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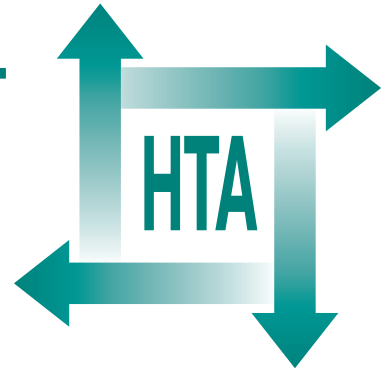

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Abstract

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

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Objectives: To investigate the clinical effectiveness and cost-effectiveness of naltrexone for relapse prevention in detoxified formerly opioid-dependent individuals compared with any strategy that does not use naltrexone, including treatment with placebo, other pharmacological treatments, psychosocial interventions or no treatment.
Data sources: Major electronic databases were searched from inception to September 2005.
Review methods: Selected studies were screened and quality assessed. Meta-analyses were carried out as appropriate. 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). Utility values could not be identified from the literature and so were obtained by research specially commissioned from the Value of Health Panel.
Results: The methodological quality of the 26 randomised controlled trials (RCTs) that met the inclusion criteria was poor to moderate. The results suggest that naltrexone as maintenance therapy may be better than placebo in terms of retention in treatment, but this was not statistically significant. A meta-analysis of seven included RCTs gave the relative risk (RR) of loss of retention in treatment in the naltrexone arm as 0.94. The pooled hazard ratio (HR) reported in five of the RCTs for retention in treatment data followed up to 35 weeks was calculated as 0.90 in favour of naltrexone and also did not reach statistical significance. The risk of drug abuse in naltrexone versus placebo, with or without psychological support given in both arms, gave a pooled RR of 0.72, which was a statistically significant difference in favour of naltrexone. The pooled HR from three RCTs for opioid relapse-free rates was significantly different from placebo in favour of naltrexone 0.53; however, this fell off over time and may be of limited clinical significance. The RR of reimprisonment while on naltrexone therapy showed results in favour of naltrexone in the combined two studies of parolees or people on probation, but the number of participants was small. One study of 52 participants found that the difference in improvement score for risky sexual behaviour in the naltrexone group compared with the placebo group was not statistically significant. The adverse events data reported showed no significant difference between the naltrexone and placebo arms. The quality of the nine RCTs of interventions designed to increase retention with naltrexone was poor to moderate; however, all three different modalities of enhanced care showed some evidence of effectiveness. All of the contingency management programmes used incentive vouchers; the mean duration of treatment retention was 7.4 weeks for the contingency management intervention compared with 2.3–5.6 weeks for the naltrexone treatment alone. The mean length of time for which patients stayed on naltrexone was 84–103 days with additional psychosocial therapy compared with 43–64 days for the control group. In trials with added pharmacological agents the RRs of stopping treatment were 1.63 at 6 months and 1.31 at 12 months (in favour of naltrexone plus fluoxetine). It became statistically significant at 6 months, but not at 12 months. A meta-analysis of the RR of stopping treatment at week 12 (the minimum follow-up period) was carried out using six of the nine studies. The pooled RR of stopping treatment was 0.81. The results indicated that overall the intervention groups had 19% fewer patients who stopped treatment compared with

the control group, but there was only a small number of studies and their quality was relatively poor. No existing economic evaluations were identified. The point estimate for the cost-effectiveness of naltrexone was £42,500 per quality-adjusted life-year (QALY). Sensitivity analysis was carried out and the incremental cost-effectiveness ratio varied between £34,600 and £42,500 per QALY gained.

Conclusions: Following 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 to remain abstinent, although the quality of the evidence is relatively poor and heterogeneous. The limited quality and extent of the studies precluded an analysis of subgroups likely to benefit from naltrexone prescribing. Oral naltrexone is used infrequently in current UK practice, and this review suggests that this is appropriate as there is little evidence to support its wider implementation. There is an important deficit in information about the quality of life of people who use illicit opioids and this would perhaps be a worthwhile area of research in informing policy questions about the cost-effectiveness of different programmes and interventions.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Abstinence 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 A high-affinity, partial μ-opioid agonist. Buprenorphine's profile includes a relatively long-lasting partial agonist effect that limits adverse medical reactions, opiate antagonist activity that blocks the effects of exogenously administered opiates, and slow dissociation from μ-opioid receptors that results in diminished withdrawal signs and symptoms upon discontinuation.

Clonidine An α-adrenergic agonist that acts preferentially on presynaptic α_2 neurons to inhibit noradrenergic activity. Clonidine is useful as an inhibitor of opiate withdrawal and it may have some antianxiety effects.

Cognitive behavioural therapy A psychological treatment for mental health conditions. Treatment usually takes between eight 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 to change behaviour in response to those thoughts. Cognitive techniques (e.g. challenging negative thoughts) and behavioural techniques (e.g. exposure therapy gradually to 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 that stabilises clients on a substitute drug for as long as it is necessary to help them to avoid returning to previous patterns of drug use. Community maintenance generally consists of drug administration, and the provision of psychosocial treatment and motivational interventions.

Contingency management 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 be either a short-term process (<30 days) or a long-term process (between 30 and 180 days), and often involves the prescription of other drugs to help to manage withdrawal symptoms.

Drug misuse Illegal and illicit drug-taking that can lead a person to experience social, psychological, physical or legal problems related to intoxication, regular consumption or dependence.

Heroin 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.

continued

Glossary *continued*

Information bias Systematic differences in self-reported and objectively measured outcomes.

LAAM A μ-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 A full μ-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 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 μ-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 Naturally occurring products derived from the opium poppy that act on opioid receptors. Opiates have potent analgesic effects associated with significant changes in mood and behaviour, and the potential for dependence and tolerance following repeated administration. Examples include morphine and heroin (diamorphine).

Opiate dependence A cluster of cognitive, behavioural 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 as 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 Continuous contact with the service.

Withdrawal The body's reaction to the absence of a drug to which the client has become physically dependent.

List of abbreviations

A&E	accident and emergency
BCS	British Crime Survey
BNF	British National Formulary
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CJS	criminal justice system
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DARP	Drug Abuse Reporting Program
EED	Economic Evaluation Database
HCHS	Hospital and Community Health Services
HEED	Health Economic Evaluations Database
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IDU	injecting drug user
ITT	intention-to-treat
NA	not applicable
NCIS	National Coronial Information System
NDTMS	National Drug Treatment Monitoring System
NICE	National Institute for Health and Clinical Excellence
NNH	number needed to harm
NNT	number needed to treat
NR	not reported
ns	not significant
NTA	National Treatment Agency for Substance Misuse
NTORS	National Treatment Outcome Research Study
NTX	naltrexone
PenTAG	Peninsula Technology Assessment Group
PSS	Personal Social Services
QALY	quality-adjusted life-year
RAB	Risk Assessment Battery
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
ss	statistically significant

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

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 10 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 to 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.

Objectives

The objectives of the report were:

- 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 review systematically 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.

Methods

The study systematically reviewed the literature about (1) the effectiveness of naltrexone and (2) measures to increase compliance with naltrexone, since naltrexone is only effective if taken, using established methods. Bibliographic databases were searched from database inception to September 2005. 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 with any strategy that does not use naltrexone, including treatment with placebo, other pharmacological treatments, psychosocial interventions or no treatment.

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/Personal Social Services 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.

Results

Quality

Out of 1013 identified citations, 26 studies met the inclusion criteria: nine were randomised controlled trials (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 of 940 participants) and three were controlled but non-randomised studies. The methodological quality of the RCTs was poor to moderate at best.

Effectiveness

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: in a meta-analysis of seven included RCTs the relative risk (RR) of loss of

retention in treatment in the naltrexone arm was 0.94 [95% confidence interval (CI) 0.84 to 1.06]. The pooled hazard ratio (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 to 1.17) in favour of naltrexone and also did not reach statistical significance.

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

The RR of reimprisonment while on naltrexone therapy showed results in favour of naltrexone in the combined two studies of parolees or people on probation (RR 0.5, 95% CI 0.27 to 0.91), but the number of participants was small.

One study reported results using the Risk Assessment Battery, which is a self-report instrument questionnaire measuring HIV risk. There were 52 participants in this study. The difference in improvement score for risky sexual behaviour in the naltrexone group compared with the placebo group was not statistically significant.

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

Interventions to increase compliance with naltrexone treatment

Nine RCTs 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 of 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 duration of treatment retention was 7.4 weeks for the contingency management intervention compared with 2.3–5.6 weeks for the naltrexone treatment alone.

The mean length of time for which patients stayed on naltrexone was 84–103 days with additional psychosocial therapy compared with 43–64 days for the control group.

In trials with added pharmacological agents the RRs of stopping treatment were 1.63 at 6 months and 1.31 at 12 months (in favour of naltrexone plus fluoxetine). It reached statistical significance at 6 months, but not at 12 months. There were only 13 participants in the RCT of the pharmaceutical agent sertaline and there are insufficient data to draw any conclusions.

Different studies used different outcome measures with different follow-up periods. It is debatable whether it is appropriate to combine such clinically heterogeneous interventions. This has been done for the sake of completeness, but the results should be interpreted with caution. A meta-analysis was conducted of the RR of stopping treatment at week 12 (the minimum follow-up period) using six of the nine studies. The pooled RR of stopping treatment was 0.81 (95% CI 0.71 to 0.94). The results indicated that overall the intervention groups had 19% fewer patients who stopped treatment compared with the control group. However, owing 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

The point estimate for the cost-effectiveness of naltrexone was £42,500 per quality-adjusted life-year (QALY). Sensitivity analysis was carried out and the incremental cost-effectiveness ratio varied between £34,600 and £42,500 per QALY gained. Because of the uncertainty in the estimates, the cost-effectiveness acceptability curves never went above 55% for any willingness-to-pay threshold.

Conclusions

Following 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 to 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 subgroups particularly likely to benefit from naltrexone prescribing.

Oral naltrexone is used infrequently in current UK practice, and this review suggests that this is appropriate as there is little evidence to support its wider implementation.

Recommendation for future research

There is an important deficit in information about the quality of life of people who use illicit opioids and this would perhaps be a worthwhile area of research in informing policy questions about the cost-effectiveness of different programmes and interventions.

Chapter 1

Aim of the review

The objectives of this report were:

- 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 review systematically 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.

Chapter 2
Background

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. Obtaining 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 effects 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 owing 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 years 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 maintenance and promotion of abstinence approaches. Maintenance therapy concentrates on helping individuals to 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.[2,3] Although maintenance therapy with methadone is the most common pharmacological method used currently in the UK to help to prevent relapse, it is not uncommon for people to want to try to remain opiate free. Thus, for a variety of reasons, clinicians and patients sometimes prefer the abstinence approach. The chronic relapsing nature of drug dependence makes interventions that can help to prevent relapse desirable and naltrexone (Nalorex®, Bristol-Myers Squibb Pharmaceuticals) 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 quality-adjusted life-year (QALY).

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

48–72 hours of discontinuing naltrexone, after which heroin will produce its normal physiological and psychological consequences. In such a situation naltrexone 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 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.

Place of the intervention in the treatment pathway(s)

Naltrexone is licensed as an 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 1, followed by 50 mg (one tablet) daily from day 2 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. Naltrexone is licensed as an adjunct to standard therapy.

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, in part because of 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 of mental disorders (DSM-IV)[4] 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:

- 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
- 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
- the substance is often taken in larger amounts or over a longer period than was intended
- there is a persistent desire or unsuccessful efforts to cut down or control substance use
- 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 recover from its effects
- important social, occupational or recreational activities are given up or reduced because of substance use
- 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.

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.[5]

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 years. 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.[5] 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.[6] 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.[7]

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.[8] Nevertheless, some users of dependent substances may make dramatic changes in their drug use without recourse to formal treatment.[9] 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 10–20 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.[5]

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.[10] 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 15–64 years (360,811), with 3.2 per thousand (123,498) injecting.[10]

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.[11] The 2003/04 BCS found that 35.6% of 16–59-year-olds have used one or more illicit drugs in their lifetime, 12.3% have used one or more illicit drugs in the past year and 7.5% have done so in the past month. These figures were much lower for heroin use, with 0.2% having used opiates (heroin and methadone) in the past year.[11] 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 2004/05 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.[12] Males make up over 70% of new presentations to treatment, and opiates are the most commonly used drug by those seeking treatment.

Impact of health problem

There are considerable harms associated with illicit heroin use, including increased mortality; increased infection with blood-borne viruses (HIV, hepatitis C and hepatitis B virus); 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-quarter to one-third of the mortality in an opioid-addicted population.[5] 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 with the general population.[13] However, more recent cohort studies have shown that mortality rates in drug users have improved over time.[14]

The mortality data in relation to naltrexone are 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[15] 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).[15]

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 administration and to general issues of poor nutrition and healthcare.[8] 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.[16]

Injecting drug users (IDUs) may be exposed to blood-borne infections through the sharing of infected needles, syringes or other injecting paraphernalia. The prevalence of HIV infection among IDUs in the UK has increased in recent years, although the rate is lower than in many other countries.[17] 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 past month. The sharing of other injecting equipment is more common, and few IDUs swab injecting sites before injecting.[17]

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. Before intake in NTORS, 7% were homeless and living on the street, 5% were living in squats and 8% were living in temporary hostel accommodation.[16]

Health-related quality of life

There is little evidence about the health-related quality of life in drug users. No utility estimates were found in the literature and therefore an analysis was commissioned from a Value of Health Panel to obtain estimates for this report (see Appendix 1).

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 (CJS) in the UK estimated as reaching £1 billion per annum in 1998.[18]

Psychological effects and mental illness

The Epidemiological Catchment Area study reported a 47% lifetime prevalence rate of substance abuse among patients with schizophrenia compared with 16% in the general population,[19] and these figures are confirmed in UK studies.[20,21] Substance misuse in schizophrenia is associated with exacerbation of psychotic symptoms, more frequent hospitalisation, poor social functioning, homelessness, increased suicide rate and poor treatment response. Opioid dependence is less associated with severe mental illness such as schizophrenia or bipolar disorder than stimulant drugs or alcohol. Psychosis is not a typical feature of the opioid withdrawal syndrome, but it has been reported in some cases after stopping methadone.[22] Bloom and colleagues proposed that an excess of endogenous opioids may play a role in the pathogenesis of schizophrenia.[23]

Other psychiatric co-morbidity is common in opioid-dependent populations, with anxiety, affective, antisocial and other personality disorders being particularly common.[19,24] Recent psychiatric treatment was reported by one in five of the 1075 subjects recruited to NTORS, and psychiatric symptom levels were high.[25] Clinical studies suggest that half of opioid-dependent individuals have a lifetime depressive episode, while one-third have depressed mood at intake to addiction treatment.[8]

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 CJS, including inpatient or residential, day-patient or outpatient settings.

The government's 10-year national drug strategy, *Tackling drugs to build a better Britain* (1998), identified treatment as one of the four key areas for action.[18] 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.[12]

The UK government spending review in 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 CJS
- to 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
- to reduce the use of class A drugs and the frequent use of any illicit drug among people under the age of 25 years, especially by the most vulnerable young people.

Direct expenditure for tackling drugs in the 2003/04 financial year was £1244 million, with £503 million of this spent on treating drug misuse.[10]

The NTA Annual Report 2004/05[26] reports that in 2004/05:

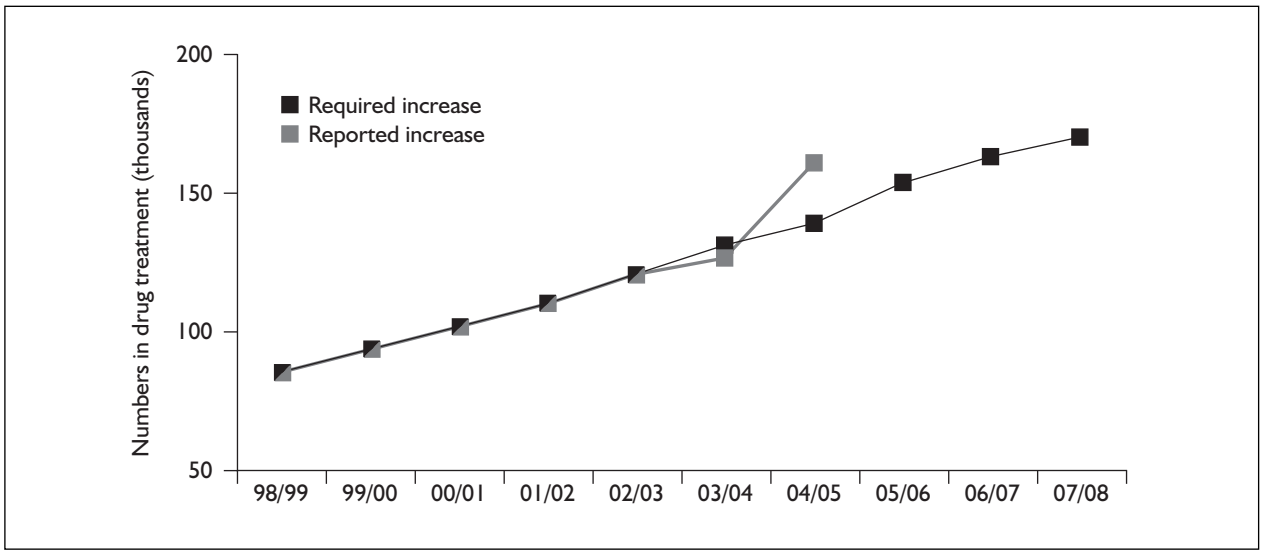

FIGURE 1 *Numbers in drug treatment: required and reported increase 1998/99 to 2007/08 (taken from the National Treatment Agency for Substance Misuse Annual Report 2004/05)*[26]

- 160,450 people received specialist drug treatment, up 27% from 2003/04 and 89% from 1998/99
- 53% of people who left treatment had stayed for at least 12 weeks
- 75% either successfully completed or were still in treatment as at 31 March 2005
- 2–4 weeks was the average time that 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*.

