Technology assessment report commissioned by the HTA Programme on behalf of The National Institute for Health and Clinical Excellence

Oral naltrexone as a treatment for relapse prevention in formerly opioid dependent drug users – a systematic review and economic evaluation

Produced by West Midlands Health Technology Assessment Collaboration

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Date completed February 2006

Expiry date December 2007

INSIDE TITLE PAGE

PUBLICATION INFORMATION

ABOUT "HOME UNIT"

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively undertake research synthesis to produce health technology assessments. Most of our members are based in the Department of Public Health & Epidemiology, University of Birmingham, however other members are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility, University of Birmingham, and pharmacists and methodologists from the Department of Medicines Management, Keele University.

WMHTAC produce systematic reviews, health technology assessments and economic evaluations for NHS R&D HTA programme (NCCHTA), the National Institute for Health and Clinical Excellence (NICE), and for the health service in the West Midlands. WMHTAC also undertakes methodological research on research synthesis, and provides training in systematic reviews and health technology assessment.

CONTRIBUTIONS OF AUTHORS

Dr Yaser Adi coordinated the clinical evidence aspects of the review, applied the inclusion and exclusion criteria, extracted data, appraised studies, conducted meta-analysis and contributed to the drafting of the clinical effectiveness, results and discussion sections of the report and helped in sorting out references.

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Ms Sue Jowett contributed to the development of the Birmingham economic model and contributed to the writing of the economic sections of the report.

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Dr Ed Day drafted the introduction section and commented on all other sections of the report, particularly the conclusions.

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Dr Amanda Burls supervised the project, wrote sections of the report, commented on all sections and compiled and edited the final report .

CONFLICTS OF INTEREST: NONE

Source of funding:
This report was commissioned by NHS R&D HTA Programme as project number (04 23)

Relationship of reviewers with sponsor
None

ACKNOWLEDGEMENTS

We are grateful to the following individuals for their help and advice during the writing of this report:

Linda Briscoe, Department of Public Health & Epidemiology, University of Birmingham for her administrative assistance.

Dr Nick Lintzeris, National Addiction Centre, Institute of Psychiatry, Kings College, London for clinical advice.

Ms Josie Sandercock for methodological advice on handling of survival data and helpful peer reviewer comments on a draft version of this report.

Ms. Hege Korner, Psychologist, Norwegian Knowledge Centre for Health Services, Oslo for helpful peer reviewer comments on a draft version of this report.

Dr. Chris Hyde, Department of Public Health & Epidemiology, University of Birmingham for helpful peer reviewer comments on a draft version of this report.

Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. The authors of the updated but yet unpublished Cochrane systematic review "*Oral naltrexone maintenance treatment for opioid dependence*"

Dr Pelham Barton, Health Economics Facility, University of Birmingham for advice on assessment group economic model

Ms Guiqing Lily Yao, Health Economics Facility, University of Birmingham for advice on assessment group economic model

Mr Duncan McFarland for attending meetings, proof-reading draft reports and for providing a patient perspective.

The responsibility for the content of this report rests with the authors and does not necessarily reflect the views of those who have been acknowledged for their help.

Dr Amanda Burls is guarantor

CONTENTS

TABLES

FIGURES

APPENDICES

ABBREVIATIONS

BCS	British Crime Survey
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence Interval
CJS	Criminal Justice System
CM	Contingency Management
CRD	Centre for Review and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DARP	Drug Abuse Reporting Program
EED	Economic Evaluation Database
HBV	Hepatitis B Virus
HCHS	Hospital and Community Health Services
HEED	Health Economic Evaluation Database
HIV	Human Immunosuppressive Virus
HR	Hazard Ratio
ICER	Incremental Cost Effectiveness Ratio
IDUs	Injecting Drug Users
MMT	Methadone Maintenance treatment
NDTMS	National Drug Treatment Monitoring System
NNH	Number needed to harm
NNT	Number needed to treat
NTORS	National Treatment Outreach Study
NTX	Naltrexone
PenTag	Peninsula Technology Assessment Group
PSA	Public Service Agreement
PSS	Personal Social Service
QALY	Quality Adjusted Life Year
QoL	Quality of life
RCT	Randomized Controlled Trial
RR	Relative Risk
SD	Standard Deviation

DEFINITIONS

Abstinence	Refers to the complete absence of drug use. For the purpose of this review, heroin users are considered to be abstinent if they have ceased all opioid drug use.
Buprenorphine	Is a high affinity, partial mu-opioid agonist. Buprenorphine's profile includes a relatively long-lasting partial agonist effect which limits adverse medical reactions, opiate antagonist activity which blocks the effects of exogenously administered opiates, and slow dissociation from mu-opioid receptors which results in diminished withdrawal signs and symptoms upon discontinuation.
Clonidine	Is an alpha-adrenergic agonist that acts preferentially on presynaptic alpha-2 neurons to inhibit noradrenergic activity. Clonidine is useful as an inhibitor of opiate withdrawal and it may have some anti-anxiety effects
Cognitive behavioural therapy	Cognitive Behavioural Therapy (CBT) is a psychological treatment for mental health conditions. Treatment usually takes between 8 and 20 sessions. It is a combination of cognitive therapy, which can modify or eliminate unwanted thoughts and beliefs, and behavioural therapy, which can help change behaviour in response to those thoughts. Cognitive techniques (such as challenging negative thoughts) and behavioural techniques (e.g. exposure therapy to gradually desensitise people to their phobias or relaxation techniques) are used to relieve symptoms of anxiety and depression by changing thoughts, beliefs and behaviour.
Community maintenance	Treatment which stabilises clients on a substitute drug for as long as it is necessary to help them avoid returning to previous patterns of drug use. A longer term aim can be to gradually reduce the quantity prescribed until the client does not experience withdrawal symptoms and is drug free. Community maintenance generally consists of drug administration, and the provision of psychosocial treatment and motivational interventions.
Contingency management	This refers to programmes of patient management that reward patients when they comply with treatment (e.g. by giving vouchers or money) and do not reward them when they do not. These may have escalating rates of reward for continuous compliance which may go back to the original reward level with an episode of non-compliance (e.g. missed dose of naltrexone).
Cost-utility analysis	An economic evaluation where benefits are measured by health-related measures that combine quality of life in and duration of each health state, such as quality-adjusted life years.

Detoxification	The process of alleviating the short-term symptoms of withdrawal from drug dependence. This may either be a short-term process (less than 30 days) or a long-term process (between 30 and 180 days), and often involves the prescription of other drugs to help manage withdrawal symptoms.
Drug misuse	Illegal and illicit drug taking which can lead a person to experience social, psychological, physical or legal problems related to intoxication, regular consumption, or dependence (see section 2.3.1 for formal definitions).
Heroin	Is a naturally occurring substance extracted from the seedpod of the Asian poppy plant (opium) which acts on opioid receptors and produces a sense of euphoria and lessens sensitivity to painful stimuli. Heroin usually appears as a white or brown powder.
Information bias	Refers to systematic differences in self-reported and objectively measured outcomes.
LAAM	Is a mu-opioid agonist used as a pharmacotherapy for the treatment of opioid dependence. LAAM has a long duration of action and produces opioid blockade. It has a longer half-life than methadone, thus potentially reducing dosing frequency to three times a week.
Methadone	Is a full mu-opioid agonist used in the treatment of opioid dependence. This long-acting synthetic opioid analgesic relieves craving for opioids and blocks the euphoric effects of additionally used heroin. It has a half-life of approximately 35 hours, which enables once-daily dosing.
Naltrexone	Is a synthetic opioid antagonist used especially to maintain detoxified opioid dependent users in a drug-free state. Naltrexone inhibits the effects of opioids by blocking the mu-opioid receptors and thus takes away the desired effect of the illicit drug. Naltrexone does not produce any opioid-like effects or cause psychological or physical dependence.
Opiates	Are naturally occurring products derived from the Opium poppy which act on opioid receptors. Opiates have potent analgesic effects associated with significant changes in mood and behaviour, and with the potential for dependence and tolerance following repeated administration, examples include morphine and heroin (diamorphine).
Opiate dependence	A cluster of cognitive, behavioral, and physiological symptoms in which the client continues use of opiates despite significant opiate-induced problems. Opiate dependence is characterised by repeated self-administration that usually results in opiate tolerance, compulsive drug-taking and withdrawal symptoms if the drug is not taken.
Opioid	A synthetic product with the same pharmacological properties to opiates, e.g. methadone.

Psychosocial treatment	Treatment techniques based on one or more theories of human behaviour. They involve a close relationship between therapist and client, within which issues relating to development, experience, relationships, cognition, emotion or behaviour are considered. The goal is usually to make changes in the client's cognition, emotion or behaviour. Examples include cognitive behaviour therapy, motivational interviewing and relapse prevention.
Retention in treatment	Defined as continuous contact with the service.
Withdrawal	The body's reaction to the absence of a drug to which the client has become physically dependent.

EXECUTIVE SUMMARY

Background

Naltrexone is an opiate antagonist that is licensed for use orally as adjunctive therapy in the treatment of detoxified formerly opioid-dependent individuals (after around ten days of being opiate free). It is taken in a dose of 50 mg per day and blocks the pleasurable and euphoric effects of heroin and other opiates. It works to help former opioid dependent individuals stay off drugs through the knowledge that these drugs will produce no positive effects. It does not increase motivation to stay abstinent and thus if people choose not to take the dose daily it will not work.

It is not widely used in England and Wales and the current cost to the NHS in England is around £500,000 per annum and there is no evidence of an increasing trend in use. Moreover not all of these prescriptions will be for use in the prevention of relapse in formerly opioid dependent individuals as it is also used in alcohol misuse and other conditions.

Method

We systematically reviewed the literature about the effectiveness of naltrexone and, since naltrexone is only effective if taken, measures to increase compliance with naltrexone, using established methods. The focus of this review was to investigate the clinical and cost effectiveness of naltrexone for relapse prevention in detoxified formerly opioid-dependent individuals compared to any strategy that does not use naltrexone, including treatment with placebo, other pharmacological treatments, psychosocial interventions, or no treatment.

Results

Quality

Out of 1013 identified citations, 26 studies met the inclusion criteria: nine were RCTs of interventions to increase compliance with naltrexone (with a total number of 841 participants) and 17 were studies considering the effectiveness of naltrexone. Of the latter 17, one was a systematic review, 13 were RCTs (with a total number 940 participants) and three were controlled but non-randomised studies. The methodological quality of the RCTs was poor to moderate at best.

Effectiveness

A. Naltrexone

The results suggest that naltrexone as maintenance therapy for relapse prevention in opioid addicts may be better than placebo in terms of retention in treatment but this was not statistically significant - a meta-analysis of 7 included RCTs shows that the relative risk of loss of retention in treatment in the naltrexone arm is 0.94, 95% CI (0.84, 1.06). The pooled HR reported in five of the RCTs for retention in treatment data followed up to 35 weeks was calculated as 0.90 95% CI (0.69, 1.17) in favour of naltrexone and also did not reach statistical significance.

With respect to the risk of drug abuse in naltrexone vs placebo, with or without psychological support given in both arms, the pooled relative risk from six RCTs was 0.72, 95% CI (0.58 , 0.90) which was a statistically significant difference in favour of naltrexone. The Pooled HR from 3 RCTs for opioid relapse-free was significantly different from placebo in favour of naltrexone 0.53, 95%CI (0.34, 0.82). However this effect can be seen to fall off over time and may be of limited clinical significance.

The relative risk of re-incarceration in naltrexone shows results in favour of naltrexone in the combined two studies of parolees or people on probation RR 0.5 95% CI (0.27, 0.91), but the number of participants was small.

One study reported results by using Risk Assessment Battery (RAB), which is a self report instrument questionnaire measured HIV risk. This study reported a statistically significant improvement score in naltrexone for risky sexual behaviour. The number of participants in this study was 52.

The adverse events data reported in the included studies showed no significant difference between naltrexone and placebo arm.

B. Interventions to increase compliance with naltrexone treatment

Nine randomised controlled trials of interventions designed to increase retention with naltrexone (three RCTs for contingency management programmes, four RCTs for psychosocial therapy and two RCTs for additional pharmaceutical agents) were identified and

analysed. The quality of these studies was poor to moderate at best, with calculation errors in one study and one study only reporting data driven analyses, rather than randomised comparisons. All three different modalities of enhanced care showed some evidence of effectiveness in improving retention on naltrexone.

All the contingency management programmes used incentive vouchers that could be exchanged for goods or services to reward participants when they complied with treatment, The mean time of treatment retention was 7.4 weeks for the contingency management intervention compared to 2.3 to 5.6 weeks for the naltrexone treatment alone. The mean length of time patients stayed on naltrexone was 84-103 days for the psychosocial therapy intervention compared to 43-64 days for the control. The relative risks of abandonment proportion were 1.63 at 6 months (corrected figures) comparing a pharmaceutical agent (fluoxetine) and the control at 6 months and 12 months respectively. All the above effects were statistically significant. The difference in mean length of time that patients stayed on naltrexone was not significant over 21 months.

There were only 13 participants in the RCT of the pharmaceutical agent sertaline and the difference of the rates of retention in treatment between intervention and control was only significant at week 2, not at week 10.

Different studies used different outcome measures with different follow-up periods. It is debatable whether it is appropriate to combine such clinically heterogeneous interventions. However we have done so for completeness sake but the results should be interpreted with caution. We did a meta-analysis of the relative risk of stopping treatment at week 12 (the minimum follow-up period) using six of the nine studies. The pooled relative risk of stopping treatment was 0.81 (95%CI 0.71, 0.94). The results indicated that overall the intervention groups had 19% less patients who stopped treatment compared to the control group. However, due to the small number of studies and the relatively poor quality of the studies, it is difficult to estimate the real effectiveness of these interventions.

Economic evaluation

Existing economic evaluations

No existing economic evaluations were identified.

De novo cost-utility analysis

A decision analytic model using Monte Carlo simulation was developed that compared naltrexone as an adjunctive therapy to no naltrexone. It assumed compliance rates that were not enhanced by contingent management rewards (because this is current UK practice). It took an NHS/PSS perspective and was modelled to 12 months. Given the time horizon no discounting was applied. Utility values could not be identified from the literature and so were obtained by research specially commissioned from the Value of Health Panel.

The point estimate for the cost-effectiveness of naltrexone was £42,500 per QALY. Sensitivity analysis was carried out and the ICER varied between £34,600 to £42,500, per QALY gained. Because of the uncertainty in the estimates the CEAC curves never get above 55% for any willingness to pay threshold.

Conclusion

Following the successful withdrawal from opioids, naltrexone may be administered on a chronic basis to block any future effects of opioids. Naltrexone appears to have some limited benefit in helping formerly opioid dependent individuals remain abstinent although the quality of the evidence is relatively poor and heterogeneous. The limited quality and extent of the studies found in this review precluded an analysis of sub-groups particularly likely to benefit from naltrexone prescribing. It is poorly cost-effective using current UK criteria.

Oral naltrexone is used infrequently current UK practice and our systematic review of the evidence for effectiveness and modelling for cost-effectiveness suggest that this is appropriate - there is little evidence to support its wider implementation.

1. AIM OF THE REVIEW

- To undertake a systematic review of the clinical effectiveness of oral naltrexone for helping to prevent formerly opioid dependent people from returning to illicit drug use.
- To systematically review enhanced treatment packages designed to improve compliance with oral naltrexone treatment.
- To review published economic evaluations and undertake a *de novo* cost-utility analysis of oral naltrexone.
- To see whether the evidence allows particular subgroups of opioid users or particular settings or care packages to be identified in which oral naltrexone is likely to be more effective or cost-effective.

It is *not* the purpose of this review to consider

- the use of naltrexone in detoxification
- the use of naltrexone for other conditions, e.g. in alcohol abuse
- the relative merits of maintenance versus abstinence methods for the treatment of opioid dependence
- depot or other unlicensed preparations of naltrexone

2. BACKGROUND

2.1 Description of health problem

Heroin and other opioids are powerful drugs that can induce a sense of well-being, deliver a boost to self esteem and increase tolerance to pain. People taking opioids, whether for recreational use or for a medical condition, may become dependent on these drugs. Getting the next dose can then become an important part of each day and may take over people's lives. Drug dependence can have many negative effects such as inadvertent overdose, increased risk of infections (e.g. HIV or hepatitis), family distress, adverse effect on the opioid dependent person's children, disruption at work, and involvement in criminal activities. It is difficult to stop using these drugs and remain abstinent due to a combination of craving, unpleasant withdrawal symptoms, and the continued or worsening personal circumstances that led to illicit drug use in the first place. Even when a dependent opioid

user manages to become abstinent, there is a high probability that he or she will return to using drugs within a short time.

Opioid dependent users constitute a small proportion of the world population (less than 1% of those aged 15 or over)[1], but the regular and sustained use of heroin accounts for a substantial proportion of drug-related problems in Western countries.

Several treatment approaches are currently used to help people who are opioid dependent and a broad distinction can be made between harm reduction versus promotion of abstinence approaches. Harm reduction concentrates on helping individuals gain control over their lives by replacing the illicit opioid with a stable, long-term, legally prescribed, opioid, such as methadone or buprenorphine, both of which can be taken orally. The evidence suggests that the provision of opiate substitutes, is more effective than naltrexone for preventing illicit drug use[2]. Although maintenance therapy with methadone is the commonest pharmacological method used currently in the UK to help prevent relapse it is not uncommon for people to want to try and remain opiate free. Thus, for a variety of different reasons, clinicians and patients sometimes prefer the abstinence approach. The chronic relapsing nature of drug dependence makes interventions that can help prevent relapse desirable and naltrexone (Nalorex®, Bristol-Myers Squibb Pharmaceuticals Ltd) is licensed as an adjunctive prophylactic therapy in the maintenance of detoxified, formerly opioid-dependent patients.

This report does not address the question of the relative merits of naltrexone therapy versus maintenance with opiate substitutes, rather, it looks at how effective and cost-effective naltrexone is when used as an adjunctive prophylactic therapy to prevent relapse in detoxified, formerly opioid-dependent, individuals who want to remain opiate free. It systematically collates and evaluates the existing research evidence about whether oral naltrexone is effective in preventing people who were formerly opioid dependent from returning to illicit drug use. It also reviews the evidence about interventions to enhance compliance with naltrexone therapy. An economic evaluation of oral naltrexone is undertaken to estimate an incremental cost per QALY.

2.2 Naltrexone

Naltrexone is an opioid antagonist with a high affinity for opioid receptors. It competitively displaces opioid agonists (e.g. heroin or methadone), blocking the euphoric and other effects of opioid use and thereby minimising the positive rewards of heroin or opioid use. It is usually taken orally at a dose of 50 mg per day.

Naltrexone is used to help prevent patients going back to opioid use following detoxification. as they know that if they take the daily therapeutic dose of naltrexone, using heroin or other opioid drugs will have no effect. Therefore naltrexone can be seen as a form of 'insurance' and a protection against a sudden temptation to use opioids. It does not stop people wanting to use heroin or maintain their motivation to remain abstinent.

Those who take naltrexone regularly after detoxification have high abstinence rates from heroin use. However, the blockade wears off within 48 to 72 hours of discontinuing naltrexone after which heroin will produce its normal physiological and psychological consequences. In such a situation it loses its "deterrent" or protective effect. Issues concerning concordance with the naltrexone regimen are therefore very important.

One problem associated with naltrexone treatment is the increased risk of death from heroin overdose in patients who return to opioid use after being treated with naltrexone. After discontinuing naltrexone, the dose of heroin that a user had been accustomed to inject during their last period of addiction, can prove fatal. Furthermore, there is a serious risk of overdose if a patient who has taken naltrexone in the previous few days tries to take larger doses of heroin in order to overcome the blockade to achieve a pleasurable effect.

Naltrexone has been used in the management of opioid dependence since the 1980s to assist relapse prevention following detoxification. More recently, naltrexone has been used as a detoxification medication, for 'precipitated' or 'rapid' detoxification, and in the management of alcohol dependence. This review is only concerned with naltrexone as a relapse prevention agent for opioid dependence.

2.3 Place of the intervention in the treatment pathway(s):

Naltrexone is licensed as and adjunct to therapy for use in detoxified formerly opioid-dependent patients (who have remained opioid-free for at least 7–10 days).

As naltrexone competitively binds to opioid receptors, it can precipitate a severe opioid withdrawal reaction if taken while opioid dependent. Therefore it is recommended that naltrexone only be commenced in individuals at least 5-7 days after the last use of heroin, and 7-14 days after the last methadone use. As a precaution against the inadvertent precipitation of withdrawal symptoms, an intravenous or intramuscular naloxone challenge may precede oral naltrexone administration, as this has a shorter duration of action.

The initial dose of naltrexone should be 25 mg (half a tablet) on day one, followed by 50 mg (one tablet) daily from day two onwards. A three-times-a-week dosing schedule may be considered if it is likely to result in better compliance e.g. 100 mg on Monday, 100 mg on Wednesday and 150 mg on Friday.[1]

Concomitant administration of naltrexone with an opioid-containing medication should be avoided. Patients should be warned that attempts to overcome the blockade may result in acute opioid intoxication which may be life threatening. In an emergency requiring opioid analgesia an increased dose of opioid may be required to control pain. The patient should be closely monitored for evidence of respiratory depression or other adverse symptoms and signs.

It is recommended that patients prescribed naltrexone also engage in psychosocial interventions, such as relapse prevention counselling and attendance at self-help groups. It is licensed as an adjunct to standard therapy.

2.3.1 Definitions

The opiates are a group of psychoactive substances derived from the poppy plant that includes opium, morphine and codeine. The term ‘opiate’ is also used for the semi-synthetic drug heroin that is produced from poppy compounds. The term ‘opioids’ refers to opiates

and other semi-synthetic and synthetic compounds with similar properties. Opioids are generally consumed by injection or inhalation of the fumes produced by heating ('chasing'). Regular use of opioids can lead to opioid dependence.

Physical and psychological dependence can occur with any opioid drug, but illicit or 'street' heroin presents the greatest problems due in part to its potency and illegality. Opioid dependence tends to be a chronic, relapsing-remitting condition with physical, psychological and social dimensions. It is typically characterised by a loss of control over one's drug use, and is usually associated with unsuccessful attempts to cut down or control use. Opioids are taken in larger amounts or over a longer period than was intended, and considerable time is spent in obtaining, using, or recovering from the effects of the drugs. This leads to a reduction in other social, occupational, or recreational activities, but use continues despite the drug-related problems. Physical tolerance to opioids and a withdrawal syndrome on reduction or cessation of use are usually present.

The diagnosis of dependence has been operationalised in the Diagnostic and Statistical Manual[3] as a maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. tolerance, as defined by either of the following:
    - a need for markedly increased amounts of the substance to achieve intoxication or desired effect
    - markedly diminished effect with continued use of the same amount of the substance
2. withdrawal, as manifested by either of the following:
    - the characteristic withdrawal syndrome for the substance
    - the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
3. the substance is often taken in larger amounts or over a longer period than was intended
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use

5. a great deal of time is spent in activities necessary to obtain the substance (e.g. visiting multiple doctors or driving long distances), use the substance, or recovering from its effects
6. important social, occupational, or recreational activities are given up or reduced because of substance use
7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

2.3.2 Aetiology, pathology and prognosis

The aetiology of opioid dependence is uncertain. Studies of twins, families, and people who have been adopted show that vulnerability to drug abuse may be a partially inherited condition but it is not clear whether for a given individual repeated use begins as a result of genetic predisposition or whether socioeconomic and psychological factors lead an individual to try and then later to use opioids compulsively. Once an individual is dependent on opioids, such dependence constitutes a medical disorder.[4]

Initiation into heroin use does not lead inevitably to regular and problematic use for many people. Vulnerability to use is highest among young people, with most problem heroin users starting before the age of 20. Biological, psychological, sociological, and economic factors influence when and why a person will start taking opioids. However, it is clear that when use begins, it often escalates to abuse (repeated use with adverse consequences) and then to dependence (opioid tolerance, withdrawal symptoms, compulsive drug-taking). Once dependence is established there are usually repeated cycles of cessation and relapse extending over decades.[4] In one long-term outcome study that conducted a 24-year follow-up of 581 male opioid users, 29% were currently abstinent, but 28% had died, 23% had positive urine tests for opiates and 18% were in prison.[5] The Drug Abuse Reporting Program (DARP), a longitudinal data collection project over 12 years in the USA, found that the average time from first to last opioid use was 9.9 years, with 40% addicted for over 12 years.[6]

For many people, the relapsing nature of drug misuse means that they will have extensive treatment histories. Treatment for people with established substance-use problems is rarely a

discrete, single event. Rather several episodes of treatment may be provided over several years.[7] Nevertheless, some users of dependent substances may make dramatic changes in their drug use without recourse to formal treatment.[8] The natural history of heroin users attending treatment services suggests that most individuals develop dependence in their late teens and early twenties, several years after their first use of heroin, and continue use over the next 10 to 20 years. Treatment can alter the natural history of opiate dependence, most commonly by prolonging periods of abstinence. As a cohort of persons addicted to opiates ages, the percentage who are still addicted decreases.[4]

2.3.3 Epidemiology

Information on the incidence of heroin and other opioid use is available from several sources, including national and regional surveys, and data from specialist treatment agencies. Population-based surveys are considered to be of limited use in estimating the full extent of heroin use in the UK, mainly because of the hidden nature of problem drug use.[9] Instead, national prevalence estimates can be derived from a range of methods, with the multivariate indicator method being the favoured approach. This combines local prevalence estimates along with routinely available indicator data. Using such methods, the latest UK estimate of problem drug use is 9.35 per thousand of the population aged 15 to 64 years (360,811), with 3.2 per thousand (123,498) injecting.[9]

The British Crime Survey (BCS) is a large national survey of adults who live in a representative cross-section of private households in England and Wales. In addition to asking respondents about their experiences of crime, the BCS also asks about a number of other crime-related topics. Since 1996 the BCS has included a self completion module of questions on illicit drug use.[10] The 2003/4 BCS found that 35.6% of 16 to 59 year olds have used one or more illicit drugs in their lifetime, 12.3% used one or more illicit drugs in the last year and 7.5% in the last month. These figures were much lower for heroin use, with 0.2% having used opiates (heroin and methadone) in the last year.[10] However this is likely to be an underestimate, as it is less than the number of people who were involved in the drug treatment system which itself will be only a proportion of all drug users. Analysis of the 2004/5 data from The National Drug Treatment Monitoring System (NDTMS), which collects, collates and analyses information from those involved in the drug treatment system, suggests that there were an estimated 160,450 people in contact with treatment services in

England, the majority for primary opioid problems.[11] Males make up over 70% of new presentations to treatment, and opiates are the most commonly used drug by those seeking treatment.

