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Methadone and Buprenorphine for the Management of Opioid Dependence: A Systematic Review and Economic Evaluation

Produced by

West Midlands Health Technology Assessment Collaboration

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About 'home unit'

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

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

Contributions of authors

Ariadna Juarez-Garcia developed the Birmingham economic model, reviewed the previous economic evaluations and industry model and contributed to the writing of the economic sections of the report.

Martin Connock coordinated the clinical evidence aspects of the review, applied the inclusion and exclusion criteria, extracted data, appraised studies, conducted meta-analysis and contributed to the drafting of the clinical effectiveness section of the report.

Ed Day drafted the background section, provided clinical advice throughout the project, and assisted in the construction of the utility scenarios.

Emma Frew contributed to the review of economic evaluations, collected and summarised the cost data for use in the model and contributed to the definition of health states.

Anne Fry-Smith designed and executed the searches of bibliographic databases and other electronic sources and wrote the literature searching sections.

Sue Jowett contributed to the development of the Birmingham economic model, reviewed the previous economic evaluations and industry model and contributed to the writing of the economic sections of the report.

Zulian Liu contributed to the review of the clinical effectiveness evidence.

Tracy Roberts supervised the economic section of the project, contributed to the review of economic evaluations and to the writing of the economic sections of the report.

Rebecca Taylor undertook the review of the previous economic evaluations, applied the inclusion and exclusion criteria, extracted data and appraised studies.

Nick Linzeris provided access to an unpublished systematic review regarding the safety of buprenorphine and provided clinical advice during the project.

Rod Taylor supervised the project, contributed to the review of clinical effectiveness and drafted the clinical effectiveness and discussion sections of the report.

All authors contributed to the editing of the report.

Conflicts of interest

Nick Linzeris has been supported to attend an international conference, and has been paid to deliver educational programs for health professionals by Schering Plough.

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

ARIF Aggressive Research Intelligence Facility
BDT buprenorphine detoxification therapy
BMT buprenorphine maintenance therapy
CEAC cost effectiveness acceptability curve
CI confidence interval
CJS criminal justice system
DoH Department of Health
EQ-5D Euroquol
ES effect size
HCB/HCV hepatitis B/C virus
HIV human immunodeficiency virus
HR hazard ratio
ICER incremental cost effectiveness ratio
IDU injecting drug user
LAAM MT Levo α-acetyl methadol maintenance therapy
MD mean difference
MDT methadone detoxification therapy
mg milligram
MMT methadone maintenance therapy
NICE National Institute for Health & Clinical Excellence
NR not reported
NS not statistically significant at P≤0.05
NTORS National Treatment Outcome Research Study
QALY quality adjusted life year
RCT randomised controlled trial
SD standard deviation
SE standard error
SPC summary product characteristics
WMD weighted mean difference
OR odds ratio
RD risk difference (or absolute risk reduction)
RR relative risk

Maintenance - Process whereby an individual who is physically dependent on a drug is taken off that drug and a substitute drug is prescribed instead

Detoxification - Process whereby an individual who is physically dependent on a drug is taken off that drug either abruptly or gradually.

2 EXECUTIVE SUMMARY

Background
Opiate dependence is becoming increasingly prevalent, with associated increases in the spread of infectious disease (e.g., HIV, hepatitis B and C) and overdose deaths. Methadone has traditionally been the mainstay drug used in the management of opioid dependent individuals. Buprenorphine has been reported as an alternative to methadone.

Objectives
The primary objective of this assessment report was to assess the clinical and cost effectiveness of buprenorphine maintenance therapy (BMT) and methadone maintenance therapy (MMT) for the management of opioid dependent individuals from the perspective of the National Health Service and Personal Social Services.
Although methadone is the mainstay drug used in current practice, for the purposes of this report we sought to address three specific questions:

- Is methadone maintenance therapy (MMT) effective and cost effective compared no drug therapy?
- Is buprenorphine maintenance therapy (BMT) effective and cost effective compared to no drug therapy?
- Is MMT or BMT more effective and cost effective?

We also sought to: explore the variation in effectiveness of BMT and MMT acrossdrug doses, patient subgroups and treatment settings; assess the cost effectiveness of BMT and MMT buprenorphine from a wider societal perspective; and compare the effectiveness of BMT to buprenorphine detoxification therapy (BDT) and MMT compared to methadone detoxification therapy (MDT).

Methods
Comprehensive bibliographic searches were undertaken to identify clinical and cost effectiveness studies. Given the number of systematic reviews already published in this area, the assessment of clinical effectiveness was based on a review of these reviews plus an updated search for randomised controlled trials (RCTs). Industry submissions to the National Institute for Health and Clinical Excellence were searched for additional clinical and cost effectiveness evidence. We developed a decision tree with Monte Carlo simulation model to assess the cost effectiveness of BMT and MMT. This model was designed to estimate costs, from the perspective of the UK National Health Service and Personal Social Services and outcomes in terms of quality adjusted life year (QALYs) for 1-year for the three strategies. Retention in treatment and opiate abuse parameters were sourced from the meta-analysis of RCTs directly comparing flexible MMT to flexible dose BMT. Utilities were derived from a panel representing a wider societal perspective.

Results
Clinical effectiveness
31 systematic reviews (including either RCT & non RCT evidence) met the inclusion criteria of this report. Many of the studies included in these reviews overlap. In addition, we identified an additional 28 RCTs published more recently (since 2001). The majority of systematic reviews and RCTs were of moderate to good quality, focused on short-term (up to 1-year follow up) outcomes of retention in treatment and the level of opiate use (self-report or urinalysis) in those individuals retained in treatment. Most studies employed a trial design that compared a fixed dose strategy (i.e. all individuals received a standard dose) of MMT or

BMT and were conducted in predominantly young men who fulfilled DSM-IV criteria as opiate abusers or heroin dependent, without significant co-morbidities. However, flexible dosing (i.e. individualised doses) of MMT and BMT is more reflective of real world practice and was therefore focused on in this report.

MMT vs. no drug therapy/placebo: A number of RCT meta-analyses have consistently shown that fixed dose MMT has superior levels of retention (e.g. 20-97mg vs. placebo: pooled relative risk [RR] - 3.91, 95% CI: 1.17 to 13.2) in treatment and opiate use (e.g. 35-97mg vs. no treatment: pooled effect size - 0.65, 0.41 to 0.89) than placebo or no treatment, with higher fixed doses of MMT being more effective than lower fixed doses (retention in treatment e.g. ≥50 mg vs. <50mg: pooled RR - 1.25, 0.94 to 1.67). There was evidence, primarily from non-randomised observational studies, that fixed dose MMT reduces mortality, HIV risk behaviour and levels of crime compared to no therapy.

BMT vs. no drug therapy/placebo: Two RCT meta-analyses show that fixed dose BMT has superior levels of retention in treatment (e.g. 6-12mg vs. placebo: pooled RR- 1.74, 1.06 to 2.87) and opiate use (6-16mg vs. placebo: pooled RR - 1.74, 1.06 to 2.87) than placebo or no therapy, with higher fixed doses of BMT being more effective than lower fixed doses (e.g. retention in treatment e.g. 8-16mg vs. 1-4mg: effect size - 0.21, 0.12 to 0.31. One small RCT has shown that the level of mortality with fixed dose BMT to be significantly less than placebo.

BMT vs. MMT: A number of RCT meta-analyses have consistently shown that fixed doses of MMT had superior retention in treatment and opiate abuse than comparable fixed doses of BMT. A recently updated and unpublished Cochrane systematic review of 7 RCTs directly compared flexible dosing MMT to flexible dosing BMT in 976 opiate dependent individuals. Amongst RCTs employing flexible dose regimens the allowable daily equivalent dose commonly ranged from 20 or 30mg to 60 or 120mg for methadone and 2 or 4mg to 8 or 16 mg for buprenorphine. No further RCTs comparing flexible MMT and BMT were identified through our searches. Retention in treatment was superior for flexible MMT than flexible BMT dosing (pooled hazard ratio: 1.40, 95% CI: 1.15 to 1.69) although there was no significant difference in opiate use (standardised mean difference: 0.12, 95% CI: -0.02 to 0.26). Indirect comparison of data from population cross sectional studies, suggest that the level of mortality with BMT may be lower than that of MMT. A pooled RCT analysis showed no significant difference in the rate of serious adverse events with MMT compared to BMT.

Treatment modifiers: - Although the amount of evidence on treatment modifiers was limited, adjunct psychosocial and contingency interventions (e.g. financial incentives for opiate free urine samples) appeared to enhance the effects of both MMT and BMT. Also, MMT and BMT appear to be similarly effective whether delivered in primary care or outpatient clinic setting.

MMT vs. MDT and BMT vs. BDT:

Two RCTs demonstrated MMT to have superior retention in treatment and opiate use than MDT. One RCT has shown BMT to be superior to BDT.

Cost-effectiveness

Previous economic evaluations

11 economic evaluations met the inclusion criteria of this report. Eight studies assessed the cost effectiveness of MMT and two BMT for opiate abuse. Direct comparisons of the results between the studies is not readily possible because of their different approaches to modelling, different time horizons, comparators and perspective, country of origin, source of preference weights and effectiveness data used. Although most of the included papers were considered

to be of high quality, none used all of the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context.

Industry economic evidence
One company (Schering-Plough) submitted cost effectiveness evidence. This submission was based on an economic model that had a 1-year time horizon and sourced data from a single RCT of flexible dose MMT compared to flexible BMT and utility values obtained from the literature.
MMT vs. no drug therapy: Incremental cost effectiveness (ICER) £12,584/quality adjusted life year (QALY) and
BMT vs. no drug therapy: £30,048/QALY respectively. In a direct comparison,
MMT vs. BMT: MMT was found to be slightly more effective (QALY difference of 0.00055) and less costly than BMT.
Assessment group model
MMT vs. no drug therapy: ICER £13,697/QALY
BMT vs. no drug therapy: £26,429/QALY.
MMT vs. BMT: As with the industry model, in direct comparison, MMT was slightly more effective (QALY difference 0.0126) and less costly than BMT (-£520).
When considering social costs, both MMT and BMT gave more health gain and were less costly than no drug treatment. These findings were robust to deterministic and probabilistic sensitivity analyses.

Neither the assessment group nor industry model assessed the cost effectiveness of MMT compared to MDT or BMT compared to BDT.

Discussion
Strengths, limitations & uncertainties
The principle strengths of this report are that its cost effectiveness analysis were based on: retention in treatment and opiate abuse outcomes sourced from a systematic review and meta-analysis of RCT evidence directly comparing flexible dose MMT to BMT (more reflective of real world clinical practice than fixed dose design trials); this pooling was based on a meta-analysis using the time-dependent nature (i.e. hazard ratios) of the outcomes; utilities were derived from a panel representing a wider societal perspective; and inclusion of wider societal costs. Potential limitations and uncertainties included: the small sample size and potential representativeness of the utility panel sample; the short-time horizon of the cost effectiveness analysis; and the lack of data to allow the exploration of the cost effectiveness across opiate abuser sub-groups and treatment settings.

Conclusions
Implications for service provision
Both flexible dose MMT and BMT appear to be more clinically effective and more cost effective than no drug therapy in opiate abusers. In direct comparison, a flexible dosing strategy with MMT (daily dose equivalent 20 to 120mg) was found be somewhat more effective in maintaining individuals in treatment than flexible dose BMT (daily dose equivalent 4 to 16mg) and therefore associated with a slightly higher health gain and lower costs. However, this needs to be balanced by the more recent experience of clinicians in the use of buprenorphine, the possible risk of higher mortality of MMT and individual opiate abuser's preferences.

Suggested research priorities

Future research should be directed towards: the safety and effectiveness of MMT and BMT as it is delivered in the UK; potential safety concerns regarding methadone and buprenorphine ─
specifically mortality and key drug interactions; efficacy of substitution medications (in particular patient subgroups, such as within the criminal justice system, or within young people); uncertainties in cost effectiveness identified by current economic models.

3 BACKGROUND

3.1 Description of health problem

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

It is reported that some 185 million people worldwide – 3.1 % of the global population or 4.3% of people aged 15 years and above - were consuming drugs in the late 1990s. In the UK it is estimated that around 4 million people use illicit drugs each year [1], and the most commonly used drugs are cannabis and ecstasy. Opioid dependent users constitute a small proportion of the world population (less than 1% of those aged 15 or over[2]), but the regular and sustained use of heroin accounts for a substantial proportion of drug-related problems in Western countries.

The opioids are a group of psychoactive substances derived from the poppy plant that includes opium, morphine, codeine, and others. 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. [2] Opioids are generally consumed by injection or inhalation of the fumes produced by heating ('chasing'). Regular use of opioids can lead to opioid dependence.

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

3.2 Diagnosis

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

1. Tolerance, as defined by either of the following:

- a need for markedly increased amounts of the substance to achieve intoxication or desired effect
- markedly diminished effect with continued use of the same amount of the substance

2. Withdrawal, as manifested by either of the following:
   - the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for withdrawal from the specific substances)
   - the same (or a closely related) substance is take to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer period than was intended
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use
5. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects
6. Important social, occupational, or recreational activities are given up or reduced because of substance use
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g. current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

3.3 Aetiology, pathology and prognosis

The aetiology of opioid dependence is multifactorial. 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.