According to *Models of care*, services for drug misusers can be grouped into four broad tiers:[12]

- 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 in a context in which the heroin user's coexisting physical and emotional, social and legal problems are addressed as far as possible.[12] Prescribing must be complemented by counselling or structured psychotherapy, as well as other services such as welfare advice, and 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 2 weeks and 4 weeks for accessing most specialist services, but there is much improvement on 5 years ago, as shown in *Figure 2*.

Identification of important subgroups

Several important subgroups 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.[28] Good results have been shown in the treatment of healthcare professionals in uncontrolled studies,[29–31] 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,[29] and this suggests that linking naltrexone compliance with retaining a job or professional registration may be

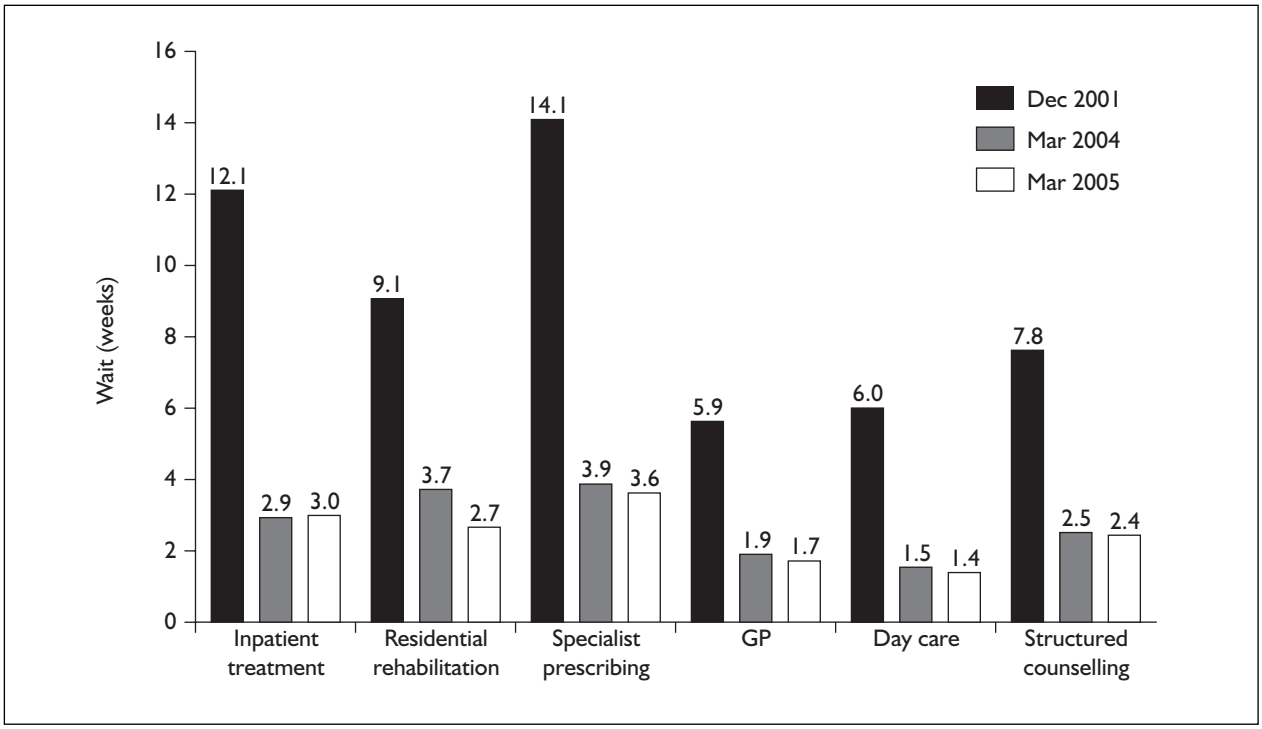

FIGURE 2 *National average waiting times for treatment (taken from the National Treatment Agency for Substance Misuse Annual Report 2004/05).*[26] *One week equals five working days.*

a useful strategy that merits further investigation through randomised controlled trials (RCTs). The study by Cornish and colleagues[32] also suggests that further research on the efficacy of naltrexone treatment for populations of opioid-dependent individuals in the CJS is needed.

The addition of specific behavioural therapies to a prescription of naltrexone may significantly enhance its efficacy,[33,34] 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.

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.[18] The strategy defines three groups: children (aged 12 years or less), young people (aged 13–17 years) and young adults (aged 18–24 years). There are significant challenges in designing appropriately matched treatments and support for young people, and there is little experience of service delivery.

Pregnancy

Dependent heroin use during pregnancy is associated with a reduction of foetal growth, resulting in low birth weight, prematurity and foetal 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]

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 2004/05. 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.[12]

Treatment using oral naltrexone is not common, with a total of only 11,000–14,000 prescriptions being issued per annum in England and no trend towards increasing use (*Figure 3*). 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

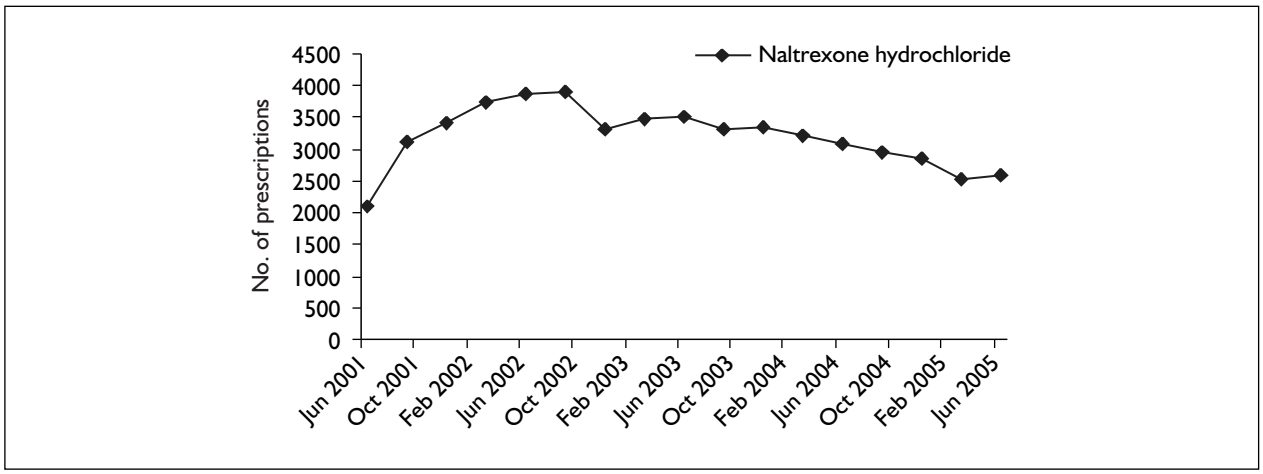

FIGURE 3 *Total quarterly prescriptions for naltrexone in England from PACT data, 2001–2005*

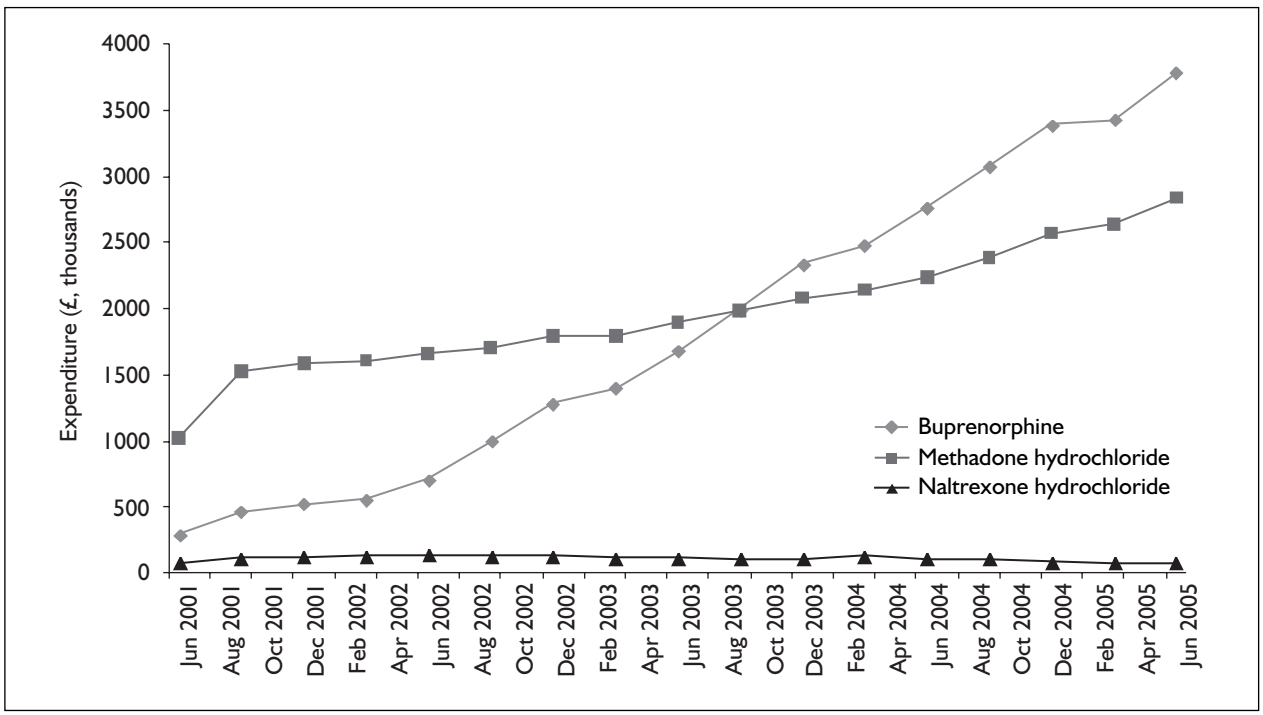

FIGURE 4 *Quarterly expenditure on methadone, buprenorphine and naltrexone in England, 2001–2005*

possible to distinguish the indication for use from Prescription Analyses and Cost (PACT) data.

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*. [The analysis in the figure is for all formulations in British National Formulary (BNF) sections 4.10, 4.7 and 3.9.]

Chapter 3

Methods for reviewing effectiveness

The methods used in this review were in accordance with explicit quality standards agreed by the Technology Assessment Service Collaboration (InterTASC) and the National Coordinating Centre for Health Technology Assessment (NCCHTA).

Search strategy

Clinical effectiveness review

For the clinical effectiveness review the following sources were searched:

- bibliographic databases: Cochrane Library (Wiley) 2005 Issue 2, MEDLINE (Ovid) 1966 to July week 4 2005 and MEDLINE In-Process (Ovid) at 3 August 2005, EMBASE (Ovid) 1980 to 2005 week 36 and CINAHL (Ovid) 1982 to July week 5 2005, PsycINFO (Ovid) 1967 to August week 1 2005, Science Citation Index/Social Science Citation Index (Web of Science) 1970 to 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 2.

Experts were also contacted.

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 to July week 4 2005, EMBASE (Ovid) 1980 to 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.

Searches were not limited by date, except for the quality of life searches (2004–2005) owing to the large volume of material retrieved. There were no language restrictions. Details of search strategies may be found in Appendix 2.

Experts were also contacted.

Inclusion and exclusion criteria

Inclusion criteria were:

- controlled trials of the use of oral naltrexone compared with 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
- RCTs of any intervention designed to enhance compliance with naltrexone treatment with the same naltrexone regimen in both arms.

Exclusion criteria were:

- 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.

Outcomes to be examined

Primary outcomes were:

- changes in illicit drug use
- drug-related morbidity
- drug-related mortality
- health-related quality of life.

Secondary outcomes were:

- proportion of individuals being maintained opioid free
- concordance with and retention to treatment
- adherence to treatment, treatment dropout
- societal function
- criminal activity, (re)incarcerations

- utilisation of healthcare system
- mean duration of treatment
- serious adverse effects of treatment.

Data extraction strategy

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

Quality assessment strategy

The quality of the clinical effectiveness studies were assessed according to criteria based on NHS CRD Report No. 4[37] 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.

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 (RRs), including hazard ratios (HRs) if appropriate, and risk differences with 95% confidence intervals (CIs) 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 from the graphs 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 non-retention-treatment events of the primary studies at weekly time-points and censoring patients who were 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 tests.
4. The pooled hazard ratio and its 95% confidence interval were derived by meta-analysing the individual hazard ratios using equation (1).[38]

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

$$\ln(\mathrm{HR}) = \frac{\sum_i \frac{\ln(\mathrm{HR}_i)}{\mathrm{Var}[\ln(\mathrm{HR}_i)]}}{\sum_i \frac{1}{\mathrm{Var}[\ln(\mathrm{HR}_i)]}} \qquad (1)$$

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

Chapter 4

Results of effectiveness reviews

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* for the flowchart giving the study selection.

Twenty-seven studies did not meet the criteria for inclusion in this review: three did not have a population of participants of opioid-dependent individuals, 14 had no relevant results, eight had no comparator and two were not obtainable. Details of the studies and reasons for exclusion are given in Appendix 3.

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

No systematic reviews of analytical observational studies were identified.

Details of the naltrexone effectiveness studies

Quality of naltrexone studies

Of the 17 studies looking at effectiveness, one was a systematic Cochrane review.[39,40] The details are summarised in *Table 1*. It included ten RCTs and was of good quality (see Appendix 4). However, the summary result is only expressed as the relative risk of retention in treatment rather than the hazard ratio. Thirteen studies were RCTs (for details see *Table 2*) and three were comparative but not randomised studies (for details see *Table 3*).

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 29* (Appendix 5). 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 3 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 greater than 20% or not reported. None of the three non-randomised studies adjusted for the possible confounding variables. Full details are given in *Table 30* (Appendix 6).

Characteristics of identified studies

A summary of the characteristics of the naltrexone RCTs is given in *Table 2* and Appendices 7 and 8 and the characteristics of the non-randomised studies are summarised in *Table 3*.

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,[32,41] the participants were people on probation and parolees.

Comparators in RCTs

Several comparators were used in the included studies:

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

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 reincarceration rates.