2.3.4 Impact of health problem

There are considerable harms associated with illicit heroin use, including increased mortality; increased infection with blood-borne viruses (HIV, HCV, HBV); high levels of depression and anxiety disorders; social problems such as disrupted parenting, employment and accommodation; and increased participation in income-generating crime. Even when users become drug free there is a high probability of their returning to drug use within a few months.

Increased Mortality

Addiction-related deaths, including unintentional overdose, drug-related injuries, and many illnesses directly attributable to chronic drug dependence, explain one fourth to one third of the mortality in an opioid-addicted population.[4] One long-term follow-up study of dependent heroin users reported in 1994 estimated that this population has a 12-fold increased risk of mortality compared to the general population.[12] However, more recent cohort studies have shown that mortality rates in drug users have improved over time.[13]

The mortality data relation to naltrexone is an important issue as naltrexone blocks the actions of opioids, naltrexone will rapidly remove the person's tolerance to opioids so that a given dose of opioids would have more effects than previously. Therefore the lack of naltrexone not its presence, exposes a naltrexone-maintained patient to the risk of opioid overdose and consequently increased death rate. In a recently published report[14] the National Coronial Information System (NCIS) revealed 32 deaths related to the use of naltrexone in the period 2000-2003 in Australia. When expressed as deaths per number of treatment episodes, it was estimated that naltrexone had mortality rate of 10.1 per 1000 treatment episodes and the mortality rate was 22.1 per 100 person years during the period of high risk (2 weeks post-treatment), and 1 per 100 person years during the period of low risk (during treatment)[14].

Physical Health Effects

Individuals may experience physical health problems and medical complications that relate to the action of the drug taken, to the route of their administration and to general issues of poor nutrition and health care.[7] The majority of subjects recruited to the National Treatment Outcome Research Study (NTORS) in the UK reported problems with their physical health, most commonly sleep disturbance, weight loss and chest pain.[15]

Injecting drug users may be exposed to blood-borne infections through the sharing of infected needles, syringes or other injecting paraphernalia. The prevalence of HIV infection among injecting drug users (IDUs) in the UK has increased in recent years, although the rate is lower than in many other countries.[16] Approximately one in every 65 injectors is infected, but the figure is substantially higher in London than the rest of the country with around one in 25 IDUs infected. Overall more than two in five IDUs in the UK have been infected with hepatitis C. In England and Wales hepatitis C transmission among IDUs is high with one in six of those who had started to inject since the beginning of 2002 having become infected. Transmission of both hepatitis A and B continues among IDUs even though there are effective vaccines. Needle and syringe sharing increased in the late 1990s, and since then has been stable with around one in three IDUs reporting this activity in the last month. The sharing of other injecting equipment is more common and few IDUs swab injecting sites prior to injecting.[16]

Social Functioning

The nature of the opioid withdrawal syndrome and the associated psychological craving for the drug may mean that the need to obtain supplies takes precedence over all other priorities. This may lead to mistakes at work, lost productivity or unemployment. Personal relationships are placed under considerable strain by dependent drug use, and problems with accommodation are common. Prior to intake in NTORS, 7% were homeless and living on the street, 5% were living in squats, and 8% were living in temporary hostel accommodation.[15]

Health-related quality of life

There is little evidence about the health-related quality of life in drug users. We undertook our own analysis using a citizen's value of health panel in order to obtain estimates for this report.

Criminal Activity

Many opioid dependent individuals become involved in crime to support their drug use. It is estimated that half of all recorded crime is drug related, with associated costs to the criminal justice system in the UK estimated as reaching £1 billion per annum in 1998.[17]

Psychological Effects and Mental Illness

Psychiatric co-morbidity is common in opioid dependent populations, with anxiety, affective, antisocial and other personality disorders particularly common.[18,19] Recent psychiatric treatment was reported by one in five of the 1075 subjects recruited to NTORS, and psychiatric symptom levels were high.[20] Clinical studies suggest that half of opioid-dependent individuals have a lifetime depressive episode, while a third have depressed mood at intake to addiction treatment.[20]

The Epidemiological Catchment Area study reported a 47% lifetime prevalence rate of substance abuse among patients with schizophrenia compared to 16% in the general population[18], and these figures are confirmed in UK studies[21,22]. The consequences of substance misuse in schizophrenia are substantial, as misuse of alcohol, cannabis and stimulants is associated with exacerbation of psychotic symptoms, more frequent hospitalisation, poor social functioning, homelessness, increased suicide rate and poor treatment response. However, psychosis is not a typical feature of the opioid withdrawal syndrome, but it has been reported in some cases after stopping methadone[23]. Bloom and others have proposed that an excess of endogenous opioids may have a role in the pathogenesis of schizophrenia[24], and it is sometimes more practical to maintain opioid-dependent schizophrenic patients on a combination of antipsychotic medication and methadone than attempting a detoxification process. Relatively little research has been done on pharmacological treatment of patients with coexisting schizophrenia and substance-use disorders, with many studies focusing on psychosocial treatment and providing patients with standard pharmacotherapy.

There is a strong link between bipolar disorder and substance misuse, with the ECA study showing that more than 60% of people with a diagnosis of bipolar I disorder had a lifetime diagnosis of substance use disorder.[1] Symptoms of depression are common in people that misuse drugs and alcohol, and diagnostic issues are often difficult to clarify. Developments in diagnostic criteria and improved trial methodology have led some authors to conclude that any substance-dependent person who meets criteria for a depressive disorder stands a good chance of improvement on medication.[25] However, it is important to remember that most depressive symptoms observed in substance dependent individuals resolve with abstinence, and are probably substance-induced mood disorders. A variety of studies on the use of tricyclic antidepressants in opioid dependent patients with depressive symptoms have given inconclusive results. Plasma level monitoring is important, as methadone-maintained patients often have plasma levels of tricyclic drugs twice as high as prior to methadone administration. More recently SSRIs have been recommended as the antidepressant of choice in depressed injecting drug users, but only where there is a clear depressive disorder[26].

2.3.5 Current service provision

The UK has a well-established range of treatment services across statutory and non-statutory sectors to help affected individuals. Various medications and other psychosocial interventions can be provided in a range of different settings within the community and the criminal justice system, including inpatient or residential, day-patient or outpatient settings.

The Government's ten-year national drug strategy, Tackling Drugs to Build a Better Britain (1998), identified treatment as one of the four key areas for action.[17] It covered all illicit drugs, but gave priority to the reduction of use of and harm by opioids, cocaine, amphetamine and amphetamine-type stimulants, sedative/hypnotics, hallucinogens and volatile substances (solvents and inhalants). The Updated Drug Strategy (drugs Strategy Directorate 2002) set the target for England to continue to expand drug treatment as well as to improve its quality and the retention of users in treatment. It is the responsibility of the National Treatment Agency for Substance Misuse (NTA) to improve the quality, availability, accessibility and effectiveness of drug treatment in England. To ensure effective delivery of drug treatment services, the Models of Care document was developed to provide guidance on the optimal models of care for drug treatment services.[11]

The UK Government Spending Review 2004 saw agreement of a new Public Service Agreement (PSA) for the Government's Drug Strategy. This included targets to

- reduce the harm caused by illegal drugs including substantially increasing the number of drug misusing offenders entering treatment through the Criminal Justice System
- increase the participation of problem drug users in drug treatment programmes by 100% by 2008 and increase year on year the proportion of users successfully sustaining or completing treatment programmes
- reduce the use of Class A drugs and the frequent use of any illicit drug among young people under the age of 25, especially by the most vulnerable young people.

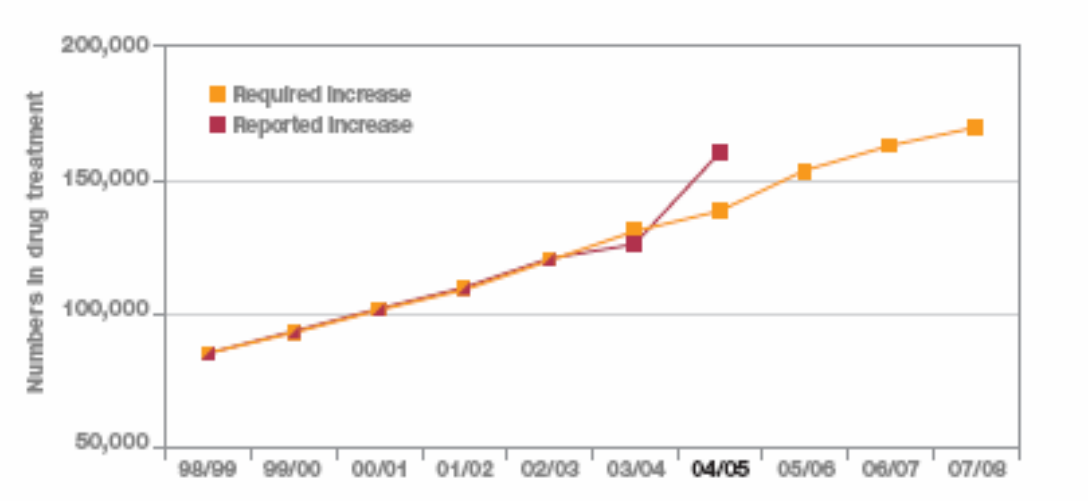
Direct expenditure for tackling drugs in the 2003/4 financial year was £1,244 million, with £503 million of this spent on drug treatment.[9]

The National Treatment Agency for Substance Misuse Annual Report 2004/5 reports that in 2004/5

- 160,450 people received specialist drug treatment
- Up 27 per cent from 2003/04, and 89 per cent from 1998/99
- 53 per cent of people who left treatment had stayed for
- at least 12 weeks
- 75 per cent either successfully completed or were still in treatment as
- at 31 March 2005
- weeks was the average time someone waited for treatment
- 10,025 people were working in the drug treatment sector.

The numbers currently and predicted as being in treatment are given in Figure 1, below

Figure 1 Numbers in drug treatment – required and reported increase 1998/9 to 2007/8



(taken from the National Treatment Agency for Substance Misuse Annual Report 2004/5)

According to Models of Care, services for drug misusers can be grouped into four broad tiers:[11]

Tier 1 – non-substance-misuse-specific services requiring interface with drug and alcohol treatment

Tier 2 – open access drug and alcohol treatment services

Tier 3 – structured community-based drug treatment services

Tier 4 – residential services for drug and alcohol misusers

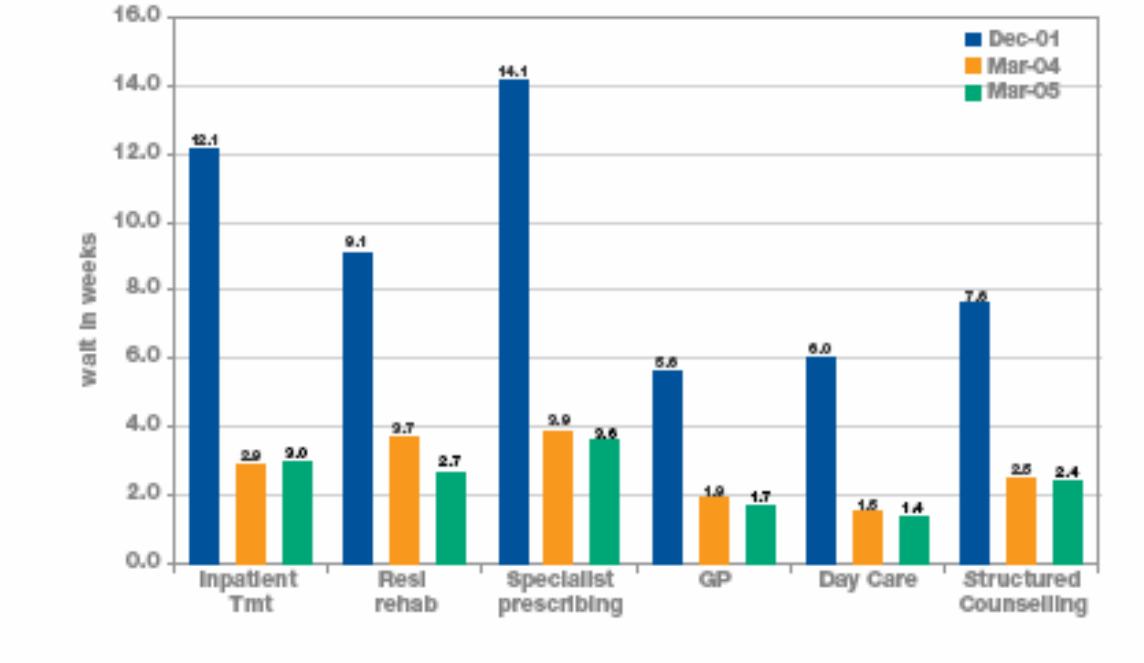
Maintenance programmes vary widely in terms of the nature and quantity of psychosocial support delivered in addition to the medication, and in terms of the degree of supervision of methadone consumption.[27] Substitute opioids and naltrexone are mainly prescribed in tier 3 (community prescribing programme) settings, although increasing use is being made of prescribing in primary care. UK policy recommends that community prescribing takes place within a context in which the heroin user's co-existing physical and emotional, social and legal problems are addressed as far as possible.[11] Prescribing must be complemented by counselling or structured psychotherapy, as well as other services such as welfare advice, help with housing or employment.[27]

Waiting times continue to be an important problem for people wishing to access drug services with waits averaging between just under two weeks to four weeks for accessing most

specialist services but there is much improvement on five year ago as shown in Figure 2, below.

Figure 2 National average waiting times for treatment

(1 week s five working days)



(taken from the National Treatment Agency for Substance Misuse Annual Report 2004/5)

2.3.6 Identification of important sub-groups

There are a number of important sub-groups who have particular risk factors or particular problems such as the homeless, people with co-morbidity (e.g. mental illness), young people and pregnant women.

It has been suggested that patients involved in meaningful relationships, in full-time education or employment, or living with family members are most likely to benefit from naltrexone treatment (Resnick 1979).[28] Good results have been shown in the treatment of health care professionals in uncontrolled studies (Washton et al 1984,[29] Ling et al 1984,[30] Roth 1997[31]), and addicted professionals have high rates of accepting naltrexone and remaining in treatment. High earning business executives have also shown high rates of

treatment retention and low rates of relapse to opioid use (Washton 1984),[29] and this suggests that linking naltrexone compliance with retaining a job or professional registration may be a useful strategy that merits further RCT investigation. The study by Cornish et al[32] also suggests that further research on the efficacy of naltrexone treatment for populations of opioid dependent individuals in the criminal justice system are needed.

The addition of specific behavioural therapies to a prescription of naltrexone may significantly enhance its efficacy (Carroll 2001,[33] Preston 1999[34]), although there is limited evidence that such contingency management strategies have so far been introduced successfully into UK services. This is possibly because the idea of using health service funds to reward people who are drug abusers with vouchers or money is politically too sensitive.

2.3.6.1 Young people

The national drugs strategy places special emphasis on preventing drug misuse among young people and on providing appropriate services for those who have drug-related problems or who are at risk of developing them.[17] The strategy defines three groups: children (aged 12 or less); young people (aged 13-17 years); young adults (aged 18-24 years). There are significant challenges in designing appropriately matched treatments and support for young people, and little experience of service delivery.

2.3.6.2 Pregnancy

Dependent heroin use during pregnancy is associated with a reduction of fetal growth, resulting in low birth weight, prematurity, and fetal and neonatal death.[27,35] The specific effects of opioids on the neonate are confounded by harm associated with the mother's lifestyle. Parental drug use during and after pregnancy can also have a serious impact on the emotional, cognitive and behavioural development of children.[36]

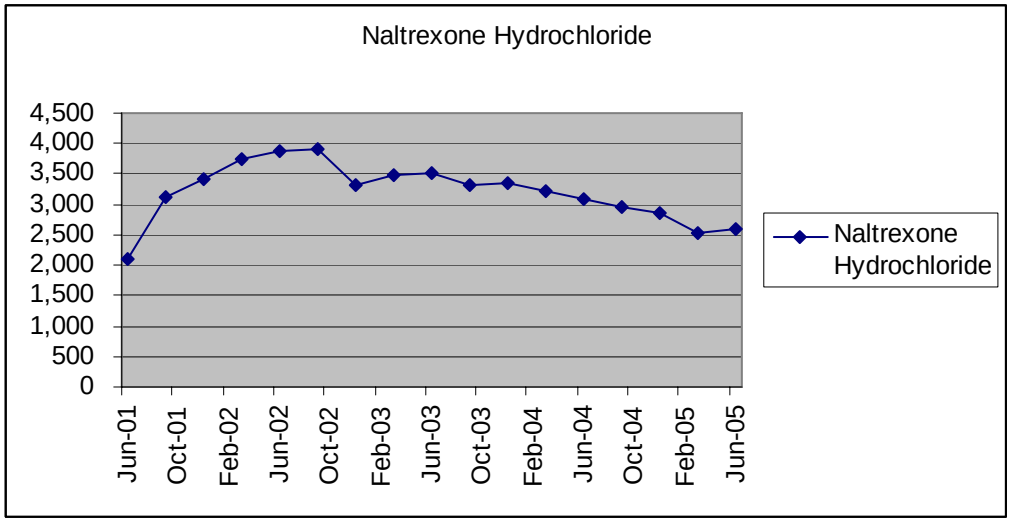
2.3.7 Current usage in the NHS

Figures produced by the NDTMS show that 160,450 individuals were recorded as in contact with structured drug treatment services in England in 2004/5. A total of 53% (55,650) of patients who were discharged remained in treatment for 12 weeks or more following triage

assessment, and 120,700 individuals (75% of those treated in the year) either successfully completed treatment or were retained in treatment.[11]

Treatment using oral naltrexone is not common with a total of only 11,000 to 14,000 scripts being issued per annum in England and no trend of increasing use (see Figure 3 below). Moreover not all of these will have been for use in formerly opioid dependent individuals as naltrexone is also used in alcoholism and other mental disorders. It is not possible to distinguish the indication for use from PACT data.

Figure 3 Total quarterly prescriptions for naltrexone in England from PACT data 2001-2005

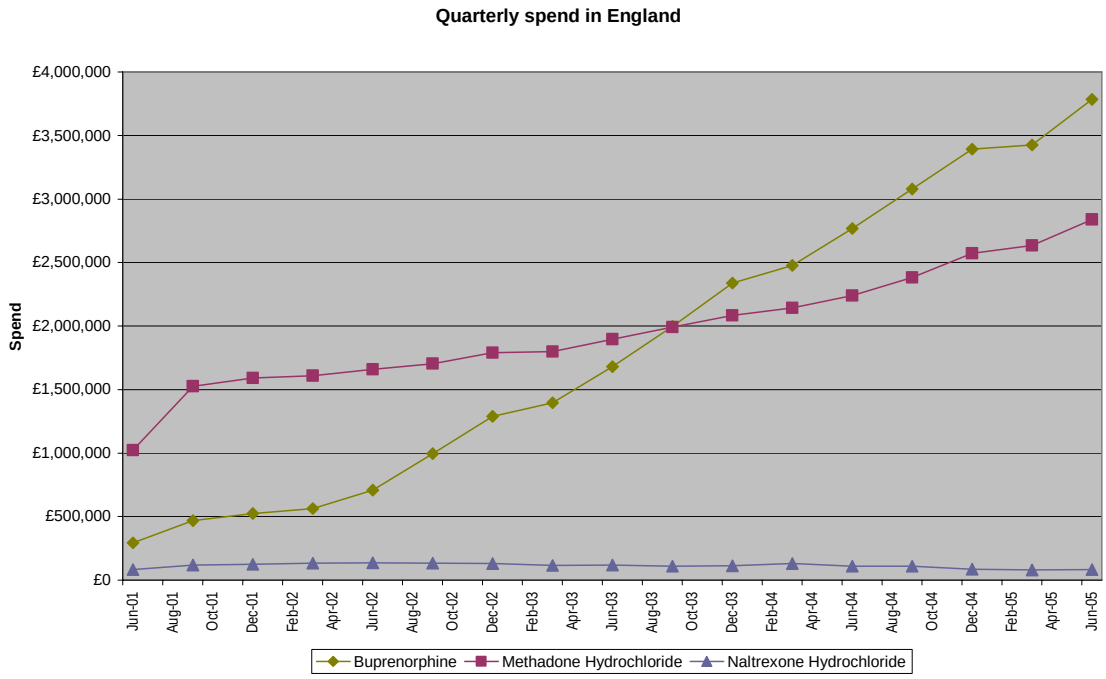


2.3.8 Anticipated costs associated with intervention

The annual drug cost per patient per year of naltrexone use is £552.50.

The total expenditure on naltrexone is less than £500,000 per annum in England. This contrasts with maintenance treatment using methadone and buprenorphine which are increasingly used, as illustrated in Figure 4 below. (The analysis in the figure is for all formulations in BNF sections 4.10, 4.7 and 3.9.)

Figure 4 Quarterly expenditure on methadone, buprenorphine and naltrexone in England 2001- 2005



3. METHODS FOR REVIEWING EFFECTIVENESS[1]

3.1 Search strategy

3.1.1 Clinical Effectiveness reviews

For the clinical effectiveness review the following sources were searched :

- Bibliographic databases: Cochrane Library (Wiley) 2005 Issue 2, MEDLINE(Ovid) 1966 – July week 4 2005 and MEDLINE In-Process (Ovid) at 3 August 2005 , EMBASE (Ovid) 1980 – 2005 week 36 and CINAHL (Ovid) 1982 – July week 5 2005 , PsycINFO (Ovid) 1967 – August week 1 2005, Science Citation Index/Social Science Citation Index (Web of Science) 1970 – 6 September 2005
- Research registries of ongoing trials including National Research Register 2005 Issue 2 and Current Controlled Trials *meta*Register and Clinical Trials.gov as at August 2005
- Citations of relevant studies
- Relevant internet sources including specialist substance abuse sites

Searches were not limited by date. No language restrictions were applied. Details of search strategies may be found in Appendix 7.

Experts were also contacted.

3.1.2 Cost-Effectiveness review and modelling

Studies on costs, quality of life and information to populate the decision analytic model were identified from the following sources:

- Bibliographic databases: MEDLINE (Ovid) 1966 – July week 4 2005, EMBASE (Ovid) 1980 – 2005 week 32, Cochrane Library (Wiley internet version) (NHS EED and DARE) 2005 issue 2, Office of Health Economics HEED database August 2005 issue
- Internet sites of national economic units

[1] In accordance with explicit quality standards agreed by InterTASC and the NCCHTA

Searches were not limited by date except for the quality of life searches (2004-2005) due to the large volume of material retrieved. There were no language restrictions. Details of search strategies may be found in Appendix 8.

Experts were also contacted.

3.2 Inclusion and exclusion criteria

Inclusion criteria:

- Controlled trials of use of oral naltrexone compared to any other relapse prevention strategy (pharmacological, psychosocial, etc) without naltrexone in detoxified formerly opioid-dependent individuals in both arms.
- Systematic reviews of analytical observational studies looking at adverse events or other outcomes, e.g. crime rates, for naltrexone use for the same indication.
- Randomised controlled trials of any intervention designed to enhance compliance with naltrexone treatment with the same naltrexone regimen in both arms.

Exclusion criteria

- Studies of naltrexone treatment outside the licensed indications such as subcutaneous implants or parenteral depot preparations.
- Studies of naltrexone use for alcohol dependence or other indication
- Case reports and case series

3.3 Outcomes to be examined

3.3.1 Primary outcomes

- Changes in illicit drug use
- Drug-related morbidity
- Drug-related mortality
- Health-related quality of life

3.3.2 Secondary outcomes

- Proportion of individuals being maintained opioid-free
- Concordance with and retention to treatment
- Adherence to treatment, treatment drop out
- Societal function
- Criminal activity, (re-)incarcerations
- Utilisation of health care system.
- Mean duration of treatment
- Serious adverse effects of treatment

3.4 Data extraction strategy

Data were extracted onto agreed pro-forma by two reviewers independently. Results were extracted, where possible for intention-to-treat populations, as raw numbers, plus any summary measures with standard deviations, confidence intervals and p-values. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary.

3.5 Quality assessment strategy

The quality of the clinical effectiveness studies were assessed according to criteria based on NHS CRD Report No. 4 by one reviewer and checked by a second reviewer. A Jadad score was used. This give a score from 0 (poorest quality) to 5 (best quality). Disagreements were resolved by consensus and where necessary a third reviewer was consulted.

