoma proximal to the implant site. b) *Possibly naltrexone related*: 10 study related unexpected adverse events (4 oral, 6 implant) – typically diarrhoea or headaches. 29 study related expected adverse events (10 oral, 19 implant) – typically opiate withdrawal symptoms (diarrhoea, nausea, vomiting), exudation redness, pain at the surgical incision site or proximal to the implant in the first 14 days after surgery. No opiate overdoses requiring hospital treatment or admission were reported during the 6 month follow up period.
NIG, naltrexone implant group						

Comparative studies

Study/ Country	N (n/group)	Population	Intervention	Comparator	Follow-up	Main Findings
Carreño 2003 Spain	440 (156/ 284)	Opioid dependent outpatients	ROD using a combination of antagonists followed by long term maintenance Wedgewood naltrexone implant (1000mg) and CBT	Classic detoxification followed by maintenance with oral naltrexone and CBT	12 months	a) *Site related*: 7 (4.5%) had local allergic tissue reactions. 3 (1.9%) had local wound infection, but no implants had to be removed.
Hulse 2005a^ Australia	361	Opioid dependent outpatients	Go Medical naltrexone implant (2200mg) simultaneously with ROD	6 months pre treatment	6 months	a) *Site related*: 3 implant removals in the first week at the patients request, 2 for psychological reasons and 1 due to infection at the wound site. Another removal at 169 days post implant due to an allergic reaction. b) *Mortality*: 1 death due to head trauma, coroners report not available
*Ngo 2008b^* Australia	836 (314/ 522)	Opioid dependent outpatients	Go Medical naltrexone implant (2200mg) simultaneously with ROD	MMT (methadone syrup prescribed by medical practitioners and dispensed by pharmacists)	3.5 years (plus 6 months pre treatment)	a) *Site related*: as per Hulse 2005a b) *Mortality:* 1 drug related death in the NIG vs 6 in the MMT group. In the MMT group 2 deaths were opioid related, 1 was a combined drug overdose, and 2 were non-opioid drug overdoses. The mortality in the NIG was from an opioid overdose in a participant previously treated with MMT.
*Tait 2008b^* Australia	894 (341/ 553)	Opioid dependent outpatients	Go Medical naltrexone implant (2200mg)	MMT	3.5 to 5.5 years	*a) Site related:* as per Hulse 2005a *b) Mortality*: 6/341 (1.8%) versus 15/553 (2.7%). The age standardized mortality rate ratio for naltrexone compared to methadone was 0.645 [95% CI 0.123, 1.17]. The mortality rates for the initial 14 day period', 'stable treatment (0-6 months) and overall' were 0.0, 4.21 and 3.76 vs 94.47, 0.0 and 5.83/1,000 p-y. In the NIG 2 deaths were drug related and 1 self inflicted. In the MMT group 5 cases were drug related and 2 were self-inflicted.

Study/Country	N	Population	Intervention		Follow-up	Main Findings
Waal 2006 Australia	13	Opioid dependent outpatients	Go Medical naltrexone implant (1800mg single, double or single + double)	1 week pre treatment	11.3 months	a) *Site related:* 2 local tissue reactions, 1 was mild and responded to antihistamines, the other (of which the patient had had 4 earlier implants) developed necrosis and required removal. At 12 weeks post treatment 9 could still feel their implant on palpitation and 6 felt some anxiety or discomfort by the lump. b) *Possibly naltrexone related:* Side effects (on a checklist including cephalgia, nausea, diarrhoea, muscle and articular pain or discomfort, anxiety and irritability) were recorded for all 13 participants. In the first week pre treatment, diarrhoea, muscle pain and irritability were the most frequency reported vs muscle pain, irritability and anxiety in the first week post treatment. The mean value of all side effect scores was in the range of 'not at all' to 'small' throughout the post implant observation period.
MMT, methadone maintenance treatment; NIG, naltrexone implant group; ROD, rapid opioid detoxification; CBT, cognitive behavioural psychotherapy; ^ same base cohort						

Studies with no control group

Study/Country	N	Population	Intervention	Follow-up	Main Findings
Olsen 2004 Norway	10	Opioid dependent outpatients	Wedgewood naltrexone implant (1000mg single, 3 or 4)	80 days	a) *Site related*: 3 implant removals (one each due to necrosis, local tissue reactions, on patient request due to mixed abstinence phenomena and desperation). First 2 removals were after repeated implantation. b) *Possibly naltrexone related*: the most prevalent side effects were irritability and dysphoria in the first week post implant (reported as 6/10 in Lobmaier 2008 not reported in study itself). Also reports of slight cephalagia, nausea and muscular discomfort (numbers not reported).
Foster 2003 England	101 (55/46)	Opioid dependent patients	Wedgewood implant (1000mg single, double or single + double) 1st cohort: ROD under general anesthesia followed by implant 2nd cohort: ROD (non-iv sedation) followed by implant	12 weeks	a) *Site related*: 15/101 (15%) had local tissue reactions. Most were mild and resolved without surgical treatment. b) *Mortality*: 2 deaths deemed to be unrelated to implant- 1 pulmonary embolism, 1 suicide in a participant with a history of depression.
ROD, rapid opioid detoxification					