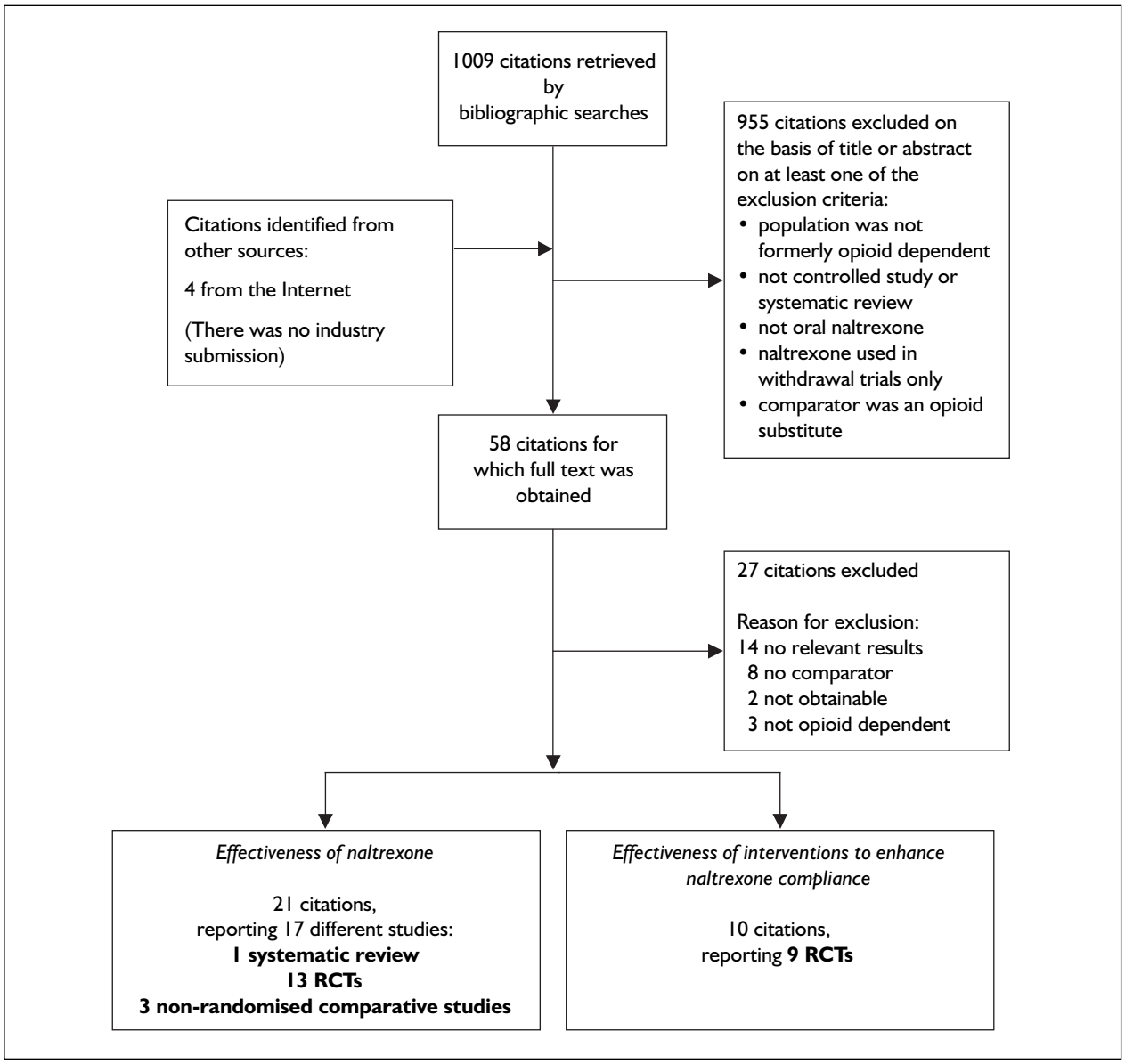

FIGURE 5 *Flowchart for study selection*

TABLE 1 *Summary table of systematic review*

Study	Sample size	Population	Intervention	Comparator	Follow-up	Main findings
Kirchmayer, 2002, 2003.[39,40] The update, 2005, was later published as: Minozzi, 2006[75]	Ten studies with total of 696 participants	All inpatients and outpatients 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: 6 months (range 1–10 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)

TABLE 2 *Summary table of RCTs*

Study	Country	*N* (*n*/group)	Population	Intervention	Comparator	Jadad score	Follow-up	Main findings
Krupitsky, 2004[42,43]	Russia	52 (27/25)	Opioid-dependent patients	Naltrexone plus fortnightly drug counselling (6 months)	Placebo plus fortnightly drug counselling	2	6 months	Relapse to heroin: 8/27 (29.6%) naltrexone vs 18/25 (72%) placebo ($p < 0.01$) Retention in treatment: significantly higher in naltrexone patients from 1 month throughout the study. At the end of 6 months 12 naltrexone patients 12/27 (44.4%) vs 4/25 (16%) in the control ($p < 0.05$) Retention in treatment: HR (naltrexone/placebo) 0.45 (95% CI 0.23 to 0.87)
Grinenko, 2003[44]	Russia (translation)	52 (25/27)	Heroin addicts in south Petersburg regional hospital	Naltrexone plus fortnightly psychotherapy (6 months)	Placebo plus fortnightly psychotherapy	2	Not clear, probably all until 6 months	Remission at 6 months: 16% naltrexone vs 44% control
Guo, 2001[45]	China	49 (35/14)	Heroin addicts	Naltrexone (6 months)	Placebo	2	6 months	Abstinence rate: at 6 months in the RCT study 31.4% naltrexone vs 7.1% placebo Average abstinence period for naltrexone group was significantly longer
Cornish, 1997[32]	USA	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 months	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[46]	Italy	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 at meetings was significantly higher in opiate antagonist treatment
Shufman, 1994[47]	Israel	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: 36% naltrexone at 12 weeks vs 19% placebo (ns) Retention rate: ns in naltrexone vs placebo at 12 weeks of 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)

continued

TABLE 2 *Summary table of RCTs (cont'd)*

Study	Country	*N* (*n*/group)	Population	Intervention	Comparator	Jadad score	Follow-up	Main findings
Lerner, 1992[48]	Israel	31 (15/16)	Opioid-dependent patients	Naltrexone plus psychotherapy and counselling (2 months)	Placebo plus psychotherapy and counselling	3	1 year	Success rate: 9/15 naltrexone vs 8/16 placebo at 2 months, 8/15 vs 6/16 at 1 year Retention rate: ns in naltrexone vs placebo at 2 months and at 1 year ($t = 0.54$, df = 29, $p = 0.59$) at 2 months and ($t = 0.87$, df = 27, $p = 0.373$) at 1 year Craving: naltrexone 12/15, 3/15 in moderate and severe scale, placebo 3/16, 13/16 in moderate and severe scale Attempting opioid taking: naltrexone 7, 1, 3, 4 (no attempt, 1 attempt, 2 attempts, ≥3 attempts), placebo 8, 8, 0, 0 (no attempt, 1 attempt, 2 attempts, ≥3 attempts), ns ($t = 0.18$, df = 29, $p = 0.85$)
San, 1991[49]	Spain	50 (28/22)	Heroin addicts	Naltrexone (6 months)	Placebo	2	1 year	Overall retention rate at 6 months: 27.9% with dropouts excluded, but 4/23 (17.4%) naltrexone and 8/20 (40%) 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[50]	Switzerland	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 programme	Basic psychosocial programme alone	1	Mean 69 days (naltrexone group), 49 days (control group)	Length of treatment: mean 69 days naltrexone vs 49 days control
Brahen, 1977, 1979[51,52]	USA	40 (20/20)	Former opiate addicts	Naltrexone (20 days)	Cyclazocine; placebo	2	20 days	Postplacebo naltrexone produced fewer effects than initial exposure to naltrexone, but ns Incidence of adverse effects: 298 cyclazocine vs 67 naltrexone
Rawson, 1979[53]	USA	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

continued

TABLE 2 *Summary table of RCTs (cont'd)*

Study	Country	*N* (*n*/group)	Population	Intervention	Comparator	Jadad score	Follow-up	Main findings
Hollister, 1978[54]	USA	192[a] (60/64)	Street addicts; methadone users; 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[41]	USA	38 (19/19)	American dependent parolees or probationers	Naltrexone (92 days)	Placebo	2	9 months	Successful completion: 2/19 naltrexone vs 2/19 placebo Total length of treatment: 80 days naltrexone vs 92 days placebo

[a] The total sample size was reported as 192 in the study, but a table showed sample sizes for naltrexone and placebo as 60 and 64, respectively. The proportion of patients who remained in treatment was measured manually on the survival curve, and the measurement confirmed the sample sizes reported in the table; therefore, the sample sizes of 60 for naltrexone and 64 for placebo were used in these analyses.

ns, not significant.

TABLE 3 *Summary table of comparative controlled studies*

Study	Country	*N* (*n*/group)	Population	Intervention	Comparator	Follow-up	Main findings
Arnold-Reed, 2003[55]	Australia	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), ns ($\chi^2 = 1.28$, $p = 0.26$)
Sivolap, 1998[56]	Russia	120 (60/60)	Opioid-dependent patients	Naltrexone	Nothing	>6 months	Abstinence rate: 12/60 naltrexone vs 24/60 placebo Leaving the programme: 42/60 naltrexone vs 22/60 placebo
Judson, 1984[57]	USA	117 (40/77)	Heroin addicts	Naltrexone after 6-month LAAM programme (1 year)	No naltrexone after 6-month LAAM programme	1 year	No significant correlation between total duration in naltrexone treatment and post-treatment outcomes such as heroin use, arrests, incarcerations: 5/40 vs 15/77, or mortality preceding the 1-year follow-up

Results reported in naltrexone studies

Retention in treatment

Systematic review

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

RCTs

Data on retention in treatment were provided by seven trials that compared naltrexone with placebo. The length of follow-up varied between trials; therefore, the relative risk may not be a representative estimate of retention in treatment and hazard ratio would be a better estimate. However, a meta-analysis is initially presented 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 are also presented graphically in *Figure 6*.

The results suggest that the risk of not being in treatment retention in naltrexone group compared with the placebo group is reduced by 6%, but this

TABLE 4 *Relative risks of stopping treatment: naltrexone treatment versus placebo (with or without psychological support given in both arms)*

Study	NTX *n/N*	Placebo *n/N*	RR (fixed) (95% CI)
Curran, 1976[41]	17/19	17/19	1.00 (0.75 to 1.33)
San, 1991[49]	24/28	14/22	1.35 (0.98 to 2.03)
Lerner, 1992[48]	6/15	8/16	0.80 (0.35 to 2.44)
Shufman, 1994[47]	8/16	7/16	1.14 (0.54 to 1,73)
Krupitsky, 2004[42]	15/27	21/25	0.66 (0.43 to 0.93)
Hollister, 1978[54]	53/60	58/64	0.97 (0.85 to 1.11)
Cornish, 1997[32]	16/34	11/17	0.73 (0.44 to 1.25)
Total	**139/199**	**136/179**	**0.94 (0.84 to 1.06)**

Q test for heterogeneity, $p = 0.1537$.
NTX, naltrexone.

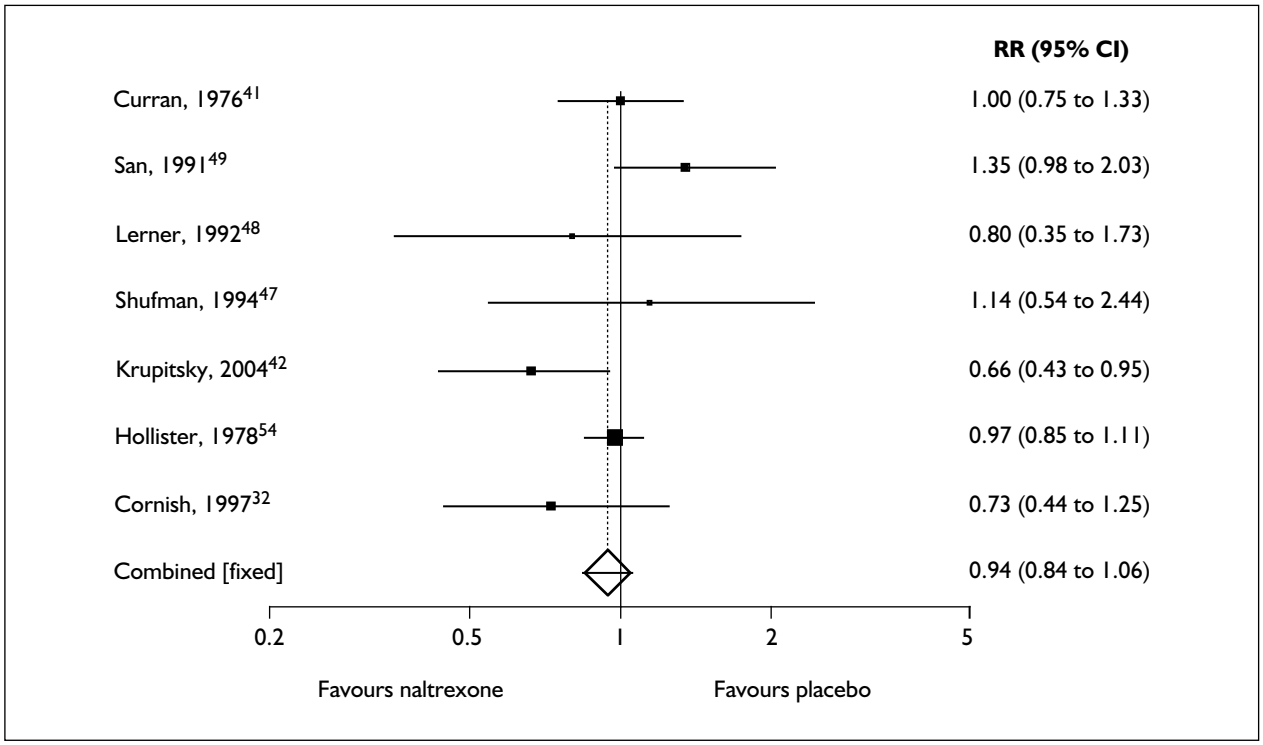

FIGURE 6 *Relative risk of stopping treatment (meta-analysis plot, fixed effects)*

was not statistically significant, with a 95% confidence interval from 0.84 to 1.06. This is consistent with the finding of the Cochrane review.

The reviewers also looked at the hazard ratios as these generally 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) (Chapter 3) and is 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 adding together all events where participants were no longer retained in treatment. Patients still in treatment when a study ended were treated as censored at that point in time (i.e. as lost to follow-up). This is shown in *Figure 7*.

For the retention-rate studies, $\chi^2 = 11.08$ (df = 4, $p = 0.03$), showing 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 performed for retention-rate studies. The random effect analysis gave a hazard ratio of 0.90 (95% CI 0.55 to 1.48), compared with 0.90 (95% CI 0.69 to 1.17) from the fixed effect analysis.

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 the analysis presented in *Table 6* and *Figure 8*.

The pooled relative risk of 0.72 indicates that naltrexone significantly reduces the use of opioids by 28% compared with the control and gives an

TABLE 5 *Pooled and individual hazard ratios for stopping treatment*

Study	HR	95% CI lower	95% CI upper	Favours	Time of follow-up	*p*
Shufman, 1994[47]	1.18	0.43	3.25	Placebo	12 weeks	0.74
Krupitsky, 2004[42]	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[54]	0.88	0.60	1.27	NTX	9 months	0.46
San, 1991[49]	2.06	1.06	4.00	Placebo	1 year	0.03
Pooled studies (fixed)	**0.90**	**0.69**	**1.17**	**NTX**		**0.41**

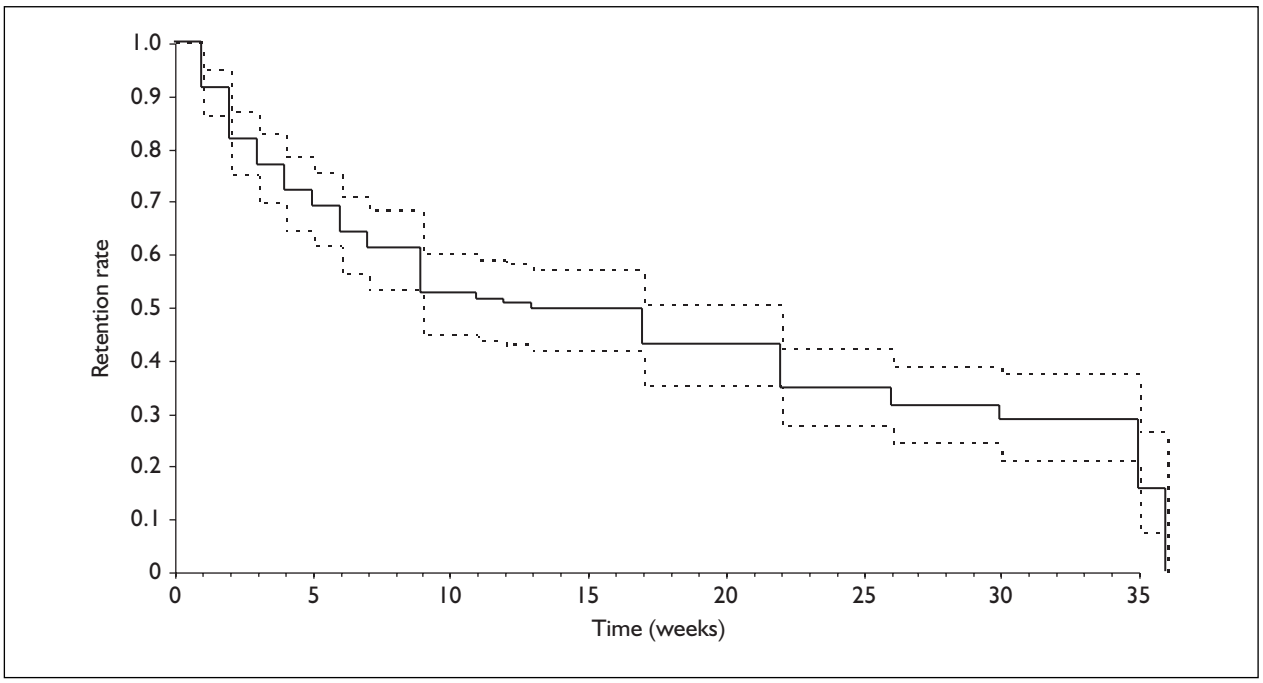

FIGURE 7 *Combined retention rate and 95% CI in naltrexone treatment*

TABLE 6 *Risk of drug abuse in naltrexone versus placebo (listed in order of length of follow-up)*

Study	NTX *n/N*	Placebo *n/N*	Absolute risk reduction	NNT (NNH)	Time of follow-up	RR (fixed) (95% CI)
Shufman, 1994[47]	10/16	13/16	0.188	6	12 weeks	0.77 (0.46 to 1.20)
Krupitsky, 2004[42]	8/27	18/25	0.424	3	6 months	0.41 (0.21 to 0.74)
Guo, 2001[45]	23/34	11/12	0.240	5	6 months	0.74 (0.54 to 1.09)
Curran, 1976[41]	3/19	7/19	0.211	5	9 months	0.43 (0.13 to 1.29)
San, 1991[49]	16/28	12/22	0.026	(39)	1 year	1.05 (0.64 to 1.78)
Lerner, 1992[48]	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, $p = 0.2007$.
NNT, number needed to treat; NNH, number needed to harm.