3.6 Data analysis

The main results are placed in tables. Studies are grouped according to outcome and comparison groups. Where possible the results are summarised by calculating relative risks (including hazard ratios if appropriate) and risk differences with 95% confidence intervals for dichotomous outcomes. Meta-analysis was carried out where appropriate. Analysis by subgroups (e.g. settings, patient characteristics) is explored.

Survival analysis for treatment retention rates were carried out in the following steps:

1. the treatment retention rates from primary studies were measured manually and linearly interpolated in weekly time points
2. the combined survival analysis curves for the intervention group and the control group were generated by summing not-retention-treatment events of the primary studies at weekly time points and censoring patients who still retained in treatment at the end of follow-up of the studies
3. the logarithm of the hazard ratios and their variances were obtained by performing log-rank test.
4. the pooled hazard ratio and its 95% confidence interval were derived by meta-analysing the individual hazard ratios using Equation 1.[37]

The same analysis was done for proportion who refrained from use of illicit drugs in each group.

Equation 1 The pooled hazard ratios

$$\ln(HR) = \frac{\sum_i \frac{\ln(HR_i)}{Var[(\ln(HR_i)]}}{\sum_i \frac{1}{Var[(\ln(HR_i)]}}$$

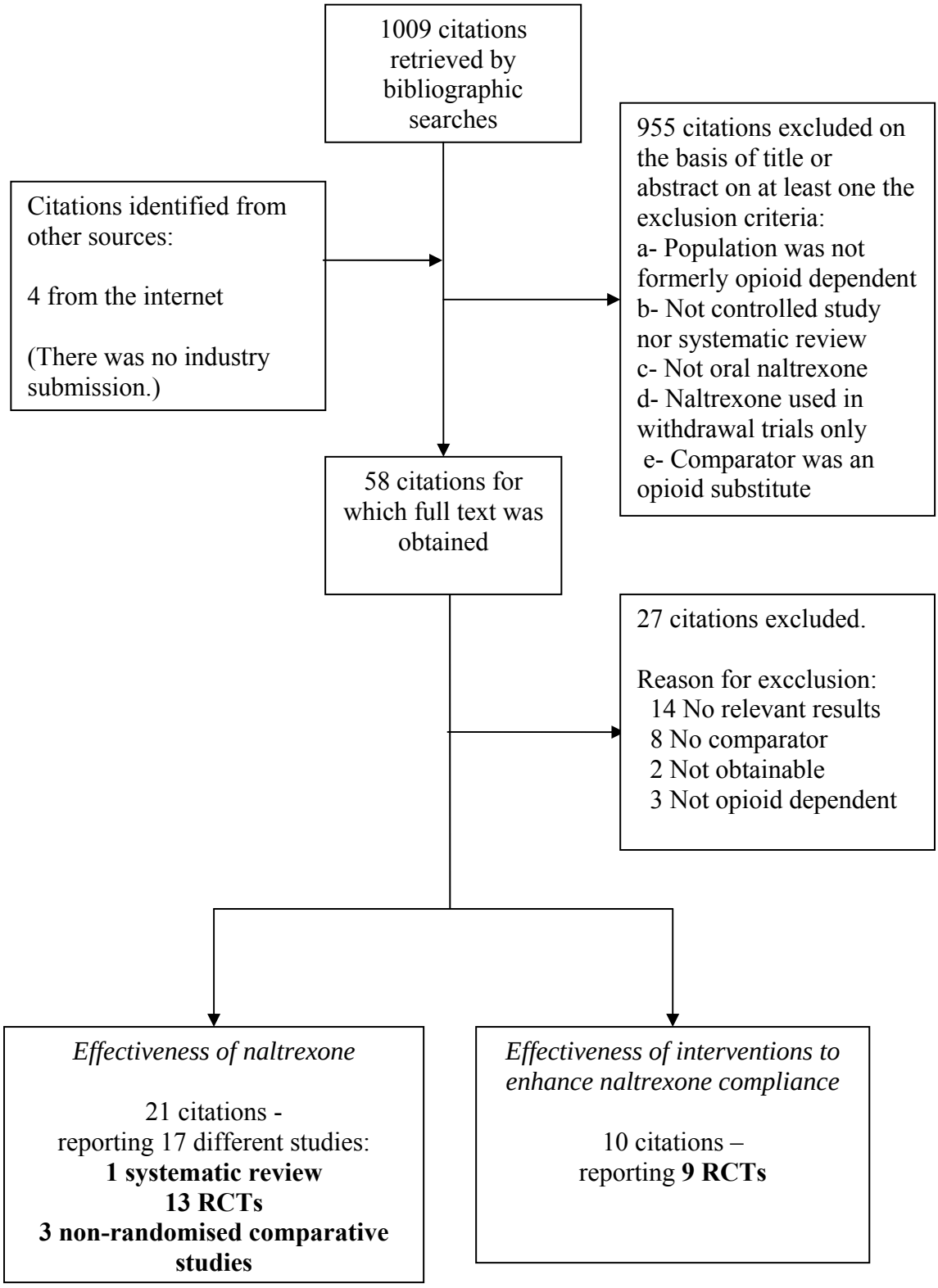
$$Var[\ln(HR)] = \frac{1}{\sum_i \frac{1}{Var[(\ln(HR_i)]}}$$

4. RESULTS OF EFFECTIVENESS REVIEWS

4.1 Quantity of evidence available

The searches produced 1013 citations, of which 955 citations could be excluded on the basis of the title and abstracts as they did not fulfil one or more of the inclusion criteria in terms of the population, the intervention or design of the studies. The full text was obtained for 58 citations for further assessment. See Figure 5 below for the flowchart giving the study selection.

Figure 5 Flow chart for study selection



Twenty-seven studies did not meet the criteria for inclusion in this review: three did not have the population of participants of opioid-dependent individuals, 14 had no relevant results, eight had no comparator; two were not obtainable. Details of the studies and reasons for exclusion are given in Appendix 7, page 114.

Thirty-one papers, representing 26 studies, fulfilled the inclusion criteria. Seventeen looked at the effectiveness of oral naltrexone and studies looked at interventions to improve compliance with naltrexone therapy.

4.2 Details of the naltrexone effectiveness studies

4.2.1 Quality of naltrexone studies

Of the 17 studies looking at effectiveness, one was systematic review[38,39], 13 were RCTs (for details see Table 2, below) and 3 were comparative but not randomised studies (for details see Table 3, below).

The systematic review was a Cochrane review. The details are summarised in Table 1, below. It included 10 RCTs and was of good quality. However the summary result is only expressed as the relative risk of retention in treatment rather than the hazard ratio.

Table 1 Summary table of systematic review

Author	Sample size	Population	Intervention	Comparator	Follow up	Main Findings
Kirchmayer 2003 & update 2005[38,39]	Ten studies with 696 total participants	All in-patients and out-patients dependent on heroin, or former heroin addicts dependent on methadone and participating in a naltrexone treatment programme are considered. No distinction is made between addicts dependent on heroin alone or on multiple drugs.	Naltrexone, and/or psychosocial therapy.	Placebo and/or psychosocial therapy or psychosocial therapy alone	mean duration : six months (range 1 to 10 months)	Use of primary substance of abuse: six combined studies, RR 0.72 (95%CI 0.58 to 0.90) Retention in treatment: five studies, RR 1.08 (95%CI 0.74 to 1.57).

The quality of the other included studies tended to be low. A full summary of the quality of the RCTs of naltrexone use is given in Table 28, page 106. In only one out of the 13 included RCTs was the method of randomisation satisfactorily described. Only one RCT described the allocation of intervention as concealed. Nine were reported as double-blind. Twelve of the 13 studies scored less than three on the Jadad scale. Only four trials gave withdrawal rates. None of the trials described the power or gave a sample size calculation.

In the three non-randomised comparative studies, the population was adequately described, however the loss to follow up was either >20% or was not reported. None of the three non-randomised studies adjusted for the possible confounding variables. Full details are given in Table 29, page 108.

4.2.2 Characteristics of identified studies

A summary of the characteristics of the naltrexone RCTs is given in Table 2, below and the characteristics of the non-randomised studies in Table 3, below.

4.2.2.1 Participants in RCTs

The total number of opioid users in the 13 included trials was 940. The mean length of follow up was 29 weeks (range 3-52 weeks). In two studies, Cornish 1977[32] and Curran 1976[40] the participants were people on probation and parolees.

4.2.2.2 Comparators in RCTs:

A number of comparators were used in the included studies:

- placebo
- placebo plus psychosocial therapy
- clonidine
- cyclazocine
- behavioural therapy

4.2.2.3 Outcomes reported in RCT trials:

Seven studies reported retention in treatment as the main outcome comparing either naltrexone to placebo or naltrexone plus psychosocial support to placebo plus psychosocial support. The other reported outcomes were the return to use of primary substance, adverse events and re-incarceration rates.

Table 2: Summary table of RCTs

Author	Country	N (n/group)	Population	Intervention	Comparator	Jadad Score	Follow up	Main Findings
Krupitsky[41,41,42] 2004	Russia	N=52 (27/25)	Opioid dependant patients	Naltrexone plus biweekly drug counselling (6 months)	Placebo plus biweekly drug counselling	2	6 months	Relapse to heroin: 8/27 (29.6%) on naltrexone versus 18/25 (72%) on placebo, p<0.01 Retention in treatment: Significantly higher in naltrexone patients from one month throughout the study. At the end of 6 months 12 naltrexone patients 12/27 (44.4%) versus 4/25 (16%) in the control P<0.05 Retention in treatment: HR (Naltrexone/Placebo) 0.45, 95%CI (0.23 to 0.87)
Grinenko 2003 [43] translation	Russia	N=52 (25/27)	Heroin addicts in S Peterburg regional hospital	Naltrexone plus biweekly psychotherapy (6 months)	placebo plus biweekly psychotherapy	2	Not clear, probably all till 6 months	Remission at 6 month 16% in naltrexone versus 44% control
Guo 2001 [44]	China	N=49 (35/14)	Heroin addicts	Naltrexone (6 month)	Placebo	2	6 months	Abstinence rate: At six months in the RCT study 31.4% in naltrexone vs 7.1% in placebo Average abstinence period for naltrexone group was significantly longer

Author	Country	N (n/group)	Population	Intervention	Comparator	Jadad Score	Follow up	Main Findings
Cornish 1997 [32]	USA	N=51 (34/17)	probationers or parolees with a history of opioid addiction;	Naltrexone and minimal counselling and probation programme (6 months)	Probation programme and minimal counselling	1	6 month	Retention rate was not statistically significantly higher than that of control 52% naltrexone vs 33% control. Retention in treatment: HR (Naltrexone/Control) 0.66, 95%CI (0.29 to 1.49)
Gerra 1995 [45]	Italy	N=152 (42/33/58/19)	Heroin-abusing patients	Naltrexone and Clonidine (3 months)	Clonidine only; Naloxone and Clonidine; Placebo	1	6 months	Subjects' and relatives' attendance to the meetings was significantly higher in opiate antagonists treatment.
Shufman 1994 [46]	Israel	N=32 (16/16)	Heroin addicts	Naltrexone plus behavioural and supportive psychotherapy (12 weeks)	Placebo plus behavioural and supportive psychotherapy	2	12 weeks	*Drug free survival curves*: shows 36% in naltrexone at 12 weeks vs 19% in placebo, not statistically significant. Retention rate: was not significant in naltrexone vs placebo at 12 weeks treatment. 55% for both arms estimated from Kaplan-Meier curves. Retention in treatment: HR (Naltrexone/control) 1.18, 95%CI (0.43 to 3.25)

Author	Country	N (n/group)	Population	Intervention	Comparator	Jadad Score	Follow up	Main Findings
Lerner 1992 [47]	Israel	N=31 (15/16)	Opioid dependants	Naltrexone plus psychotherapy and counselling (2 months)	Placebo plus psychotherapy and counselling	3	1 year	Success rate naltrexone vs. placebo 9/15 vs 8/16 at 2 months 8/15 vs. 6/16 at 1 year. Retention rate was not significant in naltrexone arm compared with placebo at 2 months and at 1 year (t=0.54, df=29, p=0.59) at 2 month and (t=0.87, df=27, p=0.373) at 1 year. Craving in naltrexone 12/15, 3/15 in moderate and severe scale, while craving in placebo 3/16, 13/16 15 in moderate and severe scale. Attempting opioid taking for naltrexone (7,1,3,4 for no attempt, 1 attempt, 2 attempt, 3 or more attempt), for placebo, (8,8,0,0 for no attempt, 1 attempt, 2 attempt, 3 or more attempt), not sig. (t=0.18, df=29, p=0.85)

Author	Country	N (n/group)	Population	Intervention	Comparator	Jadad Score	Follow up	Main Findings
San 1991 [48]	Spain	N=50 (28/22)	Heroin addicts	Naltrexone (6 months)	Placebo	2	1 year	Overall retention rate at 6 months was 27.9% with drop out excluded, but 4/23 (17.4%) in naltrexone and 8/20 (40%) in placebo ; no significant difference at 6 months or at 1 year Retention in treatment: HR (Naltrexone/Placebo) 2.06, 95%CI (1.06 to 4.00)
Ladewig 1990 [49]	Switzerland	N=20 (15/5)	Detoxified opioid addicts male and female; age range: 20-35 years; opioid free for at least 10 days;	Naltrexone plus basic psychosocial program	Basic psychosocial program alone	1	Mean 69 days (Naltrexone group) Mean 49 days (control group)	Length of treatment in naltrexone mean 69 days vs 49 days in control
Brahen 1977,1979[50,51]	USA	N=40 (20/20)	Former opiate addicts	Naltrexone (20 days)	Cyclazocine; Placebo	2	20 days	Post placebo naltrexone produced fewer effects than initial exposure to naltrexone but not significantly. Incidence of adverse effects 298 in cyclazocine vs 67 incidence in naltrexone

Author	Country	N (n/group)	Population	Intervention	Comparator	Jadad Score	Follow up	Main Findings
Rawson 1979[52]	USA	N=181 (55/55/71)	Heroin addicts	Naltrexone or Naltrexone plus behaviour therapy (30 weeks)	Behaviour therapy	2	1 year	Opiate free urine sample: 10/23 naltrexone vs 4/15 behaviour therapy Incarcerated: 6/23 naltrexone vs 6/15 behaviour therapy
Hollister 1978,[53]	USA	N=192 * (60/64)	(1) street addicts (2) methadone users (3) post addicts	Naltrexone (9 months)	Placebo	2	9 months	Retention rate: only 7 patients on naltrexone and 6 on placebo completed 8 months trial Retention in treatment: HR (Naltrexone/Placebo) 0.87, 95% CI (0.60 to 1.27)
Curran 1976[40]	USA	N=38 (19/19)	American dependant parolees or probationers;	Naltrexone (92 days)	Placebo	2	9 months	Successful completion: 2/19 vs 2/19 Total length of treatment 80 days in naltrexone vs 92 in placebo

* The total sample size was reported as 192 in the study, but a table showed sample sizes for Naltrexone and placebo were 60 and 64 respectively. We manually measured the proportion of patients who retained in treatment on survival curve, and the measurement confirmed the sample sizes reported in the table, therefore, the sample size of 60 for Naltrexone, and sample size of 64 for placebo were used in our analyses.

Table 3 Summary table of comparative controlled studies

Author	Country	N (n/group)	Population	Intervention	Comparator	Follow up	Main Findings
Arnold-Reed [54]2003	Australia	N=92 (21/71)	Death-related heroin users	Naltrexone	Non-naltrexone	2 years	Registered cause of death in the study population which is heroin related: Naltrexone 63.6% (21/33), Non-naltrexone 74% (71/96), not significant different (chi2=1.28, p=0.26);
Sivolap 1998 [55]	Russia	N=120 (60/60)	Opioid dependents	Naltrexone	Nothing	> 6 months	Abstinence rate 12/60 Naltrexone v 24/60 placebo Leaving the programme 42/60 naltrexone vs 22/60 placebo
Judson 1984 [56]	USA	N=117 (40/77)	Heroin addicts	Naltrexone after 6-month LAAM program (1 year)	Not enter naltrexone after 6-month LAAM program	1 year	No significant correlation between total duration in naltrexone treatment and post treatment outcomes such as: heroin use, arrests, incarcerations5/40 vs 15/77 or mortality preceding to the 1 year follow up.

4.3 Results reported in naltrexone studies

4.3.1 Retention in treatment

Systematic review

In the systematic review (Table 1) the summary relative risk of retention in treatment was RR 1.08 (95%CI 0.74 to 1.57).

RCTs

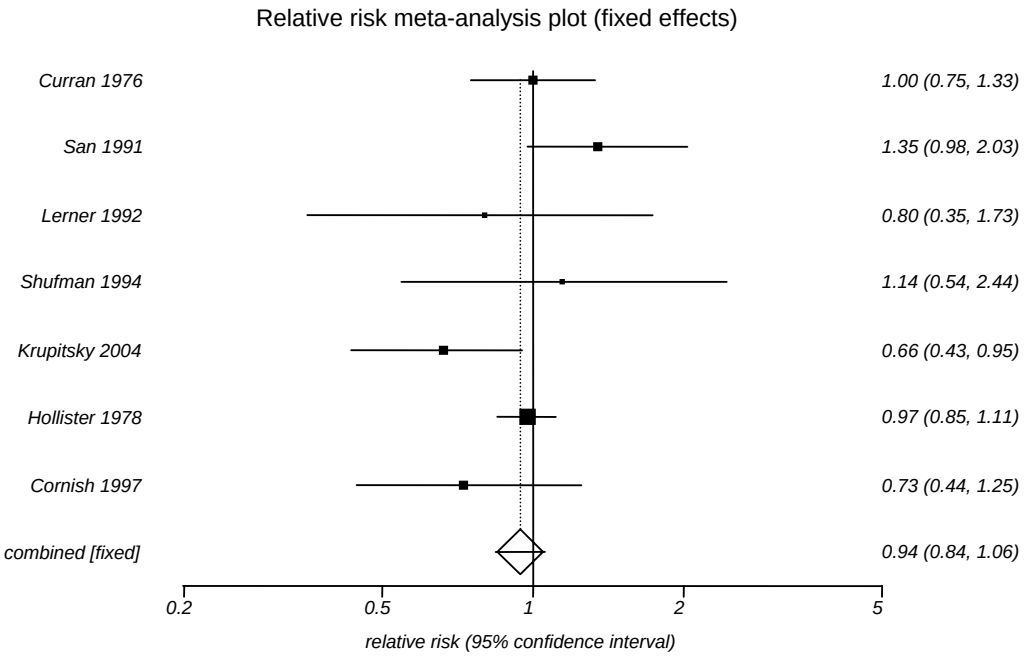
Data on retention in treatment was provided by seven trials that compared naltrexone with placebo. The length of follow up varied between trials and therefore the RR may not be a representative estimate of retention in treatment and hazard ratio will be a better estimate. However, we initially present a meta-analysis of seven studies giving the relative risk of retention to allow these results to be compared with those of the Cochrane review. The results are given in Table 4. The data is also present graphically in Figure 6 below.

Table 4 RR of stopping treatment naltrexone treatment vs placebo (with or without psychological support given in both arms)

Study	Naltrexone n/N	Placebo n/N	RR (Fixed) 95% CI
Curran 1976 [40]	17/19	17/19	1.00 (0.75, 1.33)
San 1991 [48]	24/28	14/22	1.35 (0.98, 2.03)
Lerner 1992 [47]	6/15	8/16	0.80 (0.35, 244)
Shufman 1994 [46]	8/16	7/16	1.14 (0.54, 1,73)
Krupitsky 2004 [41]	15/27	21/25	0.66 (0.43,0.93)
Hollister 1978 [53]	53/60	58/64	0.97 (0.85, 1.11)
Cornish 1997 [32]	16/34	11/17	0.73 (0.44, 1.25)
Total	**139/199**	**136/179**	**0.94 (0.84, 1.06)**

Q test for heterogeneity P = 0.1537

Figure 6 Relative risk of stopping treatment



Favour Naltrexone Favour Placebo

The results suggest that the risk of not being in treatment retention in naltrexone group compared to the placebo group is reduced by 6% but this was not statistically significant with 95% CI from 0.84 to 1.06. This is consistent with the finding of the Cochrane review.

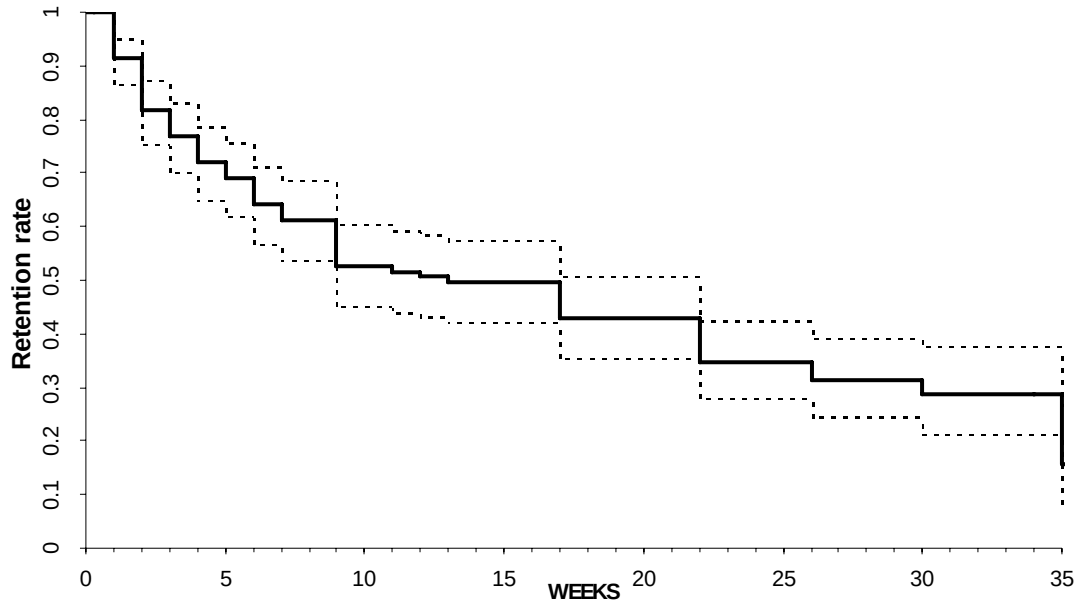
However we also looked at the hazard ratios as these general incorporate more information. Survival data could only be extracted from five primary studies. Survival analyses were performed and the log-rank tests were carried out for these individual studies. The pooled hazard ratio for retention rate was derived using Equation 1 and shown in Table 5. The results showed that patients in the naltrexone treatment arm had a better retention rate with a hazard ratio of 0.90 which was not statistically significant (95%CI 0.69 to1.17). A combined survival curve was obtained by summing not-retention-treatment events and censoring patients who were retained in treatment at the end of studies and is shown in Figure 7.

Table 5 Pooled and individual hazard ratios for retention in treatment.

Study	HR	95% CI Lower	95% CI Upper	Favour	Time of follow up	p-value
Shufman 1994 [46]	1.18	0.43	3.25	Placebo	12 weeks	0.74
Krupitsky 2004 [41]	0.45	0.23	0.87	NTX*	6 months	0.01
Cornish 1997 [32]	0.66	0.29	1.49	NTX	6 months	0.27
Hollister 1978 [53]	0.88	0.60	1.27	NTX	9 months	0.46
San 1991 [48]	2.06	1.06	4.00	Placebo	1 year	0.03
Pooled Studies (fixed)	**0.90**	**0.69**	**1.17**	**NTX**		**0.41**

*NTX=naltrexone

Figure 7 Combined retention rate and 95% CI in naltrexone treatment



For the retention rate studies, $\chi 2 = 11.08$ (df=4, p=0.03), showed heterogeneity between these studies (see Table 5 for the individual hazard ratios and the pooled hazard ratio). Therefore, in addition to the fixed effect meta-analysis, random effect meta-analysis was also performed for retention rate studies. The random effect analysis gave a hazard ratio of 0.90 (95%CI, 0.55, 1.48), compared to 0.90 (95%CI, 0.69, 1.17) from the fixed effect analysis.

4.3.2 Relapse rates

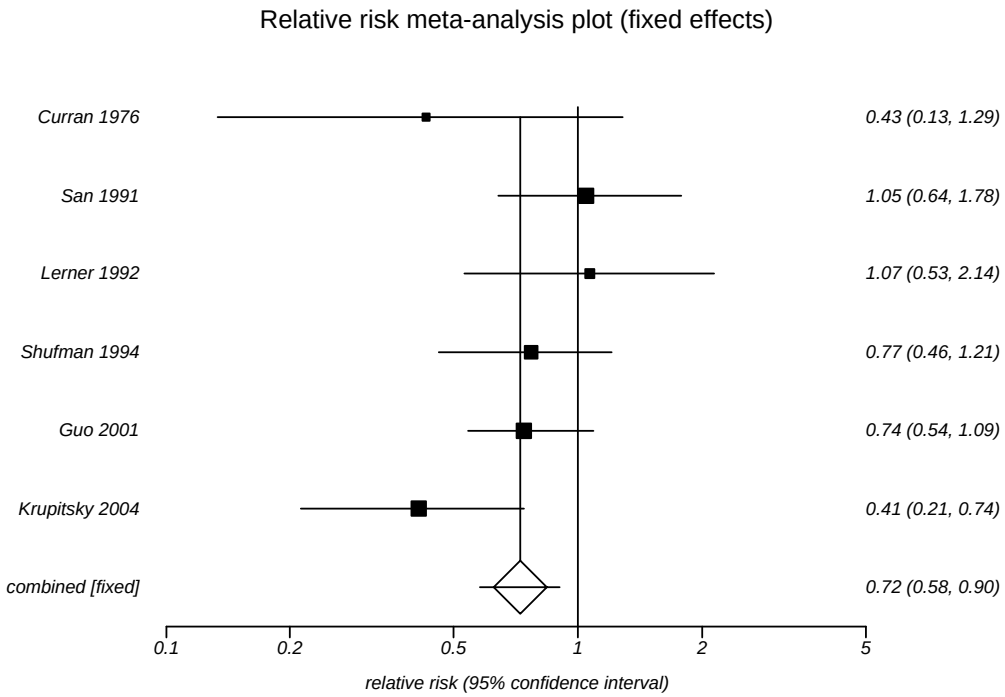
The systematic review reported a combined relative risk of use of primary substance of abuse of 0.72 (95%CI 0.58 to 0.90) which was confirmed by our analysis, presented in Table 6 and Figure 8, below.