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 initiating before the age of 20. Individuals addicted to opioids often become dependent on these drugs in their early twenties and remain intermittently dependent for decades. Biological, psychological, sociological, and economic factors determine when a person will start taking opioids. However, it is clear that when use begins, it often escalates to abuse (repeated use with adverse consequences) and then to dependence (opioid tolerance, withdrawal symptoms, compulsive drug-taking). Once dependence is established there are usually repeated cycles of cessation and relapse extending over decades.[4] In one long-term outcome study that conducted a 24-year follow-up of 581 male opioid users, 29% were currently abstinent, but 28% had died, 23% had positive urine tests for opioids and 18% were in prison[5]. The Drug Abuse Reporting Program, a longitudinal data collection project over 12 years in the USA, found that the average time from first to last opioid use was 9.9 years, with 40% addicted for over 12 years.[6]

For many people, the relapsing nature of drug misuse means that they will have extensive treatment histories. Treatment for people with established substance-use problems is rarely a discrete, single event, with several episodes of treatment often provided over several years.[7] Nevertheless, some users of dependent substances may make dramatic changes in their drug use without recourse to formal treatment.[8] The natural history of heroin users attending treatment services suggests that most individuals develop dependence in their late teens and

early twenties, several years after their first use of heroin, and continue use over the next 10 to 20 years. Treatment can alter the natural history of opioid dependence, most commonly by prolonging periods of abstinence from illicit opioid abuse. As a population of persons addicted to opioids ages, the percentage who are still addicted decreases.[4]

3.4 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. For example, 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 has included a self completion module of questions on illicit drug use since 1996.[9] The 2003/4 BCS found that 35.6% of 16 to 59 year olds have used one or more illicit drugs in their lifetime, 12.3% used one or more illicit drugs in the last year and 7.5% in the last month. These figures were much lower for heroin use, with 0.2% having used opioids (heroin and methadone) in the last year. [9]

However, 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. Instead, national prevalence estimates can be derived from a range of methods, with the multivariate indicator method being the favoured approach. This combines local prevalence estimates along with routinely available indicator data. Using such methods the latest UK estimate of problem drug use is 9.35 per thousand of the population aged 15 to 64 years (360,811), with 3.2 per thousand (123,498) injecting.[9] Analysis of the 2004/5 data from The National Drug Treatment Monitoring System (NDTMS), which collects, collates and analyses information from those involved in the drug treatment system, suggests that there were an estimated 160,450 people in contact with treatment services in England, the majority for primary opioid problems.[10] Males make up over 70% of new presentations to treatment, and opioids are the most commonly used drug by those seeking treatment.

3.5 Impact of health problem

There are considerable harms associated with illicit heroin use, including increased mortality (approximately 10 to 20 times greater than age and gender matched non-users); increased infection with blood-borne viruses (HIV, HCV, HBV); high levels of depression and anxiety disorders; social problems such as disrupted parenting, employment and accommodation; and increased participation in income-generating crime. Even when users become drug free there is a high probability of their returning to drug use within a few months.

Increased Mortality

Addiction-related deaths, including unintentional overdose, drug-related injuries, and many illnesses directly attributable to chronic drug dependence, explain one fourth to one third of the mortality in an opioid-addicted population.[4] One long-term follow-up study reporting in 1994 of dependent heroin users estimated that this population has a 12-fold increased risk of mortality compared to the general population[11], however, more recent cohort studies have shown that mortality rates in drug users has improved over time.[12]

Physical Health Effects

Individuals may experience physical health symptoms and medical complications that relate to the action of the drug taken, to the route of their administration and to general issues of poor nutrition and health care.[7] The majority of subjects recruited to the National Treatment Outcome Research Study (NTORS) in the UK reported problems with their physical health, most commonly sleep disturbance, weight loss and chest pain.[13]

Injecting drug users may be exposed to blood borne infections through the sharing of infected needles, syringes or other injecting paraphernalia. The prevalence of HIV infection among injecting drug users (IDUs) in the UK has increased in recent years, although the rate is lower than in many other countries.[14] Approximately one in every 65 injectors is infected, but the figure is substantially higher in London than the rest of the country with around one in 25 IDUs infected. Overall more than two in five IDUs in the UK have been infected with hepatitis C. In England and Wales hepatitis C transmission among IDUs is high with one in six of those who had started to inject since the beginning of 2002 having become infected. Transmission of both hepatitis A and B continues among IDUs even though there are effective vaccines. Needle and syringe sharing increased in the late 1990s, and since then has been stable with around one in three IDUs reporting this activity in the last month. The sharing of other injecting equipment is more common and few IDUs swab-injecting sites prior to injecting.[14]

Psychological Effects

Psychiatric co-morbidity is common in opioid dependent populations, with anxiety, affective, antisocial and other personality disorders particularly common.[15,16] Recent psychiatric treatment was reported by one in five of the 1075 subjects recruited to NTORS, and psychiatric symptom levels were high.[17] Clinical studies suggest that half of opioid-dependent individuals have a lifetime depressive episode, while a third have depressed mood at intake to addiction treatment.[7]

Mental Illness

The Epidemiological Catchment Area study reported a 47% lifetime prevalence rate of substance abuse among patients with schizophrenia compared to 16% in the general population,[18] and these figures are confirmed in UK studies. [19,20]The consequences of substance misuse in schizophrenia are substantial, as misuse of alcohol, cannabis and stimulants is associated with exacerbation of psychotic symptoms, more frequent hospitalisation, poor social functioning, homelessness, increased suicide rate and poor treatment response. However, psychosis is not a typical feature of the opioid withdrawal syndrome, but it has been reported in some cases after stopping methadone.[21] Bloom and others have proposed that an excess of endogenous opioids may have a role in the pathogenesis of schizophrenia,[22] and it is sometimes more practical to maintain opioid-dependent schizophrenic patients on a combination of antipsychotic medication and methadone than attempting a detoxification process. Relatively little research has been done on pharmacological treatment of patients with coexisting schizophrenia and substance-use disorders, with many studies focusing on psychosocial treatment and providing patients with standard pharmacotherapy.

There is a strong link between bipolar disorder and substance misuse, with the ECA study showing that more than 60% of people with a diagnosis of bipolar I disorder had a lifetime

diagnosis of substance use disorder.[18] Symptoms of depression are common in people that misuse drugs and alcohol, and diagnostic issues are often difficult to clarify. Developments in diagnostic criteria and improved trial methodology have led some authors to conclude that any substance-dependent person who meets criteria for a depressive disorder stands a good chance of improvement on medication.[23] However, it is important to remember that most depressive symptoms observed in substance dependent individuals resolve with abstinence, and are probably substance-induced mood disorders. A variety of studies on the use of tricyclic antidepressants in opioid dependent patients with depressive symptoms have given inconclusive results. Plasma level monitoring is important, as methadone-maintained patients often have plasma levels of tricyclic drugs twice as high as prior to methadone administration. More recently SSRIs have been recommended as the antidepressant of choice in depressed injecting drug users, but only where there is a clear depressive disorder.[24]

Social Functioning
The nature of the opioid withdrawal syndrome and the associated psychological craving for the drug may mean that the need to obtain supplies takes precedence over all other priorities. This may lead to mistakes at work, lost productivity or unemployment. Personal relationships are placed under considerable strain by dependent drug use, and problems with accommodation are common. Prior to intake in NTORS, 7% were homeless and living on the street, 5% were living in squats, and 8% were living in temporary hostel accommodation.[13]

Impact on Children and Families
Concern has recently been raised about the potentially negative impact of problem drug use by parents upon children and families in the UK.[25] It is estimated that 2-3% of all children under the age of 16 years have parents with drug problems, although not all of these problems relate exclusively to opioids. Using opioid drugs does not necessarily impact on parenting capacity, and the complex nature of the problems faced by many opioid users often makes it difficult to disentangle the specific contribution of drugs.[26] However, parental drug use has the potential to impede parenting and the provision of a nurturing environment. Preoccupation with obtaining and using opioids during an intensive period of drug use by parents may lead to children not being properly fed, clothed or cared for, and an inconsistent regard for child safety and supervision. Registration on UK child protection registers for neglect has been correlated strongly with parental heroin use, and parental problem drug use has been shown to be one of the commonest reasons for children being received into the care system.[26]

Health-related quality of life
There is little evidence about the health-related quality of life in drug users. We undertook our own analysis using a citizen's value of health panel in order to obtain estimates for this report. These are reported below in Appendix 12.

Criminal Activity
There is a clear association between illicit drug use and crime, although this link can arise in several ways. Many opioid dependent individuals become involved in crime to support their drug use, but crime may also provide the money and the contacts to buy drugs. It is estimated that half of all recorded crime is drug related, with associated costs to the criminal justice system in the UK estimated as reaching £1 billion per annum in 1996. [27] However, the

majority of those who steal to buy drugs were involved in crime before their drug use became a problem for them.

Illicit drug use is much more common amongst known offenders in Great Britain than amongst the young population as a whole. In a sample of 1,435 arrestees drug-tested and interviewed by Bennett et al 2001[28], 24% tested positive for opiates. The average weekly expenditure on drugs (heroin and crack/cocaine) was £290, and the main sources of illegal income were theft, burglary, robbery, handling stolen goods and fraud. High levels of criminal activity are also found in populations of people dependent on heroin. The National Treatment Outcome Research Study (NTORS) found 61% of a drug misuse treatment sample reported committing crimes other than drug possession in the three months prior to starting treatment, with the most commonly reported offence shoplifting.[16] Drug treatment led to significant reductions in offending levels.[29]

3.6 Management of opioid abuse

Methadone

Methadone is a synthetic opioid mμ-receptor agonist with pharmacological activity similar to morphine. The Summary Product Characteristics (SPC) for methadone states that it is indicated for *"use in the treatment of opioid drug addictions (as a narcotic abstinence syndrome suppressant)"*. Methadone is used in opioid dependence at a dose of 10-40mg daily, increased by 10-20mg per week until no signs of withdrawal or intoxification; the usual dose range is 60-120 mg daily, although larger doses may be employed. Methadone is available in tablet, oral solution or injectable ampoules, but only the oral route will be considered in this report.

Methadone has a high bioavailability when ingested orally, with 80-90% absorbed through the gastro-intestinal tract. Once absorbed into the bloodstream 90% of the methadone is bound to blood proteins and after repeated administration accumulates in various tissues in the body, including the brain. The elimination half-life has been estimated to be 24-36 hours, but most studies show considerable variation across individuals (from 10 to 80 hours)[30]. The half-life of morphine has been estimated to be about 3 hours. The liver is the main site of biotransformation of methadone, and it is eliminated in the form of the metabolites resulting from biotransformation and by excretion of the drug itself in urine and faeces.[30]

The pharmacological profile of methadone makes it ideal for use as a maintenance drug. The oral route avoids the risks associated with injecting, its long half-life allows for a single daily dosing schedule, and the accumulation in the body means that steady state plasma levels are easily achieved after repeated administration. Methadone appears to have no serious long-term side effects associated with chronic administration.[31] In stabilised methadone maintenance patients, methadone does not have the pronounced narcotic effects seen with shorter acting opioids such as heroin. Some drugs have been shown to influence the amount of methadone present in blood plasma by induction of microsomal liver enzyme activity, and so speeding up the elimination of methadone from the body. Such drugs include rifampicin, phenytoin, the barbiturates, and some antiviral drugs used in the treatment of HIV infection. Other drugs, such as fluvoxamine, may have the opposite effect on methadone metabolism and so increase plasma levels. Knowledge of these interactions usually allows the appropriate adjustment of methadone dose for effective treatment.

Induction with methadone presents a potential risk of respiratory depression and should be undertaken with care. The risk of death during methadone induction has been calculated as

nearly 7-fold greater than the risk of death prior to entering maintenance treatment.[32] The relatively slow onset of action and long half-life mean that methadone overdose can be deceptive and toxic effects may become life threatening several hours after taking a dose. During the induction phase careful adjustments of the methadone dose are made in order to eliminate drug craving and prevent withdrawal, while avoiding the risk of intoxication or overdose. Such a process requires monitoring by a doctor or trained nurse, and may require regular visits to a community-prescribing centre. Initially patients may need to be seen at least fortnightly, but when stable the frequency of medical assessment can be reduced. A more thorough review every three months may be useful to consider what has been achieved and to set new goals. Where possible, co-existing physical, emotional, social and legal problems should be addressed.

Buprenorphine

Buprenorphine is a partial opioid agonist at the μ opioid receptors, and a κ opioid receptor antagonist. It has low intrinsic agonist activity, only partially activating μ opioid receptors, and providing a milder, less euphoric and less sedating effect than full opioid agonists such as heroin or methadone.33 The SPC for buprenorphine states that it is indicated for *"substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment"*. Buprenorphine is used in opioid dependence by sublingual tablet administration at an initial recommended single daily dose of 0.8-4mg, adjusted according to response. In practice a starting dose of over 4 mg/day is often used. The maximum daily dose is 32mg.

Buprenorphine has a number of differences in its mode of action to methadone.[33] As it has a high affinity for μ opioid receptors it reduces the impact of additional heroin or other opioid use by preventing heroin from occupying these receptors. Furthermore, the high affinity of buprenorphine for μ opioid receptors combined with its high lipohilicity means that it has a prolonged duration of action at higher doses, which potentially allows alternate-day and even 3-days-a-week dispensing regimes. Buprenorphine also has a relatively good safety profile, and doses many times greater than normal therapeutic doses appear to rarely result in clinically significant respiratory depression. However, the safety of buprenorphine mixed with high doses of other sedative drugs such as alcohol or benzodiazepines is till unclear, with deaths having been reported.[33]

3.7 Detoxification (or withdrawal)

A clear goal for many opioid dependent individuals is to stop using opioid drugs altogether and a range of medical and psychosocial strategies have been developed that aim to achieve this goal of abstinence. A person who is physically dependent on opioids will experience a characteristic set of signs and symptoms if they stop taking the drug abruptly, including yawning, sweating, dilated pupils, anorexia, abdominal pain, irritability, tremor, and insomnia. Although rarely life threatening, this range of symptoms is extremely unpleasant, and most opioid users will try very hard to avoid it. Detoxification is the process whereby an individual who is physically dependent on a drug is taken off that drug either abruptly or gradually.[34] Prescribing opioid medication allows this process to occur in a relatively comfortable and controlled manner, and detoxification is usually the first stage of an abstinence programme. It aims to reduce or eliminate withdrawal symptoms and help the patient reach a drug-free state in a safe and humane way. Prior to maintenance approaches detoxification was the only treatment available to those dependent on opioids. The last 25

years have seen the introduction of new approaches to assist withdrawal including such as alpha-2-agonists (clonidine and lofexidine).