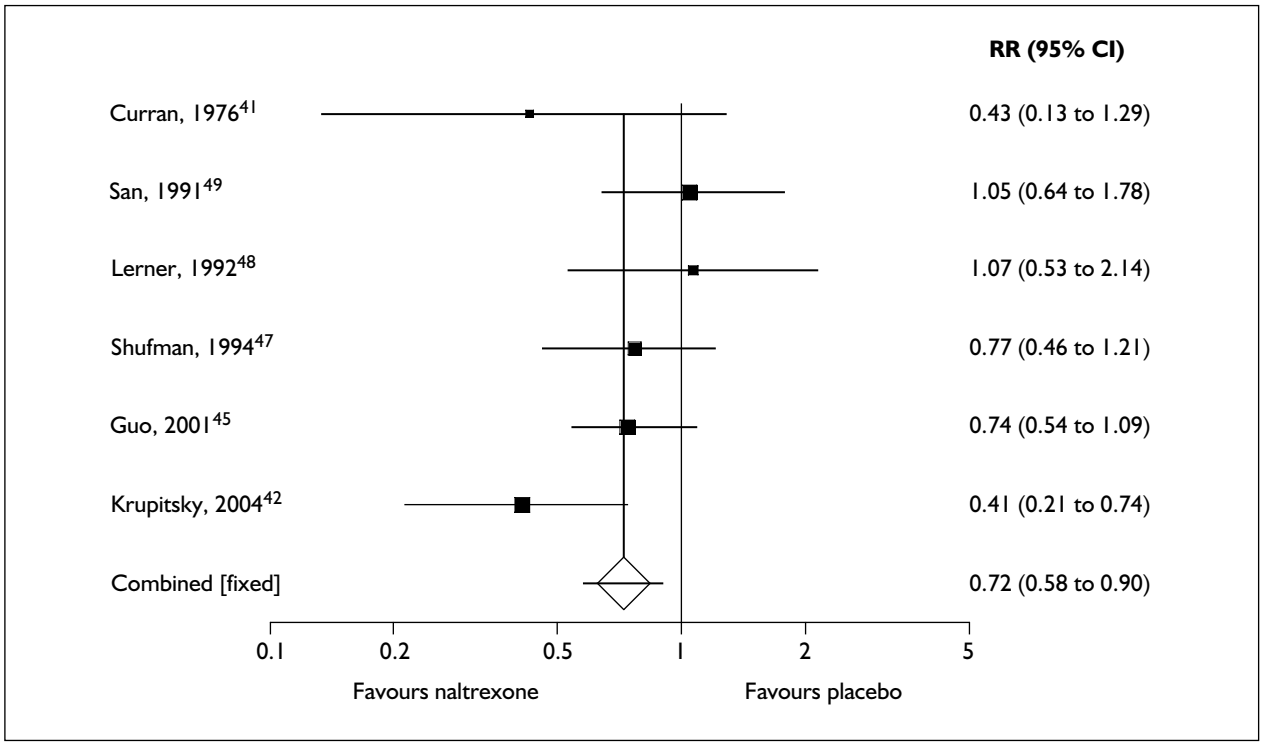

FIGURE 8 *Relative risk of returning to illicit drug use (meta-analysis plot, fixed effects)*

NNT of 8. However, the effect drops off over time. *Figure 9* shows the relapse-free rates in the naltrexone treatment arm at different time-points. The solid line represents 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 rates are shown in *Table 7* and *Figure 9*. The hazard ratio for relapse-free rates between naltrexone and control arms was 0.53 (95% CI 0.34 to 0.82), and was significantly in favour of naltrexone.

Chi-squared tests were performed to test for heterogeneity between trials. For the opioid relapse-free studies, $\chi^2 = 0.59$ (df = 2, $p = 0.75$), suggesting that there was no statistical heterogeneity between trials. The fixed model gave a pooled hazard ratio of 0.53 (95% CI 0.34 to 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, $p = 0.03$), showing heterogeneity between these studies (see

TABLE 7 *Pooled and individual hazard ratios for no opioid relapse*

Study	HR	95% CI lower	95% CI upper	Favours	Time of follow-up	*p*
Shufman, 1994[47]	0.67	0.30	1.53	NTX	12 weeks	0.29
Guo, 2001[45]	0.53	0.23	1.22	NTX	6 months	0.06
Krupitsky, 2004[42]	0.45	0.23	0.87	NTX	6 months	0.01
Pooled studies (fixed)	**0.53**	**0.34**	**0.82**	**NTX**		**0.00**

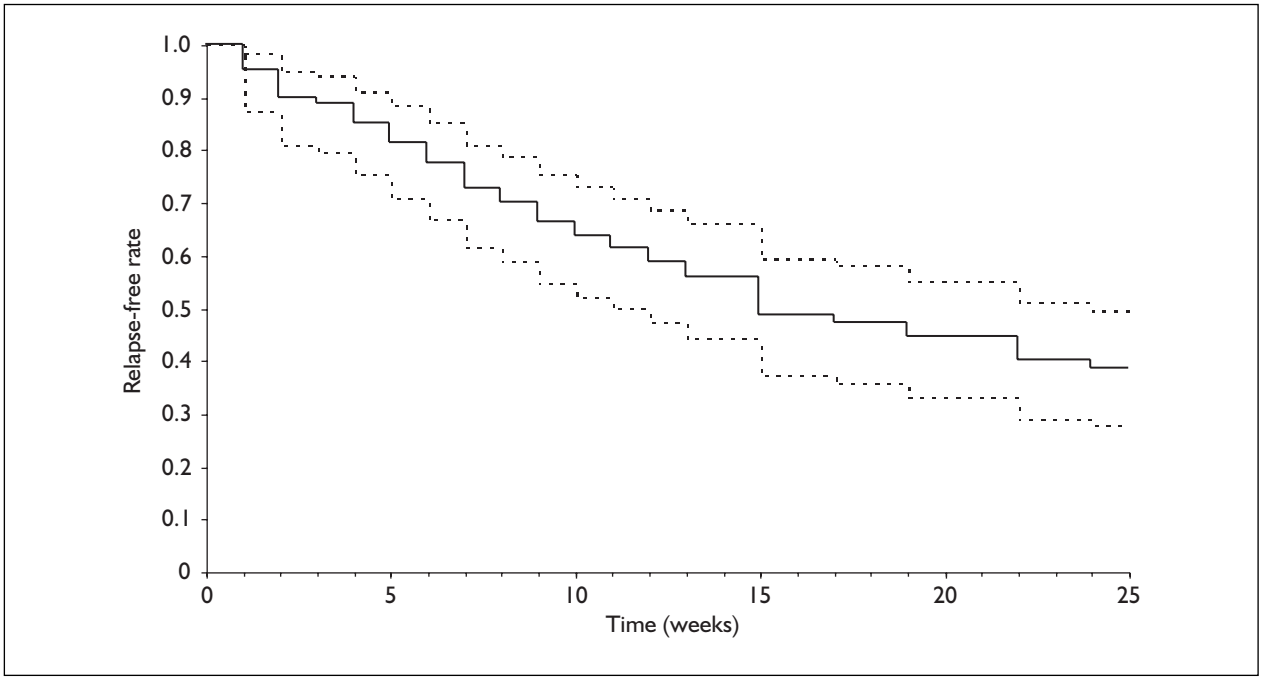

FIGURE 9 *Combined relapse-free rate and 95% CI in naltrexone treatment*

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 performed for retention-rate studies. The random effects analysis gave a hazard ratio of 0.90 (95% CI 0.55 to 1.48), compared with 0.90 (95% CI 0.69 to 1.17) from the fixed effect analysis.

Owing to the limited number of studies and poor quality of these studies, it is very difficult to evaluate factors that resulted in heterogeneity between studies. There were no great differences in age and gender between studies. The mean age of participants was 22–39 years in the naltrexone arm and 21–39 years in the placebo arm. One study[54] did not report age and gender at all. The proportion of men and women in the studies was also comparable: 79–100% and 72–100% male in the naltrexone and placebo arms, respectively. Other factors could be the length of treatment, duration of opiate use, level of education and 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 6 years, while one study reported that the participants had opiate use of less than 3 years before they were recruited for the trials. Two subgroups were analysed according to the duration of opiate use (i.e. duration of opiate use ≥6 years, or <6 years or not reported); the F test gave a p-value of 0.10 ($F = 5.57$, df of 1 and 3), which 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.

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[42] reported both the proportion remaining on treatment and the proportion remaining drug free (*Table 8*). There was no striking relationship, as shown in *Figure 10*.

TABLE 8 *Proportion drug free in those who remained in treatment (from Krupitsky* et al.*, 2004[42])*

Time (weeks)	No. of subjects with heroin-positive urine (% of those who are opioid free and retained in naltrexone treatment), *n* = 27	No. of subjects with heroin-positive urine (% of those who are opioid free on placebo), *n* = 25
2	7 (71)	8 (61.9)
4	4 (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)

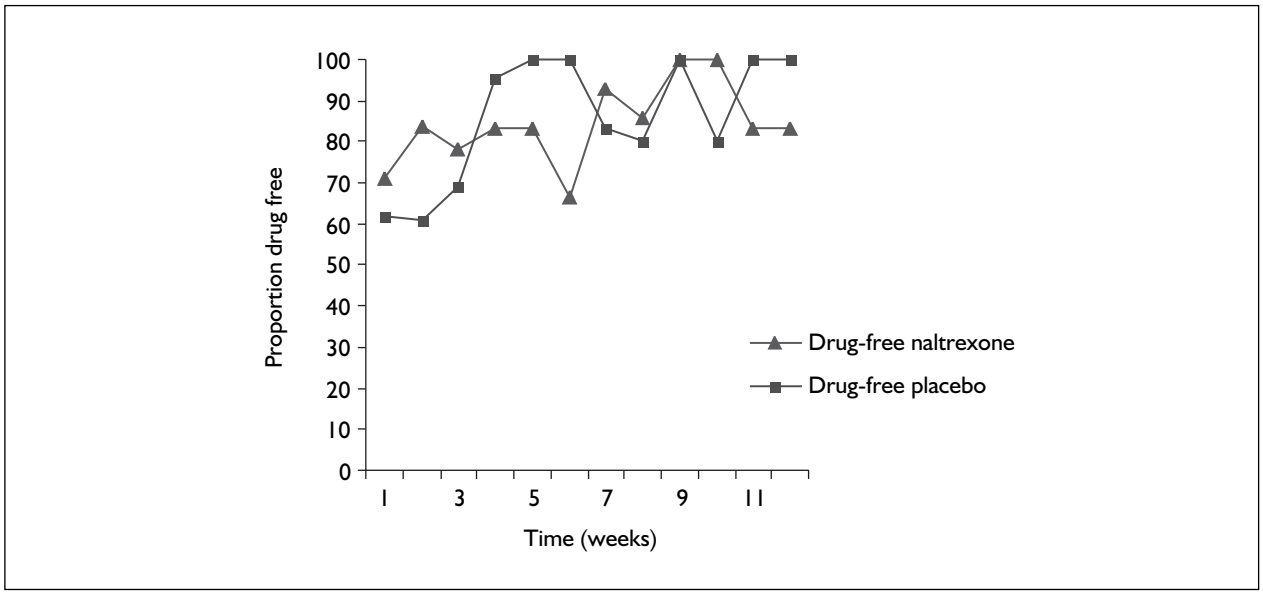

FIGURE 10 *Proportion drug free in those who remained on treatment (from Krupitsky* et al.*, 2004[42])*

Adverse effects

Guo[45] 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 6 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 flushes in naltrexone-treated participants.

HIV-related outcomes

Only one study[42] 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 6 months. The RAB drug risk scores for naltrexone patients who remained in the study reduced from 8.2 at baseline to 1.5 at 3 months and 1.4 at 6 months. The placebo patients reduced from 7.0 at baseline to 0.9 at 3 months and 0.0 at 6 months. Although within-group changes were significant at $p < 0.05$, there were no differences between groups. No significant difference was found in the score for risky sexual behaviour compared with placebo.

Reincarceration rate

Two studies reported a significant reduction in reincarceration rate when using oral naltrexone plus psychosocial treatment versus psychosocial

TABLE 9 *Reincarceration rate in naltrexone plus psychosocial versus psychosocial alone*

Study	NTX *n/N*	Placebo *n/N*	RR (fixed) (95% CI)	Significance status	Favours
Rawson, 1979[53]	4/20	6/15	0.50 (0.17 to 1.46)	ns	NTX
Cornish, 1997[32]	9/34	9/17	0.50 (0.24 to 1.02)	ns	NTX
Total	**13/54**	**15/32**	**0.50 (0.27 to 0.91)**	**ss**	**NTX**

ns, not significant; ss, statistically significant difference.

treatment alone. *Table 9* shows the two studies combined. Although the naltrexone group seems to show a lower rate of reincarceration, this result would need to be further researched as the sample size is very small.

Results from non-RCTS

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

Mortality

No mortality data were reported in the RCTs. A retrospective audit of clinical records, toxicology reports and registered coronial findings[55] 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).

RCTs of interventions to enhance naltrexone treatment

Nine RCTs of interventions designed to increase retention with naltrexone were identified.

Characteristics of RCTs of intervention to enhance retention on naltrexone treatment

The characteristics of these studies are shown in *Table 10*. Three RCTs looked at contingency management programmes. These are programmes that 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.

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*. The Ball trial[58] failed to report any outcomes by randomised group and all reported results are data-driven analyses.

Results of the studies designed to enhance retention on naltrexone

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 study[34] 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 starting level). A participant who complied fully with treatment over 12 weeks could earn a total of $1155. The rate of reimbursement in the Carroll study[33] 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 study,[58] but participants could earn up to $561 worth of goods if they completed the full

TABLE 10 *Characteristics of RCTs looking at interventions to improve naltrexone retention*

Study	Country	*N* (*n*/group)	Population	Comparator	Intervention	Follow-up
Contingency management (with or without additional psychosocial therapies)						
Preston, 1999[34]	USA	58 (19/19/20)	Patients who had recently completed opioid detoxification who were interested in continuing treatment to maintain abstinence	(a) Naltrexone (b) Naltrexone + non-contingency vouchers	Naltrexone plus incentive vouchers	12 weeks
Carroll, 2001[33]	USA	127 (35/48/44)	Outpatients who had completed outpatient detoxification (95%)	Naltrexone	Comparator plus incentive vouchers Comparator plus incentive vouchers plus significant other involvement	12 weeks
Ball, 2004[58]	USA	125	Opioid-dependent patients at outpatients who were detoxified for 5 days	Naltrexone + relapse prevention group counselling	Comparator plus incentive vouchers Comparator plus incentive vouchers plus relationship counselling	12 weeks
Psychosocial therapies						
Callahan, 1980[59]	USA	104 (56/48)	Male opioid-dependent patients	Naltrexone	Comparator plus behavioural therapy	21 months
Rawson, 2001[60]	USA	81 (41/40)	Detoxified opioid-dependent patients meeting DSM-IV criteria	Naltrexone	Naltrexone plus cognitive behavioural therapy	52 weeks
Fals-Stewart, 2003[61,62]	USA	124 (62/62)	Male opioid-dependent users meeting DSM-III-R criteria, 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 regarding detoxification not clear	Naltrexone + individual-based treatment	Comparator plus behavioural family counselling	24 weeks
Tucker, 2004[63]	Australia	97 (52/45)	Opioid-dependent patients according to DSM-IV, inpatients and outpatients recruited via advertisement who were 18 years or older. Detoxification for a minimum of 5 days	Naltrexone	Comparator plus group counselling which used cognitive behavioural approach	12 weeks
Pharmaceutical agents						
Landabaso, 1998[64]	Spain	112 (56/56)	Opioid-dependent patients with DMS-IV criteria following outpatient detoxification programme, severe mental psychology cases excluded	Naltrexone (no placebo)	Comparator plus fluoxetine	12 months
Farren, 2002[65]	USA	13	Opioid-dependent patients with no co-morbid psychopathology. Detoxification was for 5–30 days	Naltrexone + placebo	Naltrexone plus sertaline	12 weeks

TABLE 11 *Quality assessment of RCTs of interventions to enhance naltrexone retention*

Study	Assignment of treatment described as random?	Was method of randomisation 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 (with or without 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[58]	Y	Y	CT	CT	NA	NA	Y	Y	CT	N	Y	N	N	2
Psychosocial therapies														
Callahan, 1980[59]	Y	N	CT	CT	NA	NA	Y	CT	CT	N	N	N	N	1
Rawson, 2001[60]	Y	Y	Y	Y	NA	NA	Y	Y[a]	CT	N	Y	N	N	3
Fals-Stewart, 2003[61,62]	Y	N	CT	CT	NA	NA	Y	Y	CT	N	Y	N	N	2
Tucker, 2004[63]	Y	N	CT	CT	NA	NA	Y	CT	CT	Y	Y	N	N	2
Pharmaceutical agents														
Landabaso, 1998[64]	Y	N	CT	CT	CT	CT	Y	Y	CT	N	Y	N	N	2
Farren, 2002[65]	Y	N	CT	CT	Double-blinded	N	Y	Y	Y	N	Y	Y	N	3

[a] Except for the years of education.
CT, can't tell; N, no; NA, not applicable; Y, yes.