Table 6 Risk of drug abuse in naltrexone vs placebo (listed in order of length of follow up)

Study	Naltrexone n/N	Placebo n/N	Absolute risk reduction	NNT (NNH)	Time of follow up	RR (Fixed) 95% CI
Shufman 1994[46]	10/16	13/16	0.188	6	12 weeks	0.77 [0.46 to 1.20]
Krupitsky 2004[41]	8/27	18/25	0.424	3	6 months	0.41 [0.21 to 0.74]
Guo 2001[44]	23/34	11/12	0.240	5	6 months	0.74 [0.54 to 1.09]
Curran 1976[40]	3/19	7/19	0.211	5	9 months	0.43 [0.13 to 1.29]
San 1991[48]	16/28	12/22	0.026	(39)	1 year	1.05 [0.64 to 1.78]
Lerner 1992[47]	8/15	8/16	0.033	(30)	1 year	1.07 [0.53 to 2.14]
Total	**68/139**	**69/110**	**0.138**	**8**		**0.72 [0.58 to 0.90]**

Q test for heterogeneity P = 0.2007

Figure 8 Relative risk of returning to illicit drug use



Favour Naltrexone Favour Placebo

The pooled relative risk of 0.72 indicates that naltrexone significantly reduces the use of opioid by 28% compared with the control and gives an NNT of 8. However the effect drops off over time.

Figure 9, below, the relapse-free rates in naltrexone treatment arm at different time points. The solid lines represent the combined rates, while the dashed lines represent the 95% confidence interval limits. The retention rates were 31.5% and 15.7% at week 26 and week 35, respectively. The relapse-free rate at week 26 was 37.3%.

Three studies were used to investigate the relapse-free rate between patients in naltrexone and control arms. These results for relapse-free are shown in Table 7 and Figure 9. The hazard ratio for relapse-free between naltrexone and control arms was 0.53, 95%CI (0.34, 0.82), and was significantly in favour of naltrexone.

$\chi 2$ tests were performed to test for heterogeneity between trials. For the opioid relapse-free studies, $\chi 2 = 0.59$ (df=2, p=0.75), suggested that there was no statistical heterogeneity between trials. The fixed model gave a pooled hazard ratio of 0.53, with 95%CI, (0.34, 0.82) (see Table 7 for the individual hazard ratios and the pooled hazard ratio). For the retention rate studies, $\chi^2 = 11.08$ (df=4, p=0.03), showed heterogeneity between these studies (see Table 5 for the individual hazard ratios and the pooled hazard ratio). Therefore, in addition to the fixed effect meta-analysis, random effect meta-analysis was also performed for retention rate studies. The random effects analysis gave a hazard ratio of 0.90 (95%CI, 0.55, 1.48), compared to 0.90 (95%CI, 0.69, 1.17) from the fixed effect analysis.

Due to the limited number of studies and poor quality of these studies, it is very difficult to evaluate factors which resulted in heterogeneity between studies. There were not big differences in age and sex between studies. The mean ages of participants were 22 to 39 years old in the naltrexone arm, and 21 to 39 years old in the placebo arm. One study, Hollister 1978 did not report age and sex at all. The proportion of male and female in the studies were also comparable, 79-100% and 72-100% male in the naltrexone and placebo arms, respectively. Other factors could be the length of treatment period, the duration of opiate use, the education level and the number of previous treatments, but they were not comparable as different studies reported different baseline variables. Two studies reported that the participants had opiate use of more than six months, one study reported that the participants had opiate use of less than three months before they were recruited for the trials. We analysed two subgroups according to the duration of opiate use, i.e., the duration of opiate use was greater than or equal to 6 months, or less than six months or not reported, the F test gave a p-value of 0.10, (F=5.57, with df of 1 and 3), was not statistically significant, but the trend was still strong. More studies are

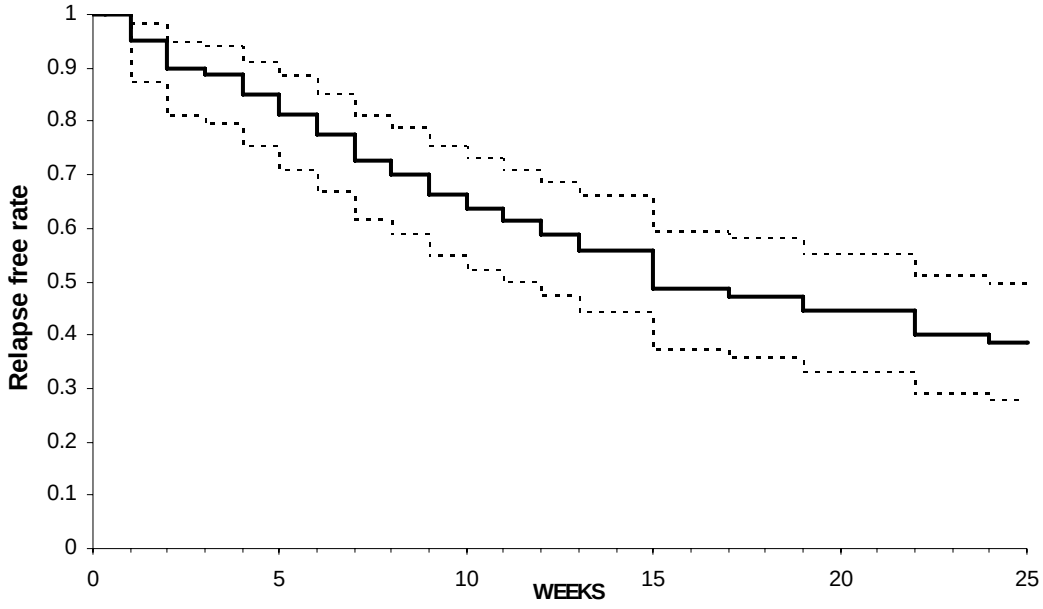
needed to confirm whether the heterogeneity might just be a chance effect or result from other factors.

Table 7 Pooled and individual hazard ratios for no opioid relapse

Study	HR	95% CI Lower	95% CI Upper	Favour	Time of follow up	p-value
Shufman 1994 [46]	0.67	0.30	1.53	NTX*	12 weeks	0.29
Guo 2001 [44]	0.53	0.23	1.22	NTX	6 months	0.06
Krupitsky 2004 [41]	0.45	0.23	0.87	NTX	6 months	0.01
Pooled Studies (fixed)	**0.53**	**0.34**	**0.82**	**NTX**		**0.00**

*NTX=naltrexone

Figure 9 Combined relapse-free rate and 95% CI in naltrexone treatment



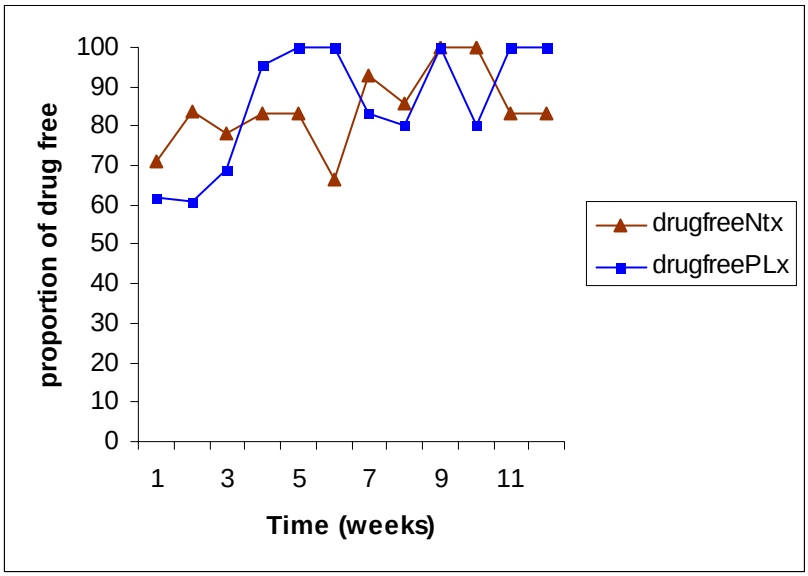
4.3.3 Relationship between retention in treatment and relapse rates

Although the pathophysiological reasoning underlying the rationale for naltrexone use would suggest that retention rates and relapse rates will be correlated, only one study, Krupitsky 2004[41], reported both the proportion remaining on treatment and the proportion remaining drug free (see Table 8, below). There was no striking relationship as shown in Figure 10, below.

Table 8 Proportion drug free in those who remained in treatment (from Krupitsky 2004[41])

Time (weeks)	Number of subjects with heroin positive urines, (%) of those who are opioid free and retained in naltrexone treatment, n=27	Number of subjects with heroin positive urines, (%) of those who are opioid free on placebo, n=25
2	7 (71)	8 (61.9)
4	16 (84)	7 (61.1)
6	5 (78.2)	4 (69.2)
9	3 (83.4)	1 (95.5)
11	3 (83.4)	0 (100)
13	6 (66.7)	0 (100)
15	1 (92.9)	1 (83.4)
17	2 (85.8)	1 (80)
19	0 (100)	0 (100)
22	0 (100)	1 (80)
24	2 (83.4)	0 (100)
26	2 (83.4)	0 (100)

Figure 10 Proportion drug free in those who remained on treatment



From Krupitsky 2004[41]

4.3.4 Adverse effects

Guo 2001[44] was the only RCT that reported useful data for comparison of adverse events following treatment of naltrexone in a double blind placebo controlled trial. However this was of small sample size with 35 participants using naltrexone in one arm and 12 using placebo in the other arm. The follow up was up to six months. Although many side effects were recorded, the severity was generally mild and declined during the treatment period. Adverse events were not significantly different between the two arms for any adverse event except for cold flush in naltrexone treated participants.

4.3.5 HIV related outcomes

Only one study, Krupitsky 2004[41], reported the Risk Assessment Battery (RAB) which is a self-reported instrument that measures HIV risk and focuses on drug use during the past 30 days and injection and sexual risk during the past 6months. The RAB drug risk scores for naltrexone patients who remained in the study, reduced from 8.2 at baseline to 1.5 at 3 and 1.4 at 6 months. The placebo patients reduced from 7.0 at base line to 0.9 at 3 and to 0.0 at 6 months. Although within-group changes were significant at <0.05, there were no differences between groups. No significant difference was found between the score for risky sexual behaviour compared to placebo.

4.3.6 Re-incarceration rate

Two studies reported a significant reduction in re-incarceration rate when using oral naltrexone plus psychosocial treatment vs psychosocial treatment alone. Table 9 shows the two studies combined.

Table 9 Re-incarceration rate in Naltrexone plus psychosocial vs psychosocial alone

Study	Naltrexone n/N	Placebo n/N	RR (Fixed) 95% CI	Significance status	Favour
Rawson 1979 [52]	4/20	6/15	0.50 [0.17 to 1.46]	N	naltrexone
Cornish 1977 [32]	9/34	9/17	0.50 [0.24 to 1.02]	N	naltrexone
Total	13/54	15/32	0.50 [0.27 to 0.91]	SS	naltrexone

Although the naltrexone group seems to show lower rate of re-incarceration, this result would need to be further researched as the sample size is very small.

4.3.7 Results from non-RCTS

The results from comparative but non-randomised studies did not add any useful data regarding the effectiveness of naltrexone.

4.3.8 Mortality

No mortality data were reported in the RCTs. A retrospective audit of clinical records, toxicology reports and registered coronial findings Arnold-Reed 2003[54], presented fatalities among a cohort of 1196 heroin dependent people treated with oral naltrexone over 2 years. There were 21 fatal heroin overdoses out of 33 registered causes of deaths in naltrexone users. This gives an estimated risk of death from fatal overdose of about 1 in 114 years of patient treatment. It is difficult to say to what extent the use of naltrexone was itself a contributory factor. While the study also reports 71 fatal heroin overdoses out of 96 registered causes of deaths in users not exposed to naltrexone, no denominator information is given. However, the proportion of deaths caused by overdose in naltrexone users (0.64) is no higher than that in non-naltrexone users (0.74).

4.4 RCTs of interventions to enhance naltrexone treatment

Nine randomised controlled trials of interventions designed to increase retention with naltrexone were identified.

4.4.1 Characteristics of RCTs of intervention to enhance retention on naltrexone treatment

The characteristics of these studies are shown in Table 10, below. Three RCTs looked at contingency management programmes. These are programmes which use a variety of strategies that reward participants when they comply with treatment but have no reward when participants do not comply. All used incentive vouchers that could be exchanged for various goods. Two of these trials had additional arms that involved psychosocial therapy in addition to incentive vouchers. Four further RCTs looked at additional psychosocial therapy and two RCTs looked at adding the additional pharmaceutical agents, sertaline and fluoxetine, respectively.

Table 10 Characteristics of RCTs looking at interventions to improve naltrexone retention

Author	Country	N (n/group)	Population	Comparator	*Intervention*	Follow up
Contingency management (+/- additional psychosocial therapies)						
Preston 1999[34]	USA	58 (19/19/20)	Recently completed opioid detoxification who are interested in continuing treatment to maintain abstinence	(a) Naltrexone (b) Naltrexone + non-contingency vouchers	- Naltrexone + ***incentive vouchers***	12 weeks
Carroll 2001[33]	USA	127 (35/48/44)	Outpatients completed outpatient detoxification (95%)	Naltrexone	- Comparator + ***incentive vouchers*** - Comparator + ***incentive vouchers*** + ***significant other involvement***	12 weeks
Ball 2004[57]	USA	125	Opioid dependents at outpatients who were detoxified for 5 days	Naltrexone + relapse prevention group counselling	- Comparator + ***incentive vouchers*** - Comparator + ***incentive vouchers*** + ***relationship counselling***	12 weeks
Psychosocial therapies						
Callahan 1980[58]	USA	104 (56/48)	Males opioid dependents	Naltrexone	Comparator + ***behavioural therapy***	21 months
Rawson 2001[59]	USA	81 (41/40)	Detoxified opioid dependents meeting DSM-IV criteria	Naltrexone	Naltrexone + ***cognitive behavioural therapy***	52 weeks
Fals-Stewart 2003[60,61]	USA	124 62/62	Males opioid-dependent users meeting DSM-III-R criteria, based at a community based outpatient clinic, living with at least one parent, a spouse or a partner or a family member who is not a current user. Details re detoxification not clear.	Naltrexone + Individual-based treatment	Comparator + ***behavioural family counselling***	24 weeks
Tucker 2004[62]	Australia	97 (52/45)	Opioid dependents according to DSM-IV inpatients and outpatients recruited via advertisement who are 18 years or older, detoxification for a minimum of 5 days	Naltrexone	Comparator + ***group counselling which used cognitive-behavioural approach***	12 weeks
Pharmaceutical agents						
Landabaso 1998[63]	Spain	112 (56/56)	Opioid dependents with DMS-IV criteria following outpatient detoxification programme, severe mental psychology cases excluded	Naltrexone (no placebo)	Comparator + ***fluoxetine***	12 months
Farren 2002[64]	USA	13	Opioid dependents with no co-morbid psychopathology. Detoxification was between 5-30 days	Naltrexone + placebo	Naltrexone + ***sertaline***	12 weeks

4.4.2 Quality of RCTs to enhance retention on naltrexone treatment

The quality of these studies was poor to moderate at best. Blinding is not possible by definition in the contingency management or behavioural therapy trials and was not attempted in one of the two pharmaceutical trials (which did not use a placebo). A summary of the quality assessment is given in Table 11, below. The Ball trial[57] failed to report any outcomes by randomised group and all reported results are data driven analyses.

Table 11 Quality assessment of RCTs of interventions to enhance naltrexone retention

Study	Assign-ment of treatment described as random?	Was method of randomi-sation described?	Was the method really random?	Was allocation of treatment concealed?	Who was blinded to treatment?	Was method of blinding adequately described?	Were eligibility criteria described?	Were groups comparable at study entry?	Were groups treated identically apart from the intervention?	Was ITT used?	Were withdrawals stated?	Were reasons for withdrawals stated?	Was a power calculation done?	Jadad Score
Contingency management (+/- additional psychosocial therapies)														
Preston 1999[34]	Y	N	CT	CT	NA	NA	Y	Y	CT	N	Y	N	N	2
Carroll 2001[33]	Y	N	CT	CT	NA	NA	Y	Y	CT	N	Y	N	N	2
Ball 2004[57]	Y	Y	CT	CT	NA	NA	Y	Y	CT	N	Y	N	N	2
Psychosocial therapies														
Callahan 1980[58]	Y	N	CT	CT	NA	NA	Y	CT	CT	N	N	N	N	1
Rawson 2001[59]	Y	Y	Y	Y	NA	NA	Y	Y*	CT	N	Y	N	N	3
Fals-Stewart 2003[60,61]	Y	N	CT	CT	NA	NA	Y	Y	CT	N	Y	N	N	2
Tucker 2004[62]	Y	N	CT	CT	NA	NA	Y	CT	CT	Y	Y	N	N	2
Pharmaceutical agents														
Landabaso 1998[63]	Y	N	CT	CT	CT	CT	Y	Y	CT	N	Y	N	N	2
Farren 2002[64]	Y	N	CT	CT	Double blinded	N	Y	Y	Y	N	Y	Y	N	3

*Except for the years of education

4.5 Results of the studies designed to enhance retention on naltrexone

4.5.1 Contingency management interventions

All three contingency management studies used incentive vouchers that could be exchanged for goods or services to reward patients for compliance with treatment. In the Preston[34] study the value of vouchers began at US$2.50 with an additional incentive for each consecutive dose and penalties for a missed dose (reward dropping back to beginning level). A participant who complied fully with treatment over 12 weeks could earn a total of $1155. The rate of reimbursement in the Carroll[33] study began at $0.80 for an opiate free urine specimen and also had an incremental gain for consecutive samples. In this study a participant could earn a total of $561 worth of goods if they completed the full 12 weeks of follow up successfully.

Full details are not given of the programme in the Ball[57] study but participants could earn up to $561 worth of goods if they completed the full 12 weeks of follow up successfully. However, we believe that the results of the Ball[57] trial, which reported only data driven analyses rather than randomised comparisons, are uninterpretable for the purposes of informing the question about whether incentive vouchers enhance retention on naltrexone.

Both the other studies showed a statistically significant effect on enhanced retention (Preston[34] showing a mean additional 5.1 weeks on treatment and Carroll[33] showing a mean additional 1.8 weeks on treatment). Carroll also demonstrated a significantly reduced rate of opiate use as measured by number of opiate-free urine samples (19±14 vs. 14 ±12 p=0.04). There was no evidence to suggest that the involvement of a significant other in addition to incentive vouchers produced additional benefit. The full results for these trials are given in Table 12, below.

Table 12 Results of naltrexone verse naltrexone with contingency management

Study	Intervention	Outcome measure	Unit	Effect size	P-value or 95%CI	Direction of effect	Significant	Comments
Preston 1999[34]	incentive vouchers	Treatment retention	Weeks	7.4 ±1.2 (contingent) vs. 5.0 ±1.0 (no contingent) vs. 2.3 ±0.7 (no voucher)	P=0.02	Favours incentive vouchers	yes	
		Naltrexone ingestion	Number of naltrexone doses ingested	21.4±3.5 (contingent) vs. 11.3 ±3.0 (no contingent) vs. 4.4±1.5 (no voucher)	P<0.001	Favours incentive vouchers	yes	
Carroll 2001[33]	incentive vouchers	Treatment retention	Weeks	7.4± 4.4 vs. 5.6± 4.5	P=0.05*	Favours incentive vouchers	yes	There would appear to be no particular additional benefit from incentive vouchers plus involvement of significant other over incentive vouchers alone although no formal analysis was reported.
		Opioid use reduction	Number of opiate-free urine specimens	19±14 vs. 14 ±12	P=0.04*	Favours incentive vouchers	yes	
	incentive vouchers + significant other involvement	Treatment retention	weeks	7.4±5.1 vs. 5.6±4.5	Not reported	Favours incentive vouchers	Not reported	
		Opioid use reduction	Number of opiate-free urine specimens	20±16 vs. 14±12	Not reported	Favours incentive vouchers	Not reported	
Ball 2004[57]	incentive vouchers	Probability of opioid use (non-affective subtype)		Not reported	P<0.02*	Favours control	yes	These results were data driven sub-group analyses, caution is required in interpreting the results. Comparisons of the randomised arms were not reported.
		Probability of opioid use (antisocial-narcissistic subtype)		Not reported	P<0.01*	Favours control	yes	
		Addiction severity index in alcohol composite severity (low psychiatric cluster)		Not reported	P<0.01*	Favours control	yes	

* The comparisons were done between two combined incentive voucher groups vs. naltrexone without incentive voucher.

4.5.2 Additional behavioural therapies

Four studies looked at either individual or group behavioural therapy interventions. Three of these, all from the USA, showed statistically significant improvements in the effectiveness of naltrexone therapy. Tucker[65], an Australian trial that used a group cognitive behavioural approach, was the one trial that showed a direction of effect favouring control but this was not statistically significant. The full results are given in Table 13, below.

Table 13 Results of naltrexone verse naltrexone with psychosocial therapies

Study	Intervention	Outcome measure	Unit	Effect size	P-value or 95%CI	Direction of effect	Significant
Callahan 1980[58]	behavioural therapy	Mean length of time patients stayed on naltrexone during first 7 months	days	84 vs. 43	P<0.025	Favours behavioural therapy	yes
		Mean length of time patients stayed on naltrexone over 21 months	days	110.6 vs. 88.5	p>0.05	Favours behavioural therapy	no
		Urine test	percentage	93 vs. 92		Favours behavioural therapy	no
		Mean weekly frequency of reported side effects (7 months)	weekly frequency	1.3 vs. 3.0	P<0.05	Favours behavioural therapy	yes
Rawson 2001[59]	cognitive behavioural therapy	Treatment participation measures	Counselling sessions	13.8±10.1 vs. 1.5±3.3	P<0.01	Favours cognitive behavioural therapy	yes
		Medication compliance	Number of 50mg doses	78.7±67.6 vs. 34.7±48.3	P<0.01	Favours cognitive behavioural therapy	yes
		Retention	weeks	14.7±10.0 vs. 9.1± 8.9	P<0.01	Favours cognitive behavioural therapy	yes
		Urine test	percentage	86.2 vs. 74.6	P<0.001	Favours cognitive behavioural therapy	yes
		Opioid use (abstinent 3 consecutive weeks)	percentage	73.2 vs. 50	P<0.05	Favours cognitive behavioural therapy	yes
		Self reporting opioid free (6 months)	percentage	44.4 vs. 21.7	P>0.05	Favours cognitive behavioural therapy	no
		Self reporting opioid free (12 months)	percentage	50 vs. 50			no
Fals-Stewart 2003[60,61]	behavioural family counselling	Adherence rating	unknown	9.1±0.8 vs. 8.9±0.9		Favours behavioural family counselling	no
		Opioid-free urine	percentage	78.3±26.1 vs. 69.3±26.2	P<0.05	Favours behavioural family counselling	yes
		Abstinence from opioid (during treatment)	percentage	81.3 vs. 70.2	P<0.01	Favours behavioural family counselling	yes
		Abstinence from opioid (12 months)	percentage	69.3 vs. 56.3	P<0.01	Favours behavioural family counselling	yes
Tucker 2004[62]	group counselling which used cognitive-behavioural approach	Retention rate	percentage	28.85 vs. 35.6	P=0.35	Favours control	no
		Median survival	days	50 vs. 54	P=0.49 (95%CI, 36-64) vs. (95%CI, 34-74)	Favours control	no

4.5.3 Pharmaceutical agents

The two pharmaceutical agents that were tested in trials as enhanced care packages to naltrexone were sertaline (Farren 2002)[64] and fluoxetine (Landabaso 1998)[63]. The former trial involved only 13 patients and thus had little power to demonstrate any clinically relevant effects. The latter involved 112 patients but unfortunately there was neither blinding nor placebo and thus there are some threats to its validity which need to be borne in mind when considering the results. Fluoxetine showed an enhanced effect over the standard care package with naltrexone at both six and twelve months. The number needed to treat to have one patient still on treatment at one year was five. Full results are given in Table 14, below

Table 14 Results of naltrexone verse naltrexone with Pharmaceutical agents

Study	Intervention	Outcome measure	Unit	Effect size	P-value or 95%CI	Direction of effect	Significant
Landabaso 1998[63]	fluoxetine	Abandonment proportion(6 months)	relative risk	1.63*	95%CI, 1.00-2.70*	Favours fluoxetine	yes
		Abandonment proportion(12 months)	relative risk	1.31*	95%CI, 0.97-1.81*	Favours fluoxetine	no
		Abandonment proportion(6 months)	risk difference	0.18*	95%CI -0.002-0.35*	Favours fluoxetine	no
		Abandonment proportion(12 months)	risk difference	0.16*	95%CI, -0.02-0.33	Favours fluoxetine	no
Farren 2002[64]	sertaline	Retention rate (week 2)	percentage	100 vs. 66	P=ns	Favours sertaline	no
		Retention rate (week 10)	percentage	57 vs. 50	P=ns	Favours sertaline	no
		Craving scale (Clinical significance of this not clear)	Change in score on scale	"No difference"			no
		Side effect	percentage	28 vs. 17		Favours sertaline	no

*There were errors in calculation of relative risk and risk difference for abandonments proportion in the publication. We give the corrected figures in the table.