3.8 Maintenance (or substitution)

While some patients can achieve abstinence from opioids rapidly, others require the support of prescribed medication for longer than a few months.[35] An alternative to attempting to stop opioid use altogether is the maintenance approach, is the principle focus of this report. This intervention, by reducing craving and preventing withdrawal, virtually eliminates the hazards of needles, frees the patient from preoccupation with obtaining illicit opioids, and enhances overall function, thus enabling the patient to make use of available psychosocial interventions.[36] Substitute opioids are prescribed in doses higher than that required merely to prevent withdrawal symptoms. By doing so, it becomes harder for the patient to experience euphoria if they use heroin in addition to their prescription, and craving for opioids is reduced. By exchanging an expensive illicit drug of unknown purity and quality for a pharmaceutically produced drug of more certain dose, the user may begin to achieve some stability in their life. The prescription of methadone, or latterly buprenorphine, can act as an inducement for the patient to attend a treatment programme where other problems that originally led to drug use may be addressed (e.g. housing, relationship or employment difficulties).

The decision about which drug treatment to offer is based on local availability, on the client's previous history, current situation, social support network and expressed wishes. The decision should be taken together with the patient and based on the clinician's judgment of the required degree of structure, monitoring and support.[37]

Ultimately a stable dose is established based on the presence of desired clinical effects such as the elimination of craving and prevention of withdrawal symptoms, and the maintenance phase can be said to have begun. Department of Health prescribing guidance recommends maintaining individuals on a daily dose of methadone between 60mg and 120mg.[35] In some cases, higher doses may be necessary due to the patient's high tolerance. High doses can reduce heroin and other opioid consumption, but caution needs to be observed about high doses if there is associated alcohol or other benzodiazepine dependence. UK prescribing guidelines recommend that maintenance opioids should be dispensed on a daily basis under supervision for the first three months of treatment.[35] As the patient who is on maintenance begins to work on major life changes, the need for daily collection and supervision can change.

Prescribing may take place in a number of different settings. Traditionally tier 3/specialist drug treatment centres, usually staffed by psychiatrists have done the bulk of prescribing to opioid users, but more recently there has been a large expansion in prescribing by primary care practitioners. Access to prescribing has been increased since the advent of the National Treatment Agency, and large investment in treatment services linked to the criminal justice system. Prescribing requires a number of ancillary services to meet best recommended practice. Initial assessment should include oral fluid or urine testing, and the patient may need to be seen by a doctor or specialist drug worker a number of times within the first few weeks of induction and dose titration.

3.9 Current service provision

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

The Government's ten year national drug strategy *'Tackling Drugs to Build a Better Britain'* (1998) identified treatment as one of the four key areas for action.[27] 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.[38]

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

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

Direct expenditure for tackling drugs in the 2003/4 financial year was £1,244 million, with £503 million of this spent on drug treatment.[39]
According to Models of Care, services for drug misusers can be grouped into four broad tiers[38]:

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

Methadone and buprenorphine are mostly orally administered once daily for therapeutic purposes of preventing or substantially reducing the consumption of illicit opioids such as heroin. The primary function is to improve the health status and psychological well being of the opioid-dependent person. Substitute opioids are mainly prescribed in tier 3 (community prescribing programme) settings, although increasing use is being made of prescribing in primary care. 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.[40] UK policy recommends that community prescribing takes place within a context in which the heroin user's co-existing physical and emotional, social and legal problems are addressed as far as possible.[38] Prescribing should be complemented by counseling or structured psychotherapy, as well as other services such as welfare advice, help with housing or employment.[41]

Identification of important subgroups

There are a number of important subgroups who have particular risk factors or particular problems such as the homeless, people with comorbidity (e.g. mental illness), youg people and pregnant women.

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 at risk of developing them.[27] The strategy defines three groups: children (aged 12 or less), young people (aged 13 to17 years) and young adults (aged 18 to 24 years). There are significant challenges in designing appropriately matched treatments and support for young people, and 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.[42,43] However, 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.[44]

3.10 Current usage in the NHS

Figures produced by the NDTMS show that 160,450 individuals were recorded as in contact with structured drug treatment services in England in 2004/5. A total of 53% (55,650) of patients who were discharged remained in treatment for 12 weeks or more following triage assessment, and 120,700 individuals (75% of those treated in the year) either successfully completed treatment or were retained in treatment.[10]

Treatment using oral naltrexone is not common with a total of only 11,000 to 14,000 scripts being issues per annum in England and no trend of increasing use.

Maintenance treatment using methadone and buprenorphine are increasingly used, as illustrated in Figure 1 below. The analysis in the figure is for all formulation in BNF sections 4.10, 4.7 and 3.9.

3.11 Anticipated costs associated with intervention

The quarterly drug spend for buprenorphine summer 2005 was ~£3.8M. Assuming a unit drug cost of £0.48 /mg (BNF) and an average dose of 10 mg/day this corresponds to approximately ~0.79 million daily doses and ~8700 patients. The annual cost per patient is estimated to be ~ £4112.7 and thus the total cost for the NHS is probably about £35.8 M. However the number of patients treated appears to be increasing at a rate of about 1.36 fold per year, which projects to a 2006 spend in the region of £48.6M.

For methadone with a unit drug cost of £0.0135/mg and a quarterly spend of ~£2.8M and an average dose of 50mg/day the corresponding calculations result in 45,600 patients in methadone treatment and a total annual spend (at £2594 / patient) of £118.2M projecting at annual rise of 1.24 fold in patients treated to nearly £150M in 2006.

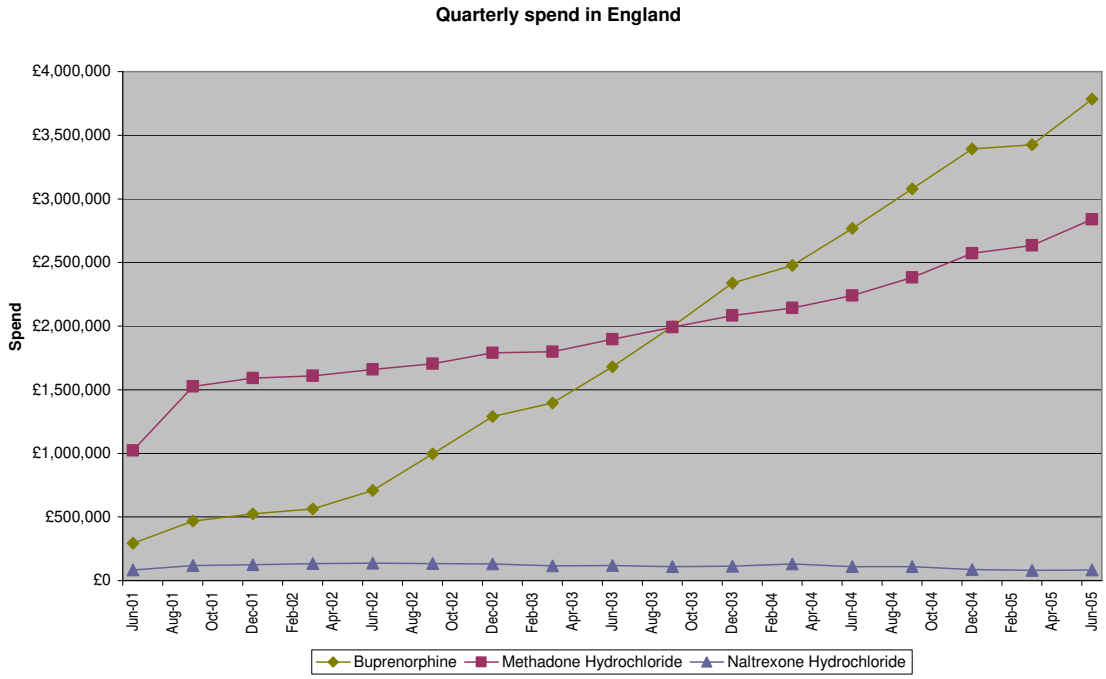


Figure 1. Quaterly expenditure on methadone, buprenorphine & naltrexone in England 2001-2005

Table 1 Annual cost of buprenorphine per patient

Item	Cost (£)
Pharmacology	1943.42
Dispensing	511.68
Counselling	444.08
Urine test	29.12
Treatment total	**2928.30**
NHS resource use	1184.40
NHS total	**4112.70**

Table 2 Annual cost of methadone treatment per patient

Item	Cost (£)
Pharmacology	274.24
Dispensing	662.22
Counselling	444.08
Urine test	29.12
Treatment total	**1409.66**
NHS resource use	1184.40
NHS total	**2594.06**

4 DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

- Interventions
  - *Methadone and buprenorphine*

  Methadone is licensed for use in opioid dependence at a dose of 10-20mg daily, increased by 10-20mg daily until no signs of withdrawal or intoxification; in the UK the usual dose 40-60mg daily however larger doses are employed elsewhere. Only oral methadone will be considered. Buprenorphine is licensed for use in opioid dependence by sublingual tablet administration at an initial dose of 0.8-4mg as a single daily dose, adjusted according to response; however in practice a starting dose is often > 4 mg/day. The maximum is 32mg daily. Licensed dose and doses used in practice are not necessarily concordant so that consideration will therefore be given to studies employing doses out with those licensed.
  - *Place of the intervention in the treatment pathway(s)*

  Each drug is licensed as an adjunct in the treatment of opioid dependence and can be used in strategies aimed at both maintenance and detoxification

- Populations including subgroups

  Opioid dependent adults (18-years and over) are the target population for this report. Where data was available this report sought to assess the impact of interventions across a range of sub-groups including drug use (e.g. injector vs. non-injector); co-morbidity (e.g. HIV vs. no HIV infection); socio-demographics (e.g. male vs. female) and treatment setting (e.g. health care vs. criminal justice).

- Relevant comparators

  The interventions are adjuncts to current treatment strategies (e.g. psychosocial interventions) and therefore the comparator will be treatment strategies without methadone (oral) or buprenorphine (sublingual), but may include an alternative drug treatment or placebo or alternative non-drug treatment in place of methadone or buprenorphine.

- Outcomes

  Changes in illicit drug use (frequency of use, type of use, dosage) or, proportion of patients remaining illicit-drug free, or retention in treatment, or compliance with recommended dose, or quality of life measures, or major adverse effects of treatment drugs (i.e. drug interactions, liver disease, cardiac abnormalities, exacerbation of co-morbidities) or illicit-drug related morbidity (e.g. blood borne virus infection), or mortality.

- Key issues

  The primary focus of this assessment will be clinical and cost outcomes from the perspective of the National Health Service and Personal Social Services. The wider societal implications including public health and safety, and costs to the criminal justice system will be considered.

4.2 Primary and secondary objectives of assessment

The primary policy objective of this report was to assess the clinical effectiveness of methadone and buprenorphine maintenance in the management of opioid dependence from a National Health Services and Personal Social Services perspective. Although methadone is the mainstay drug used in current practice, for the purposes of this report we sought to address three specific questions:

- Is methadone maintenance therapy (MMT) effective and cost effective compared no drug therapy?
- Is buprenorphine maintenance therapy (BMT) effective and cost effective compared to no drug therapy?
- Is MMT or BMT more effective and cost effective?

Secondary policy objectives were to: explore the potential variation in effectiveness of methadone and buprenorphine across drug dose, patient opioid abuser subgroups and treatment settings; assess the cost-effectiveness of methadone and buprenorphine maintenance in the management of opioid dependence from a broader societal perspective; assess the effectiveness of MMT compared to methadone detoxification (MDT) and BMT compared buprenorphine detoxification (BDT).

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

5.1.1 Rationale

Scoping searches indicated the existence of a large number of reviews on treatments for opioid-dependent individuals. These include systematic reviews as well as meta-analyses and more traditional narrative (non-systematic) reviews. It was evident that a proportion of these addressed the issues encompassed in the remit of the present review. We therefore decided to undertake a detailed search for systematic reviews and to assess their relevance, quality and to map their results to the policy questions of this report.

In order to bring this assessment of evidence up-to-date we then searched for RCTs published after the completion of the searches of these systematic reviews (taken as January 2000). The results of these RCTs were then qualitatively compared to those of the systematic reviews to check for comparability.

5.1.2 Identification of studies

Review of systematic reviews
Searches for existing systematic reviews (that included randomised controlled trials [RCTs] or non-RCTs) were undertaken using the ARIF search protocol which includes sources such as Cochrane Library, internet sites of health technology assessment organisations and MEDLINE (See Appendix 1). In addition the Cochrane Drugs and Alcohol Group were contacted to seek any recent updates of current Cochrane reviews. The searches were not restricted by date or language.