12 weeks of follow-up successfully. However, the reviewers believe that the results of the Ball trial,[58] 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 of 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[33] also demonstrated a significantly reduced rate of opiate use, as measured by the number of opiate-free urine samples (19 ± 14 versus 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*.

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,[66] 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*.

Pharmaceutical agents

The two pharmaceutical agents that were tested in trials as enhanced care packages to naltrexone were sertaline[65] and fluoxetine.[64] 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 that need to be borne in mind when considering the results. Fluoxetine showed an enhanced effect over the standard care package with naltrexone at both 6 and 12 months. The NNT to have one patient still on treatment at 1 year was five. Full results are given in *Table 14*.

Combining results for any enhanced care package

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. This has been done for the sake of completeness, but the results should be interpreted with caution.

Five out 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[33,65] evaluated the effect size using point retention rates, others[34,60,64] using mean or median survival time. The follow-up periods varied from 12 to 52 weeks. Some studies[65] only observed significant higher retention rates in early stage of the treatment, but not at a later stage. To summarise the effectiveness of additional care packages in general, a meta-analysis of the relative risk of stopping treatment at week 12 was conducted. One study[63] did not report survival curves comparing retention in treatment between naltrexone and naltrexone with care packages, but the reviewers derived the relative risk of stopping treatment at week 12 for this study. The pooled relative risk of stopping treatment was 0.81 (95% CI 0.71 to 0.94) (*Figure 11*). The results indicated that overall the intervention groups had 19% fewer patients who stopped treatment compared with the control group.

Summary and conclusion of the results for effectiveness

Naltrexone studies

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

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 showed that the relative risk of loss of retention in treatment in the naltrexone arm was 0.94 (95% CI 0.84 to 1.06) and the pooled hazard ratio from five RCTs reporting usable retention-in-treatment data followed up to 35 weeks was calculated as 0.90 (95% CI 0.69 to 1.17) in favour of naltrexone.

With respect to the risk of opioid use in naltrexone versus placebo with or without psychological support given in both arms, the pooled relative risk of six RCTs was 0.72 (95% CI 0.58 to 0.90), which was a statistically significant difference in

TABLE 12 *Results of naltrexone versus 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	No. 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	$p = 0.05$[a]	Favours incentive vouchers	Yes	There appears 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	No. of opiate-free urine specimens	19 ± 14 vs 14 ± 12	$p = 0.04$[a]	Favours incentive vouchers	Yes	
	Incentive vouchers plus significant other involvement	Treatment retention	Weeks	7.4 ± 5.1 vs 5.6 ± 4.5	NR	Favours incentive vouchers	NR	
		Opioid use reduction	No. of opiate-free urine specimens	20 ± 16 vs 14 ± 12	NR	Favours incentive vouchers	NR	
Ball, 2004[58]	Incentive vouchers	Probability of opioid use (non-affective subtype)		NR	$p < 0.02$[a]	Favours control	Yes	These results were data driven subgroup analyses; caution is required in interpreting the results. Comparisons of the randomised arms were not reported
		Probability of opioid use (antisocial–narcissistic subtype)		NR	$p < 0.01$[a]	Favours control	Yes	
		Addiction severity index in alcohol composite severity (low psychiatric cluster)		NR	$p < 0.01$[a]	Favours control	Yes	

[a] The comparisons were done between two combined incentive voucher groups vs naltrexone without incentive voucher.

TABLE 13 *Results of naltrexone versus naltrexone with psychosocial therapies*

Study	Intervention	Outcome measure	Unit	Effect size	*p*-Value or 95% CI	Direction of effect	Significant
Callahan, 1980[59]	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[60]	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	No. of 50-mg 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[61,62]	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[63]	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 to 64 vs 34 to 74)	Favours control	No

TABLE 14 *Results of naltrexone versus naltrexone with pharmaceutical agents*

Study	Intervention	Outcome measure	Unit	Effect size	*p*-Value or 95% CI	Direction of effect	Significant
Landabaso, 1998[64]	Fluoxetine	Stopping treatment (6 months)	RR	1.63[a]	95% CI 1.00 to 2.70[a]	Favours fluoxetine	Yes
		Stopping treatment (12 months)	RR	1.31[a]	95% CI 0.97 to1.81[a]	Favours fluoxetine	No
		Stopping treatment (6 months)	Risk difference	0.18[a]	95% CI –0.002 to 0.35[a]	Favours fluoxetine	No
		Stopping treatment (12 months)	Risk difference	0.16[a]	95% CI –0.02 to 0.33	Favours fluoxetine	No
Farren, 2002[65]	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

[a] There were errors in calculation of relative risk and risk difference for abandonment proportion in the publication. The corrected figures are given in this table.

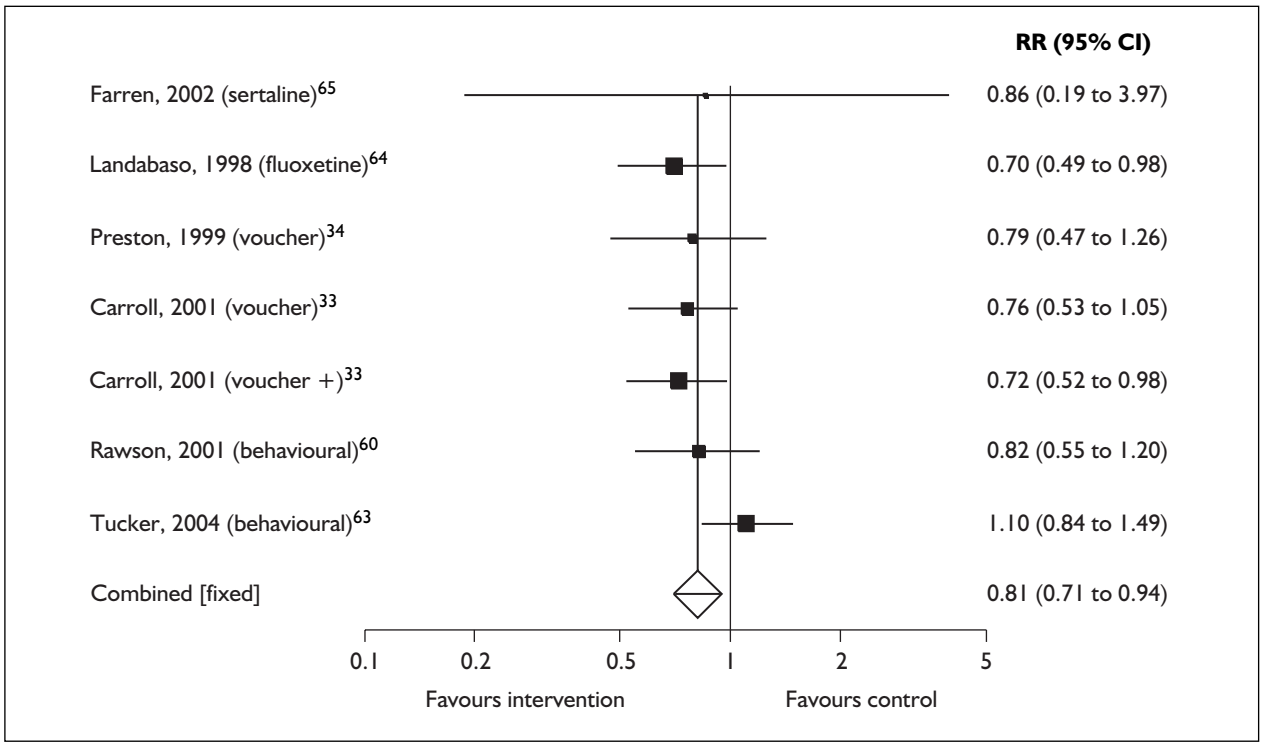

FIGURE 11 *Relative risk of stopping treatment: naltrexone versus naltrexone with care packages (meta-analysis plot, fixed effects)*

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

The relative risk of reincarceration in naltrexone showed results in favour of naltrexone in the combined two studies of parolees or people on probation (RR 0.50, 95% CI 0.27 to 0.91). The number of participants was small and the 95% confidence interval is wide.

One study[42] reported results using the RAB, which is a self-report instrument questionnaire measuring HIV risk. There was no significantly different improvement score between placebo and 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 arms.

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*.

All three modalities of enhanced care package, for which RCTs were identified, namely contingency management, behavioural therapy and pharmaceutical agents, showed 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 was 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 was too small to be able to draw any conclusions about its effectiveness or otherwise, and the results of the trial of fluoxetine

TABLE 15 *Summary of results for naltrexone trials*

Outcome measure	Estimate (95% CI)
Pooled RR of loss of retention in treatment in the naltrexone of seven RCTs	0.94 (0.84 to 1.06), ns
Pooled HR of five included RCTs for stopping in treatment data followed up to 35 weeks	0.90 (0.69 to 1.17), ns
Pooled RR of opioid use (from six RCTs)	0.72 (0.58 to 0.90), ss in favour of naltrexone
Pooled HR for no opioid relapse (from three RCTs)	0.53 (0.34 to 0.82), ss in favour of naltrexone
Pooled RR of reincarceration in naltrexone from two studies	0.50 (0.27 to 0.91)
RAB	Statistically significant improvement score in naltrexone for risky sexual behaviour
Adverse events reported in two RCTs	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 individuals
Any particular population of opioid users shown to benefit from naltrexone	No data

TABLE 16 *Summary of results for naltrexone with enhanced care packages*

Care package	Outcome measure	Estimate
Contingency management	Treatment retention (two RCTs)	7.4 weeks (mean) for intervention vs 2.3–5.6 weeks for control, favours intervention, ss
Psychosocial therapy	Length of time patients stayed on naltrexone (three RCTs)	84–103 days (mean) for intervention vs 43–64 days for control, favours intervention, ss within 52 weeks; 111 days (mean) for intervention vs 89 days for control, favours intervention, ns over 21 months; 50 days (median) for intervention vs 54 days for control, favours control, ns
	Opiate-free urine (three RCTs)	78–86% for intervention vs 69–75% for control, favours intervention, ss within 52 weeks; 93% for intervention vs 92% for control, favours intervention, ns over 21 months
Pharmaceutical agents	Retention in treatment (two RCTs)	RR of stopping treatment 1.63[a] and 1.31[a] at 6 months and 12 months, respectively, favours intervention, ss at 6 months, but not at 12 months; in a small study (13 patients), 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, ns
Pooled three modalities	Pooled RR of loss of retention in treatment between intervention and control (five RCTs, with one RCT having two types of intervention)	0.81 (95% CI 0.71 to 0.94), favours intervention, ss

[a] There were errors in calculating the relative risks.

may have nothing to do with enhancing the effectiveness of naltrexone, but may 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, which 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, in the Cochrane Library or on MEDLINE.)

Chapter 5
Economic analysis

Introduction

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

Methods

A decision tree (see Appendix 9) with Monte Carlo simulation was used which models drug use to 12 months, as data to support modelling beyond this period are not available and evidence suggests that naltrexone is rarely used long term by patients. The model estimates costs, from the perspective of the UK NHS and Personal Social Services (PSS), 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 that 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.

Description of the model

The model follows patients for 1 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 dropout rate is higher. The combined data show that dropout appears to stabilise around the 6-month stage. For each period, a utility value and cost are 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 were 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.

Estimation of model parameters

Retention in treatment

Data on retention in treatment were available in five trials that compared naltrexone with placebo, with or without psychosocial support given in both arms. The method for deriving the combined hazard ratios is discussed in the section 'Data analysis' (p. 12). Meta-analysis gave a hazard ratio for treatment retention at end of follow-up of 0.90 (95% CI 0.69 to 1.17) 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 were combined for the five trials identified in the review using Kaplan–Meier analysis with censoring of retained patients at end of follow-up (*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, to estimate retention in treatment for placebo (*Table 17*).

Level and nature of drug misuse

As some detoxified patients retained within a programme will still use drugs, data on the proportion of patients using drugs are required. The nature of their drug use, specifically if they are injecting drug users, is also important. Both parameters are required by the model to assign appropriate use of healthcare resources and utility values. The method of assigning resource use and utilities to different patient groups will be described in the relevant subsections.

Opioid-positive or opioid-negative urine data were reported in only one trial[42] and results from this trial are shown in *Table 8* (p. 22). It is important to note that as these data were only available from one trial, they should be viewed with some caution. The analysis assumes that having a

TABLE 17 *Retention in treatment with naltrexone versus placebo*

	Naltrexone			Placebo		
Week	**Retained**	**95% CI lower**	**95% CI upper**	**Retained**	**95% CI lower**	**95% CI upper**
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

negative urine means that the participants are drug free. For those not retained in treatment it was assumed that patients return to drug misuse irrespective of their period in the postdetoxification programme.

The estimates for the number of individuals injecting and not injecting were taken from the study by NTORS.[16] 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).

Resource use and costs

The perspective adopted for the reference case evaluation is that of the NHS and PSS, and the cost-effectiveness is expressed in terms of incremental cost per QALY. A non-reference case analysis also includes cost implications as far as possible for a societal perspective, which includes the CJS 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 estimate accurately 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 for weeks 2–4 and off treatment for weeks 4–6.

TABLE 18 *Naltrexone and placebo therapy resource use*

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

[a] Mattick *et al*. (2003).[67]

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 of 20 minutes' duration 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 were obtained from the Mattick trial,[67] and where no published standard deviations were available, the standard deviations for the probabilities were based on SD = rate/$\sqrt{(N)}$ (*Table 18*).

Data on resource use for the reference cases, required for the model, were extracted using data supplied by 'problem drug-users' within NTORS, which covered healthcare services, the CJS and employment. This study, described in detail by Gossop and colleagues,[16] 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 those reported by the NTORS participants in the 12 months before entering treatment and that drug misusers in naltrexone treatment have consequences experienced from the treatment programmes described in NTORS. No data were available on the social services costs of drug misuse; therefore, these costs are zero in the model.

NTORS recorded resource use of substance misusers and found higher rates of GP contacts and inpatient stays among those in short-term treatment. These items are presented in *Table 19*. Where published standard deviations were not available, the same approach as detailed above was used.

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.[69] The unit costs for an accident and emergency (A&E) visit and for inpatient hospital stays have been calculated using estimates provided by Godfrey and colleagues[70] and updated to 2004 figures using the Hospital and Community Health Services (HCHS) pay and prices index. Based on Godfrey,[70] the A&E cost assumes that many of these visits would be serious and therefore would involve an overnight stay. Godfrey and colleagues note 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 BNF (2005),[71] with naltrexone costing £1.52 per 50-mg tablet.