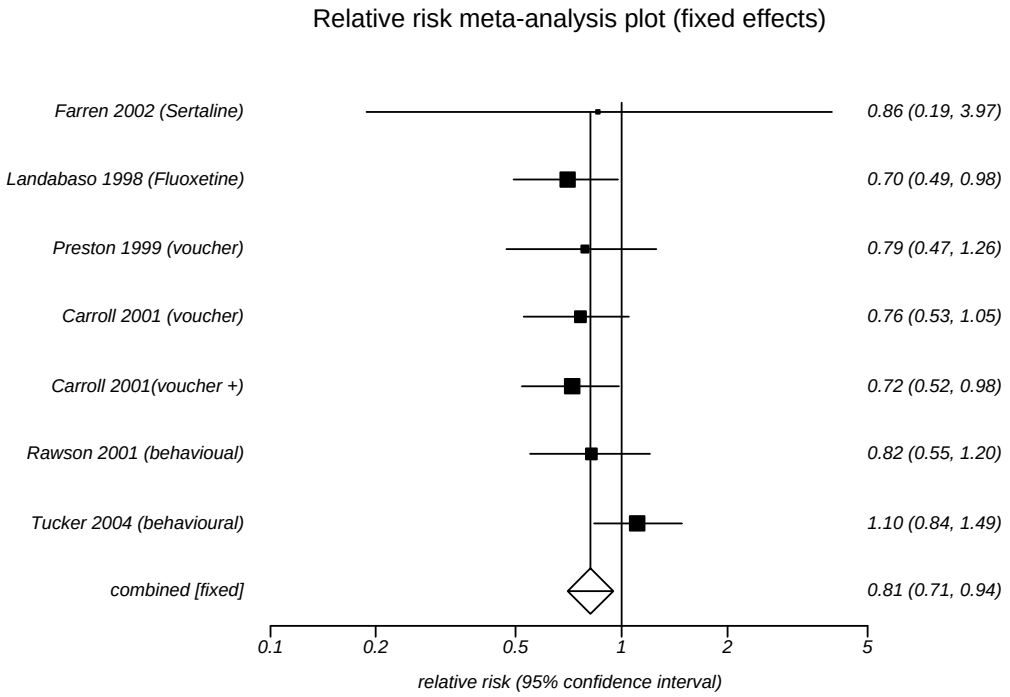
4.5.4 Combining results for any enhanced care package

We have seen that all three different modalities of enhanced care show some evidence of effectiveness in improving retention on naltrexone. It is debatable whether it is appropriate to combine such clinically heterogeneous interventions. However we have done so for completeness sake but the results should be interpreted with caution.

Five of nine studies reported survival curves comparing retention in treatment between naltrexone and naltrexone with care packages. These included contingency management, psychological therapies and pharmaceutical agents. Some studies (Farren 2002[64], Carroll 2001[33]) evaluated the effect size using point retention rates, others (Rawson 2001[59], Landabaso 1998[63] and Preston 1999[34]) using mean or median survival time. The follow-up periods varied from 12 weeks to 52 weeks. Some studies (Farren 2002)[64] only observed significant higher retention rates in early stage of the treatment, but not at later stage. In order to summarise the effectiveness of additional care packages in general, we did a meta-analysis of the relative risk of stopping treatment at week 12. One study (Tucker 2004)[62] did not report survival curve comparing retention in treatment between naltrexone and naltrexone with care packages, but we derived the relative risk of stopping treatment at week 12 for this study. The pooled relative risk of stopping treatment was 0.81 with 95% confidence interval (0.71, 0.94) (see Figure 11, below). The results indicated that overall there the intervention groups had 19% less patients who stopped treatment compared to the control group.

.

Figure 11 Relative risk of stopping treatment between naltrexone vs. naltrexone with care packages



4.6 Summary and conclusion of the results for effectiveness

4.6.1 Naltrexone studies

The results and effect sizes for naltrexone are summarised in Table 15, below.

- Thirteen relevant RCTs of naltrexone were identified with 940 participants. Three non-randomised studies were also identified. The methodological quality of the studies was generally poor.
- There was no clear evidence that naltrexone as maintenance therapy for relapse prevention in opioid addicts is any better than placebo in terms of retention in treatment. A meta-analysis of seven included RCTs shows that the relative risk of loss of retention in treatment in the naltrexone arm is 0.94, 95% CI (0.84, 1.06) and the pooled HR from five RCTs reporting usable retention in treatment data followed up to 35 weeks was calculated as 0.90, 95% CI (0.69 1.17) in favour of naltrexone.
- With respect to the risk of opioid use in naltrexone vs placebo with or without psychological support given in both arms, the pooled relative risk of six RCTs is 0.72, 95% CI (0.58, 0.90) which was a statistically significant difference in favour of

naltrexone. The pooled HR from 3 RCTs for opioid relapse-free was significantly different from placebo in favour of naltrexone. 0.53, 95%CI (0.34, 0.82). However this effect can be seen to fall off over time and may be of limited clinical significance.

- Relative risk of re-incarceration in naltrexone shows results in favour of naltrexone in the combined two studies of parolees or people on probation RR 0.50, 95% CI (0.27, 0.91). The number of participants was small and the 95% CI is wide.
- One study (Krupitsky 2004)[41] reported results by using Risk Assessment Battery (RAB), which is a self report instrument questionnaire measuring HIV risk. This study reported a statistically significant improvement score in naltrexone for risky sexual behaviour. The number of participants in this study was 52.
- The adverse events data reported in the included studies showed no significant difference between naltrexone and placebo arm.

Table 15 Summary of results for naltrexone trials

Outcome measure	Estimate
Pooled relative risk of loss of retention in treatment in the naltrexone of seven RCTs	0.94 (95% CI 0.84, 1.06). NS
Pooled HR of five included RCTs for retention in treatment data followed up to 35 weeks	0.90 (95% CI 0.70, 1.17) NS
Pooled Relative risk of opioid use (from six RCTs)	0.72 (95% CI 0.58, 0.90) SS in favour of naltrexone
Pooled HR for no opioid relapse (from 3 RCTs)	0.53 (95% CI 0.34, 0.82) SS in favour of naltrexone
Pooled relative risk of re-incarceration in naltrexone from two studies	0.50 (95% CI 0.27, 0.91)
Risk Assessment Battery (RAB)	Statistically significant improvement score in naltrexone for risky sexual behaviour.
The adverse events Two RCTs reported	No statistically significant difference in adverse events in the two arms.
Mortality Rate in RCTs	No data from RCTs. Although individual deaths from overdose are associated with naltrexone use there is no evidence that the overall fatality rate from overdose is higher than in non-naltrexone exposed individual
Any particular population of opioid users shown to benefit from naltrexone	No data

NS Not significant
SS Statistically significant difference

4.6.2 Studies of interventions to enhance retention on naltrexone treatment

The results and effect sizes for naltrexone with enhanced care packages are summarised in Table 16, below.

Table 16 Summary or results for naltrexone with enhanced care packages

Care packages	Outcome measure	Estimate
Contigency management	Treatment retention (2 RCTs)	7.4 weeks (mean) for intervention vs. 2.3-5.6 weeks for control, favours intervention, statistically significant
Psychosocial therapy	Length of time patients stayed on naltrexone (3 RCTs)	84-103 days (mean) for intervention vs. 43-64 for control, favours intervention, statistically significant within 52 weeks; 111 days (mean) for intervention vs. 89 days for control, favours intervention, not statistically significant over 21 months; 50 days (median) for intervention vs. 54 days for control, favours control, not statistically significant
	Opiate free urine (3 RCTs)	78-86% for intervention vs. 69-75% for control, favours intervention, statistically significant within 52 weeks; 93% for intervention vs. 92% for control, favours intervention, not statistically significant over 21 months
Pharmaceutical agents	Retention in treatment (2 RCts)	Relative risk of abandonment proportion 1.63* and 1.31* at 6 months and 12 months, respectively, favours intervention, statistically significant at 6 months, but not at 12 months; in a small study (13 pateints), retention rates of 100% for intervention vs. 66% for control, and 57% for intervention vs. 50% for control at 2 weeks and 10 weeks, favours intervention, not statistically significant.
Pooled three modalities	Pooled relative risk of loss of retention in treatment between intervention vs. control (5 RCTs, with one RCT having two types of interventions)	0.81 with 95% CI (0.71, 0.94), favours intervention, statistically significant

* There were errors in calculating the relative risks

- All three modalities of enhanced care package, for which RCTs were identified, viz. contingency management, behavioural therapy and pharmaceutical agents, show clinically and statistically significant improvements over the comparator of naltrexone care package.
- It is difficult to estimate whether, and if so how much, these interventions would alter estimates of effectiveness of oral naltrexone derived from the previous systematic review. It seems reasonable to assume that the introduction of incentive vouchers would as these are unlikely to have formed part of the standard care package to which oral naltrexone was added as an adjunctive treatment. The trial that included a non-contingent voucher arm shows that this effect is not simply due to increased access to goods. The point estimate of effect size is consistent across the studies with relative risks of stopping treatment of 0.72, 0.76 and 0.79.
- However most of the naltrexone studies already include an element of counselling or pyschosocial therapy as part of the basic care package and so may actually resemble the "enhanced care package" of the behavioural therapy trials reviewed.

- The trial of sertaline is too small to be able to draw any conclusions about its effectiveness or otherwise and the results of the trial of fluoxetine may have nothing to do with enhancing the effectiveness of naltrexone but simply be a consequence of the effectiveness of fluoxetine *per se*. A systematic review of RCTs of the effectiveness of fluoxetine as an adjunctive treatment in treatment of opioid-dependent individuals, that included all studies whether or not they used naltrexone in the comparator arm, would be needed to address this question. (No such review was found in the York CRD database, the Cochrane Library or on Medline.)

5. ECONOMIC ANALYSIS

5.1 Introduction

This section provides details of the model we developed to evaluate the cost-effectiveness of naltrexone (plus psychosocial support) compared to standard treatment psychosocial support for treatment of detoxified patients who were previously opioid dependent. The model draws upon a range of published sources to provide data for assessment of the value for money afforded by naltrexone treatment.

5.2 Methods

A decision tree with Monte Carlo simulation was used and models drug use to 12 months as data to support modelling beyond this period are not available and evidence suggests that it is rarely used long term by patients. The model estimates costs, from the perspective of the UK National Health Service and Personal Social Services and outcomes in terms of QALYs for 12 months for both strategies. The model incorporates uncertainty in probabilities, resource use and utilities by incorporating the input parameters of the model as probability distributions which are then used in a Monte Carlo simulation. The model was developed in TreeAge Pro(™) 2005. All costs are presented in 2004 UK pounds. Costs and benefits are not discounted as the model assesses only 12 months.

5.2.1 Description of the model

The model follows patients for one year and the main parameter is retention in treatment. The model considers the proportion of patients retained in treatment at 2 weeks, 6 weeks, 13 weeks, 25 weeks and finally at 12 months. Follow up is more frequent in the early stages of treatment

because at this stage the drop out rate is higher. The combined data show that drop out appears to stabilise around the 6 month stage. For each period of time, a utility value and cost is attached to each arm of the tree.

The comparator 'psychosocial support alone' represents non-pharmacological support for detoxified patients and is the relevant comparator for detoxified individuals who wish to remain opiate free. The parameter data for effectiveness was obtained from the trials, reported in this review, where naltrexone was compared with placebo and where both arms of the trials provided psychosocial support, as naltrexone is licensed as an adjunctive treatment.

5.2.2 Estimation of model parameters

5.2.2.1 Retention in treatment

Data on retention in treatment was available in five trials that compared naltrexone with placebo, with psychosocial support given in both arms. The method for deriving the combined hazard ratios is discussed in section 3.6, page 37. Meta-analysis of hazard ratio for treatment retention at end of follow up was 0.90 (95% CI 0.69 to1.17) in favour of naltrexone.

The length of follow up varied between trials and relative risk is difficult to use for representation of retention through time. To obtain a representative estimate of retention in treatment, data was combined for the five trials identified in the review using Kaplan-Meier analysis with censoring of retained patients at end of follow up, see Table 17. A survival curve for retention in naltrexone treatment was calculated using the Kaplan-Meier analysis. The hazard ratio was applied to the survival curve of naltrexone, to which a Weibull distribution had been fitted, in order to estimate retention in treatment for placebo, see Table 17, below.

Table 17 Retention in treatment with naltrexone vs placebo

	Naltrexone			Placebo		
Week	Retained	95% LCI	95% UCI	Retained	95% LCI	95% UCI
1	0.92	0.86	0.95	0.93	0.87	0.96
2	0.82	0.75	0.87	0.83	0.76	0.89
3	0.77	0.70	0.83	0.76	0.69	0.83
4	0.72	0.65	0.78	0.68	0.60	0.75
5	0.69	0.61	0.76	0.64	0.55	0.71
6	0.64	0.56	0.71	0.58	0.50	0.66
7	0.61	0.53	0.68	0.56	0.47	0.63
8	0.61	0.53	0.68	0.52	0.44	0.60
9	0.53	0.45	0.60	0.51	0.42	0.59
10	0.53	0.45	0.60	0.48	0.40	0.56
11	0.52	0.44	0.59	0.44	0.36	0.52
12	0.51	0.43	0.58	0.42	0.34	0.50
13	0.50	0.42	0.57	0.40	0.32	0.48
14	0.50	0.42	0.57	0.40	0.32	0.48
15	0.50	0.42	0.57	0.40	0.32	0.48
16	0.50	0.42	0.57	0.40	0.32	0.48
17	0.43	0.35	0.50	0.28	0.20	0.35
18	0.43	0.35	0.50	0.28	0.20	0.35
19	0.43	0.35	0.50	0.28	0.20	0.35
20	0.43	0.35	0.50	0.28	0.20	0.35
21	0.43	0.35	0.50	0.28	0.20	0.35
22	0.35	0.27	0.42	0.26	0.19	0.34
23	0.35	0.27	0.42	0.26	0.19	0.34
24	0.35	0.27	0.42	0.26	0.19	0.34
25	0.35	0.27	0.42	0.26	0.19	0.34
26	0.31	0.24	0.39	0.23	0.16	0.30
27	0.31	0.24	0.39	0.23	0.16	0.30
28	0.31	0.24	0.39	0.23	0.16	0.30
29	0.31	0.24	0.39	0.23	0.16	0.30
30	0.29	0.21	0.37	0.23	0.16	0.30
31	0.29	0.21	0.37	0.23	0.16	0.30
32	0.29	0.21	0.37	0.23	0.16	0.30
33	0.29	0.21	0.37	0.23	0.16	0.30
34	0.29	0.21	0.37	0.23	0.16	0.30
35	0.16	0.08	0.26	0.18	0.10	0.27

5.2.2.2 Level and nature of drug misuse

As some detoxified patients retained within a program will still use drugs, data on the proportion of patients using drugs is required. In addition, the nature of their drug use, specifically if they are injecting drug users is also important. Both parameters are required by the model in order to

assign appropriate use of health care resources and utility values. The method of assigning resource use and utilities to different patient groups will be described in the relevant sub-sections.

Opioid positive or opioid negative urine data was reported in only one trial (Krupitsky 2004)[41] and results from this trial are shown in Table 18. It is important to note that as this data was only available from one trial, it should be viewed with some caution. The analysis assumes that the percentage of negative urines is equivalent to the percentage of the retained patients at each time point that are drug free at that time. For those not retained in treatment it was assumed that patients return to their pre-treatment habits irrespective of their period in the post-detoxification program.

The estimates for the number of individuals injecting and not injecting was taken from the study by NTORS (national treatment outcome research study). The proportion of individuals who are injecting but not in treatment was estimated to be 61% (39% were not injecting and not in treatment). The proportion of individuals injecting and on treatment was estimated to be 44% (56% of patients in treatment were not injecting).

Table 18 Proportion of patients free of opioids

Week	% who are opioid free and retained in naltrexone treatment	% who are opioid free on placebo (with psychosocial support)
2	71.0	61.9
4	84.0	61.1
6	78.2	69.2
9	83.4	95.5
11	83.4	100
13	66.7	100
15	92.9	83.4
17	85.8	80.0
19	100	100
22	100	80.0
24	83.4	100
26	83.4	100

5.2.3 Resource use and costs

The perspective adopted for the reference case evaluation is that of the National Health Service and Personal Social Services (NHS/PSS) and the cost-effectiveness is expressed in terms of

incremental cost per quality adjusted life year. In a non-reference case analysis we also include cost implications as far as possible for a societal perspective which includes the criminal justice system and victim costs of crime. Therefore the identification of costs for the model has been conducted from both the NHS/PSS and the societal perspective. Every effort has been made to use the information available to accurately estimate the magnitude of these costs. The estimation of costs for the model is divided into costing the treatment programmes and costing the consequences of drug misuse. The model uses a half-cycle correction for costs, therefore, if a patient who is in treatment at 2 weeks then drops out of treatment at 6 weeks, it is assumed they have been in treatment from weeks 2-4 and off treatment for weeks 4-6.

NHS/PSS perspective (Reference case)

Naltrexone therapy included both pharmacological treatment and counselling, and placebo included counselling alone. In this model, naltrexone therapy was assumed to be a 50 mg tablet taken daily. It was assumed patients in treatment attended one counselling session per week and had one urine test per fortnight to monitor treatment success. When patients dropped out of treatment, counselling and urine testing did not occur. Data was obtained from the Mattick (2003)[66] trial, and where no published standard deviations (SD) were available, the SDs for the probabilities were based on: SD = rate/√(N). Unit cost information used in the industry submission was also used here.

Table 19 Naltrexone and placebo therapy resource use

	Mean	SD	Unit cost (£)
Naltrexone daily dose	50mg	-	1.52
Counselling sessions per week	1*	0.050	8.54
Urine tests in maintenance period per week	0.5*	0.025	1.12

(* Mattick *et al* 2003) [66]

Data on resource use for the reference cases, required for the model, was extracted using data supplied by 'problem drug-users' within the National Treatment Outcomes Research Study (NTORS) that covered health care services, the criminal justice system and employment. This study, described in detail in Gossop et al 1998[15], is the largest prospective longitudinal cohort study of treatment outcome for drug misusers ever conducted in the UK. The study collected

data on drug-taking behaviour, health, criminal activity and service use before and after entry to a treatment programme. The model assumes that drug misusers not on treatment have experiences similar to that reported by the NTORS participants in the twelve months prior to entering treatment and that drug misusers in naltrexone treatment have consequences experienced from the treatment programmes described in the NTORS study.

The NTORS study recorded resource use of substance misusers and found higher rates of GP contacts and inpatient stays amongst those in short term treatment. These items are presented in Table 20. Where published standard deviations were not available, the same approach as detailed above was used.

Table 20: NHS/PSS perspective resource use and costs

SUCCESSFUL HEALTH STATES					
Successful/drugs free/ reduction/<1 year					
Health care costs breakdown	**Resource use**	**Source**	**Unit cost**	**Source**	**Total**
GP visits per year	5.6	Gossop et al, 2001[67]	£21	Curtis and Netten 2004[68]	£118
Rate of A&E visits per year	0.8	Gossop et al, 2001[67]	£318	Godfrey et al, 2002[69]	£254.40
Rate of inpatient hospital stays per year	2.8	Gossop et al, 2001[67]	£251	Godfrey et al, 2002[69]	£702.80
Rate of outpatient mental health visits per year	0.8	Gossop et al, 2001[67]	£56	Godfrey et al, 2002[69]	£45
Rate of inpatient mental health visits per year	0.4	Gossop et al, 2001[67]	£162	Godfrey et al, 2002[69]	£64.80
Total annual health care costs					**£1,184**
UNSUCCESSFUL HEALTH STATES					
Unsuccessful/drugs misused					
Health care costs breakdown	**Resource use**	**Source**	**Unit cost**	**Source**	**Total**
GP visits per year	3.6	Gossop et al, 2001[67]	£21	Curtis and Netten, 2004 [68]	£76
Rate of A&E visits per year	0.7	Gossop et al, 2001[67]	£318	Godfrey et al, 2002[69]	£222.60
Rate of inpatient hospital stays per year	1.75	Gossop et al, 2001[67]	£251	Godfrey et al, 2002[69]	£439
Rate of outpatient mental health visits per year	1.3	Gossop et al, 2001[67]	£56	Godfrey et al, 2002[69]	£72.80
Rate of inpatient mental health visits per year	1.5	Gossop et al, 2001[67]	£162	Godfrey et al, 2002[69]	£243
Total annual health care costs					**£1,053**

Unit costs for the model were taken from a range of sources. All costs are presented in UK pounds for 2004. The resource use was multiplied by the appropriate unit cost to calculate the total cost of health service use. For GP visits, the unit cost was estimated using Curtis and Netten 2004.[68] The unit cost for an A&E visit and for inpatient hospital stays have been calculated using estimates provided by Godfrey et al (2002)[69] and updated to 2004 figures using the Hospital and Community Health Services (HCHS) pay and prices index. Based on Godfrey et al (2002)[69], the A&E cost assumes that many of these visits would be serious therefore would involve an overnight stay. Godfrey et al notes that the unit cost for community health visits may be an underestimate as it does not take into account expensive outpatient visits to a psychiatrist. Drug costs are taken from the British National Formulary (No. 50, September 2005) with naltrexone costing £1.52 per 50 mg tablet.

Societal Perspective (Non-Reference Case analysis)

The NTORS study (Gossop 1998, 2001)[15,67] provides the most detailed source of information of criminal consequences associated with drug misuse. The study asked clients to recall experiences related to criminal behaviour and thus covered the following: drug arrests; arrests for acquisitive crimes; stays in police custody; appearances in court; and stays in prison. As before, the data from the NTORS study is combined with unit cost information to estimate the total social costs associated with drug misuse. It is assumed that information supplied by clients prior to treatment will be similar to users not on treatment. The model also assumes that drug misusers in either treatment have consequences experienced from the treatment programmes described in the NTORS study. Godfrey et al, 2002[69], Godfrey et al, 2002[70] provide the unit cost information for drug arrests (assuming no victim costs are included), police detention costs, court appearances, prison and victim costs. The level of arrests for drug offences and acquisitive crime were higher for users in treatment in the first year than those not in treatment. For the police detention costs it is assumed that users are held in police custody on average for 2 nights, 1.2 nights and 0.8 nights for no treatment, treatment < 1 year and treatment > 1 year respectively. The cost of overnight stays are estimated at £69 per stay. Godfrey et al, 2002[69] used estimates provided by Brand and Price (2000)[71] and the pattern of offences self reported by NTORS clients to estimate the victim costs associated with criminal behaviour. Victim costs refer to an estimated average cost per drug addict or patient in treatment imposed on and incurred by victims of crime. This includes measures in anticipation of crime such as security

measures and direct costs such as material or physical damage or loss. Resource use and costs are presented in Table 21.

Table 21: Societal perspective resource use and costs

SUCCESSFUL HEALTH STATES					
CJS = Criminal Justice System					
Successful/Drugs free/reduction/< 1year					
CJS costs breakdown	**Resource use**	**Source**	**Unit cost**	**Source**	**Total**
Rate of drug arrests per year	0.8	NTORS study	£3,551	Godfrey et al, 2002[69]	£2,840.80
Rate of acquisitive crime arrests per year	1.6	NTORS study	£1,346	Godfrey et al, 2002[69]	£2,153.60
Average time held in policy custody per year (nights)	1.2	NTORS study	£69	Godfrey et al, 2002[70]	£82.80
Rate of court appearances in 1 year	1.4	NTORS study	£699	Harries, 1999[72]	£978.60
Time spent in prison per year (days)	34	NTORS study	£68.86	Godfrey et al, 2002[70]	£2,341
Total annual CJS costs					**£8,397.04**
Annual victim costs			£8,893	Godfrey et al, 2002[69]	**£8,893.00**
Total annual social costs					**£17,290.04**
Unsuccessful					
CJS costs breakdown	**Resource use**	**Source**	**Unit cost**	**Source**	**Total**
Rate of drug arrests per year	0.3	NTORS study	£3,551	Godfrey et al, 2002[69]	£1,065.30
Rate of acquisitive crime arrests per year	1.35	NTORS study	£1,346	Godfrey et al, 2002[69]	£1,817.10
Average time held in policy custody per year (nights)	2	NTORS study	£69	Godfrey et al, 2002[70]	£138
Rate of court appearances in 1 year	2.2	NTORS study	£699	Harries, 1999[72]	£1,537.80
Time spent in prison per year (days)	36	NTORS study	£68.86	Godfrey et al, 2002 [70]	£2,479
Total annual CJS costs					**£7,037**
Annual victim costs			£30,827	Godfrey et al, 2002[69]	**£30,827**
Total annual social cost					**£37,864**

5.2.4 Estimation of QALYs

In the literature review process for a parallel evaluation of drug abuse, there appeared to be very limited published data available on the associated quality of life. Many of the available data were irrelevant because they specifically related to quality of life for patients suffering some of the potential consequences of drug abuse such as HIV or AIDS. It was considered appropriate to seek some entirely new data from the experimental health utilities panel co-ordinated by the Peninsula Technology Assessment Group (PenTAG). This allowed specific data to be collected relevant to the specific health states that were considered most relevant to the evaluation and modelling process. We use the results of our own utility exercise co-ordinated by PenTAG in the reference case analysis of the current TAR.