Review of recent randomised controlled trials
The following sources were searched for RCTs:

- Bibliographic databases: Cochrane Library (CENTRAL)(Wiley internet interface) 2005 Issue 3, MEDLINE (Ovid) 2001 – Aug 2005, MEDLINE In-Process & Other Non-Indexed Citations (Ovid) 12 Aug 2005, EMBASE (Ovid) 2001 – Aug 2005, PsycINFO (Ovid) 2001 – Aug 2005, International Bibliography of the Social Sciences(BIDS) 2001 – Aug 2005, Sociological Abstracts (CSA Illumina) 2001 – 2005. Searches were based on text words and index terms, where available, which encompassed methadone, buprenorphine; opioid misuse, dependence and withdrawal. No language restrictions were applied. (see Appendix 1 for full search strategies)
- Citations of relevant studies
- Further information was sought from contact with author reports where necessary
- Research registers of ongoing studies were searched as follows: National Research Register 2005 Issue 3, Current Controlled Trials and ClinicalTrials.gov.
- Invited industry submissions to NICE for this appraisal

5.1.3 Inclusion exclusion criteria

Review of systematic reviews
A systematic review was defined for the purposes of this report as a review that stated that at least one substantial database (e.g. EMBASE) had been scrutinised in conjunction with appropriate search terms. Meta-analyses were also included if they satisfied this criterion. In addition reviews were included if their inclusion criteria encompassed:

- Studies of opioid dependent individuals
- Studies (RCTs or non RCTs) of methadone and or buprenorphine as maintenance therapy or detoxification strategies

Foreign language reviews were excluded, but those of potential relevance were identified and commented upon. Two reviewers independently undertook the selection of reviews with a third reviewer resolving any disagreement.

Review of recent randomised controlled trials
RCTs were included if they had not already been analysed and considered within included systematic reviews. Further inclusion criteria for RCTs were that they encompassed:

- A population of opioid dependent individuals
- Study of methadone and or buprenorphine as maintenance therapy or detoxification strategies

RCTs were excluded if the population was a mixture of cocaine abusers and opioid abusers, or if the population were in methadone or buprenorphine maintenance, temporarily switched prior to randomisation to an alternative, and subsequently randomly allocated back to methadone or buprenorphine maintenance (with or without supplementary pharmacotherapy or other therapy). Two reviewers undertook selection of RCTs and a third reviewer resolved disagreement.

5.1.4 Critical appraisal strategy

Review of systematic reviews
The methodological quality and quality of reporting of the included systematic reviews and meta-analyses was assessed using the validated OQAC (Overview Quality Assessment Questionnaire) instrument developed by Oxman et al 1991.[45]

Review of recent randomised controlled trials
The methodological quality of included RCTs was assessed on the basis of randomisation, adequate concealment of randomisation, level of blinding, use of intention-to-treat-analysis, and description of loss to follow up. An overall quality score (Jadad) was assigned to each RCT using a modified Jadad[46] instrument (Appendix 5).

5.1.5 Data extraction

One reviewer extracted data from systematic reviews and RCTs into pre-designed data forms. Extracted data was checked by at least one other reviewer and disagreement resolved by discussion. Data from studies with multiple publications were reported as a single study, but the source of publications noted.

For both included systematic reviews and RCTs, the following outcomes were sought:

- Drug use i.e. changes in illicit drug use; concordance with, and retention in treatment
- Health of drug user i.e. drug-related mortality; drug-related morbidity (e.g. blood-borne virus infection rates); health-related quality of life; use of health care system; Major adverse effects of treatment (i.e. drug interactions, liver disease, cardiac abnormality, exacerbation of comorbidity)
- Social effects i.e. effects on employment; effects on family
- Effects on criminal justice system i.e. rates of crime; recidivism

5.2 Results

5.2.1 Quantity of research available

Review of systematic reviews
A total of 192 citations were identified in our search for systematic reviews. Of these, 31 systematic reviews were included in this report. The inclusion and exclusion process is summarised in Figure 2.

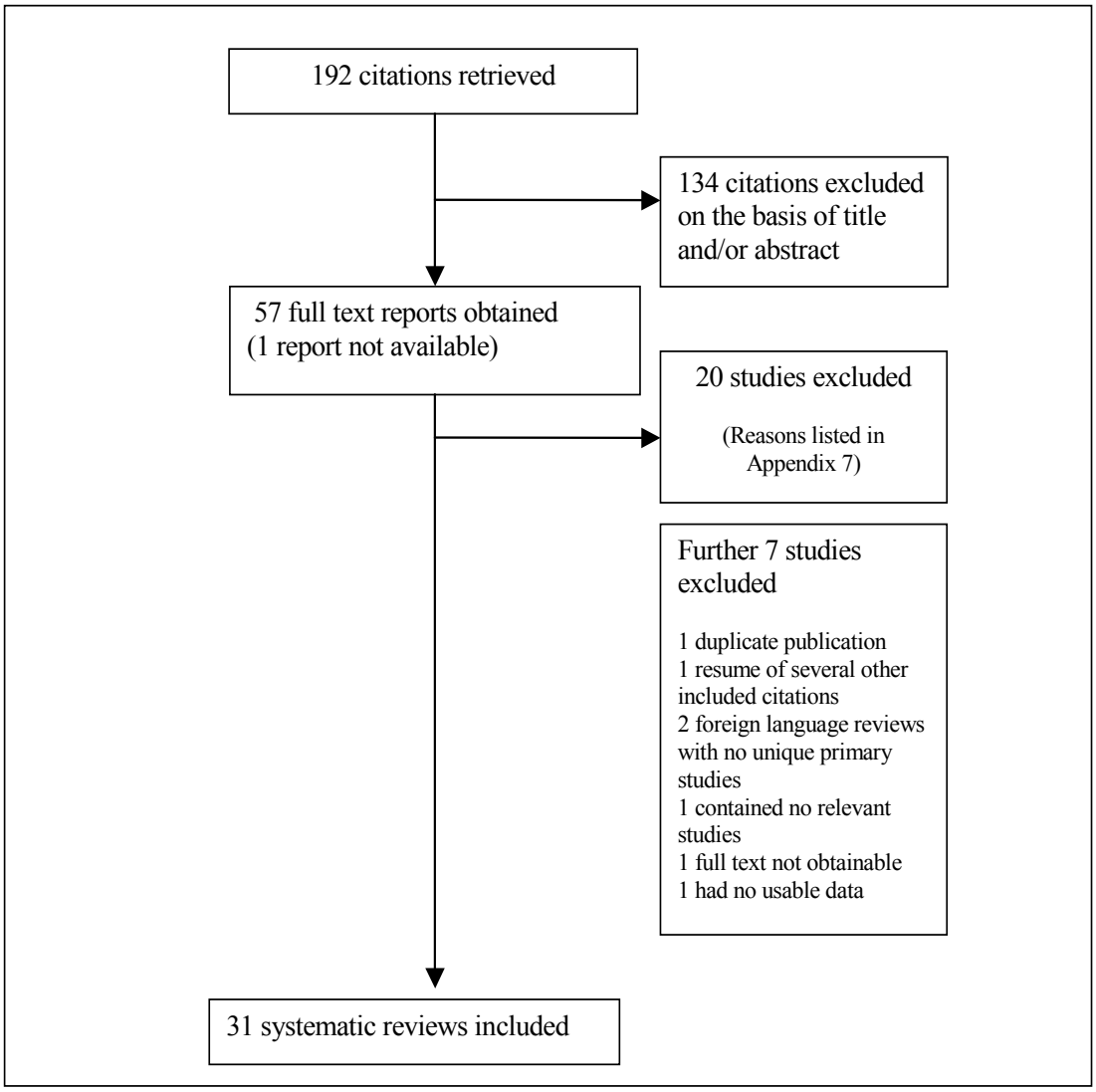


Figure 2 Flow diagram of retrieval of systematic reviews

Review of recent randomised controlled trials
A total of 1616 citations were identified in our search RCTs. Of these, 27 RCTs were included in this report. The inclusion exclusion process is summarised in Figure 3. Excluded studies and reasons for exclusion are listed in Appendix 11.

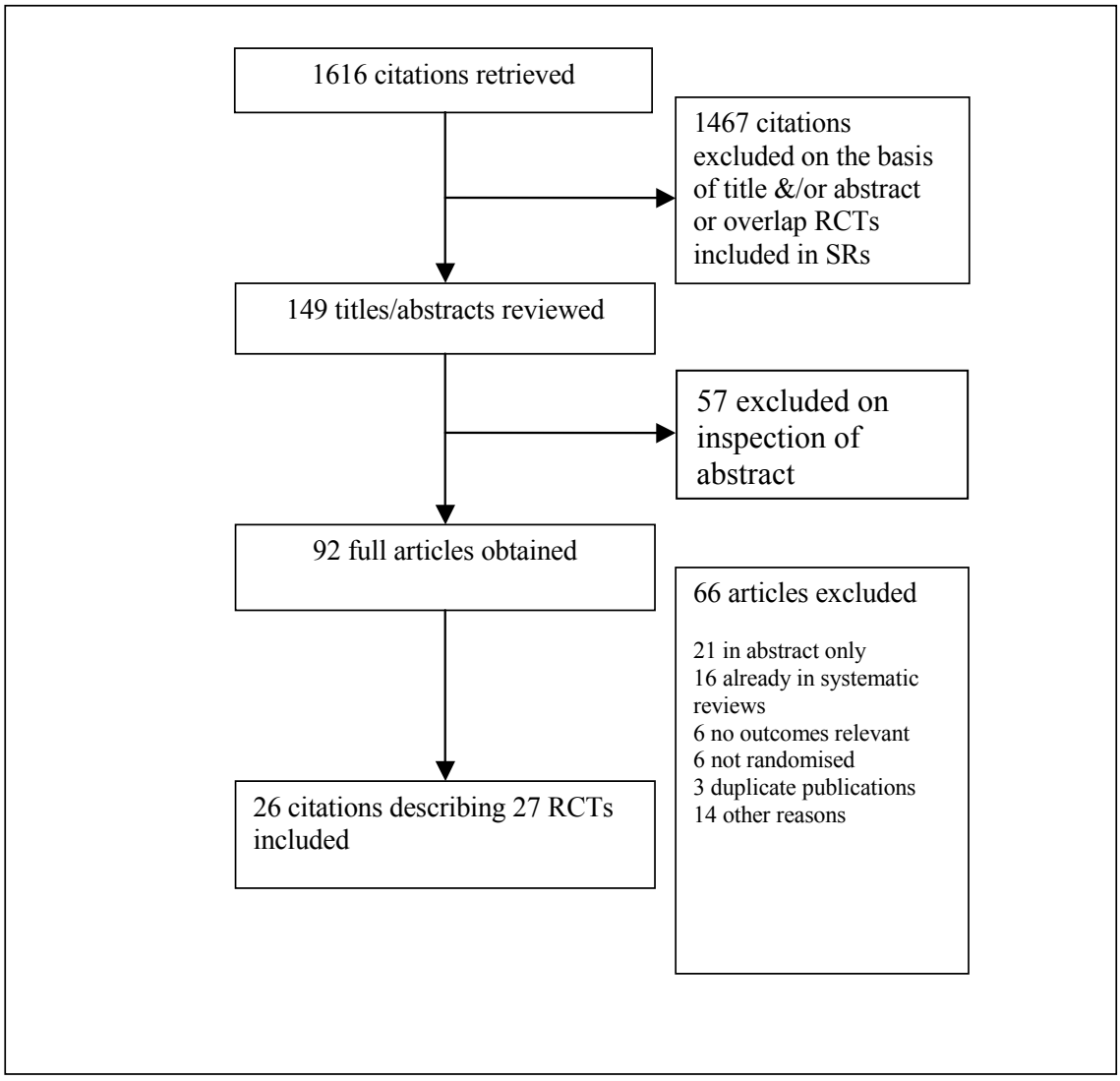


Figure 3 Flow diagram of retrieval of RCTs

5.2.2 Scope and quality of included systematic reviews

Given the number of systematic reviews and RCTs identified in this report, details are provided as appendices:

- Appendix 3 – characteristics of systematic reviews
- Appendix 4– characteristics of RCTs
- Appendix 6 – quality of systematic reviews
- Appendix 7 – quality of RCTs

- Appendix 9 – findings of systematic reviews
- Appendix 4 – findings of RCTs

The remainder of this clinical effectiveness section aims to provide a focused summary of the scope, quality and findings of this evidence base according to the policy questions of this report. Table 3 and Table 4 provide a mapping of the systematic reviews and RCTs to the policy questions of this report.