Societal perspective (non-reference case analysis)

NTORS[16,68] 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 NTORS are combined with unit cost information to estimate the total social costs associated with drug misuse. It is assumed that information supplied by clients before 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 NTORS. Godfrey and colleagues[70,72] 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 was higher for users in treatment in the first year than for 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

TABLE 19 *NHS/PSS perspective resource use and costs*

Healthcare costs	Resource use	Source	Unit cost (£)	Source	Total (£)
Successful health states					
(successful/drugs free/reduction/< 1 year)					
GP visits per year	5.6	Gossop, 2001[68]	21	Curtis and Netten, 2004[69]	118
Rate of A&E visits per year	0.8	Gossop, 2001[68]	318	Godfrey, 2002[70]	254.40
Rate of inpatient hospital stays per year	2.8	Gossop, 2001[68]	251	Godfrey, 2002[70]	702.80
Rate of outpatient mental health visits per year	0.8	Gossop, 2001[68]	56	Godfrey, 2002[70]	45
Rate of inpatient mental health visits per year	0.4	Gossop, 2001[68]	162	Godfrey, 2002[70]	64.80
Total annual healthcare costs					**1,184**
Unsuccessful health states					
(unsuccessful/drugs misused)					
GP visits per year	3.6	Gossop, 2001[68]	21	Curtis and Netten, 2004[69]	76
Rate of A&E visits per year	0.7	Gossop, 2001[68]	318	Godfrey, 2002[70]	222.60
Rate of inpatient hospital stays per year	1.75	Gossop, 2001[68]	251	Godfrey, 2002[70]	439
Rate of outpatient mental health visits per year	1.3	Gossop, 2001[68]	56	Godfrey, 2002[70]	72.80
Rate of inpatient mental health visits per year	1.5	Gossop, 2001[68]	162	Godfrey, 2002[70]	243
Total annual healthcare costs					**1,053**

treatment, treatment of less than 1 year and treatment of more than 1 year, respectively. The cost of overnight stays is estimated at £69 per stay. Godfrey and colleagues[70] used estimates provided by Brand and Price[73] 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 20*.

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 coordinated 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. The results of the reviewers' own utility exercise coordinated by PenTAG are used in the reference case analysis of the current TAR.

The Value of Health Panel is coordinated 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 the National Institute for Health and Clinical Excellence (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 five health states was 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.

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 according to the proportion of patients in each possible health state while on treatment. The QALY was obtained from the utilities provided by using the average proportion of patients in treatment still taking drugs, taking into account the percentage injecting, and the proportion of patients drug free while on treatment. However, it is important to note that the data providing the proportion of opioid-positive patients while on treatment 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 21*.

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

Assessment of cost-effectiveness

Data on the incremental cost per QALY are presented in two ways. First, mean costs and QALYs for the alternative interventions are presented and the incremental cost per QALY is calculated where appropriate. The second mode of presentation uses the results of the probabilistic sensitivity analysis and shows cost-effectiveness acceptability curves (CEACs) and scatterplots 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 that a strategy is cost-effective at

TABLE 20 *Societal perspective resource use and costs*

Social costs	Resource use	Source	Unit cost (£)	Source	Total (£)
Successful health states					
(successful/drugs free/reduction/<1 year)					
CJS costs					
Rate of drug arrests per year	0.8	NTORS[16]	3,551	Godfrey, 2002[70]	2,840.80
Rate of acquisitive crime arrests per year	1.6	NTORS[16]	1,346	Godfrey, 2002[70]	2,153.60
Average time held in policy custody per year (nights)	1.2	NTORS[16]	69	Godfrey, 2002[72]	82.80
Rate of court appearances in 1 year	1.4	NTORS[16]	699	Harries, 1999[74]	978.60
Time spent in prison per year (days)	34	NTORS[16]	68.86	Godfrey, 2002[72]	2,341
Total annual CJS costs					**8,397**
Annual victim costs			**8,893**	**Godfrey, 2002[70]**	**8,893**
Total annual social costs					**17,290**
Unsuccessful health states					
(unsuccessful/drugs misused)					
CJS costs					
Rate of drug arrests per year	0.3	NTORS[16]	3,551	Godfrey, 2002[70]	1,065.30
Rate of acquisitive crime arrests per year	1.35	NTORS[16]	1,346	Godfrey, 2002[70]	1,817.10
Average time held in policy custody per year (nights)	2	NTORS[16]	69	Godfrey, 2002[72]	138
Rate of court appearances in 1 year	2.2	NTORS[16]	699	Harries, 1999[74]	1,537.80
Time spent in prison per year (days)	36	NTORS[16]	68.86	Godfrey, 2002[72]	2,479
Total annual CJS costs					**7,037**
Annual victim costs			**30,827**	**Godfrey, 2002[70]**	**30,827**
Total annual social cost					**37,864**

TABLE 21 *Estimated QALYs for patients in treatment*

Treatment	Mean	SD
Naltrexone	0.8351	0.1607
Placebo	0.8383	0.1599

TABLE 22 *Distributions and parameter values used in probabilistic sensitivity analysis*

Parameter	Normal distributions	
	Mean	**SD**
Survival analysis		
Log of HR 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
No. of urine tests (per week)	0.5	0.025

Parameter	Beta distributions		
	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

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 22*. The model was run for 10,000 simulations.

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 CJS and victims of crime. The associated resource-use and unit costs have been described previously.

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 the 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) (£8893) and those who have dropped out of treatment (£30,827). Therefore, the impact of the inclusion of these costs was assessed by conducting the societal perspective evaluation with costs to the CJS only.

Results

Reference case

Table 23 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 incremental cost-effectiveness ratio (ICER) of £42,500 per QALY gained.

TABLE 23 *Cost-effectiveness results of naltrexone (with psychosocial support) versus placebo (with psychosocial support)*

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

TABLE 24 *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 (£ per QALY)
Naltrexone	31,244		0.7161		
Placebo	31,716	472	0.7105	–0.0056	Dominated

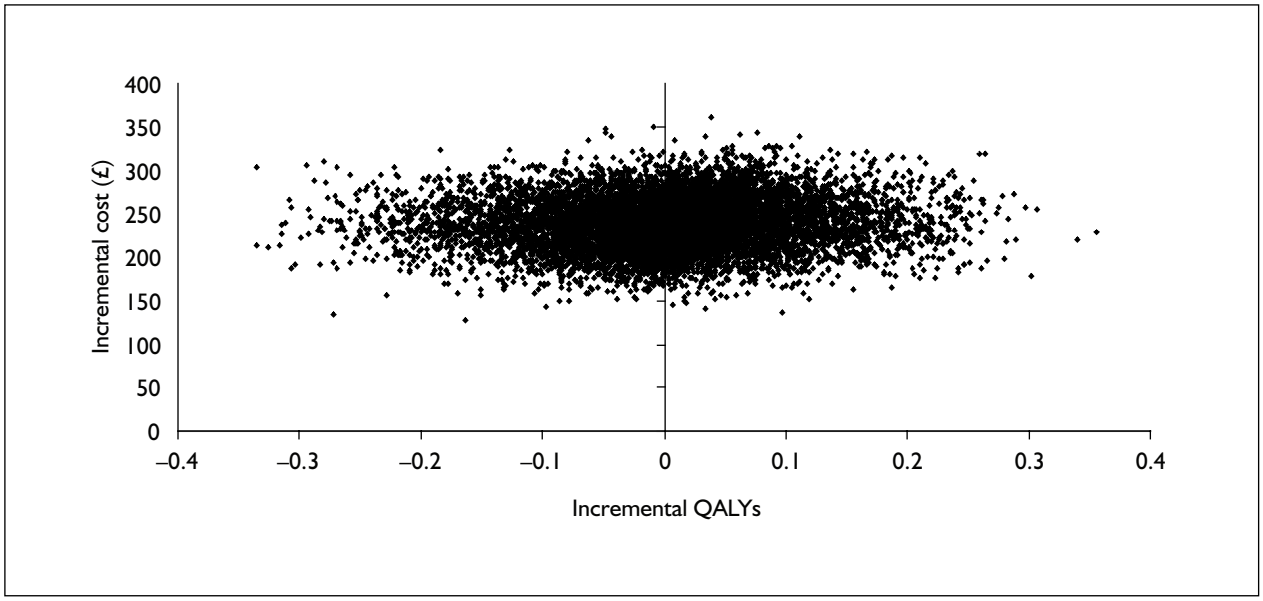

FIGURE 12 *Incremental cost-effectiveness plane for naltrexone versus placebo*

Non-reference case analysis: societal perspective

Costs to the CJS 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 24* and show that treatment with naltrexone dominates placebo.

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.

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 25*). 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.

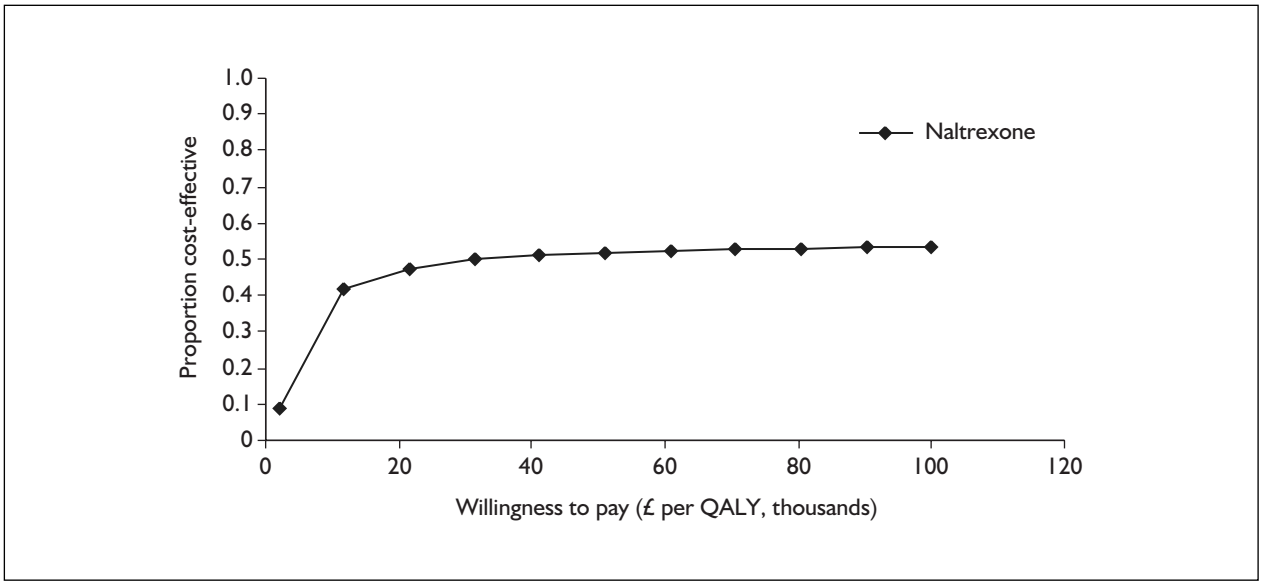

FIGURE 13 *CEAC for naltrexone compared with placebo*

TABLE 25 *Sensitivity analysis: cost-effectiveness results of naltrexone (with psychosocial support) versus placebo (with psychosocial support)*

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

TABLE 26 *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 (£ per QALY)
Placebo	8799		0.7105		
Naltrexone	9085	286	0.7161	0.0056	51,071

Removing victim costs of crime changed the result from naltrexone dominating placebo to naltrexone having an ICER of £51,071 per QALY gained (*Table 26*), demonstrating the considerable impact that the level of victim costs has on the results.

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, no quality of life data were available for this treatment. To the authors' knowledge, this 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 few data are currently available; 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. The authors consider this to be a reasonable non-pharmacological comparator and the second systematic review of interventions to enhance the effect of naltrexone shows this to be appropriate. As there were no

data on the pathway of patients who drop out of either treatment, the model assumes that in both arms patients who drop out of treatment return to their pretreatment behaviour. The effect on the cost-effectiveness estimates is uncertain; therefore, follow-up of patients dropping out of treatment should be considered in future research.

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 the model outcomes. In addition, the values had the advantage of being population-based estimates rather than 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.

Subgroup analysis, for example, concentrating on patients with mental health problems or different detoxification pathways would undoubtedly be of value. However, owing 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. This reflects the fact that patients in the naltrexone arm spend slightly longer in treatment. Less crime is likely to be committed while on treatment; therefore, CJS costs are lower overall for these patients. 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. It is important to note that the CJS costs alone were higher for patients in treatment than those out of treatment. The report containing these 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 owing to slightly higher retention in treatment (and therefore higher CJS costs) and cost of naltrexone. The inclusion of victim costs reverses the cost difference owing to these costs being very much higher when patients have dropped out of treatment. It is important to note that wider social impacts of drug use were not considered in this model because of a lack of data; these include the impact on family life, unemployment and social services costs.

Only one trial reported data on the level of drug use while on treatment. As these data were required to determine both resource use and utilities to calculate QALYs, the uncertainty surrounding these data could have a major impact on the results. The sensitivity analysis 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 makes naltrexone appear dominant over psychological support; however, the proportion of patients incurring the higher victim costs will be only marginally different for naltrexone and placebo.

In conclusion, the authors have some serious concerns 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 are available for subgroup analysis. The data on CJS resource-use and victim costs are also of some concern. Therefore, extreme caution is required when using the modelling results to inform policy decisions. More, better quality evidence is required.

Given the uncertainty already in the model, it was felt that it would not add value to proceed to model the use of a contingency management programme. These programmes 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%.

Chapter 6
Discussion

Twenty-six studies fulfilled the inclusion criteria for this report: one systematic review, 22 RCTs and three comparative but not randomised studies. There were no economic evaluations.

The methodological quality of the RCTs was generally poor. Only three out of 22 had a Jadad score of 3, and the rest scored 2 or less. Only three out of 22 reported that allocation was concealed and none reported a power calculation or the required sample size before 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 seven included RCTs showed that the relative risk of loss of retention in treatment in the naltrexone arm was 0.94 (95% CI 0.84 to 1.06). The pooled hazard ratio from the 5 included RCTs for retention in treatment data followed up to 35 weeks was calculated as 0.90 (95% CI 0.69 to 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 versus placebo with or without psychological support given in both arms. The pooled relative risk from six RCTs was 0.72 (95% CI 058 to 0.90), which is a statistically significant difference favouring naltrexone. The pooled hazard ratio from three RCTs for being free of opioid relapse was significantly different from placebo in favour of naltrexone (HR 0.53, 95% CI 0.34 to 0.82). However, this effect can be seen to fall off over time and its clinical significance is unclear.

The relative risk of reincarceration in the two studies of parolees or of people on probation also favoured naltrexone (combined RR 0.5, 95% CI 0.27 to 0.91), although the number of participants was small. There was no statistically significant difference in improvement in score on a self-report instrument from measuring risky sexual behaviour between the naltrexone and placebo groups; however, there were only 52 participants in this study.[42]

The adverse events data reported in the included studies showed no significant difference between naltrexone and placebo arm for any serious adverse event.[41,45]

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

The updated, but at the time unpublished, Cochrane systematic review included ten RCTs (personal communication with the authors), all of which plus three additional trials were included in the review on the effectiveness of naltrexone. The authors of the Cochrane review 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 the present authors' conclusions.

The present review added three extra trials, the survival analysis of data for loss of retention in treatment, 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: 25 mg (half a tablet) on day 1, followed by 50 mg (one tablet) daily from day 2 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 of contingency management programmes has also been shown to increase compliance. However, this is a rapidly changing clinical area and refinements to care packages by introducing such changes will probably be overtaken by the new formulations with alternative routes of administration. Subcutaneous implants are already being used unlicensed by private clinics and are likely to be licensed for use in the near future.

The economic evaluation was a *de novo* cost–utility analysis for the use of naltrexone. It is a decision-analytic model using Monte Carlo simulation and compares naltrexone as an adjunctive therapy with 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 were found in relation to societal function, utilisation of the healthcare system or heroin overdose in association with naltrexone.

The model, for the NICE reference case, gave an estimate for the cost-effectiveness of naltrexone of £42,500 per QALY. Sensitivity analysis was carried out and the ICER varied from £34,600 to £42,500 per QALY gained. Because of the uncertainty in the parameters, the CEACs never went 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 studies 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 hazard ratios for retention in treatment on naltrexone in five RCTs was not reported in any other systematic review or any of the primary included RCTs. Furthermore, the very limited useful published literature data on quality of life associated with illicit drug use led to entirely new data being commissioned 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 were no primary data that enabled the mortality rate associated with oral naltrexone treatment to be quantified. The mortality data are 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 NCIS report showed 32 deaths related to the use of naltrexone in one year.[15] 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.

It was not possible to identify specific population at risk who will benefit most from naltrexone within the studies of randomised controlled design. However, the increased effectiveness of contingency management programmes suggests 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 reincarceration rates did. Naltrexone may 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. Some uncontrolled studies[29,31] claim a particular benefit of naltrexone as an adjunct in the maintenance of an opioid free state in professional groups. For example, in a retrospective study of 20 health professionals who were formerly opioid dependent, treated over a 5-year-period, the mean overall duration of naltrexone administration was 8 months and the mean duration in the programme was 1.9 years.[31] Ninety-four per cent of referred clients had long-term abstinence and 66% were working in their profession during the programme. These results are better than the rates shown in the RCTs. Thus, naltrexone in the setting of a structured programme may be helpful in the treatment and professional reinstatement of opioid-abusing professionals.[31] However, such evidence is far from conclusive.