The Value of Health Panel is co-ordinated by PenTAG which is part of the Universities of Exeter and Plymouth. Their experimental study is funded jointly by the UK Department of Health, NHS Quality Improvement Scotland (NHSQS) and NICE. The panel uses a randomly selected group of individuals who are members of the public who have given their consent to involvement in this process. These individuals make valuations on given health states via the Value of Health Panel Website using the standard gamble method.

A total of 10 health states were defined to describe a range of alternative health states that could be experienced by individuals abusing drugs. The health states were defined by the team and involved considerable input from one clinician (ED) with expertise in this area. An iterative process followed this first stage with further advice from PenTAG. The health states were then provided to the panel and the QALYs derived from PenTAG based on the results of this panel are presented in Appendix 1, page 96.

The final QALY was obtained by weighting the QALY results from the panel by the proportion of patients in relevant health scenarios: On treatment and drug free; On treatment with drug reduction (injecting drug misusers); On treatment with drug reduction (non- injectors); Not on treatment and injecting drug misusers; and Not on treatment but non-injecting drug misusers.

Patients retained in treatment were assigned an average weighted QALY obtained from the utilities provided by using the average proportion of patients in treatment consuming drugs for

both injectors and non injectors and the proportion of patients drugs free while on treatment. However, it is important to note that these proportions were obtained from one trial alone, therefore they and the mean weighted QALYs obtained should be viewed with some caution. The mean weighted QALYs are presented in Table 22.

Table 22: Estimated QALYs for patients in treatment

Treatment	Mean	SD
Naltrexone	0.8351	0.1607
Placebo	0.8383	0.1599

For those not retained in treatment we assumed that patients returned to their pre-treatment habits irrespective of their period of naltrexone or placebo treatment for which the same QALY was used in both cases. We obtained an average weighted QALY from the results obtained by the health panel by considering the average proportion consuming drugs that are injectors and the average proportion consuming drugs that are non injectors. The weighted QALY obtained had a mean value of 0.64 (SD 0.21). In order to obtain a beta distribution for QALYs we used the method of moments methodology.

5.2.5 Assessment of cost-effectiveness

Data on the incremental cost per QALY are presented in two ways. Firstly, mean costs and QALYs for the alternative interventions are presented and the incremental cost per QALY calculated where appropriate. The second mode of presentation uses the results of the probabilistic sensitivity analysis and shows cost-effectiveness acceptability curves (CEACs) and scatter plots of incremental costs and outcomes. CEACs were used to illustrate uncertainty in results due to statistical variability around the parameter estimates. The curves demonstrate the likelihood a strategy is cost-effective at different threshold values of willingness to pay for an additional QALY. The probabilistic sensitivity analysis was undertaken using appropriate distributions for all model variables, shown in Table 23. The model was run for 10,000 simulations.

In order to consider the wider costs and benefits of each strategy to society, a non-reference case analysis was undertaken, taking into account the cost to the criminal justice system and victims of crime. The associated resource use and unit costs have been previously described.

Table 23 Distributions and parameter values used in probabilistic sensitivity analysis

Normal distributions		
Parameter	**Mean**	**SD**
Survival analysis		
log of hazard ratio for naltrexone-placebo	0.111	0.136
log of lambda (λ) for naltrexone	-2.161	0.058
log of lambda (λ) for placebo	-2.179	0.071
gamma (γ) for naltrexone	0.701	0.021
gamma (γ) for placebo	0.786	0.026
Resource use (per patient per year)		
A&E visits (in treatment)	0.8	0.003
A&E visits (not in treatment)	0.7	0.002
Outpatient mental health services (in treatment)	0.8	0.003
Outpatient mental health services (not in treatment)	1.3	0.004
GP visits (in treatment)	5.6	0.022
GP visits (not in treatment)	3.6	0.010
Inpatient mental health services (in treatment)	0.4	0.002
Inpatient mental health services (not in treatment)	1.5	0.004
Inpatient stay (in treatment)	2.8	0.011
Inpatient stay (not in treatment)	1.75	0.005
Counselling sessions (per week)	1.0	1
Number of urine tests (per week)	0.5	0.025

Beta distributions			
Parameter	**Expected value**	**α**	**β**
QALY value not on treatment	0.638	2.737	1.550
QALY value on naltrexone	0.835	3.619	0.715
QALY value on placebo	0.838	3.608	0.696

5.2.6 Deterministic sensitivity analysis

The sensitivity analysis focused on varying the value on one parameter. Further details and justification are provided below.

QALYs

There was uncertainty around the data on proportion of drug misusers in each strategy as the data came from one trial alone, thus impacting on the weights used to calculate the QALYs. Therefore to determine the impact of QALYs on the cost-effectiveness of naltrexone, the model was run with the QALY value (0.8383) for the placebo strategy for both strategies.

Societal costs

The victim costs of crime differ greatly between patients in a treatment programme (naltrexone or psychosocial support) and those who have dropped out of treatment. Therefore the impact of the inclusion of these costs was assessed by conducting the societal perspective evaluation with costs to the criminal justice system only.

5.3 Results

Reference case

Table 24 presents the results of the deterministic analysis. Naltrexone with psychosocial therapy is more expensive but more effective than placebo with psychosocial therapy alone, giving an ICER of £42,500 per QALY gained.

Table 24 Cost-effectiveness results of naltrexone (with psychosocial support) versus placebo (with psychosocial support)

Strategy	Cost £	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Placebo	1271		0.7105		
Naltrexone	1510	239	0.7161	0.0056	42,500

Non-reference case analysis: Societal perspective

Costs to the criminal justice system and victims of crime were included in the analysis to assess the cost-effectiveness of naltrexone compared with placebo from a wider societal perspective. The results are presented in Table 25 and show treatment with naltrexone dominates placebo.

Table 25: Cost-effectiveness results of naltrexone (with psychosocial support) versus placebo (with psychosocial support) from a societal perspective

Strategy	Cost £	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Naltrexone	31244		0.7161		
Placebo	31716	473	0.7105	-0.0056	Dominated

5.3.1 Sensitivity analysis

Reference case probabilistic sensitivity analysis

The incremental cost-effectiveness plane for naltrexone versus placebo is shown in Figure 12 and demonstrates there is a great deal of variability in both cost and QALY difference, although costs are always higher for naltrexone. The CEAC in Figure 13 shows that compared with placebo, naltrexone has a probability of being cost-effective of approximately 50% for any threshold over around £30,000 per QALY gained. This reflects the extensive uncertainty in the model results.

Figure 12 Incremental cost-effectiveness plane for naltrexone versus placebo

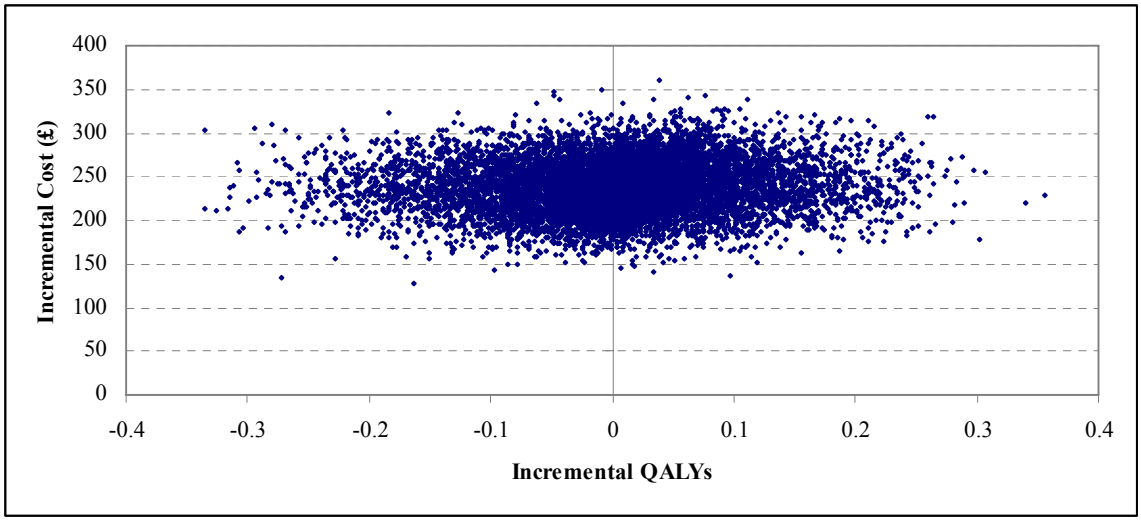
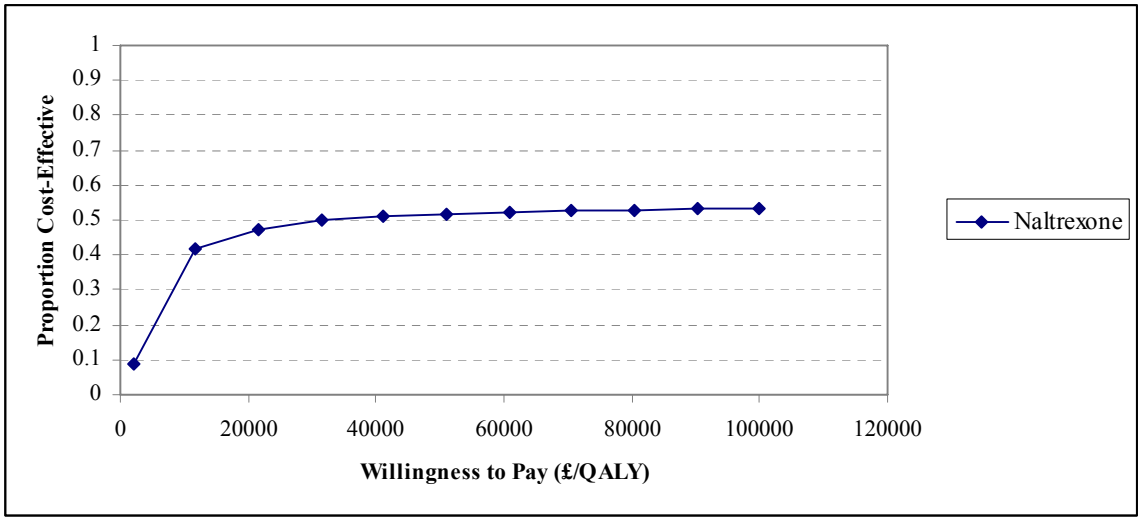


Figure 13 Cost-effectiveness acceptability curve for naltrexone compared with placebo



Deterministic sensitivity analysis

By using the same QALY value for both strategies, the ICER for naltrexone versus placebo was £34,600 per QALY gained (Table 26). This demonstrates how sensitive the ICER is to a very small change (0.0032) in the QALY used for naltrexone. This small difference has a substantial impact on the ICER, changing it from £42,500 to £34,600 per QALY gained.

Table 26 Sensitivity analysis: Cost-effectiveness results of naltrexone (with psychosocial support) versus placebo (with psychosocial support)

Strategy	Cost £	Cost difference	QALYs	QALY difference	ICER (£/QALY)
QALYs					
Placebo	1271		0.7105		
Naltrexone	1510	239	0.7174	0.0069	34,600

Removing victim costs of crime changed the result from naltrexone dominating placebo to naltrexone having an ICER of £51,071 per QALY gained (Table 27), demonstrating the considerable impact the level of victim costs have on the results.

Table 27 Sensitivity analysis: Cost-effectiveness results of naltrexone (with psychosocial support) versus placebo (with psychosocial support) from a societal perspective excluding victim costs

Strategy	Cost £	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Placebo	8799		0.7105		
Naltrexone	9085	286	0.7161	0.0056	51,071

Summary of evidence on cost-effectiveness

There is no previous evidence available on the cost-effectiveness of naltrexone. No economic evaluations have been published in the literature and no industry submission was provided. In addition, there was no quality of life data available for this treatment. To the best of our knowledge it is the first and only model to evaluate the cost-effectiveness of naltrexone in detoxified patients previously on opioids. Its strengths are that it uses data from an up-to-date systematic review and meta-analysis of the available clinical evidence, which has taken into account the time-related nature of the data on retention in treatment. However, very little data is currently available and the review only found five trials with appropriate data to include in the review, and the quality of these trials was variable.

The analysis used placebo with psychosocial support as the comparator we consider this to be a reasonable non-pharmacological comparator and the second systematic review of interventions to enhance the effect of naltrexone show this to be appropriate.

Given the limited data on appropriate utilities associated with drug abuse in the published literature, new utilities were derived from a panel of members of the general public. The advantage of this process was the ability to derive utility values for specific health states appropriate for our model outcomes. In addition, the values had the advantage of being population based estimates rather than being patient specific values and using the latter is a common criticism of QALY estimates. Although new utility values for specific health states have been derived, the panel used to derive these estimates was relatively small.

Sub-group analysis, for example, concentrating on patients with mental health problems, or different detoxification pathways would undoubtedly be of value. However, due to the paucity

of data for the reference case analysis and no data on subgroups, further analysis would not be appropriate.

By conducting a non-reference case analysis from a societal perspective including victim costs, the result changed. The reference case gave an ICER of £42,500, but from a societal perspective naltrexone was dominant. As the level of victim costs differed greatly between patients in treatment (pharmacological or psychological) and those who dropped out of either treatment, victim costs were omitted and naltrexone had an ICER of over £50,000 per QALY. Firstly, it is important to note that the criminal justice system (CJS) costs alone were higher for patients in treatment than those out of treatment. The report containing this data highlights this unexpected result but does not give any further explanation, and states that additional analysis of the data was not possible within the project. The higher cost per QALY for naltrexone when victim costs are excluded is not surprising due to slightly higher retention in treatment (therefore higher CJS costs) and cost of naltrexone. The inclusion of victim costs reverses the cost difference due to these costs being very much higher when patients have dropped out of treatment.

Only one trial reported data on the level of drug use whilst on treatment. As this data was required to determine both resource use and utilities to calculate QALYs, the uncertainty surrounding these data could have a major impact on the results. In our sensitivity analysis we used the placebo QALY value for both strategies, which changed the ICER dramatically, even though the change in initial QALY value was incredibly small.

Naltrexone demonstrated slightly higher retention in treatment than placebo but this was not significantly different. Therefore, it appears that small changes in costs or QALYs have a large impact on the results. For example, inclusion of victim costs of crime make naltrexone appear dominant over psychological support, however the proportion of patients incurring the higher victim costs will only be marginally different for naltrexone and placebo.

In conclusion we have some serious concerns about over interpretation of the results based on this model because of its extreme sensitivity to the smallest changes in the parameter values which are in themselves highly uncertain. In addition, limited data exist for the reference case analysis and no specific data is available for sub-group analysis. The data on criminal justice system resource use and victim costs are also of some concern. Therefore we recommend

extreme caution when using the modelling results to inform policy decisions. More better quality evidence is required.

Given the uncertainty in the model already, it was felt that it would not add value to proceed to model the use of a contingency management programme. These are currently not widely accepted within NHS service provision and the costs associated with them would depend on the value of the vouchers and repayment strategy chosen. The review of effectiveness suggests that they would enhance retention by about 19%.

6. DISCUSSION

Twenty six studies fulfilled the inclusion criteria for this report:1 systematic review, 22 randomised controlled studies and 3 comparative but not randomised studies. There were no economic evaluations.

The methodological quality of the RCTs were generally poor. Only 3/22 had Jadad score of 3, and the rest scored 2 or less. Only 3/22 reported that allocation was concealed and none reported a power calculation or the required sample size prior to the trials.

Naltrexone as maintenance therapy for relapse prevention in opioid addicts may be better than placebo in terms of retention in treatment but this was not statistically significant: a meta-analysis of 7 included RCTs shows that the relative risk of loss of retention in treatment in the naltrexone arm is 0.94, 95% CI (0.84, 1.06). The pooled HR from the 5 included RCTs for retention in treatment data followed up to 35 weeks was calculated as 0.90, 95% CI (0.69, 1.17) in favour of naltrexone and did not reach statistical significance.

However naltrexone appears to have some effect in improving the risk of opioid use in naltrexone vs placebo with or without psychological support given in both arms. The pooled relative risk from six RCTs is 0.72 (95%CI 058, 0.90) which is a statistically significant difference favouring naltrexone. The pooled HR from 3 RCTs for being free of opioid relapse was significantly different from placebo in favour of naltrexone: 0.53 (95%CI 0.34, 0.82). However this effect can be seen to fall off over time and its clinical significance is unclear.

The relative risk of re-incarceration in the two studies of parolees or of people on probation also favoured naltrexone, combined RR 0.5 (95%CI 0.27, 0.91), although the number of participants was small. There was also evidence from one study of a statistically significant improvement in score on a self-report instrument from measuring risky sexual behaviour, however, there were only 52 participants in this study.[41]

The adverse events data reported in the included studies showed no significant difference between naltrexone and placebo arm for any serious adverse event.[40,44]

There were no published data about drug-related morbidity, drug related morbidity, or health related quality of life that would have enabled us to estimate the cost per QALY gained.

The updated, but at the time unpublished, Cochrane systematic review included 10 RCTs (personal communication with the authors), all of them plus three additional trials were included in the review on the effectiveness of naltrexone. The authors of Cochrane review's concluded "…*The studies did not provide an objective evaluation of naltrexone treatment in the field of opioid dependence. The conclusions are also limited due to the heterogeneity of the trials both in the interventions and in the assessment of outcomes*". This is not inconsistent with our conclusions.

Our review added three extra trials and the survival analysis of the data for loss of retention in treatment and the survival analysis for the use of illicit opioids and a systematic review of all trials looking at enhanced care packages used to support naltrexone treatment.

The initial doses of naltrexone in the included studies were fairly standard of 25 mg (half a tablet) on day one, followed by 50 mg (one tablet) daily from day two onwards. A three-times-a-week dosing schedule may be considered if it is likely to result in better compliance e.g. 100 mg on Monday, 100 mg on Wednesday and 150 mg on Friday. The use if contingency management programmes have also shown been to increase compliance. However, this is a fast changing clinical area and probably refinements to care packages by introducing such changes will be overtaken by the new formulations with alternative routes of administration. Sub-cutaneous implants are already being used unlicensed by private clinics and are likely to be licensed for use in the next year or so.

Our economic evaluation was a *de novo* cost utility analysis for the use of naltrexone. It is decision analytic model using Monte Carlo simulation and compares naltrexone as an adjunctive therapy to no naltrexone. It takes an NHS/PSS perspective and was modelled to 12 months. Given the time horizon no discounting was applied. Utility values were not available in the literature and so were obtained by research commissioned from the Value of Health Panel.

No helpful data from RCTs was found in relation to societal function, utilization of health care system or heroin overdose in association with naltrexone.

The model, for the NICE reference case, give an estimate for the cost-effectiveness of naltrexone of £42,500 per QALY. Sensitivity analysis was carried out and the ICER varied between £34,600 to £42,500 per QALY gained. Because of the uncertainty in the parameters the CEAC curves never get above 55% for any willingness to pay threshold.

A strength of this technology assessment report is the systematic search and review of evidence which included RCTs and controlled but non-randomised for oral naltrexone as a treatment for relapse prevention in formerly opioid dependent drug users and of studies to enhance naltrexone retention. Survival analysis using pooled HR for retention in treatment in naltrexone in five RCTs was not reported in any other systematic review or any of the primary included RCTs. Further more the very limited useful published literature data on quality of life associated with the illicit drug use led us to commission an entirely new data from the Value of Health panel to obtain an estimate for the incremental cost per QALY.

The major limitation of the review is the paucity and poor quality of the primary research evidence. The included RCTs are generally poor and not adequately powered and the sample size was not calculated in any of the primary studies.

There was no primary data that enabled us to quantify the mortality rate associated with oral naltrexone treatment. The mortality data a potentially important issue as naltrexone decreases a formerly opioid dependent user's tolerance to opioids and thus there is a risk of opioid overdose if people return to their previous usage patterns. The National Coronial Information System (NCIS) report showed 32 deaths related to the use of naltrexone inone year.[14] However, although these deaths were in people using naltrexone it was not possible to determine whether

this was any higher than it would have been in a similar population had they not been using naltrexone.

We were unable to identify specific population at risk who will benefit most from naltrexone within the studies of randomized controlled design. However, the increased effectiveness of contingency management programmes suggest that providing people with an incentive to remain opioid free helps retention in treatment. This is consistent with the findings of the two studies of people on probation and parolees. Although in these studies the suggested improvement in retention did not reach statistical significance, the reduction in re-incarceration rates did. Naltrexone may possibly be particularly effective in this group if remaining opiate-free is a way of staying out of prison which would give people an additional incentive to remain on naltrexone treatment. There are uncontrolled studies (e.g. Washton[29] or Roth[31]) that claim particular benefit of naltrexone as an adjunct in the maintenance of an opioid-free state in professional groups. Fore example in the latter study, a retrospective study of 20 health professionals who were formerly opioid dependent who were treated over a 5-year-period, the mean overall duration of naltrexone administration was eight months, and the mean duration in the program was 1.9 years. Ninety-four percent of referred clients had long term abstinence, and 66% were working in their profession during the program. These results are better than the rates shown in the RCTs. Thus naltrexone in the setting of a structured program may be helpful in the treatment and professional reinstatement of opioid abusing professionals.[31] However such evidence is far from conclusive.

7. FURTHER RESEARCH

No ongoing trials of oral naltrexone were identified during the searches.

Further RCTs comparing oral naltrexone with placebo would seem to be of limited value, however, if these are carried out they should be adequately powered RCTs and possibly should target specific populations where there is a particular incentive to remain opiate free (i.e. people for whom an opiate substitute is not acceptable), e.g. professional people or those wishing to avoid further contact with the criminal justice system.

Depot preparations are likely to be licensed within the next year or so and it will be important to systematically review the evidence for the safety and effectiveness of naltrexone used by this route of administration. New RCTs may well be required in this area.

The lack of mortality rate associated with stopping naltrexone use would merit systematic monitoring of deaths associated with naltrexone. (Naltrexone is not typically detected at autopsy and coroners and police are unlikely to be aware of the relevance of a recently terminated treatment of naltrexone.) This may also be particularly important as longer lasting routes of administration such as sub-cutaneous pellets are used. (In such circumstances an opioid dependent individual may try to overcome the effects of naltrexone by taking larger doses of opiates although they may be unaware of how much naltrexone they still have "on board" with a greater potential risk of overdose.)

There is an important deficit in information about the QoL of life of people who use illicit opioids.

8. FACTORS RELEVANT TO THE NHS

It is clear from prescription data (see Section 2), that naltrexone is currently not used widely within the NHS. Based on current cost, estimated average dose and dose duration, probably between 1,500 and 2,000 patients use naltrexone and not all of these will be using it for opioid dependence.

There is no evidence that use is on the increase. In contrast, uptake of buprenorphine and methadone appears to be increasing and a larger number of patients are being treated with these drugs within the NHS (>50,000 on the basis of prescriptions issued).

Because of the availability of these alternatives to naltrexone and their perceived cost-effectiveness (versus standard therapy), it is unlikely that naltrexone uptake will increase in the foreseeable future. The cost-effectiveness analysis undertaken in the present report failed to show that naltrexone treatment for formerly opioid-dependent individuals is a clearly worthwhile policy that should be actively promoted within the NHS. However, the budget

impact on the NHS is likely to be minimal if naltrexone is approved for use in the NHS by NICE.

9. CONCLUSIONS

Following the successful withdrawal from opioids in an opioid dependent individual, naltrexone may be administered on a chronic basis to block any future effects of opioids. Naltrexone may have some limited benefit in helping formerly opioid dependent individuals remain abstinent although the quality of the evidence is relatively poor and heterogeneous and this does not reach conventional levels of statistical significance. There is limited evidence that naltrexone can help reduce re-incarceration rate and opiate use.

Our cost-effectiveness model does not, however, demonstrate that naltrexone is clearly cost-effective from an NHS perspective. The point estimate compared to placebo was £42.5k/QALY and the probabilistic sensitivity analysis showed that naltrexone never has a probability of above ~ 50% for being cost-effective for any threshold over £30k/QALY. This reflects the huge uncertainty within the data. Nonetheless the applicability of estimates of effectiveness from the trials to the actual situation in which naltrexone is currently used in the NHS treatment of formerly opioid dependent individuals is open to question. In particular, the trials were generally undertaken in populations who were recently detoxified but not particularly selected for a high motivation to take remain opiate free. However, most such individuals are currently treated in the NHS by the use of opiate substitutes, naltrexone is infrequently used and when it is used this tends to be in the much smaller subset of individuals who prefer to remain opiate free. Thus the external generalisability of the trial estimates to current usage can be debated. Since such evidence as there is (which is far from conclusive) suggests that naltrexone is more effective in highly motivated individuals, the effectiveness in the people for whom it is currently being prescribed will be probably be higher than that estimated from the trials and the ICER correspondingly lower. Given the uncertainty in the data, the huge sensitivity of the ICER to estimates of quality of life, the fact that drug cost of naltrexone is small (it costs ~£500 to treat one patient for one year), the highly restricted way the drug is currently used by health professionals with a consequent minimal impact on the NHS budget (which is unlikely to increase), it may be inappropriate to change current policy of highly selected used on the basis of the results from the cost-effectiveness model. This conclusion is strengthened when one

takes into account that if a societal perspective including victim costs is used in the economic model, naltrexone actually becomes cost saving.