Table 3 Mapping of systematic reviews to policy questions

Author & Year	MMT* vs. placebo/no therapy	BMT* vs. placebo/no therapy	MMT* vs. BMT*	Other comparisons
Amato 2004[47]	X	X	X	MMT + co-therapies vs MMT
Barnett 2001 [48]	X	X	✓	X
Capelhorn 1995[49]	✓	X	X	X
Clark 2002 [50]	X	X	X	MMT vs LAAM MT
Davids 2004 [51]	X	✓	✓	BMT + co-therapies vs BMT; BMT vs LAAM MT
Faggiano 2003[52]	✓	✓	✓	MMT + co-therapies vs MMT; MMT and BMT vs LAAM MT; MMT vs MDT (1 study)
Farre 2002[53]	✓	✓	✓	MMT vs LAAM MT
Ferri 2005 [54]	X	X	X	MMT + heroin v MMT
Fridell 2003[55]	X	X	X	MMT + co-therapies vs MMT
Glanz 1997 [56]	✓	X	X	MMT vs LAAM MT; MMT vs MDT (1 study)
Gowing 2004[57]	✓	X	X	MMT vs MDT (1 study)
Griffith 2000 [58]	X	X	X	MMT + co-therapies vs MMT
Hopfer 2002[59]	✓	X	X	MMT vs MDT (3 studies)
Hulse 1998[43]	✓	X	X	X
Johansson 2003 [60]	✓	✓	✓	MMT + co-therapies vs MMT; MMT vs LAAM MT; MMT vs MDT (2 studies)
Kirchmayer 2003[61]	X	X	X	MMT vs Naltrexone MT
Layson-Wolf 2002[62]	✓	✓	✓	MMT and BMT vs LAAM MT;
Lintzeris 2004[63]	X	✓	✓	BMT in different settings.
Marsch 1998[64]	✓	X	X	X
Mattick 2003a[65]	✓	X	X	MMT vs MDT (3 studies)
Mattick 2005[66]	✓	✓	✓	BMT vs BDT (1 study)
Prendergast 2000[67]	✓	X	X	X
Prendergast 2002[68]	✓	X	X	X
Raisch 2002[69]	X	✓	✓	BMT vs LAAM MT; BMT oral vs subcutaneous administration
Roozen 2004[70]	X	X	X	MMT + co-therapies vs MMT + usual care
Simoens 2005[71]	✓	✓	✓	MMT or BMT + cotherapies vs MMT or BMT
Simoens 2002[72]	✓	✓	✓	MMT or BMT + cotherapies vs MMT or BMT; MMT vs MDT (1 study)
Sorensen 2000[73]	✓	X	X	X
Stanton 1997[74]	X	X	X	MMT + co-therapies vs MMT
van Beusekom 2001[75]	✓	X	X	MMT + cotherapies vs MMT; MMT vs MDT (1 studies)
West 2000[76]	✓	✓	✓	X

*At various doses (studies comparing various doses)

Table 4 Mapping of RCTs to policy questions**

Author (year)	MMT* vs. placebo/no therapy	BMT* vs. placebo/no therapy	MMT* vs. BMT*	Other comparisons
Ahmadi 2003a[77]	X	X	✓	BMT and MMT vs clonidine MT
Ahmadi 2003b[78]	X	✓	X	X
Ahmadi 2003c[79]	X	✓	X	X
Avants 2004[80]	X	X	X	MMT + harm reduction programme vs MMT
Blanken 2005¥[81]	X	X	X	MMT + heroin vs MMT
Brooner 2004 [82]	X	X	X	MMT + standard stepped care vs MMT + enhanced stepped care
Chutuape 2001[83]	X	X	X	MMT + contingency enhancement vs MMT
Cornish 2002[84]	X	X	X	MMT + dextromethorphan vs MMT
Dean 2002 [85]	X	X	X	MMT + fluoxetine vs MMT
Dijkgraaf 2005¥¥[86]	X	X	X	MMT + heroin vs MMT
Dolan 2003[87]	✓	X	X	X
Eder 2005[88]	X	X	X	MMT vs slow release morphine
Giacomuzzi 2001 [89]	X	X	X	Morphine vs MMT
Grabowski 2004†[90]	X	X	X	MMT + amphetamine vs MMT
Jones 2001 [91]	X	X	X	MMT + incentives vs MMT
King 2002[92]	X	X	X	MMT in different settings
Kosten 2003 [93]	X	X	X	BMT + desipramine vs BMT
Kristensen 2000 [94]	X	X	✓	X
Lidz 2004 [95]	X	X	X	MMT + behavioural therapy vs MMT
Loftwall 2005 [96] [Update of Strain, 1996]	X	X	✓	X
Margolin 2003 [97]	X	X	X	MMT + magnesium asparttae vs MMT
Marsch 2005 [98]	X	✓	X	X
Pollack 2002[99]	X	X	X	MMT + enhanced counselling vs MMT + behavioural therapy
Ritter 2003 [100]	X	X	X	MMT vs LAAM MT
Sigmon 2004 [101]	X	X	X	MMT +reinforcement vs MMT
Zanis 2001[102]	X	X	X	MMT + behavioural therapy vs MMT

*At various doses. ¥ Outcomes & prognostic analysis based on RCTs of van den Brink 2003[103] describing 2 RCTs (included in the systematic review by Ferri). ¥¥ Economic study based on RCTs of van den Brink 2003[103]. † Reports two RCTs. ** Several studies performed RCTs that contributed to more than one policy question.

As can be seen from Table 3 and Table 4, the majority of evidence was in the form of direct comparisons of MMT (2-100mg/day) and to placebo/no therapy (19 systematic reviews and 1 recent RCT), BMT (1-32mg/day) and compared to placebo/no therapy (11 systematic reviews and 3 recent RCTs) and the comparison of MMT to BMT (12 systematic reviews and 3 recent RCTs). This evidence base spanned a variety of doses of methadone (5 to 110 mg/day) and buprenorphine (≤5 to 32 mg/day). It should be noted that many systematic reviews included the same studies. Little evidence comparing MMT versus MDT (3 RCTs) or BMT versus BDT (1 RCT). A small number of systematic reviews explored potential treatment modifiers.

Much of the evidence came from studies that use the traditional design of comparing fixed doses of MMT or BMT i.e. all patients in the study were given the same dose of drug. However, flexible dose design studies, where patients receive an individualised dose of drug,

are more reflective of real world practice. However, with the exception of the recently updated (as yet unpublished) Cochrane systematic review completed by Mattick and colleagues in August 2005,[66] we found no other RCT evidence of flexible dosings outcomes in other reviews. Furthermore, our updated search of published RCTs identified only one potentially relevant RCT employing a flexible dose design that compared MMT and LAAM.

5.2.3 Quality of evidence

The majority of included systematic reviews and RCTs were of moderate to good quality although some were poor. The median quality score for systematic reviews was 11, with 10 reviews scoring 15 or more and 12 scoring 10 or less (where minimum quality score was 0 & maximum quality score was 18). The median Jadad score across the trials was 3 (out of a possible maximum score of 5) indicating they were generally of 'moderate' quality. Few trials reported details of randomisation (7/26) or concealment (2/26). However, nearly half were double-blind (9/26) and most reported the number of drops out and withdrawals (18/26).
Details of quality assessment are presented in Appendix 5, Appendix 6, and Appendix 7.

5.2.4 Characteristics of included individuals

Systematic reviews often reported few details of their component studies such as the opioid abuse history of participants. However, there were a number of general statements that can be made. Trials on MMT and BMT generally enrolled males aged 30 to 49 years, in good health who met Diagnostic and Statistical Manual III or IV criteria for opioid dependence, had no serious psychiatric or medical co-morbidities and had not been undergoing drug therapy for their misuse treatment in the months prior to maintenance. Although participants were of a wide range of ethnicities they usually pertained to US i.e. Hispanic, African-American. Most trials excluded individuals who had failed previous drug treatment for opioid abuse, pregnant women and those who were less than 18 years old (Simeons et al, 2005)[71]. Few studies recruited HIV-infected or AIDS individuals or polydrug users, especially alcohol and cocaine.

5.2.5 Settings & delivery

Most studies were conducted in the US or Australia and virtually all were undertaken in outpatient, inpatient or specialised treatment centres. Methadone doses ranged from 50 to 150mg/day and buprenorphine from 1 to 15mg/day. As discussed above although a number of trials have compared the relative effectiveness of differing doses of methadone and buprenorphine, the majority of these trials have been based on a fixed dose design where all patients in the trial receive the same dose. Although these fixed dosing trials have been included in this assessment report, the focus of the review of evidence comes from flexible dose trials, as these are more reflective of routine practice. The wide range of individual patient doses used in these flexible dosing strategy trials are summarised in the table below.

Table 5 Flexible dose ranges used in RCTs comparing MMT and BMT

STUDY	Structure of dose regime	Details of dosage procedure		Daily equivalent dose (mg) possible & / or *observed*	
		Methadone	Buprenorphine	Methadone	Buprenorphine
Johnson 2000	Induction wk 1 - 2	Daily: start 20 mg then increase at 10 mg/day to 60 mg/day	Days 1 to 7: daily start at 4 mg rising to 8 mg/day by day 7. Then 16mg on 3 days of wk to day 14.	20 to 60 mg	4 to 8 mg
	Maintenance wk 3-17 [take-away doses permitted]	Increases possible from 60 to 100 mg/day. Mean** dose = 90 mg	Active doses on 3 days a wk. Four increases possible (one every other week) from 16 to 32 mg on Mons & Wens. (Frid dose 50% higher). Mean** dose = 27 mg	60 to 100 mg	8 to 16 mg
Mattick 2003	"Induction" wk 1 - 6	Daily dose: 20 to 40 mg/day.	Daily dose: 2 to 6 mg/day.	20 to 40 mg	2 to 6 mg
	"Post induction" wk 7- 13 [no take-away doses]	Daily dose adjustable up to 150 mg/day (only in units of 10mg). Mean not reported	Alternate day dosing: Start at 2x dose of wk 6; adjustable up to 32 mg/dose. Mean not reported	20 to 150 mg	4 to 16 mg
Petit-jean 2001	"Flexible" wk 1- 3	Daily: day 1 to 3, 30mg; increase possible (30 mg steps) up to 120 mg by day 15.	Daily: day 1 to 3, 4mg; increase possible (4mg steps) up to 16 mg by day 15.	30 to 120 mg	4 to 16 mg
	"Maintenance" 4 – 6 wk [no take away doses]	Maintained on dose reached in flexible phase. Mean 69.8 mg/day	Maintained on dose reached in flexible phase. Mean 10.5 mg/day	30 to 120 mg *Mean 69.8 mg*	8 to 16 mg *Mean 10.5 mg*
Lintzeris 2004	Wk 1-12	Mean dose 37.8 (SD 13.1) mg/day	Mean dose 15.9 (SD 12.7) mg/day	*Mean 37.8 (SD 13.1) mg*	*Mean 15.9 (SD 12.7) mg*
	Wk 13-24 [Take away doses not routine]	Mean dose 51.2 (SD 17.6) mg/day	Mean dose 15.7 (SD 14.7) mg/day	*Mean 51.2 (SD 17.6) mg*	*Mean 15.7 (SD 14.7) mg*
Fischer 1999	"Induction" day 1 to 6	Start at 20 mg/day rising (20 mg steps) to 80 mg/day.	Start at 2 mg/day rising up to 8 mg/day.	20 to 80 mg	2 to 8 mg
	"Post induction" wk 2-24 [take-away doses permitted]	Last induction dose maintained: Mean dose = 63 mg/day	Last induction dose maintained: Mean dose = 7.5 mg/day	*Mean 63 mg*	*Mean 7.5 mg*
Strain 1994 b	"Induction" day 1 to 4	Days 1-4: 20, 30, 40, 50 mg/day	Days 1-4: 2, 4, 6, 8 mg/day	20 to 50 mg	2 to 8 mg
	"Stabilisation " to end of wk 2	50 mg/day	8 mg/day	50 mg	8 mg
	"Post stabilisation" wk 3 – 16	Dose increases (& decreases) [10 mg steps] permitted up to 90 mg/day. Mean dose = 83 mg/day	Dose increases (& decreases) [2 mg steps] permitted up to 16 mg/day. Mean dose = 15 mg/day	50 to 90 mg *Mean 83 mg*	8 to 16 mg *Mean 15 mg*
Strain 1994 a	"Induction" day 1 to 4	Days 1-4: 20, 30, 40, 50 mg/day	Days 1-4: 2, 4, 6, 8 mg/day	20 to 50 mg	2 to 8 mg
	"Stabilisation " to end of wk 2	50 mg/day	8 mg/day	50 mg	8 mg
	"Post stabilisation" wk 3 – 16	Dose increases (& decreases) [10 mg steps] permitted up to 90 mg/day. Mean dose = 54 mg/day	Dose increases (& decreases) [2 mg steps] permitted up to 16 mg/day. Mean dose = 8.9 mg/day	50 to 90 mg *Mean 54 mg*	8 to 16 mg *Mean 8.9 mg*
** authors report "mean maximal Monday and Wednesday doses".					

Although a small number of studies included within systematic reviews and included RCTs were conducted in the community or a laboratory setting most were set in an outpatient clinic. A range of delivery options were reported but in general delivery of MMT and BMT was characterised by fixed doses of medication, no take-home medication, discharge of individuals who missed 3 consecutive days of treatment, limited adjuvant psychosocial therapy, no rewards for treatment compliance, intensive monitoring and limited length of treatment and relatively short periods of follow up (Simeons et al, 2005[71]). The recently updated Cochrane review by Mattick et al (2005)[66], in addition to comparing various fixed doses also reported trials comparing flexible doses of MMT versus BMT. More recent studies have moved toward the provision of MMT and BMT in primary care. Few studies were conducted in prisons.

Reviews provided little information about the providers who deliver maintenance therapy. The administration of MMT and BMT was generally conducted and supervised by a physician or nurse often with specific training in the management of opioid abuse (Simeons et al, 2005[71]).
The potential impact on treatment outcomes of individual characteristics at entry, the delivery setting and the intensity of MMT and BMT programmes (MMT or BMT alone or combined with psychosocial interventions) will be returned to later (see page 43 "Treatment outcome modifiers").

5.2.6 Treatment outcomes

The main outcomes reported by systematic reviews and RCTs were retention in treatment and illicit use of opioids. The methodological issues associated with these is discussed in Appendix 2. Less extensive data was available on HIV-related outcomes, side effects/adverse events and mortality, the latter usually coming from observational comparative studies. Limited outcome data on non-health outcomes of criminal activity and employment was available. These latter outcomes were often sourced from non-randomised observational studies with a cohort, before and after or cross sectional design.

The summary of treatment results below focuses particularly on those systematic reviews that reported pooled numerical outcome data. One of the challenges in presenting these findings was the variety of outcome metrics used both across outcomes and also reported by different reviewers. Broadly these metrics fell into three categories – relative risk (RR), mean difference (MD) and standardised effect size (standardised mean difference [SMD] and Glass's g).

MMT vs. placebo/no therapy

Retention in treatment

All doses of MMT (20 to 97mg/day: RR 3.91, 95% CI; 1.17 to 13.2) and BMT (≤ 5mg to 18mg/day – RR 1.74, 95% CI: 1.06 to 2.87) used in trials were more effective in retaining individuals in treatment than placebo or no therapy (Appendix 9, Table 36, page 164). Higher doses of MMT (60mg or more) were almost invariably found to be more effective than lower doses (e.g. 60-109mg vs. 1-39mg – RR: 1.36, 95% CI: 1.13 to 1.63) (see Appendix 9, Table 36, page 164).