Chapter 7
Further research

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

There is an important deficit in information about the quality of life of people who use illicit opioids and this would seem to be a worthwhile area of research in that it would inform many different policy questions about the cost-effectiveness of different programmes and interventions.

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 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), such as professional people or those wishing to avoid further contact with the CJS.

Depot preparations are likely to be licensed in the future and it will be important to review systematically 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 rates 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. Such monitoring may also be particularly important as longer lasting routes of administration such as subcutaneous 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.

In addition, further economic evaluations of treatments for drug misuse that collect data on use of health services, social services and contacts with the CJS would be of great value for future evaluations.

Chapter 8

Factors relevant to the NHS

It is clear from prescription data (see Chapter 2) that naltrexone is currently not used widely within the NHS. Based on current cost, estimated average dose and dose duration, probably fewer than 1500 patients use naltrexone each year (about 500 person-years of use per annum) and not all of this is 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 is being treated with these drugs on 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 greatly 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 in the NHS. However, the data are consistent with naltrexone's being potentially useful in those for whom maintenance therapy is not an option, and the budget impact on the NHS is likely to be minimal if naltrexone is approved for use in the NHS by NICE.

Chapter 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 to 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 to reduce reincarceration rates and opiate use.

The cost-effectiveness model presented here does not, however, demonstrate that naltrexone is clearly cost-effective from an NHS perspective. The point estimate compared with placebo was £42,500 per QALY and the probabilistic sensitivity analysis showed that naltrexone never has a probability of above around 50% for being cost-effective for any threshold over £30,000 per 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 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 higher than that estimated from the trials and the ICER will be correspondingly lower. Given the uncertainty in the data, the huge sensitivity of the ICER to estimates of quality of life, the fact that the drug cost of naltrexone is small (it costs around £500 to treat one patient for 1 year) and 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 the 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.

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Contribution of authors

Yaser Adi (Systematic Reviewer) coordinated the clinical evidence aspects of the review, applied the inclusion and exclusion criteria, extracted data, appraised studies, conducted meta-analysis, contributed to the drafting of the clinical effectiveness, results and discussion sections of the report, and helped in sorting out references. Ariadna Juarez-Garcia (Research Fellow) developed the Birmingham economic model and contributed to the writing of the economic sections of the report. Dechao Wang (Systematic Reviewer) applied the inclusion and exclusion criteria, extracted data, appraised studies, conducted the survival analysis, contributed to the drafting of the clinical effectiveness section of the report and helped in sorting out references. Sue Jowett (Research Fellow) contributed to the development of the Birmingham economic model and contributed to the writing of the economic sections of the report. Emma Frew (Research Fellow) collected and summarised the cost data for use in the model and contributed to the definition of health states. Ed Day (Senior Lecturer) drafted the introduction section and commented on all other sections of the report, particularly the conclusions. Sue Bayliss (Information Specialist) carried out the searches and wrote up part of the methods section and appendices in the final report in relation to the searches. Tracy Roberts (Senior Lecturer) supervised the economic section of the project and contributed to the writing of the economic sections of the report. Amanda Burls (Senior Lecturer) supervised the project, wrote sections of the report, commented on all sections, and compiled and edited the final report.

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Appendix 1

Health states and utilities derived from the Value of Health Panel

TABLE 27 *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	0.525–1
On treatment: drugs reduction (injectors)	22	0.6332	0.2075	0.6875	0.275–0.935
On treatment: drugs reduction (non-injectors)	22	0.6834	0.2037	0.7250	0.325–0.98
Not on treatment: drug misusers, injectors	22	0.5880	0.2115	0.6375	0.125–0.96
Not on treatment: drug misusers, non-injectors	22	0.6780	0.2069	0.7375	0.275–0.98

Health state scenarios

Assume on treatment

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.

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.

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

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.

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

Clinical effectiveness and cost-effectiveness searches

Clinical effectiveness searches

Systematic reviews

MEDLINE (Ovid) 1966 to July week 4 2005

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

EMBASE (Ovid) 1980 to 2005 week 36

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

Cochrane Library search (Wiley version) 2005 Issue 2 (CDSR, DARE, HTA databases)

#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)

RCTs

MEDLINE(Ovid) 1966 to July week 4 2005

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

MEDLINE(R) In-Process and Other Non-Indexed Citations (Ovid) at 3 August 2005

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

Cochrane Library (Wiley version) 2005 Issue 2 (CENTRAL)

See Cochrane Library search in Clinical effectiveness searches (Systematic reviews), above.

EMBASE (Ovid) 1980 to 2005 week 36

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

CINAHL (Ovid) 1982 to July week 5 2005

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

PsycINFO (Ovid) 1967 to August week 1 2005

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"

Science Citation Index and Social Science Citation Index (Web of Science) 1970 to 6 September 2005

(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)

Cost-effectiveness, quality of life and outcomes searches

MEDLINE cost search

MEDLINE (Ovid) 1966 to July week 4 2005

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

MEDLINE (Ovid) 1966 to July week 4 2005

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

MEDLINE (Ovid) 1966 to July week 4 2005

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

EMBASE (Ovid) 1980 to 2005 week 32

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

EMBASE (Ovid) 1980 to 2005 week 32

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

OHE HEED August 2005 issue

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

Cochrane Library (Wiley version) (NHS EED) 2005 Issue 2

See Cochrane Library search in Clinical effectiveness searches (Systematic reviews).

Appendix 3

Characteristics of excluded studies

Reasons for exclusion are given in parentheses.

Amato L, Davoli M, Perucci AC, Ferri M, Faggiano F, Mattick PR. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat* 2005;**28**:321–9. (No relevant data.)

Berglund M. A better widget? Three lessons for improving addiction treatment from a meta-analytical study. *Addiction* 2005;**100**:742–50. (No relevant data.)

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.)

Rayburn WF, Bogenschutz MP. Pharmacotherapy for pregnant women with addictions. *Am J Obstet Gynecol* 2004;**191**:1885–97. (No relevant data.)

Tucker T, Ritter A, Maher C, Jackson H. Naltrexone maintenance for heroin dependence: uptake, attrition and retention. *Drug Alcohol Rev* 2004;**23**:299–309. (No comparator.)

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. *Addiction* 2002;**97**:1395–404. (No comparator.)

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 Depend* 2002;**66** (Suppl 1): S152. (No comparator.)

Study ID Numbers: NIDA-09262-4; P50-09262-4; 2002. (No relevant data.)

Study ID Numbers: NIDA-09260-2; P50-09260-2. (No relevant data.)

McCance-Katz EF, Rainey PM, Friedland G, Kosten TR, Jatlow P. Effect of opioid dependence pharmacotherapies on zidovudine disposition. *Am J Addict* 2001;**10**:296–307. (No relevant data.)

Rothenberg JL, Sullivan MA, Church SH, Nunes EV. Retention in treatment: a controlled trial of behavioral naltrexone therapy (BNY) vs compliance enhancement. *Drug Alcohol Dependence* 2001;**63**(Suppl 1):135. (No relevant comparator.)

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 Anaesthesiol Scand* 2000;**44**:326–33. (No comparator.)

Jelovac N, Milas M, Golik-Gruber V. Naltrexone is efficient in maintaining heroin abstinence of selected groups of addicts. *Alcoholism* 2000;**36**:73–7. (Not obtainable.)

Schmitt JM, Stotts AL, Rhoades HM, Grabowski J. Naltrexone combined with relapse prevention for the treatment of cocaine dependence. *NIDA Res Monogr* 2000;**180**:112. (No opioid-dependent patients.)

Schuh KJ, Walsh SL, Stitzer ML. Onset, magnitude and duration of opioid blockade produced by buprenorphine and naltrexone in humans. *Psychopharmacology* 1999; **145**:162–74. (No relevant data.)

Study ID Number: IAAABRA11747; 1999. (No relevant data.)

Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. 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**:465–8. (No relevant data.)

Rounsaville BJ, Carroll KM, Fenton LR. Enhancing naltrexone treatment after detoxification. *151st Annual Meeting of the American Psychiatric Association Toronto*, Ontario, Canada, 30 May–4 June 1998 (No. 112E). (No comparator.)

Seracini AM, Kleber HD, Rothenberg J, Sullivan M, Collins E, Nunes EV. Behavior naltrexone therapy for opiate dependence preliminary report. *NIDA Res Monogr* 1998;**179**:131. (Not obtainable.)

Study ID Numbers: NIDA-5-0012-5; Y01-5-0012-5; 1996. (No relevant data.)

Allen JP, Litten RZ, Fertig JB. NIDA–NIAAA workshop: efficacy of therapies in drug and alcohol addiction. Strategies for treatment of alcohol problems. *Psychopharmacol Bull* 1995;**31**:665–9. (Alcohol only.)

Kleber HD, Kosten TR, Gaspari J, Topazian M. Nontolerance to the opioid antagonism of naltrexone. *Biol Psychiatry* 1985;**20**(1):66–72. (No comparator.)

Kleber HD, Kosten TR, Gaspari J, Topazian M. Nontolerance to the opioid antagonism of naltrexone. *Biol Psychiatry* 1985;**20**:66–72. (No comparator.)

Kosten TR. Buprenorphine for benzodiazepine-abusing heroin addicts. *Am J Psychiatry* 1994;**151**:151. (No relevant data.)

Mello NK, Mendelson JH, Kuehnle JC, Sellers MS. Operant analysis of human heroin self-administration and the effects of naltrexone. *J Pharmacol Exp Ther* 1981; **216**:45–54. (No relevant data.)

Bradford A, Hurley F, Golondzowski O, Dorrier C. Interim report on clinic intake and safety data collected from 17 NIDA-funded naltrexone studies. *NIDA Res Monogr* 1976;(9):163–71. (Review.)

Keegan J, Lavenduski C, Schooff K. Comments and findings from a naltrexone double blind study. *NIDA Res Monogr* 1976;(9):74–6. (No relevant data.)

Appendix 4

Quality assessment of systematic reviews

TABLE 28 *Quality assessment of systematic reviews*

Questions	Score	Kirchmayer, 2003[39]
Search methods reported and comprehensive search? (Q1 and Q2)	Score Q1: 2 Yes Score Q2: 2 Yes	Many databases were searched, including MEDLINE (1997–2000) and EMBASE (1974–2000); some sources were handsearched and references of relevant lists studies were searched. Authors and pharmaceutical industry were contacted. Updated search was conducted in February 2003
Inclusion criteria reported? (Q3)	Score Q3: 2 Yes	Extensive criteria were clearly defined. Only controlled trials were considered in humans. The populations were opioid dependent. 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 was considered, and the control group was treated with placebo or other treatment without naltrexone. Four main outcomes were stated: three dichotomous outcomes and one continuous outcome
Selection bias avoided? (Q4)	Score Q4: 1 Partially	Two reviewers independently assessed the inclusion criteria. A third reviewer was consulted if there was 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 (adequately allocation concealment), B as a 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 Q5 were 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-analytical 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 was 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 populations may benefit is not supported by the data analysed by this review The main results stated were: treatment dropout: 0.78 (0.24 to 1.75), opioid use under treatment: 0.85 (0.45 to 1.62), reincarcerations 0.30 (0.12 to 0.76) and mean duration of treatment 20.30 (–1.59 to 42.19)

Quality assessment of systematic reviews

A modified version of the Oxman and Guyatt assessment tool and scale was used to assess the quality of reviews. This consists of nine quality interrogations, each answerable as 'yes', 'no' or 'partially/can't tell', carrying scores of 2, 0 and 1, respectively. The nine 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 computerised 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 was 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***, inclusion and exclusion criteria clearly defined. ***2 points***
   - ***Partially***, reference to inclusion 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 5

Quality assessment of included RCTs

TABLE 29 *Quality assessment of included RCTs*

Study	Was assignment of treatment described as random?	Was method of randomisation 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,[43] 2004[42]	Y	Y	Y	CT	DB	N	Y	Y	Y	Y	Y	Y	N	2
Grinenko, 2003[44]	Y	N	Y	Y	DB	N	Y	Y	Y	Y	N	N	N	2
Guo, 2001[45]	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[46]	Y	N	N	N	N	N	CT	Y	Y	CT	CT	N	N	1
Shufman, 1994[47]	Y	N	CT	CT	DB	N	Y	Y[a]	Y	Y	CT	CT	N	2
Lerner, 1992[48]	Y	N	Y	Y	DB	Y	Y	CT	Y	Y	N	N	N	3
San, 1991[49]	Y	N	CT	CT	DB	N	Y	Y	Y	Y	Y	Y	N	2
Ladewig, 1990[50]	Y	N	CT	CT	N	CT	Y	CT	CT	N	Y	N	N	1
Brahen, 1977,[52] 1979[51]	Y	N	CT	CT	DB	N	N	Y	CT	N	N	N	N	2
Rawson, 1979[53]	Y	N	CT	CT	N	N	Y	CT	CT	N	N	N	N	2
Hollister, 1978[54]	Y	N	N	CT	DB	N	Y	CT	CT	N	N	N	N	2
Curran, 1976[41]	Y	CT	CT	CT	DB	N	CT	Y	CT	CT	N	N	N	2

[a] Except for average working days in the preceding year placebo > naltrexone.
CT, can't tell; DB, double blinded; N, no; Y, yes.

Appendix 6

Quality assessment of included comparative studies

TABLE 30 *Quality assessment of included comparative studies*

Study	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?	Were missing data (group or time-point data) accounted for?
Arnold-Reed, 2003[55]	Y	Y	CT	N	CT	N	CT
Sivolap, 1998[56] (translation)	Y	N	N	N	CT	CT	CT
Judson, 1984[57]	Y	N	CT	Y	CT	N	CT

Appendix 7

Characteristics of included studies

TABLE 31 *Characteristics of included studies*

Study	Design	Population	Sample size (*N*)	Intervention	Comparator	Outcomes	Period of follow-up
Systematic reviews							
Kirchmayer, 2002, 2003.[39,40] The update, 2005, was later published as: Minozzi, 2006[75]	Systematic review of RCTs and controlled clinical trials on naltrexone treatment for opioid dependence. Cross-over studies have been excluded	All inpatients and outpatients 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	Ten studies, 696 participants	Naltrexone; naltrexone plus psychosocial therapy	Several comparators: Naltrexone vs placebo and naltrexone plus psychosocial therapy vs placebo plus psychosocial therapy: seven studies, 444 participants Naltrexone vs placebo: four studies, 329 participants Naltrexone plus psychosocial therapy vs placebo plus psychosocial therapy: three studies, 115 participants Naltrexone vs psychosocial therapy: two studies, 146 participants Naltrexone vs naltrexone plus psychosocial therapy: one study, 110 participants Naltrexone plus psychosocial therapy vs psychosocial therapy alone: two studies, 177 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 participants reincarcerated during the treatment	Mean duration: 6 months (range 1–10 months)

continued

TABLE 31 *Characteristics of included studies (cont'd)*

Study	Design	Population	Sample size (*N*)	Intervention	Comparator	Outcomes	Period of follow-up
RCTs							
Krupitsky, 2004[42,43] (Russia)	RCT (double-blind); naltrexone and placebo prepared by the pharmacy in identical capsules; code of randomisation kept by the pharmacy	Opioid-dependent patients abstinent from heroin for ≥ 1 week. Mean age: 22 years; patients dependent on heroin for 2.5 years on average; male: 80%; patients who completed secondary school: 88%	52	Naltrexone plus fortnightly drug counselling; doses and frequency of administration not specified (6 months)	Placebo and fortnightly drug counselling	Relapse rate; retention rate; side-effects; HIV risk; alcohol use; other drugs; craving for heroin	6 months
Grinenko, 2003[44] (Russia) (translation)	RCT	Heroin addicts in south Petersburg regional hospital	52	Naltrexone plus psychotherapy (6 months)	Placebo plus psychotherapy	Remission at 6 months	Not clear, probably all until 6 months
Guo, 2001[45] (China)	Randomised, placebo-controlled trial; used random number tables. Ratio of patients receiving naltrexone to those receiving placebo: 2:1 Double-blind, metacentre study	Heroin addicts who completed detoxification without using opiates for ≥ 5–7 days before naltrexone treatment. Mean age: 24.96 years naltrexone, 26.76 years placebo; male: 88.57% naltrexone, 92.86% placebo	49	Naltrexone (6 months)	Placebo	Urine tests; adverse effects; euphoric effects of heroin; duration of abstinence; relationship between heroin effects and naltrexone dose	6 months
Cornish, 1997[32] (USA)	RCT. Ratio of patients receiving naltrexone to those receiving placebo: 2:1 Not blinded	Historical opioid addicts	51	Naltrexone plus minimal counselling and probation programme (6 months)	Probation programme and minimal counselling	Retention rate; urine test (opioid use); drug-free rate; probation status	6 months