10. APPENDICES

Appendix 1 Health states and utilities derived from the Value of Health Panel

Table A: Health states and utilities derived from the Value of Health Panel

Health state	Responders	Mean	SD	Median	Range
On treatment: drugs free	22	0.8673	0.1524	0.9300	0.525 to 1
On treatment: drugs reduction (injectors)	22	0.6332	0.2075	0.6875	0.275 to 0.935
On treatment: drugs reduction (non injectors)	22	0.6834	0.2037	0.7250	0.325 to 0.98
Not on treatment: drug misusers, injectors	22	0.5880	0.2115	0.6375	0.125 to 0.96
Not on treatment: drug misusers, non-injectors	22	0.6780	0.2069	0.7375	0.275 to 0.98

Health state scenarios

Assume on treatment:

1. Drugs free

- You may have difficulty getting off to sleep
- You have no pain or discomfort
- You hardly ever feel tired
- Your condition does not affect your work life
- You will have to develop a new group of friends
- You hardly ever have problems concentrating
- You may have reduced libido or an irregular menstrual cycle
- You will have to collect medication from your community pharmacy at least once a week and possibly every day

2. Drugs reduction (injectors)

- You may have difficulty getting off to sleep.
- You may experience moderate pain or discomfort, sweats and shakes on most days. You may develop skin abscesses or painful swollen legs. You will be at risk of developing a blood borne infectious disease. You may suffer from loss of appetite, weight loss and dental problems.
- You hardly ever feel tired
- You may find it difficult to obtain and hold down a job. You might incur debts that you find difficult to pay
- You may find it difficult to be punctual and reliable, leading to disagreements with family and friends
- You hardly ever have problems concentrating
- You may have reduced libido or an irregular menstrual cycle
- You will have to collect medication from your community pharmacy at least once a week and possibly every day. You may accidentally overdose and require urgent medical attention.

3. Drugs reduction (non-injectors)

- You may have difficulty getting off to sleep. You may have occasional pain and discomfort, sweats and shakes.
- You may experience chest infections and shortness of breath
- You hardly ever feel tired
- You may find it difficult to obtain and hold down a job. You might incur debts that you find difficult to pay
- You may find it difficult to be punctual and reliable, leading to disagreements with family and friends
- You may be unable to concentrate due to being constantly preoccupied with your problems
- You may have reduced libido or an irregular menstrual cycle
- You will have to collect medication from your community pharmacy at least once a week and possibly every day

Assume not on treatment:

4. Drug misusers (injectors)

- You may experience moderate anxiety or low mood on most days. You may have difficulty in getting off to sleep
- You may experience moderate pain or discomfort, sweats and shakes on most days. You may develop skin abscesses or painful swollen legs. You will be at risk of developing a blood borne infectious disease. You may suffer from loss of appetite, weight loss and dental problems.
- You hardly ever feel tired
- You may find it difficult to obtain and hold down a job. You might incur debts that you find difficult to pay.
- You may find it difficult to be punctual and reliable, leading to disagreements with family and friends
- You hardly ever have problems concentrating
- You may have reduced libido or an irregular menstrual cycle
- You may need to attend your GP or an A&E service to obtain emergency relief for your symptoms on a regular basis. You may accidentally overdose and require urgent medical attention.

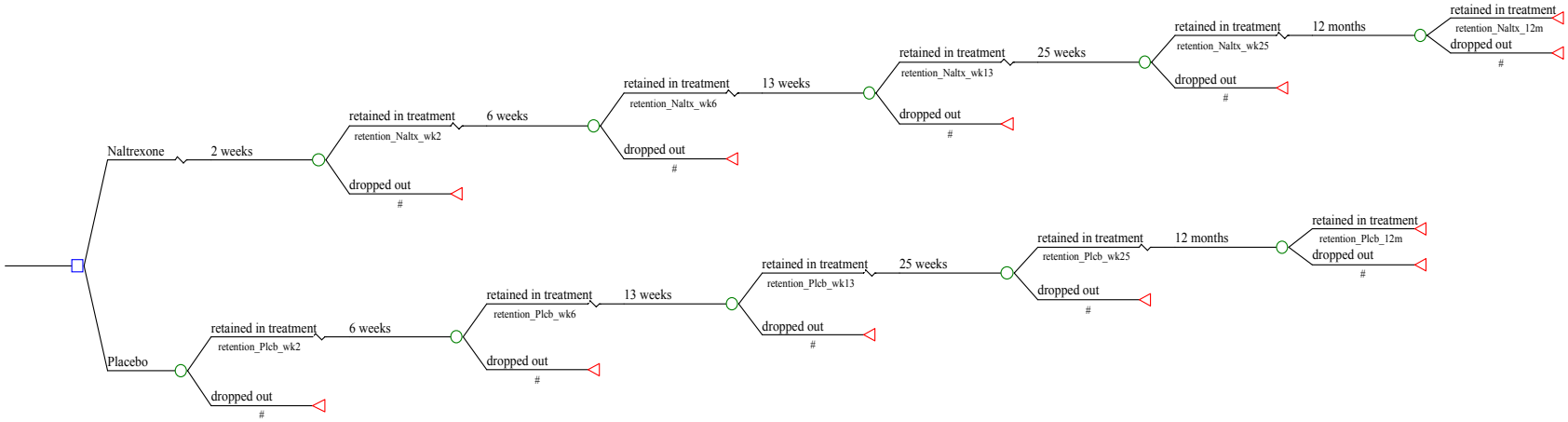
5. Drug misusers (non-injectors)

- You may experience moderate anxiety or low mood on most days. You may have difficulty getting to sleep.
- You may experience moderate pain or discomfort, sweats and shakes on most days. You may experience chest infections and shortness of breath
- You hardly ever feel tired
- You may find it difficult to obtain and hold down a job. You might incur debts that you find difficult to pay.
- You may find it difficult to be punctual and reliable, leading to disagreements with family and friends
- You hardly ever have problems concentrating

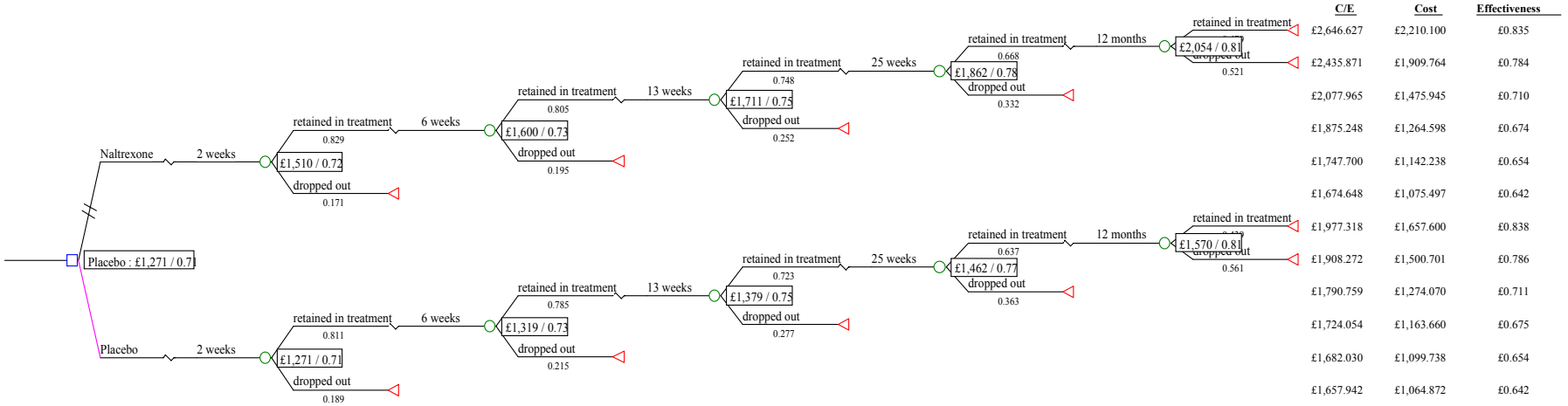
- You may have reduced libido or an irregular menstrual cycle
- You may need to attend your GP or an A&E service to obtain emergency relief for your symptoms on a regular basis

Appendix 2 Decision tree for naltrexone versus placebo

Decision tree for naltrexone versus placebo



Decision tree of naltrexone versus placebo (with results)



C/E	Cost	Effectiveness
£2,646.627	£2,210.100	£0.835
£2,435.871	£1,909.764	£0.784
£2,077.965	£1,475.945	£0.710
£1,875.248	£1,264.598	£0.674
£1,747.700	£1,142.238	£0.654
£1,674.648	£1,075.497	£0.642
£1,977.318	£1,657.600	£0.838
£1,908.272	£1,500.701	£0.786
£1,790.759	£1,274.070	£0.711
£1,724.054	£1,163.660	£0.675
£1,682.030	£1,099.738	£0.654
£1,657.942	£1,064.872	£0.642

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Appendix 3 The quality assessment of the systematic reviews

The quality assessment of the systematic reviews

Questions	Score	Kirshmayer et al 2003 ID1080
Search methods reported and comprehensive search? (Q1 and Q2)	Score Q1: 2 Yes Score Q2: 2 Yes	Many databases searched including MEDLINE (1997-2000), EMBASE (1974-2000); hand searched some sources and references of relevant lists studies were searched. Authors and pharmaceutical industry were contacted. Updated search was Feb 2003.
Inclusion criteria reported? (Q3)	Score Q3: 2 Yes	Extensive criteria clearly defined. Only controlled trials were considered in human. The populations were OD. No distinction was made between dependent on heroin alone or on multiple drugs. The intervention was oral naltrexone at any dosage after detoxification. Naltrexone alone or with other treatment considered and the control group treated with placebo or other treatment without naltrexone. Four main outcomes stated. Three were dichotomous outcomes and one continuous outcome.
Selection bias avoided? (Q4)	Score Q4: 1 PARTIALLY	Two reviewers independently assessed the inclusion criteria. A third reviewer if there is any disagreement.
Validity criteria reported? (Q5)	Score Q5: 2 Yes	The quality assessment tool was described as three levels of risk of selection: A as a low risk (a adequately allocation concealment), B as moderate risk (some doubt about allocation concealment or blinding and C as a high risk of bias (inadequate allocation concealment)
Validity for each study assessed appropriately? (Q6)	Score Q6: 2 Yes	The validity criteria described in Q 5 was applied to each included study.

Methods for combining reported and findings combined appropriately? (Q7 and Q8)	Score Q7: 2 Yes Score Q8: 2 Yes	Meta-analytic procedures were provided for four different outcomes. However, because meta-analysis was done for a limited number of studies and outcomes only, a qualitative summary of the included studied provided. Heterogeneity of studies was not statistically significant for all summary estimates stated.
Conclusions supported by data ?(Q9)	Score Q9: 1 PARTIALLY	The overall conclusion stated that the available trials do not allow a final evaluation of the naltrexone maintenance treatment yet. A trend in favour of treatment with naltrexone was observed for certain target groups particularly people who are highly motivated. As there was no subgroup analysis in the review, the authors' statement that highly motivated population may benefit is not supported by the data analysed by this review. The main results stated were : - Treatment drop out was: 0.78[0.24-1.75] - Opioid use under treatment was: 0.85[0.45=to 1.62] - Re-incarcerations 0.30[0.12-0.76] - Mean duration of treatment 20.30[-1.59-42.19]

Quality assessment of systematic reviews

A modified version of the Oxman & Guyatt assessment tool and scale was used to assess the quality of reviews. This consists of 9 quality interrogations each answerable as "yes", or "no", or "partially / can't tell" carrying scores of 2, 0 and 1 respectively. The 9 questions are listed below.

1. Were the search methods used to find evidence on the primary question(s) stated?
    - ***Yes***, description of databases searched, search strategy, and years reviewed. ***2 points***

- ***Partially***, description of methods not complete. ***1 point***
- ***No***, no description of search methods. ***0 points***

2. Was the search for evidence reasonably comprehensive?
    - ***Yes***, at least one computerized database searched as well as a search of unpublished or non-indexed literature. ***2 points***
    - ***Can't tell***, search strategy partially comprehensive, at least one of the strategies were performed. ***1 point***
    - ***No***, search not comprehensive or not described well. ***0 points***
3. Were the criteria used for deciding which studies to include in the review reported?
    - ***Yes*****,** in- and exclusion criteria clearly defined. ***2 points***
    - ***Partially***, reference to in- and exclusion criteria can be found but are not defined clearly enough**.** ***1 point***
    - ***No***, no criteria defined. ***0 points***
4. Was bias in the selection of articles avoided?
    - ***Yes*****,** issues influencing selection bias were covered. Two of three of the following bias avoiding strategies were used: two or more assessors independently judged study relevance and selection using predetermined criteria, reviewers were blinded to identifying features of the study, and assessors were blinded to treatment outcome. ***2 points***
    - ***Can't tell***, only one of the strategies used. ***1 point***
    - ***No***, selection bias was not avoided or was not discussed. ***0 points***
5. Were the criteria used for assessing the validity for the studies that were reviewed reported?
    - ***Yes***, criteria defined. ***2 points***
    - ***Partially***, some discussion or reference to criteria. ***1 point***
    - ***No*****,** validity or methodological quality criteria not used or not described. ***0 points***
6. Was the validity for each study cited assessed using appropriate criteria?
    - ***Yes*****,** criteria used addressed the major factors influencing bias. ***2 points***
    - ***Partially*****,** some discussion, but not clearly described predetermined criteria. ***1 point***
    - ***No*****,** criteria not used or not described. ***0 points***
7. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?
    - ***Yes*****,** qualitative and quantitative methods are acceptable. ***2 points***
    - ***Partially***, partial description of methods to combine and tabulate; not sufficient to duplicate. ***1 point***
    - ***No***, methods not stated or described. ***0 points***

8. Were findings of the relevant studies combined appropriately relative to the primary question of the overview?
    - ***Yes***, combining of studies appears acceptable. ***2 points***
    - ***Can't tell***, should be marked if in doubt. ***1 point***
    - ***No***, no attempt was made to combine findings, and no statement was made regarding the inappropriateness of combining findings**. *0 points***
9. Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?
    - ***Yes***, data were reported that support the main conclusions regarding the primary question(s) that the overview addresses. ***2 points***
    - ***Partially, 1 point***
    - ***No***, conclusions not supported or unclear. ***0 points***

Appendix 4 Quality assessment of included RCTs studies

Table 28 Quality assessment of included RCTs studies

	Was assign-ment of treatment described as random?	Was method of randomi-sation described?	Was the method really random?	Was allocation of treatment concealed?	Who was blinded to treatment?	Was method of blinding adequately described?	Were eligibility criteria described?	Were groups comparable at study entry?	Were groups treated identically apart from the intervention?	Was ITT used?	Were withdrawals stated?	Were reasons for withdrawals stated?	Was a power calculation done?	Jadad Score
Krupitsky 2002 [42] 2004 [41]'	Y	Y	Y	CT	DB	N	Y	Y	Y	Y	Y	Y	N	2
Grinenko 2003 [43]	Y	N	Y	Y	DB	N	Y	Y	Y	Y	N	N	N	2
Guo 2001	Y	Y	Y	CT	DB	CT	Y	Y	CT	Y	N	N	N	2
Cornish 1997 [32]	Y	N	CT	CT	N	N	Y	Y	Y	Y	CT	CT	N	1
Gerra 1995 [45]	Y	N	N	N	N	N	CT	Y	Y	CT	CT	N	N	1
Shufman 1994 [46]	Y	N	CT	CT	DB	N	Y	Y except for average working days in the preceding year placebo>naltrexone	Y	Y	CT	CT	N	2
Lerner 1992 [47]	Y	N	Y	Y	DB	Y	Y	CT	Y	Y	N	N	N	3
San 1991 [48]	Y	N	CT	CT	DB	N	Y	Y	Y	Y	Y	Y	N	2
Ladewig 1990	Y	N	CT	CT	N	CT	Y	CT	CT	N	Y	N	N	1
Brahen	Y	N	CT	CT	DB	N	N	Y	CT	N	N	N	N	2

1977, [50]1979 [51]														
Rawson 1979 [52]	Y	N	CT	CT	N	N	Y	CT	CT	N	N	N	N	2
Hollister 1978 [53]	Y	N	N	CT	DB	N	Y	CT	CT	N	N	N	N	2
Curran 1976 [40]	Y	CT	CT	CT	DB	N	CT	Y	CT	CT	N	N	N	2

Y: yes, N No, CT can't tell, DB Double blinded

Appendix 5 Quality assessment of the included comparative studies

Table 29 Quality assessment of the included comparative studies

Y Yes , N no , NC Not clear

Quality assessment for observational studies	Was the population base described?	Were recruitment / eligibility criteria reported?	Was there consideration of possible confounding factors?	Were losses to follow up reported?	Were losses to follow up > 20%?	Were other interventions received differentially during follow up?	Was missing data (group or time point data) accounted for?
Arnold-Reed 2003 [54]	Y	Y	CT	N	CT	N	CT
Sivolap 1998 [55] Translation	Y	N	N	N	CT	CT	CT
Judson 1984 [56]	Y	N	CT	Y	CT	N	CT

Appendix 6 Results of included studies

Table 30 Results of included studies

	Main findings			
Author Year	**Use of primary substance of abuse**	**Retention in treatment**	**Adverse events**	**Other**
Systematic reviews				
Kirchmayer (2002, 2003 & the yet unpublished) update 2005) [38,39]	Naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy : (six studies) combined show RR 0.72 (95%IC) 0.58 to 0.90	Naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy : five studies combined RR 1.08 (95% IC 0.74 to 1.57 Naltrexone versus placebo: (two studies) combined and (RR) 0.50 (95% CI) 0.20 to 1.24 Naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy (three studies). RR (95%CI) 0.38 (0.9 t0 2.10) Naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy : (five studies) RR 1.08 (95%IC) 0.74 to 1.57).	No statistically significant difference found in side-effects compared naltrexone with any comparators	Re- incarceration rate: no statistically significant difference but there is a trend in favour of the naltrexone treatment.

RCTs				
Krupitsky 2002, 2004 [41,42]	827 (29.6%) on naltrexone vs 1825 (72%) on placebo, p<0.01	Significantly higher in naltrexone patients from one month throughout the study. At the end of 6 months 12 naltrexone patients 12/27 (44.4%) vs 4/25 (16%) in the control P<0.05 HR Naltrexone retention in treatment: 0.445 95%CI (0.227 to 0.870)	5/27 naltrexone reported side-effects at 15 days and 3/27 reported side-effects at 1 month. The most common side-effects: abdominal pain, nausea. Allergic reaction was reported in one naltrexone patient. One attempted suicide.	*HIV risk*: Using RAB score, naltrexone dropped from 8.2 to 1.4 at 6 months vs control 0.9 p<0.05 *Craving for heroin*: reduced significantly at a 10 point scale at base line at one month, p<0.05. *Alcohol use*: increased significantly at first 4 months *Use of other illicit drugs:* no difference *Compliance*: high in those remained in the study using riboflavin positive urine *Depression, anxiety and anhedonia*: moderately elevated and gradually decreased to near normal. reduction at 15 days was statistically significant. *Opioid positive urine test:* Approximately equal in both arms except at 2.5 and 3 months in favour of naltrexone *Addiction severity index:* significant improvement in composite score at 6 months. *Overall:* CGI decreased at baseline, BPRS: decreased, and GAF increased from baseline.
Grinenko 2003 (Translation) [43]	NA .	Remission at 6 month 16% in naltrexone v 44% control	NA	NA
Guo 2001 [44]	Abstinence rate: At six months in the RCT study 31.4% in naltrexone vs 7.1% in placebo Average abstinence period for naltrexone group was	NA	Only "cold flush" in naltrexone was reported significant compared with placebo.9/35 v 0/14	*No euphoric effecs*:15 (68.18%) naltrexone vs 2 (33.3%) placebo p<0.01 *No change in euphoric effect*:3(13.64%) naltrexone vs 4 (66.67%) placebop<0.01. *In the open study*: the abstinence rate was 23.6% in naltrexone vs 1.2%in unassisted abstinence.

	significantly longer			Urine test was positive in 24.38% in naltrexone vs 40.48% placebo <0.05
Cornish 1997 [32]	NA	Retention rate was not significantly higher than that of control 52% naltrexone vs 33% control. HR for Naltrexone retention in treatment: 0.7 95%CI (0.43 to 1.5)	NA	Mean percent positive urinalysis 8% naltrexone v 30% placebo
Gerra 1995 [45]	Methadone varying dosage (average 44mg, 24% >60 mg) Naltrexone 50 mg			
Shufman 1994 [46]	*Drug free survival curves*: shows 36% in naltrexone at 12 weeks vs 19% in placebo, not statistically significant.	Retention rate: was not significant in naltrexone vs placebo at 12 weeks treatment. 55% for both arms estimated from Kaplan-Meier curves. HR for Naltrexone retention in treatment: 1.2 95%CI (0.4 to 3.23)	Adverse events: The total number of the adverse events reported for the treatment and placebo was. For depression, headaches, GI symptoms, skin and others. The number of patients with adverse events was 14 no significant difference in events.	*Social and psychological assessment*: according to BSI shows significant improvement in naltrexone compared to placebo. *Urine test for opiates*: the difference was not significant between both groups
Lerner 1992 [47]	NA	Success rate naltrexone vs. placebo 9/15 vs 8/16 at 2 months 8/15 vs. 6/16 at 1 year. Retention rate was not significant in naltrexone arm compared with placebo at 2 months and at 1 year (t=0.54, df=29, p=0.59) at 2 month and (t=0.87, df=27, p=0.373) at 1 year. Craving in naltrexone 12/15, 3/15 in moderate and severe scale, while craving in placebo 3/16, 13/16 15 in moderate and severe scale. Attempting opioid taking for naltrexone (7,1,3,4 for no attempt, 1 attempt, 2 attempt, 3 or more attempt), for placebo, (8,8,0,0 for no attempt, 1 attempt, 2 attempt, 3 or more attempt), not sig.	NA	*Craving*: naltrexone significantly decreases craving but it did not inhibit drug taking. (60%)

		(t=0.18, df=29, p=0.85)		
San 1991 [48]		Overall retention rate at 6 months was 27.9% with drop out excluded, but 4/23 (17.4%) in naltrexone and 8/20 (40%) in placebo ; no significant difference at 6 months or at 1 year HR Naltrexone retention in treatment: 2.06 95%CI (1.07 to 3.99)	101 side-effects observed in 32 naltrexone group vs 69 in placebo. The most common were: fatigue, nausea, vomiting, headache, diarrhoea, trembling and dry mouth.	Significantly higher depression scores was found in naltrexone group than placebo. Other psychometric scores in STAI, SSS were not significant.
Ladewig 1990 [49] Translation	NA	Length of treatment in naltrexone mean 69 days vs 49 days in control	7/15 patients has adverse effects in naltrexone vs 3/5 patients in control	*Urine test:* overall 29% *in* naltrexone and 58% in control were tested positive for opiates.
Brahen 1977, 1979 [50,51] RCT- crossover	NA	NA	Incidence of side-effects were significantly different from placebo. Incidence of adverse effects 298 in cyclazocine vs 67 incidence in naltrexone	Post placebo naltrexone produced fewer effects than initial exposure to naltrexone but not significantly.
Rawson 1979 [52]	NA	NA	NA	Opiate free urine sample: 10/23 naltrexone vs 4/15 behaviour therapy Incarcerated: 6/23 naltrexone vs 6/15 behaviour therapy Naltrexone plus behaviour therapy: 8/23, incarceration 4/23.
Hollister 1978 [53]		Retention rate: only 7 patients on naltrexone and 6 on placebo completed 8 months trial HR naltrexone retention in treatment : 0.87 95% CI (0.60 to 1.27)	NA	Urine test: no significant difference in detecting drug Social and psychological data: Post treatment global evaluation: significantly more improvement than placebo Craving for heroin: significantly less in naltrexone group p=.02
Curran 1976 [40]		Successful completion: 2/19 vs 2/19	Side-effects:5/19 vs 0/19 in placebo	Total length of treatment 80 days in naltrexone vs 92 in placebo
Comparative not RCT studies				
Arnold-Reed 2003 Retrospective audit of records [54]	NA	NA	Registered cause of death in the study population which is heroin related: Naltrexone 63.6% (21/33), Non-naltrexone 74% (71/96), not significant different (chi2=1.28, p=0.26);	NA
Sivolap 1998 [55]	abstinence rate 12/60	Leaving the programme 42/60 naltrexone vs	NA	NA

Translation	Naltrexone v 24/60 placebo	22/60 placebo		
Judson 1984 [56]	NA	NA	NA	*No significant correlation between total duration in naltrexone treatment and post treatment outcomes such as: heroin use, arrests, incarcerations5/40 vs 15/77 or mortality preceding to the 1 year follow up.*