Opiate Use

Doses of MMT (e.g. 60mg - RR 0.31 95% CI: 0.23 to 0.42) used in trials generally proved to be more effective in reducing self reported opioid use than placebo or no therapy (see Appendix 9, Table 37, page 168). Higher doses of MMT were more effective than low doses (e.g. ≥50 mg) vs. <50mg – RR: 0.82, 95% CI: 0.72 to 0.95). The results of urinalysis were broadly consistent with self-report results although fewer RCTs reported opioid urinalysis. Higher doses of MMT were associated with a lower number of opioid positive urines than were lower doses (e.g. 60-109mg vs. 40-59mg: Mean difference (self reported) : -1.89, 95% CI: -3.43 to -0.35), 60-109mg vs. 1-39mg RR (urine tested) 1.59 (95% CI 1.16 to 2.18) (see Table 38, page 171).

Side effects, adverse events and mortality

The frequency of side effects and adverse events associated with MMT and BMT were infrequently reported in systematic reviews other than in the form of a general statement to the effect that the frequency of adverse events was low and relatively minor. For example the systematic review of Raisch et al (2004)[69] came to the following conclusion regarding adverse events: "*the most common adverse effect reported in clinical trials of BMT for opiate dependence is headache but individuals often suffer insomnia, pain, constipation, nausea, vomiting, somnolence, asthenia, anxiety, depression, dry mouth and withdrawal symptoms*"….. and for serious adverse events "*BMT is suspected to decrease liver function but this has not been commonly reported in clinical trials*".

Compared to placebo or no therapy, MMT reduced the level of individual reported adverse events although not significantly (RR 0.59, 95% CI 0.33 to 1.04). The Linzeris and Ford[63] systematic review looked at the issue of safety outcomes of MMT and BMT in detail – based on the Australian NEPOD (National Evaluation of Pharmacotherapies for Opoid Dependence) 2004 report[104]. This report had access to individual patient level data from a number of Australian RCTs and non-RCTs of MMT and BMT. The NEPOD 2004 report quantitatively assessed the frequency of serious adverse events (i.e. resulting in death or significant disability, or are life-threatening or require hospitalisation) in 912 individuals from clinical trials who received drug therapy for opioid use – methadone, buprenorphine, LAAM and naltrexone. The rate of occurrence in four categories of serious adverse events per 100-individual-years in treatment are summarised in Table 45, page 174. The authors of the report concluded that the overall rate of SAEs was low.

Mortality

The meta-analysis of observational studies spanning publication years 1974 to 1995 (Caplehorn 1995[49], see Table 39, page 172) comparing deaths/person years at risk amongst individuals in and out of methadone treatment reported a RR of 0.25 (95% CI 0.19 to 0.33) indicating that patients in methadone treatment were 4 times less likely to die than those not in treatment or discharged from treatment. Base rates in the included studies (i.e. out of methadone treatment) varied greatly ranging from 1.65% to 8.38%.

HIV-related outcomes

A small number of systematic reviews have reported HIV-related outcomes with MMT by including non-RCT studies that encompass before and after and interrupted time series study designs. Compared to placebo or no therapy, MMT significantly improved the HIV outcomes as assessed by HIV risk behaviour/score, number of sex partners, frequency of unprotected sex and rates of seroconversion (Table 48 and page 176).

Crime outcomes
The level of criminal activity appeared to somewhat lower with MMT than placebo or no therapy, the effect size was reported to be moderate to large (mean standardised effect size: 0.54 to 0.70) (Table 47, page 175).

Other relevant outcomes
Although the level of neonatal deaths was somewhat higher in pregnant mothers on MMT (3.3%) compared to no therapy (1.7%) this difference failed to reach statistical significance (Table 53, page 177). No studies reporting quality of life were identified.

BMT vs. placebo/no therapy

Retention in treatment
All doses of BMT (≤ 5mg to 18mg/day – RR 1.74, 95% CI: 1.06 to 2.87) used in trials were more effective in retaining individuals in treatment than placebo or no therapy (Table 33, page 109). Marsch (2005)[98] compared the impact of one per day, three times per week and two times per week buprenorphine. No significant differences in retention in treatment or opioid use were observed between the three groups.

Opiate Use
Higher doses of BMT were more effective than low doses (8-16mg vs. 1-4mg - effect size [d]: -0.25, 95% CI: -0.15 to -0.35) (see Table 37, page 168).

Side effects & adverse events
See MMT vs. placebo/no therapy

Mortality
The unpublished review of Linzeris and Ford (2004)[63] indentifed one RCT (Kakko et al, 2003[105]) demonstrating the capacity of BMT to reduce mortality compared to placebo and counselling treatment over a 12-month period (0/20 deaths in BMT & 4/20 deaths in placebo).

HIV-related outcomes
No data on BMT and HIV risk behaviour was identified.

Crime outcomes
There appear to be no studies that have assessed crime outcomes of BMT compared to placebo.

Other relevant outcomes
None identified

MMT vs. BMT

Retention in treatment

Across comparable fixed doses MMT was more effective than BMT with the exception of low dose where the two drugs appeared to be equivalent (≤ 35mg MMT vs. 6-16mg BMT – RR: 1.01, 95% CI: 0.66 to 1.54) (Table 36, page 164).

A recently updated (as yet unpublished) systematic review by Mattick et al[66] identified 7 RCTs that directly compared flexible dosing MMT with BMT. Our searches identified no additional RCTs using a flexible dose design and comparing MMT and BMT. In view of this, we present here the detailed pooled retention in treatment and opioid use results from the Mattick et al, 2005 systematic review together with our reanalysis of this data as this will be utilised in the assessment group economic model. Unfortunately no RCT data was available on flexible dosing for other outcomes such as HIV risk behaviours and mortality. The forest plot below (Figure 4) summarises the relative risk for rentention in treatment in seven flexible dosing trials of methadone and buprenorphine.

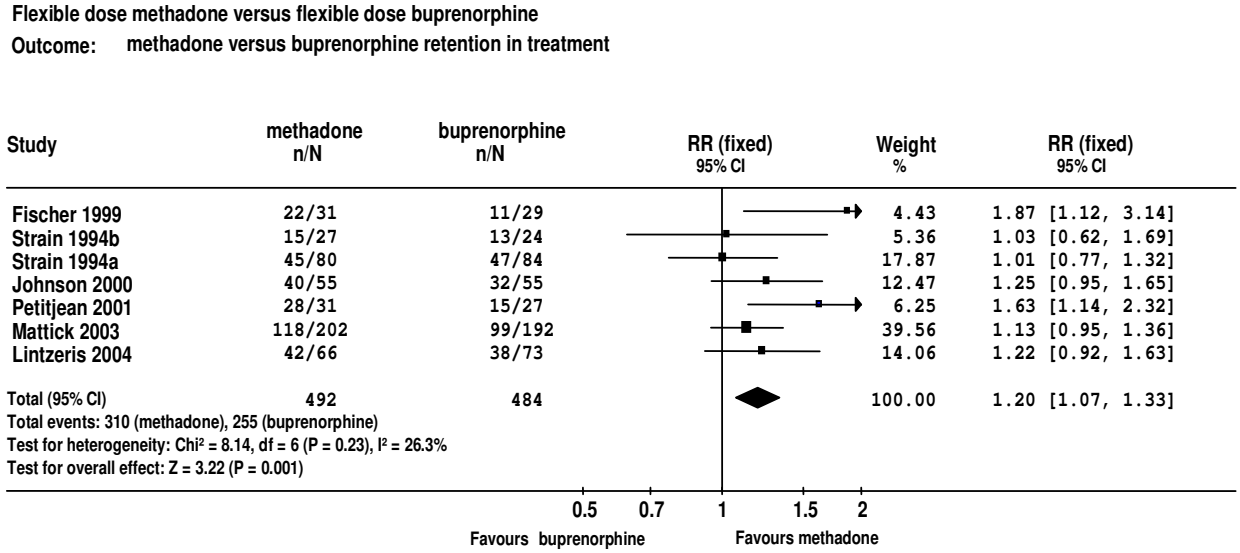


Figure 4. Retention in treatment flexible dosing of MMT vs. BMT

This data indicates statistically significant superior retention in treatment with flexible dosing MMT compared to flexible BMT. Given the time dependent nature of the retention in treatment, we constructed Kaplan Meier survival curves for BMT and MMT. It was assumed that any patients reported censored in the primary studies were unretained in treatment and weekly interpolation was used where necessary. At end of follow up in each study the patients retained in treatment were censored. The resulting survival curves are shown in Figure 5. Individual trial hazard ratios and the pooled hazard ratio are shown in Table 6 and also Figure 6. Survival curves for individual studies are shown in Appendix 10.

Table 6 Hazard Ratio of BMT vs. MMT in flexible dosing

Study	Hazard ratio	Lower confidence interval	Upper confidence interval
Mattick 2003 [106]	1.33	0.99	1.78
Lintzeris 2004[107]	1.40	0.84	2.34
Fischer 1999 [108]	2.56	1.20	5.47
Johnson 2000 [109]	1.71	0.90	3.22
Strain 1994a [110]	1.06	0.47	2.41
Strain 1994b [111]	1.03	0.67	1.60
Petitjean 2001[112]	4.21	1.47	12.03
Pooled (fixed effects)	**1.40***	**1.15**	**1.69**
* P = 0.002; Test for heterogeneity: Q = 9.44 on 6 degrees of freedom (P= 0.150)			

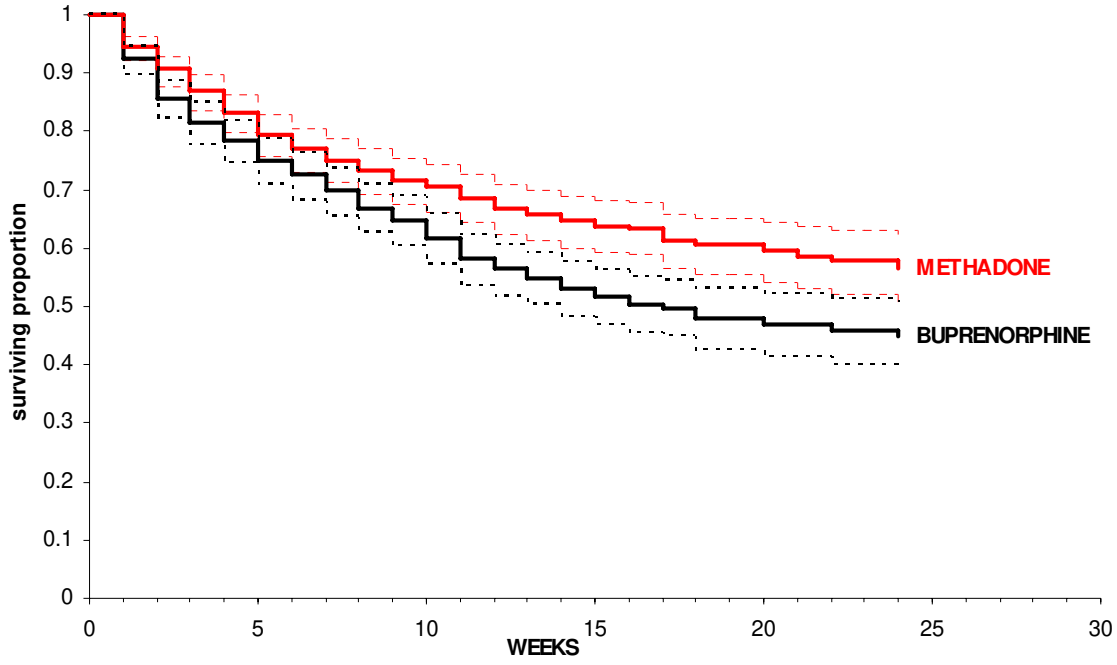


Figure 5 Patient retention with MMT and BMT in flexible dosing

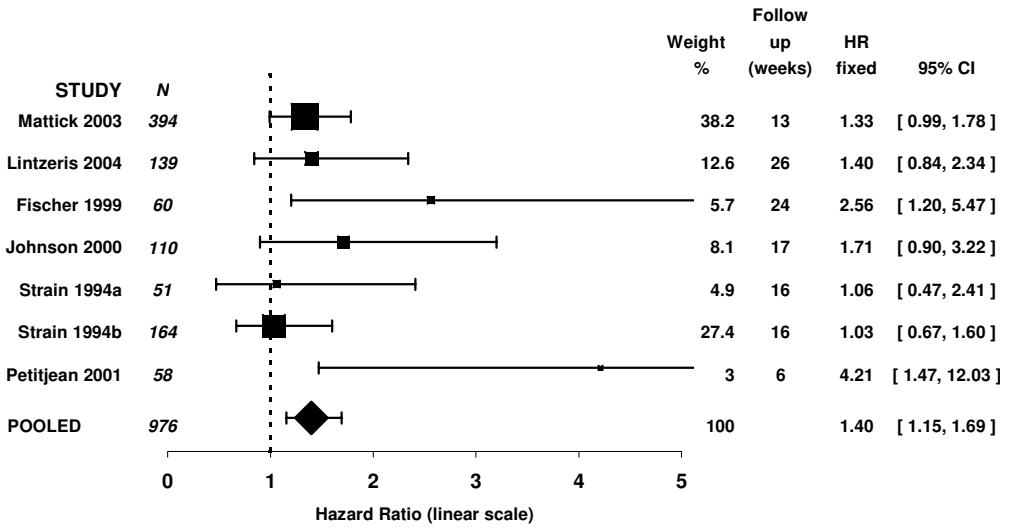


Figure 6 Hazard ratio treatment retention in flexible dosing (buprenorphine vs methadone; fixed effects)

Opiate use

There was no significant difference in the level of opiate abuse between flexible MMT and BMT groups as shown in the forest plot below (Figure 7).