continued

TABLE 31 *Characteristics of included studies (cont'd)*

Study	Design	Population	Sample size (*N*)	Intervention	Comparator	Outcomes	Period of follow-up
Gerra, 1995[46] (Italy)	RCT	Heroin-abusing patients	152	Naltrexone and clonidine (3 months)	Clonidine only; naloxone and clonidine; placebo	Dropout percentage; morphine metabolites	6 months
Shufman, 1994[47] (Israel)	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 effects; heroin-positive urine test; improvement in mental parameters	12 weeks
Lerner, 1992[48] (Israel)	Randomised, placebo-controlled trial, double-blind	Opioid-dependent patients	31	Naltrexone plus psychotherapy and counselling (2 months)	Placebo plus psychotherapy and counselling	Retention rate; craving; attempting drug	1 year
San, 1991[49] (Spain)	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[49] (Switzerland)	Open, RCT	20 detoxified opioid addicts, male and female; age range: 20–35 years; opioid free for ≥ 10 days	20	Naltrexone plus basic psychosocial programme; outpatients. Naltrexone: induction: 50 mg per day for 3 weeks; then Monday 100 mg, Wednesday 100 mg, Friday 150 mg Psychotherapy: daily group therapy plus weekly individual therapy Study duration: NR (duration of treatment of patients: range 34–124 days)	Basic psychosocial programme alone	Use of substance of abuse measured by urinalysis, adverse effects	Mean 69 days naltrexone group, mean 49 days control group

continued

TABLE 31 *Characteristics of included studies (cont'd)*

Study	Design	Population	Sample size (*N*)	Intervention	Comparator	Outcomes	Period of follow-up
Brahen, 1979[51,52] (USA)	Double-blind RCT (cross-over)	Former opiate addicts	40	Naltrexone (20 days)	Cyclazocine; placebo	Incidence of side-effects	20 days
Rawson, 1979[53] (USA)	RCT, not double-blind	Heroin addicts	181	Naltrexone *or* naltrexone plus behaviour therapy (30 weeks)	Behaviour therapy	Programme entry (probationary period); treatment duration; therapeutic assignments; urinalysis; incarceration	1 year
Hollister, 1978[54] (USA)	Multicentric, randomised, placebo-controlled, double-blind	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 programme (92)	192	Naltrexone vs placebo. Number of patients randomised to each group not specified; outpatients Detoxification with methadone at tapered doses for 21 days followed by 7–14 days with inert methadone 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 to a dose of 100 or 150 mg on the 7th day, then 100 mg per day and 150 mg on Saturday; dose not given on Sunday Study duration: 9 months	Placebo	Retention rate; urine test; acceptance; craving scale; toxicity; adverse effects	9 months

continued

TABLE 31 *Characteristics of included studies (cont'd)*

Study	Design	Population	Sample size (*N*)	Intervention	Comparator	Outcomes	Period of follow-up
Curran, 1976[41] (USA)	Randomised, placebo-controlled trial, double-blind	NR	38	Naltrexone (92 days)	Placebo	Successful completion	9 months
Controlled clinical trial							
Arnold-Reed, 2003[55] (Australia)	Historical controlled, retrospective audit records	Death-related heroin users	92	Naltrexone	Non-naltrexone	Heroin-related mortality	2 years
Sivolap, 1998[56] (Russia)	Unclear, probably a description of irregular practice	Opioid-dependent patients	120	Naltrexone	Nothing	Leaving the programme; no use of opiates at 12 months	>6 months
Judson, 1984[57] (USA)	Controlled, not randomised	Heroin addicts	117	Naltrexone after 6-month LAAM programme (1 year)	Not enter naltrexone after 6-month LAAM programme	Not using heroin, using heroin daily or less than daily; months incarcerated; use of other opiates; employment; school attendance	1 year

Appendix 8

Results of included studies

TABLE 32 *Results of included studies*

Study	Main findings			
	Use of primary substance of abuse	**Retention in treatment**	**Adverse events**	**Other**
Systematic reviews				
Kirchmayer, 2002, 2003.[39,40] The update, 2005, was later published as: Minozzi, 2006[75]	Naltrexone vs placebo and naltrexone plus psychosocial therapy versus placebo plus psychosocial therapy: six studies combined show RR 0.72 (95% CI 0.58 to 0.90)	Naltrexone vs placebo and naltrexone plus psychosocial therapy vs placebo plus psychosocial therapy: five studies combined, RR 1.08 (95% CI 0.74 to 1.57) Naltrexone vs placebo: two studies combined, RR 0.50 (95% CI 0.20 to 1.24) Naltrexone plus psychosocial therapy vs placebo plus psychosocial therapy: three studies, RR 0.38 (95% CI 0.9 to 2.10) Naltrexone vs placebo and naltrexone plus psychosocial therapy vs placebo plus psychosocial therapy: five studies, RR 1.08 (95% CI 0.74 to 1.57)	No statistically significant difference found in side-effects comparing naltrexone with any comparators	Reincarceration rate: no statistically significant difference, but there is a trend in favour of naltrexone treatment
RCTs				
Krupitsky, 2002,[43] 2004[42]	827 (29.6%) naltrexone vs 1825 (72%) placebo ($p < 0.01$)	Significantly higher in naltrexone patients from 1 month throughout the study. At the end of 6 months 12/27 naltrexone patients (44.4%) vs 4/25 (16%) in the control ($p < 0.05$) Naltrexone retention in treatment: HR 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. 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 on a 10-point scale from baseline at 1 month ($p < 0.05$) *Alcohol use*: increased significantly at first 4 months *Use of other illicit drugs*: no difference *Compliance*: high in those who 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 for 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

continued

TABLE 32 *Results of included studies (cont'd)*

Study	Main findings			
	Use of primary substance of abuse	**Retention in treatment**	**Adverse events**	**Other**
Grinenko, 2003[44] (translation)	NA	Remission at 6 months: 16% naltrexone vs 44% control	NA	NA
Guo, 2001[45]	Abstinence rate: at 6 months in the RCT study 31.4% naltrexone vs 7.1% placebo Average abstinence period for naltrexone group was significantly longer	NA	Only 'cold flush' in naltrexone was reported as significant compared with placebo: 9/35 vs 0/14	*No euphoric effects*: 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%) placebo ($p < 0.01$) *In the open study*: abstinence rate 23.6% naltrexone vs 1.2% unassisted abstinence Urine test positive in 24.38% naltrexone vs 40.48% placebo ($p < 0.05$)
Cornish, 1997[32]	NA	Retention rate was not significantly higher than that of control: 52% naltrexone vs 33% control Naltrexone retention in treatment: HR 0.7 (95% CI 0.43 to 1.5)	NA	Mean positive urinalysis 8% naltrexone vs 30% placebo
Gerra, 1995[46]	Methadone varying dosage (average 44 mg, 24% >60 mg), naltrexone 50 mg			
Shufman, 1994[47]	*Drug-free survival curves*: show 36% naltrexone at 12 weeks vs 19% placebo, ns	Retention rate: ns in naltrexone vs placebo at 12 weeks' treatment. 55% for both arms estimated from Kaplan–Meier curves Naltrexone retention in treatment: HR 1.2 (95% CI 0.4 to 3.23)	Total number of adverse events reported for the treatment and placebo was for depression, headaches, gastrointestinal symptoms, skin and others. The total number of adverse events for the treatment and control group was similar	*Social and psychological assessment*: according to BSI shows significant improvement in naltrexone compared with placebo *Urine test for opiates*: the difference was not significant between groups

continued

TABLE 32 *Results of included studies (cont'd)*

Study	Main findings			
	Use of primary substance of abuse	**Retention in treatment**	**Adverse events**	**Other**
Lerner, 1992[48]	NA	Success rate 9/15 naltrexone vs 8/16 placebo at 2 months, 8/15 vs 6/16 at 1 year Retention rate: ns in naltrexone arm vs placebo at 2 months and at 1 year (t = 0.54, df = 29, p = 0.59) at 2 months 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 in moderate and severe scale Attempting opioid taking: naltrexone 7, 1, 3, 4 (no attempt, 1 attempt, 2 attempts, ≥3 attempts), placebo 8, 8, 0, 0 (no attempt, 1 attempt, 2 attempts, ≥3 attempts), ns (t = 0.18, df = 29, p = 0.85)	NA	*Craving*: naltrexone significantly decreases craving, but it did not inhibit drug taking (60%)
San, 1991[49]		Overall retention rate at 6 months: 27.9% with dropout excluded, but 4/23 (17.4%) naltrexone and 8/20 (40%) placebo; no significant difference at 6 months or at 1 year Naltrexone retention in treatment: HR 2.06 (95% CI 1.07 to 3.99)	101 side-effects observed in 32 naltrexone vs 69 placebo. The most common were: fatigue, nausea, vomiting, headache, diarrhoea, trembling and dry mouth	Significantly higher depression scores in naltrexone group than placebo. Other psychometric scores in STAI, SSS were not significant
Ladewig, 1990[50] (translation)	NA	Length of treatment mean 69 days naltrexone vs 49 days control	7/15 patients had adverse effects in naltrexone vs 3/5 control	*Urine test*: overall 29% naltrexone and 58% control tested positive for opiates
Brahen, 1977,[52] 1979[51] RCT cross-over	NA	NA	Incidence of side-effects was significantly different from placebo Incidence of adverse effects: 298 cyclazocine vs 67 naltrexone	Postplacebo naltrexone produced fewer effects than initial exposure to naltrexone, but not significantly

continued

TABLE 32 *Results of included studies (cont'd)*

Study	Main findings			
	Use of primary substance of abuse	**Retention in treatment**	**Adverse events**	**Other**
Rawson, 1979[53]	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[54]		Retention rate: only 7 patients on naltrexone and 6 on placebo completed 8 months' trial Naltrexone retention in treatment: HR 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 ($p = 0.02$)
Curran, 1976[41]		Successful completion: 2/19 vs 2/19	Side-effects: 5/19 naltrexone vs 0/19 placebo	Total length of treatment: 80 days naltrexone vs 92 placebo
Comparative not RCT studies				
Arnold-Reed, 2003[55] Retrospective audit of records	NA	NA	Registered cause of death in the study population which is heroin related: naltrexone 63.6% (21/33), non-naltrexone 74% (71/96), ns ($\chi^2 = 1.28$, $p = 0.26$)	NA
Sivolap, 1998[56] (translation)	Abstinence rate 12/60 naltrexone vs 24/60 placebo	Leaving the programme 42/60 naltrexone vs 22/60 placebo	NA	NA
Judson, 1984[57]	NA	NA	NA	No significant correlation between total duration in naltrexone treatment and post-treatment outcomes, such as heroin use, arrests, incarcerations 5/40 vs 15/77 or mortality preceding the 1-year follow-up

BPRS, Brief Psychiatric Rating Scale; BSI, Brief Symptom Inventory; CGI, Clinical Global Impression; GAF, Global Assessment of Functioning; SSS, Symptom Severity Scale; STAI, Spielberger State Trait Anxiety Inventory.

Appendix 9

Decision tree for naltrexone versus placebo

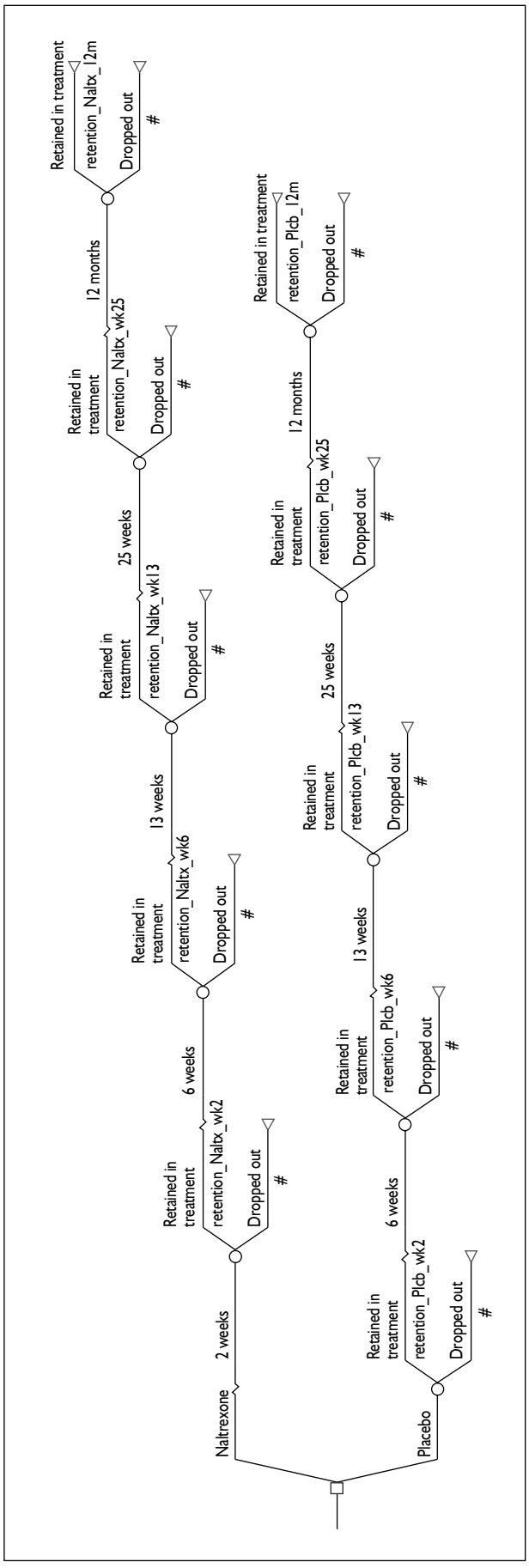

FIGURE 14 *Decision tree for naltrexone versus placebo*

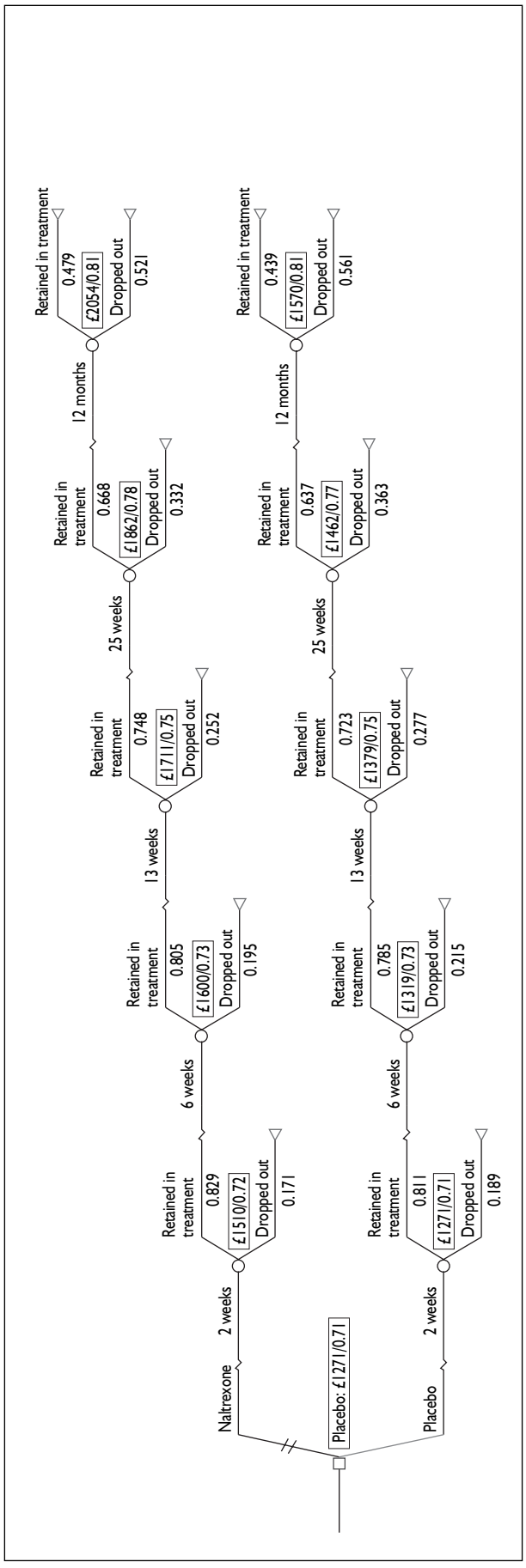

FIGURE 15 *Decision tree for naltrexone versus placebo (with results)*

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