Appendix 7 Characteristics of excluded studies

Table 31 Characteristics of excluded studies

References	Reasons for exclusion
1Amato L, Davoli M, A Perucci C, Ferri M, Faggiano F, P Mattick R. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *Journal of Substance Abuse Treatment* 2005; **28**(4):321-329.	No relevant data
2 Berglund M. A better widget? Three lessons for improving addiction treatment from a meta-analytical study.[see comment]. *Addiction* 2005; **100**(6):742-750.	No relevant data
3 Killeen T, Brady K, Faldowski R, Gold P, Simpson K. The effectiveness of naltrexone in a community treatment program. *65th Annual Scientific Meeting of the College on Problems of Drug Dependence* 2003;333.	Alcohol only
4 Rayburn WF, Bogenschutz MP. Pharmacotherapy for pregnant women with addictions. *American Journal of Obstetrics & Gynecology* 2004; **191**(6):1885-1897.	No relevant data
5 Tucker T, Ritter A, Maher C, Jackson H. Naltrexone maintenance for heroin dependence: uptake, attrition and retention. *Drug & Alcohol Review* 2004; **23**(3):299-309.	No comparator
6 Lintzeris N, Bell J, Bammer G, Jolley DJ, Rushworth L. A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal.[see comment]. *Addiction* 2002; **97**(11):1395-1404.	No comparator
7 Rothenberg JL, Sullivan MA, Bornstein G, Epstein E, Nunes EV. Behavioral naltrexone therapy: Efficacy of a new behavioral treatment for heroin dependence and future directions. *DRUG ALCOHOL DEPENDENCE* 2002; **66 Suppl 1**.	No comparator
8 Study ID Numbers: NIDA-09262-4; P50-09262-4, 2002	No relevant data
9. Study ID Numbers: NIDA-09260-2; P50-09260-2	No relevant data
10. McCance-Katz EF, Rainey PM, Friedland G, Kosten TR, Jatlow P. Effect of opioid dependence pharmacotherapies on zidovudine disposition. *American Journal on Addictions* 2001; **10**(4):296-307.	No relevant data
11 Rothenberg JL, Sullivan MA, Church SH, Nunes EV. Retention in treatment: a controlled trial of behavioral naltrexone therapy (BNY) vs compliance enhancement. *DRUG ALCOHOL*	No comparator
12 Hensel M, Kox WJ. Safety, efficacy, and long-term results of a modified version of rapid opiate detoxification under general anaesthesia: a prospective study in methadone, heroin, codeine and morphine addicts. *Acta Anaesthesiologica Scandinavica* 2000; **44**(3):326-333.	No comparator
13 Jelovac N, Milas M, Golik-Gruber V. Naltrexone is efficient in maintaining heroin abstinence of selected groups of addicts. *ALCOHOLISM* 2000; **36**(1):73-77.	Not obtainable

14 Schmitt JM, Stotts AL, Rhoades HM, Grabowski J. Naltrexone combined with relapse prevention for the treatment of cocaine dependence. *NIDA Research Monograph* 2000; **180**:112.	No opioid dependents
15 Schuh KJ, Walsh SL, Stitzer ML. Onset, magnitude and duration of opioid blockade produced by buprenorphine and naltrexone in humans. *Psychopharmacology* 1999; **145**(2):162-174.	No relevant data
16. Study ID Numbers: IAAABRA11747,1999	No relevant data
17 Lisa A Bero, Roberto Grilli, et. al. Closing the gap between research and practice: an overview of systematic reviews of systematic reviews of interventions to promote the implementation of research findings.BMJ 1998;317:465-468	No relevant data
18 Rounsaville BJ, Carroll KM, Fenton LR. Enhancing naltrexone treatment after detoxification. *151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June 1998* 1998;(No. 112E).	No Comparator
19 Seracini AM, Kleber HD, Rothenberg J, Sullivan M, Collins E, Nunes EV. Behavior naltrexone therapy for opiate dependence preliminary report. *NIDA Research Monograph* 1998; **179**:131.	Not obtainable
20 Study ID Numbers: NIDA-5-0012-5; Y01-5-0012-5, 1996	No relevant data
21 Allen JP, Litten RZ, Fertig JB. NIDA-NIAAA workshop: efficacy of therapies in drug and alcohol addiction. Strategies for treatment of alcohol problems. *Psychopharmacology Bulletin* 1995; **31**(4):665-669.	Alcohol only
22 Kleber HD. Nontolerance to the opioid antagonism of naltrexone. *Biological Psychiatry* Netherlands; **20**(1):Jan-72.	No comparator
23 Kleber HD, Kosten TR, Gaspari J, Topazian M. Nontolerance to the opioid antagonism of naltrexone. *Biological Psychiatry* 1985; **20**(1):66-72.	No comparator
24 Kosten TR. Buprenorphine for benzodiazepine-abusing heroin addicts. *American Journal of Psychiatry* 1994; **151**(1):151.	No relevant data
25 Mello NK, Mendelson JH, Kuehnle JC, Sellers MS. Operant analysis of human heroin self-administration and the effects of naltrexone. *Journal of Pharmacology & Experimental Therapeutics* 1981; **216**(1):45-54.	No relevant data
26 Bradford A, Hurley F, Golondzowski O, Dorrier C. Interim report on clinic intake and safety data collected from 17 NIDA-funded naltrexone studies. *NIDA Research Monograph* 1976;(9):163-171.	Review
27 Keegan J, Lavenduski C, Schooff K. Comments and findings from a naltrexone double blind study. *NIDA Research Monograph* 1976;(9):74-76.	No relevant data

Appendix 8 Clinical effectiveness searches

1. Systematic reviews

Database: MEDLINE (Ovid) 1966 to July week 4 2005
Search Strategy:

1 naltrexone.mp. or exp NALTREXONE/
2 nalorex.mp.
3 revia.mp.
4 naloxone.mp.
5 or/1-4
6 substance abuse$.mp. or exp Substance-Related Disorders/
7 exp Opioid-Related Disorders/ or opioid$ abuse$.mp.
8 opioid$ dependence.mp.
9 opioid addict$.mp.
10 opioid abuse$.mp.
11 exp Heroin Dependence/ or heroin addict$.mp.
12 (maintenance adj2 abstinence).mp.
13 (relapse adj2 prevent$).mp.
14 exp Substance Withdrawal Syndrome/ or substance withdrawal$.mp.
15 or/6-14
16 5 and 15
17 (systematic adj review$).tw.
18 (data adj synthesis).tw.
19 (published adj studies).ab.
20 (data adj extraction).ab.
21 meta-analysis/
22 meta-analysis.ti.
23 comment.pt.
24 letter.pt.
25 editorial.pt.
26 animal/
27 human/
28 26 not (26 and 27)
29 16 not (23 or 24 or 25 or 28)
30 or/17-22
31 29 and 30

Database: EMBASE (Ovid) 1980 to 2005 week 36
Search Strategy:

1 nalorex.mp.
2 revia.mp.
3 naloxone.mp.
4 exp NALTREXONE/ or naltrexone.mp.
5 or/1-4
6 substance abuse$.mp. or exp Substance Abuse/
7 opioid abuse$.mp. or exp Opiate Addiction/
8 opioid addict$.mp.)

9 opioid$ dependence.mp.
10 heroin addict$.mp. or exp Heroin Dependence/
11 (maintenance adj2 abstinence).mp.
12 (relapse adj2 prevent$).mp.
13 exp Withdrawal Syndrome/ or substance withdrawal.mp.
14 or/6-13
15 5 and 14
16 meta-analys$.ti,ab.
17 (systematic$ adj2 review$).ti,ab.
18 15 and 17
19 15 and 16
20 18 or 19

Database: Cochrane Library search (Wiley version) 2005 issue 2 (CDSR, DARE, HTA databases)

Search strategy:

#1 naltrexone .tw.
#2 nalorex .tw.
#3 revia.tw.
#4 naloxone.tw.
#5 exp naltrexone/
#6 (#1 or #2 or #3 or #4 or #5)
#7 exp opioid-related disorders/
#8 substance next abus*.tw.
#9 opioid next abus*.tw.
#10 opioid next addict*.tw.
#11 opioid* next dependence.tw.
#12 exp Substance withdrawal syndrome/
#13 heroin next addict*.tw.
#14 maintenance near/6 abstinence.tw.
#15 relapse near/1 prevention.tw.
#16 (#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)
#17 (#6 and #16)

Clinical effectiveness searches
2. RCTs

Database: MEDLINE(Ovid) 1966 to July week 4 2005
Search Strategy:

1 naltrexone.mp. or exp NALTREXONE/
2 nalorex.mp.
3 revia.mp.
4 naloxone.mp.
5 or/1-4
6 substance abuse$.mp. or exp Substance-Related Disorders/
7 exp Opioid-Related Disorders/ or opioid$ abuse$.mp.
8 opioid$ dependence.mp.
9 opioid addict$.mp.
10 opioid abuse$.mp.
11 exp Heroin Dependence/ or heroin addict$.mp.
12 (maintenance adj2 abstinence).mp.
13 (relapse adj2 prevent$).mp.
14 exp Substance Withdrawal Syndrome/ or substance withdrawal$.mp.
15 or/6-14
16 5 and 15
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 randomized controlled trials.sh.
20 random allocation.sh.
21 double blind method.sh.
22 single-blind method.sh.
23 or/17-22
24 (animals not human).sh.
25 23 not 24
26 clinical trial.pt.
27 exp clinical trials/
28 (clin$ adj25 trial$).ti,ab.
29 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
30 placebos.sh.
31 placebo$.ti,ab.
32 random$.ti,ab.
33 research design.sh.
34 or/26-33
35 34 not 24
36 35 not 25
37 comparative study.sh.
38 exp evaluation studies/
39 follow up studies.sh.
40 prospective studies.sh.
41 (control$ or prospectiv$ or volunteer$).ti,ab.
42 or/37-41
43 42 not 24
44 43 not (25 or 36)

45 25 or 36 or 44
46 exp COHORT STUDIES/
47 exp CASE-CONTROL STUDIES/
48 or/46-47
49 45 or 48
50 16 and 49

Database: MEDLINE(R) In-Process & Other Non-Indexed Citations (Ovid) at August 03, 2005
Search Strategy:

1 naltrexone.mp. or exp NALTREXONE/
2 nalorex.mp.
3 revia.mp.
4 naloxone.mp.
5 or/1-4
6 substance abuse$.mp. or exp Substance-Related Disorders/
7 exp Opioid-Related Disorders/ or opioid$ abuse$.mp.
8 opioid$ dependence.mp.
9 opioid addict$.mp.
10 opioid abuse$.mp.
11 exp Heroin Dependence/ or heroin addict$.mp.
12 (maintenance adj2 abstinence).mp.
13 (relapse adj2 prevent$).mp.
14 exp Substance Withdrawal Syndrome/ or substance withdrawal$.mp.
15 or/6-14
16 5 and 15

Database: Cochrane Library (Wiley version) 2005 issue 2 (CENTRAL)
Search strategy:

See Cochrane Library search in Clinical effectiveness searches section 1

Database: EMBASE (Ovid) 1980 to 2005 Week 36
Search Strategy:

1 nalorex.mp.
2 revia.mp.
3 naloxone.mp.
4 exp NALTREXONE/ or naltrexone.mp.
5 or/1-4
6 substance abuse$.mp. or exp Substance Abuse/
7 opioid abuse$.mp. or exp Opiate Addiction/
8 opioid addict$.mp.
9 opioid$ dependence.mp.
10 heroin addict$.mp. or exp Heroin Dependence/
11 (maintenance adj2 abstinence).mp
12 (relapse adj2 prevent$).mp.
13 exp Withdrawal Syndrome/ or substance withdrawal.mp.
14 or/6-13

15 5 and 14
16 randomized controlled trial/
17 15 and 16

Database: CINAHL - Cumulative Index to Nursing & Allied Health Literature (Ovid) 1982 to July Week 5 2005
Search Strategy:

1 naltrexone.mp. or exp NALTREXONE/
2 nalorex.tw.
3 revia.mp.
4 naloxone.mp. or exp NALOXONE/
5 or/1-4
6 substance abus$.tw.
7 opoioid abus$.tw.
8 exp Substance Abuse/
9 opioid addict$.tw.
10 opioid abus$.tw.
11 opioid depend$.tw.
12 exp Substance Abusers/ or heroin addict$.mp.
13 heroin depend$.tw.
14 heroin abus$.tw.
15 (maintenance adj2 abstinence).mp.
16 (relapse adj2 prevent$).mp. [
17 exp Substance Withdrawal Syndrome/ or substance withdrawal$.mp. or exp "Substance Use Disorders"/
18 or/6-17
19 5 and 18
20 exp Clinical Trials/
21 19 and 20

Database: PsycINFO (Ovid) 1967 to August Week 1 2005
Search Strategy:

1 naltrexone.mp. or exp NALTREXONE/
2 nalorex.mp.
3 revia.mp.
4 naloxone.mp. or exp NALOXONE/
5 or/1-4
6 exp Drug Abuse/ or substance abus$.mp.
7 exp Drug Dependency/ or exp Drug Abuse/ or opioid abuse$.mp.
8 exp Heroin Addiction/ or heroin addict$.mp.
9 (maintenance adj2 abstinence).mp.
10 (relapse adj2 prevention).mp.
11 exp Drug Withdrawal/ or substance withdrawal$.mp.
12 opioid dependen$.tw.
13 exp Drug Rehabilitation/ or opioid addict$.mp.
14 or/6-13
15 5 and 14
16 limit 15 to "0870 clinical trial"

Database: Science Citation Index and Social Science Citation Index (Web of Science) 1970 - 6 September 2005
Search terms used:

(Naltrexone or naloxone or revia) and (substance abuse* or drug abuse* or opioid use* or substance use* or drug use*or drug misuse* or substance misuse* or opioid misuse*) and (trial* or study)

3. Cost-effectiveness/QOL/outcomes searches

MEDLINE cost search

Database: MEDLINE (Ovid) 1966 to July Week 4 2005
Search Strategy:

1 naltrexone.mp. or exp NALTREXONE/
2 nalorex.mp.
3 revia.mp.
4 naloxone.mp.
5 or/1-4
6 substance abuse$.mp. or exp Substance-Related Disorders/
7 exp Opioid-Related Disorders/ or opioid$ abuse$.mp.
8 opioid$ dependence.mp.
9 opioid addict$.mp.
10 opioid abuse$.mp.
11 exp Heroin Dependence/ or heroin addict$.mp.
12 (maintenance adj2 abstinence).mp.
13 (relapse adj2 prevent$).mp.
14 exp Substance Withdrawal Syndrome/ or substance withdrawal$.mp.
15 or/6-14
16 5 and 15
17 economics/
18 exp "costs and cost analysis"/
19 cost of illness/
20 exp health care costs/
21 economic value of life/
22 exp economics medical/
23 exp economics hospital/
24 economics pharmaceutical/
25 exp "fees and charges"/
26 or/17-25
27 26 and 16
28 26 and 15

MEDLINE Quality of life search

Database: MEDLINE(Ovid)1966 to July Week 4 2005
Search Strategy:

1 substance abuse$.mp. or exp Substance-Related Disorders/
2 exp Opioid-Related Disorders/ or opioid$ abuse$.mp.
3 opioid$ dependence.mp.
4 opioid addict$.mp.
5 opioid abuse$.mp.
6 exp Heroin Dependence/ or heroin addict$.mp.
7 quality of life/
8 life style/
9 health status/
10 health status indicators/
11 or/7-10
12 or/1-6
13 11 and 12
14 limit 13 to yr="2004 - 2005"

MEDLINE Outcomes search

Database: MEDLINE(Ovid) 1966 to July Week 4 2005
Search Strategy:

1 naltrexone.mp. or exp NALTREXONE/
2 nalorex.mp.
3 revia.mp.
4 naloxone.mp.
5 or/1-4
6 substance abuse$.mp. or exp Substance-Related Disorders/
7 exp Opioid-Related Disorders/ or opioid$ abuse$.mp.
8 opioid$ dependence.mp.
9 opioid addict$.mp.
10 opioid abuse$.mp.
11 exp Heroin Dependence/ or heroin addict$.mp.
12 (maintenance adj2 abstinence).mp.
13 (relapse adj2 prevent$).mp.
14 exp Substance Withdrawal Syndrome/ or substance withdrawal$.mp.
15 or/6-14
16 (relapse adj rate$).mp.
17 mortality.mp. or exp MORTALITY/
18 compliance.mp. or exp COMPLIANCE/
19 adverse effect$.mp.
20 adverse event$.mp.
21 or/16-20
22 5 and 15
23 21 and 22

EMBASE cost searches

Database: EMBASE (Ovid) 1980 to 2005 Week 32
Cost-effectiveness Search Strategy 1 naltrexone :

1 nalorex.mp.
2 revia.mp.
3 naloxone.mp.
4 exp NALTREXONE/ or naltrexone.mp.
5 or/1-4
6 substance abuse$.mp. or exp Substance Abuse/
7 opioid abuse$.mp. or exp Opiate Addiction/
8 opioid addict$.mp.
9 opioid$ dependence.mp.
10 heroin addict$.mp. or exp Heroin Dependence/
11 (maintenance adj2 abstinence).mp.
12 (relapse adj2 prevent$).mp.
13 exp Withdrawal Syndrome/ or substance withdrawal.mp.
14 or/6-13
15 5 and 14
16 cost benefit analysis/
17 cost-effectiveness analysis/
18 cost minimization analysis/
19 cost utility analysis/
20 economic evaluation/
21 (cost or costs or costed or costly or costing).tw.
22 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
23 (technology adj assessment$).tw.
24 or/16-23
25 15 and 24

Database: EMBASE (Ovid) 1980 to 2005 Week 32
Cost-effectiveness Search Strategy 2 substance abuse :

1 substance abuse$.mp. or exp Substance Abuse/
2 opioid abuse$.mp. or exp Opiate Addiction/
3 opioid addict$.mp.
4 opioid$ dependence.mp.
5 heroin addict$.mp. or exp Heroin Dependence/
6 (maintenance adj2 abstinence).mp.
7 (relapse adj2 prevent$).mp.
8 exp Withdrawal Syndrome/ or substance withdrawal.mp.
9 or/1-8
10 cost benefit analysis/
11 cost-effectiveness analysis/
12 cost minimization analysis/
13 cost utility analysis/
14 economic evaluation/
15 (cost or costs or costed or costly or costing).tw.
16 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

17 (technology adj assessment$).tw.
18 or/10-17
19 9 and 18
20 limit 19 to yr="2004 - 2005"

OHE HEED Cost searches

Database: Office Of Health Economics HEED (Health Economics Evaluations Database) August 2005 issue
Search terms used:

Search 1 (Naltrexone or naloxone or revia or nalorex)

Search 2 (substance abuse* or drug abuse* or opioid use* or substance use* or drug use*or drug misuse* or substance misuse* or opioid misuse* or substance dependen* or opioid dependen* or drug dependen*)

NHS EED Cost searches

Database: Cochrane Library (Wiley version) (NHS EED) 2005 issue 2
Search strategy:

See Cochrane Library search in clinical effectiveness searches section 1

Appendix 9 characteristics of included studies

Author Year	Design	Population	Sample Size (N)	Intervention	Comparator	Outcomes	Period of follow-up
Systematic Reviews							
Kirchmayer[38,39] 2003 & update 2005	Systematic review of randomised controlled trials and controlled clinical trials on naltrexone treatment for opioid dependence. Cross-over studies have been excluded.	All in-patients and out-patients dependent on heroin, or former heroin addicts dependant on methadone and participating in a naltrexone treatment programme are considered. No distinction is made between addicts dependent on heroin alone or on multiple drugs.	Ten studies, 696 participants	Naltrexone, Naltrexone plus psychosocial therapy,	Several comparators: Naltrexone versus placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy: seven studies , 444 participants, Naltrexone versus placebo : four studies, 329 participants Naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy : three studies, 115 participants Naltrexone versus psychosocial therapy: two studies, 146 participants	(1) Retention in treatment (2) Use of primary substance of abuse measured as number of participants with positive urinalysis at the end of the study and self report data (3) Results at follow up measured as number of participants relapsed at the end of follow up (4) Side-effects measured as number of participants with at least one side-effect (5) Criminal activity measured as number of	mean duration: six months (range 1 to 10 months)

					Naltrexone versus naltrexone plus psychosocial therapy, one study, 110 participants 06 Naltrexone plus psychosocial therapy versus psychosocial therapy alone :two studies, 177 participants	participants re-incarcerated during the treatment	
Randomised Clinical Trials							
Krupitsky[41,42] 2004 (Russia)	Randomised controlled trial, (double blind); naltrexone and placebo prepared by the pharmacy in identically capsules; code of randomisation kept by the pharmacy	Opioid dependent patients abstinent from heroin for at least one week. Mean age: 22 years; Patients dependent on heroin for 2,5 years on average. male: 80%. Patients completed the secondary school: 88%	52	naltrexone plus biweekly drug counselling; doses and frequency of administration not specified (6 months)	Placebo and biweekly drug counselling	Relapse rate; Retention rate; Side-effects; HIV risk; Alcohol use; Other drugs; Craving for heroin	6 months
Grinenko 2003 [43] (Russia) translation	Randomised controlled trial	Heroin addicts in S Peterburg regional hospital	52	Naltrexone plus Psychotherapy (6 months)	placebo plus Psychotherapy	Remission at 6 months	Not clear, probably all till 6 months
Guo 2001 (China)[44]	Randomised placebo controlled trial; used the table of random number. ratio of patients receiving naltrexone to those receiving placebo: 2:1	Heroin addicts who completed detoxification without using opiates for at least 5-7 days before naltrexone treatment. Mean age: 24,96 (naltrexone) 26,76 (placebo). Male: 88,57% (naltrexone),92,86%	49	Naltrexone (6 month)s	Placebo	Urine tests; adverse effect; Euphoric effects of heroin; Duration of abstinence; relationship between heroine effects and	6 months

	double blind. Metacentre study.	(placebo).				naltrexone dose	
Cornish 1997 (USA)[32]	randomised, controlled trial. ratio of patients receiving naltrexone to those receiving placebo: 2:1 not blinding	Historical opioid addicts	51	Naltrexone and minimal counselling and probation programme (6 months)	Probation programme and minimal counselling	Retention rate; Urine test (Opioid use); Drug free rate; Probation status	6 month
Gerra 1995 (Italy)[45]	Randomised controlled trial	Heroin-abusing patients	152	Naltrexone and Clonidine (3 months)	Clonidine only; Naloxone and Clonidine; Placebo	Drop-out percentage Morphine metabolites	6 months
Shufman 1994 (Israel)[46]	randomised placebo controlled trial double-blind	Heroin addicts	32	Naltrexone plus behavioural and supportive psychotherapy (12 weeks)	Placebo plus behavioural and supportive psychotherapy	Retention rate; Adverse effect,; Heroin-positive urine test; Improvement of mental parameter;	12 weeks
Lerner 1992 (Israel)[47]	randomised placebo controlled trial double blind	Opioid dependants	31	Naltrexone plus psychotherapy and counselling (2 months)	Placebo plus psychotherapy and counselling	Retention rate; Craving; Attempting drug	1 year
San 1991 (Spain)[48]	randomised placebo controlled trial double-blind	Heroin addicts	50	Naltrexone (6 months)	Placebo	Retention rate; Side-effect; Depression score; Opioid and other consumption	1 year
Ladewig 1990 (Switzerland)[49]	Open, randomised controlled	20 detoxified opioid addicts male and female; age range: 20-35 years; opioid free for at least 10 days;	20	Naltrexone plus basic psychosocial program; outpatients. naltrexone: induction:	Basic psychosocial program alone	use of substance af abuse measured by urine analysis,	Mean 69 days (Naltrexone group)

				50 mg/day for three weeks; then Monday 100 mg, Wednesday 100 mg, Friday 150 mg. Psychotherapy: daily group therapy plus weekly individual therapy study duration: information not reported (duration of treatment of patients: min 34 max 124 days)		adverse effects	Mean 49 days (control group)
Brahen 1979 (USA)[50,51]	Double Blind, Randomised controlled (Crossover)	Former opiate addicts	40	Naltrexone (20 days)	Cyclazocine; Placebo	Incidence of side-effects	20 days
Rawson 1979 (USA)[52]	Randomised controlled (not double blind)	Heroin addicts	181	Naltrexone or Naltrexone plus behaviour therapy (30 weeks)	Behaviour therapy	Program entry (probationary period); Treatment duration; Therapeutic assignments; Urine analysis; Incarcerated.	1 year
Hollister 1978 (USA)[53]	multicentric randomised placebo controlled double blinded	192 North American male opioid addicts: (1) street addicts recently detoxified (42) (2) methadone users (58) (3) former addicts currently drug free following incarceration or participation in a drug-free therapeutic program (92)	192	naltrexone vs. placebo. Not specified the number of patients randomised to each group. Outpatients Detoxification with methadone at tapered doses for 21 days followed by 7-14 days with inert methadone	Placebo	Retention rate; Urine test; Acceptance; Craving scale; Toxicity; Adverse effect	9 months

				vehicle for heroin users. Detoxification with methadone at tapered doses for 4-8 weeks followed by 7-14 days with inert methadone vehicle for methadone users. Naltrexone: gradually increasing up to the dose of 100 or 150 mg on the seventh day. Then 100 mg /day and 150 mg on Saturday. Dose not given on Sunday. Study duration: 9 months			
Curran 1976[40] USA	randomised , placebo-controlled trial double-blind	Not mention	38	Naltrexone (92 days)	Placebo	Successful completion;	9 months
Controlled Clinical Trial							
Arnold-Reed [54]2003 (Australia)	Historical controlled, retrospective audit records	Death-related heroin users	92	Naltrexone	Non-naltrexone	Heroin-related mortality	2 years
Sivolap 1998 (Russa)[55]	CT, probably it is a description of irregular practice	Opioid dependents	120	Naltrexone	Nothing	Leaving the program and No use of opiates at 12 mo	> 6 months
Judson 1984 (USA)[56]	Controlled, not randomised	Heroin addicts	117	Naltrexone after 6-month LAAM program (1 year)	Not enter naltrexone after 6-month LAAM program	Not using heroine, using heroine daily or less than daily; Months	1 year

						incarcerated; Use of other opiates; employment; school attendance	

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