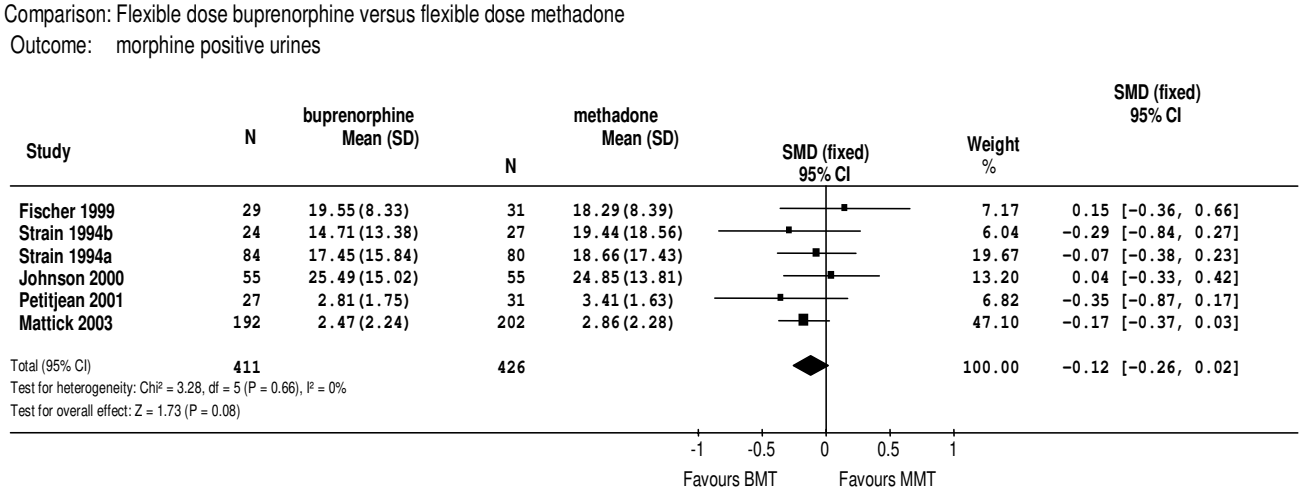


Figure 7. Opioid use in flexible dosing of MMT vs. BMT

At high doses fixed dose MMT was more effective than fixed dose BMT (≥50mg vs. <8mg: RR: 0.29, 95% CI: 0.15 to 0.79) while at lower fixed dose MMT and higher fixed dose BMT the two appeared to be more equally effective in preventing opioid use.

Side effects & adverse events

See MMT vs. placebo/no therapy

Mortality

Auriacombe et al (2001)[113] made direct comparison of drug overdose deaths in methadone and buprenorphine users in France for the years 1994 to 1998. Numbers of patients in receipt of methadone and buprenorphine were calculated indirectly from sales records provided by manufacturers and estimates regarding average dose; drug associations were ascertained from local evidence rather than lab-based tests. Total deaths and person years at risk were: methadone 19 and 9360; buprenorphine 27 and 132900. Ford and Linzeris (2004)[63] commented that although this data is unlikely to capture all related deaths, it nevertheless suggests BMT to be associated with less mortality than MMT.

HIV-related outcomes

No data on BMT and HIV risk behaviour was identified.

Crime outcomes

Flexible dosing of either MMT or BMT appear to be equally effective in their effect on criminal activity (SMD 0.14, 95% CI: -0.14 to 0.41) although this result comes from only one RCT.

Other relevant outcomes

None identified

Other MMT and BMT comparisons

MMT or BMT vs. other drugs

Compared to LAAM, MMT was more effective (RR: 1.64, 95% CI: 1.28 to 2.11) while BMT was equally effective in the one RCT where this comparison was made (no effect size reported). One RCT found MMT to more effective in retention than naltrexone while one RCT reported MMT (10-120mg) to be less effective than oral heroin (30-120mg). However, the combination of MMT and injected or oral heroin was found to be more effective than heroin alone (RR 1.24, 95% CI: 1.11 to 1.38). One RCT showed a similar level of employment of individuals receiving MMT or heroin (Table 52, page 177).

MMT or BMT plus co-therapies vs. MMT or BMT alone

Reviews provided few details of additional interventions available to individuals in trials of MMT and BMT. Moreover, where available, these additional interventions were likely to have been present in the maintenance and control arms, which make it impossible to assess their effectiveness (Stanton & Shadish, 1997[74]). However, a small number of reviews explicitly reported the treatment outcomes associated with MMT in combination with other therapies, including contingency methods (i.e. individual rewards contingent to individuals achieving a treatment compliance) and psychosocial interventions.

Fridell et al 2003[55] identified 9 RCTs that directly compared the impact of MMT plus psychosocial interventions to MMT alone (or within standard programme) (Table 36 and Table 38). The authors pooled the standardised treatment effect (d) across studies. The addition of psychosocial treatments (e.g. cognitive therapy, family therapy) to MMT reduced the opioid level of opioid misuse compared to MMT alone (d: 0.21, 95% CI: 0.08 to 0.35) although there was no significant difference in retention on treatment (d: 0.13, 95% CI: -0.24 to 0.51). Johansson (2003)[60] reported a small but non-significant improvement in opioid misuse when MMT was supplemented with community reinforcement (RR: 1.14 (0.98 to 1.31) (Table 37, page 168).

Johansson (2003)[60] identified 4 studies that directly compared drug maintenance therapy with contingency management to drug maintenance alone. Two studies found that opoid use was decreased if individuals had the option to acquire extra methadone if they submitted negative urinalysis (Higgins et al, 1986;[114] Stitzer et al, 1992[115]) while another showed that contingency management increased attendance in therapy sessions (Kidorf et al, 1994[116]). One study found no significant change in use with contingency management (Preston et al.2000[117]).

The addition of psychosocial interventions to MMT appeared to further improve individual retention rates compared to MMT alone although this additional benefit was small and not statistically significant (effect size [d][a]: 0.13, 95% CI: -0.24 to 0.51).

Treatment outcome modifiers

Four systematic reviews have specifically examined how treatment outcomes of MMT and BMT might vary by individual characteristics, treatment intensity (dose has already been discussed above), treatment setting and study design (Johnasson, 2003;[60] Simeons et al; 2005[71]; Prendergast et al, 2000[67] and 2002[68] and Lintzeris & Ford, 2004[63]).

Probably the single most comprehensive exploration of treatment modifiers in MMT are the reviews of Prendergast et al[67,68] who undertook a detailed quantitative synthesis based on meta-analysis and correlational methods. The authors identified 143 controlled studies (randomised controlled trials, 2 group non-randomised comparative studies and single group before and after studies) across a variety of different drug abuse treatments conducted between 1965 and 1996. Studies examined outcomes in adult illicit dug users comparing therapy either to no therapy or minimal therapy. The review included studies examining any drug abuse treatments. Head to head dose studies were excluded. Of 143 studies 38 (27%) specifically examined MMT. In order to combine studies, the authors converted all outcome results into a single effect size – standardised mean difference. Two outcomes were examined – substance use and crime associated outcomes, both either self-report or objectively measured.

Across the MMT studies, the mean improvement in effect size (d) with treatment was 0.78 ("moderate to large" effect) in substance use and 0.54 ("moderate" effect) in crime related outcomes. Weighted correlation analysis was used to assess the association between programme factors and effect size. For substance use, the only statistically significant predictor was methadone dose although the quality of drug programme implementation and number of weeks of treatment were also positively associated with retention. No significant predictors for criminal activity outcome were identified.

Individual characteristics

The study of any relationship between the outcome of treatment and the characteristics of individuals at entry to methadone or buprenorphine therapy is limited in RCTs. Lintzeris and Ford (2004)[63] noted that the majority of RCTs of methadone and buprenorphine have excluded individuals with significant medical or psychiatric co-morbidity. However, some studies have examined the relationship between medical and psychiatric co-morbidity and treatment outcome. Furthermore Linzeris and Ford noted no RCTs had compared the outcomes of buprenorphine and methadone treatment according to variables of duration of heroin or severity of heroin dependence. Lintzeris and Ford (2004) therefore instead used

[a] Effect size >0 indicates a greater proportion of patients retained in treatment in intervention group

three non-RCTs to examine the impact of two individual characteristics on treatment outcomes.

Gerra et al (2004)[118] examined predictors of outcome in 154 individuals entering a 12-week methadone or buprenorphine treatment programme. There was no between group difference regarding treatment retention or levels of heroin use (urine-analysis) at 12 weeks. In the methadone group, treatment retention and urinalysis results were influenced by methadone dose and level of psychosocial functioning at intake, but not by psychiatric co-morbidity or substance use history. In contrast, for the buprenorphine group, treatment retention and reductions in use were greater in individuals with a high level of depression at intake, whereas buprenorphine dose, psychosocial functioning or substance use history were unrelated to outcome.

Poirier et al (2004)[119]found the response to buprenorphine was higher in individuals with a higher psychopathological score, low disinhibition and boredom susceptibility scores, no alcohol dependence, no family history of addiction or mood disorder, and duration of opioid dependence less than 10 years.

Schottenfeld et al (1998)[120] found the reported levels of psychopathology at intake did not significantly impact upon outcomes (retention, drug use) in individuals randomised to methadone or buprenorphine. In contrast, an open label, observational study (Gerra et al, 2004[118]) identified that a history of depression was associated with better treatment response for buprenorphine individuals but not for methadone individuals.

The review of Hopfer et al (2002)[59] specifically assessed the impact of opioid use therapies in heroin dependent individuals aged 19-years or younger. Across 4 non-RCTs (registry and cross sectional designs) in 5,266 individuals they found an increase in treatment retention and reduction in opioid use with MMT.

Intensity of treatment

The review of Laysson-Wolff (2002)[62] reported one non-randomised study that compared fast induction (1-day) MMT with slow induction (14-day) MMT and found no significant difference in the level of retention at 52-weeks between groups.

The dispensing and delivery of MMT and BMT in many trials was undertaken under supervision. Lintzeris and Ford identified only one published study to directly examine the impact on treatment outcome of different supervision levels of buprenorphine dosing. Auriacombe et al (2003)[121] quasi-randomly assigned 202 individuals entering office based buprenorphine treatment into three groups - low supervision (initial 2 weeks buprenorphine supervised followed by weekly dispensing); medium supervision (three months of supervised buprenorphine, followed by weekly dispensing); and high supervision (6 months of supervised dispensing). Outcomes were most favourable in the high supervision group (retention 75% UDS positive 22%) followed by medium supervision (retention 65% UDS positive 18%), and least favourable for the low supervision group (retention 46% UDS positive 18%).

The safety and efficacy of BMT dispensed on alternate or three-day treatment compared to daily treatment has been investigated by a number of RCTs (Fudala et al 1990, [122] Amass et al 1994[123] & 1998, [124] Johnson et al 1995,[125] Bickel et al 1999,[126] Schottenfeld et al 2000[127]) and compared to daily methadone treatment (Johnson et al 2000,[109] Mattick et al 2003,[106] Linzeris et al 2004[107]). We found no studies that compared the frequency of MMT dosing.

Treatment setting
Lintzeris and Ford (2004)[63] identified two RCTs that directly compared outcomes of individuals treated in a specialist centre or in primary care setting. O'Connor et al (1998)[128] randomised 46 (presenting to primary care) and demonstrated enhanced outcome for the primary care group (less heroin use, trend toward better retention), whilst Gibson et al (2003)[129] found no significant differences amongst 101 individuals to primary care or clinic. Johansson (2003)[60] identified another two studies comparing MMT delivery in different settings. Fiellin et al (2001)[130] found in 47 individuals no difference in opioid use or retention treated with methadone by primary care physicians or by an individual narcotic treatment programme. King et al (2002)[92]randomised 73 individuals to either methadone delivery at the physician's office, in a clinic-based setting or routine care. They found no difference in urinalysis or retention between the groups at 6-months follow up.
The review by Linzeris & Ford (2004) noted growing body of RCTs indicating buprenorphine treatment can be effectively delivered in primary care compared to placebo (Fudala et al, 2003)[131] and methadone (Lintzeris et al, 2004).[107]
No reviews identified trials directly comparing MMT or BMT in prison settings to non-prison settings.

Study design
As discussed above, although the majority of studies included in reviews have been double-blind MMT and BMT randomised controlled trials, observational studies were included, particular for mortality. The bias of observational studies was quantified by Prendergast et al (2000)[67] who found the mean effect size of randomised or non-randomised two group studies to be some 3-fold less (drug use: 0.32; crime: 0.23) than single group before-after studies (drug use: 1.28; crime: 0.76).

MMT vs. MDT
The overview of Amato and colleagues (2005)[132]identified two controlled trials in 340 individuals that have compared the treatment outcome of MMT and tapered methadone (detoxification). The MMT group (76%) had a considerably higher level of retention in treatment than the MDT group (27%) - RR 3.86, (95% CI 1.09 to 13.75). Gowing et al (2004a)[57] found one RCT (Sees et al, 2000)[133] comparing 91 opioid dependent individuals on MMT to 88 in MDT. There was no difference in HIV or sex risk behaviours at 6 or 12 months follow up.

BMT v. BDT
The reviews of Mattick 2005[66] identified one RCT that compared BMT to BDT. This RCT by Kakko et al [105] compared 20 patients undergoing BDT to 20 undergoing BDT. They reported 20% mortality in the BDT group compared to 0% in BMT.

Summary

- 31 systematic reviews (including either RCT & non RCT evidence) met the inclusion criteria of this report. Many of the studies included in these reviews overlap. In addition, we identified an additional 28 RCTs published more recently (since 2001).
- The majority of systematic reviews and RCTs were of moderate to good quality, focused on short-term (up to 1-year follow up) outcomes of retention in treatment and the level of opiate use (self-report or urinalysis) in those individuals retained in treatment.
- The majority of evidence has been collected in males aged 30 to 49 years, in good health, who met Diagnostic and Statistical Manual III or IV criteria for opioid dependence, had no serious psychiatric or medical co-morbidities and had not undergoing drug therapy for their misuse treatment in the months prior to maintenance.
- The majority of trials to date have a fixed dose design where all include individuals are given the dose design of methadone and buprenorphine. More recently some studies have employed a flexible dosing design that is more reflective of real-world practice where participants receive an individualised dose of methadone or buprenorphine.
- Key findings
- MMT vs. no drug therapy/placebo: A number of RCT meta-analyses have consistently shown that fixed dose MMT has superior levels of retention (e.g. 20-97mg vs. placebo: pooled relative risk [RR] - 3.91, 95% CI: 1.17 to 13.2) in treatment and opiate use (e.g. 35-97mg vs. no treatment: pooled effect size - 0.65, 0.41 to 0.89) than placebo or no treatment, with higher fixed doses of MMT being more effective than lower fixed doses (retention in treatment e.g. ≥50 mg vs. <50mg: pooled RR - 1.25, 0.94 to 1.67). There was evidence, primarily from non-randomised observational studies, that fixed dose MMT reduces mortality, HIV risk behaviour and levels of crime compared to no therapy.
- BMT vs. no drug therapy/placebo: Two RCT meta-analyses show that fixed dose BMT has superior levels of retention in treatment (e.g. 6-12mg vs. placebo: pooled RR- 1.74, 1.06 to 2.87) and opiate use (6-16mg vs. placebo: pooled RR - 1.74, 1.06 to 2.87) than placebo or no therapy, with higher fixed doses of BMT being more effective than lower fixed doses (e.g. retention in treatment e.g. 8-16mg vs. 1-4mg: effect size - 0.21, 0.12 to 0.31. One small RCT has shown that the level of mortality with fixed dose BMT to be significantly less than placebo.
- BMT vs. MMT: A number of RCT meta-analyses have consistently shown that fixed doses of MMT had superior retention in treatment and opiate abuse than comparable fixed doses of BMT. A recently updated and unpublished Cochrane systematic review of 7 RCTs directly compared flexible dosing MMT to flexible dosing BMT in 976 opiate dependent individuals. No further RCTs comparing flexible MMT and BMT were identified through our searches. The daily equivalent doses in these flexible

dosing trials ranged from 20 or 30mg to 60 or 120mg for methadone and 2 or 4mg to 8 or 16 mg for buprenorphine. Retention in treatment was superior for flexible MMT than flexible BMT dosing (pooled hazard ratio: 1.40, 95% CI: 1.15 to 1.69) although there was no significant difference in opiate use (standardised mean difference: 0.12, 95% CI: -0.02 to 0.26). Indirect comparison of data from population cross sectional studies, suggest that the level of mortality with BMT may be lower than that of MMT. A pooled RCT analysis showed no significant difference in the rate serious adverse events with MMT compared to BMT.

- Treatment modifiers: - Although the amount of evidence on treatment modifiers was limited, adjunct psychosocial and contingency interventions (e.g. financial incentives for opiate free urine samples) appeared to enhance the effects of both MMT and BMT. Also, MMT and BMT appear to be similarly effective whether delivered in primary care or outpatient clinic setting.
- MMT vs. MDT & BMT vs. BDT: Two RCTs demonstrated MMT to have superior retention in treatment and opiate use than MDT. One RCT has shown BMT to be superior to BDT.
- Most of studies were conducted in the US and Australia and involved supervised dosing. Given the context specific nature of drug use and the effectiveness of opioid treatments, caution must be applied in the direct transferability of this evidence base in the UK.

6 ECONOMIC ANALYSIS

6.1 Systematic Review of Economic Evaluations – published evaluations

The aim of this section is to assess the cost-effectiveness of methadone or buprenorphine maintenance therapy compared to alternative available therapies or no treatment for the management of opioid dependence from a National Health Services (NHS) perspective. This section of the report has three components:

- a review of existing economic evaluations of the use of methadone and buprenorphine maintenance therapy for the management of opioid dependence
- a technical commentary on the decision-analytic models used in the economic analyses reported in the manufacturers' submissions to NICE.
- A decision analytical model developed by the assessment team.

6.1.1 Methods

Search strategy

A comprehensive search for literature on the cost and cost effectiveness of methadone and buprenorphine as substitutes opiates for opioid dependent drug misusers was conducted. The searches identified existing economic models and information on costs, cost effectiveness and quality of life from the following sources:

- Bibliographic databases: MEDLINE (Ovid) 1966- week 1 2005, EMBASE (Ovid) 1980 – Aug 2005, Cochrane Library (NHS EED and DARE) (Wiley internet interface) 2005 Issue 3, HEED database Aug 2005.
- Industry submissions.
- Internet sites of national economic units.

Full details of search strategies are contained in Appendix 1.

Inclusion and exclusion criteria

Inclusion and exclusion criteria applied for economic searches are shown in Table 7.

Table 7 Inclusion criteria for the review on cost-effectiveness

Study design	Cost-consequence analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis; cost studies (UK only), quality of life studies
Population	People who are dependent on opioids
Intervention	Burprenorphine or methadone employed in maintenance therapy irrespective of dose. The following operational definition was employed: any trial that calls itself "maintenance" OR any trial that does not include a reducing or cessation of methadone / burprenorphine dose as part of its intervention.
Comparator	Any comparator regime used in maintenance therapy (including no therapy or placebo) or the intervention drug used in withdrawal/detoxification therapy.
Outcome	Quality of life estimates, cost estimates, cost-effectiveness

Study selection, data extraction, and quality assessment strategy
An experienced health economist applied the inclusion and exclusion criteria – checked by a second health economist. Data were extracted by one reviewer using a pre-designed data extraction form and were independently check by a second reviewer. Data on the following were sought:

- Study characteristics, such as study question, form of economic analysis, population, interventions, comparators, perspective, time horizon, and modelling used.
- Clinical effectiveness and cost parameters, such as effectiveness data, health state valuations (utilities), resource use data, unit cost data, price year, discounting, and key assumptions.
- Results and sensitivity analyses.

These characteristics and the main results of included economic evaluations are summarised in subsequent tables. The quality of included studies and industry submissions was assessed using an adapted version of the Drummond and Jefferson BMJ criteria for economic evaluations[134] was used to assess non-model studies and the Phillips (2004)[135] Consensus on Health Economic Criteria quality criteria was used to assess economic model reports. The use of the predetermined quality criteria was agreed at the outset of the review. In the first instance the quality of economic aspects of the studies was assessed. Papers failing more than two quality criteria were excluded. Papers failing two items were reviewed to identify key messages contained in the papers and marked with a query. Papers that failed just one or none of the items were reviewed in full and marked with a pass.

The final data on incremental cost effectiveness ratios (ICERs) extracted from the relevant papers were converted from their respective currencies to £ (sterling) using purchasing power parities from the Organization for Economic Cooperation and development. Once converted to £ (sterling) the cost data were inflated to 2004 prices using the NHS Executive Hospital and Community Health Services Pay and Prices inflation index.

6.1.2 Results

Of the twenty eight papers that were identified and reviewed in full only 11 papers reached the final stage of our review and were considered for data extraction. The majority of papers excluded (13/28) had failed on at least two or more of the quality criteria. [b] Eleven published economic evaluations met the inclusion criteria. Key features of these studies are summarised in Table 8. A summary of the ICERs reported in the published analyses is provided in Table 9.

Eight economic evaluations considered methadone maintenance therapy (MMT) as a primary intervention, with the remaining three evaluations considering buprenorphine maintenance therapy (BMT). Each study took a different approach, for example, the evaluation

[b] Five (5/28) studies were marked with a query Five studies typically failed only one criteria item but the distinction between absolute failure and being marked with a query was considered important. Papers marked with a query often made useful points or contained useful data which might prove useful in the construction of our own model. For instance two UK based studies, Strang et al (2000) (278) and Healey et al (2003) (428), were excluded from the final stage because the perspective of their analysis was not made clear. Consequently, the full implication of the final ICERs, for these papers were difficult to interpret but the context of the description of the treatment therapy and the cost data provided useful information when structuring our own model.

undertaken, perspective taken, treatment comparators chosen and, the economic models developed. Most studies were considered to be of high quality.

Quality assessment

Phillips et al. (2004)[135] quality assessment (QA) criteria were used to measure the quality of the six studies reporting an economic model. The summary of quality results are presented in Appendix 8. All six modelling studies met at least 75% of the Philips quality criteria. The quality of these six non-model studies was judged to variable: with the exception of one study. Sirotnik & Bailey (1975)[136] met only 20% of the criteria: their study provided very limited detailed breakdown of cost data and the results, reported in terms of a 'dollar-benefit' to society, were not easily interrogated.

Economic Evaluations

Five studies were cost-utility analyses, with the ICER reported as a cost per quality adjusted life year (QALY) gained (see Table 8 & Table 9). In addition to cost per QALY, both Doran et al. (2003)[137] and Harris et al. (2005)[138] also considered cost per heroin free-day and Zaric et al. (2000a, 2000b)[139,140] considered cost per life year gained. Two studies reported outcomes in terms of life years; Barnett (1999)[141] reported a cost per life year gained and Sheerin and colleagues (2004)[142] reported a cost per life year saved. Three studies reported outcome measures other than cost per QALY or life year. These include the following: Goldschmidt (1976),[143] who reported a cost per effectiveness measure unit (i.e. successful patient) and a cost per heroin-free patient; Sirotnik & Bailey (1975),[136] who reported a dollar-benefit to society; and, Zarkin and colleagues (2005),[144] who reported a cost-benefit ratio (Table 9).

Perspective

Five studies took a societal perspective (i.e. including direct and indirect costs associated with healthcare resource use, criminal activity and earnings), these included: Dijkgraaf et al. (2005);[86] Goldschmidt (1976);[143] Harris et al. (2205);[138] Sirotnik & Bailey (1975);[136] and, Zarkin et al. (2005).[144] The remaining six studies took the perspective of a healthcare system: Barnett and colleagues (1999 & 2001)[141,145] and Zaric and colleagues (2000a & 2000b)[139,140] reported results from the perspective of the US health care system. Sheerin et al. (2004)[142] took the perspective of the New Zealand health system. Doran et al. (2003)[137] took the perspective of the Australian Health Service.

Table 8 Summary of published economic analyses

Author	Drug regimen	Form of economic analyses	Perspective taken	Model used	Time horizon	Outcome measure
Barnett (1999) [141]	MMT	Cost-effectiveness	US Healthcare system	Markov	Lifetime	Cost per life year gained
Barnett et al. (2001) [145]	BMT	Cost-utiilty	US Healthcare system	Dynamic	10 years	Cost per quality adjusted life year (QALY) gained
Dijkgraaf et al. (2005) [86]	MMT	Cost-utility	Societal	None	1 year	Cost per QALY gained
Doran et al. (2003)[137]	BMT	Cost-effectiveness	Australian Health Service Provider	None	1 year	Cost per heroin free day
Goldschmidt (1976) [143]	MMT	Cost-effectiveness	Societal	None	1 year	Cost per 'effectiveness measure unit' (EMU): 'Normabider criterion' (successful patients) and 'heroin-free' patients.
Harris et al. (2005) [138]	BMT	Cost-effectiveness and cost-utility	Societal	None	NA	Cost per heroin free day Cost per QALY gained
Masson et al (2004) [146]	MMT	Cost-effective and cost-utility	US Healthcare system	Markov	10 years	Cost per life year gained & QALY gained
Sheerin et al. (2004) [142]	MMT	Cost-effectiveness	NZ Healthcare system	Markov	10 years	Cost per life year saved
Sirotnik & Bailey (1975) [136]	MMT	Cost-benefit	Societal	None	1 year	Dollar-benefit to society
Zaric et al. (2000a) [139]	MMT	Cost-utility	US Healthcare system	Dynamic	10 years	Cost per life year gained and cost per QALY gained
Zaric et al. (2000b) [140]	MMT	Cost-utility	US Healthcare system	Dynamic	10 years	Cost per life year gained and cost per QALY gained
Zarkin et al. (2005) [144]	MMT	Cost-benefit	Societal	Monte-Carlo	Lifetime	Cost-benefit ratio

Table 9 Summary of published economic analyses reporting cost per life year saved/gained or cost per QALY

Drug regimen	Comparator	Study	Date	Time Horizon	ICER	Converted costs to UK£ 2005	Comment
Methadone maintenance therapy (MMT)	Drug-free treatment	Barnett	1999	Lifetime	US$5,250 per life year gained	£3,904 per life year gained	
	MMT plus heroin	Dijkgraaf et al.	2005	1 year	MMT + heroin MMT alone dominated		Unclear how generalisable the results are to the present report
	Methadone detoxification	Masson et al	2004	10-years	US$16,9997 per life year saved US46,217 to US$19.997 per QALY gained		
	Five treatment options	Sheerin et al.	2004	10 years	NZ$25,035-NZ$25,397 per life year saved	£10,520-£10,672 per life year saved	Study focussed on a Marori and non-Maori comparison. This population is not deemed relevant to current report
	Four populations determined by prevalence of HIV: 5%, 10%, 20%, 40%	Zaric et al.	2000a	10 years	US$9,700-$17,200♣ per life year gained US$6,300-$10,900♣ per QALY gained	£3,684-£6,533 per life year gained £2,393-£4,140 per QALY gained	Dynamic model incorporating population effects associated with an infectious diseases and therefore not appropriate for direct comparison with other static models.
	Expansion of 10% of individuals receiving MMT, within a high HIV prevalence (40%) and low HIV prevalence (5%) population	Zaric et al.	2000 b	10 years	US$8,200-$10,900♣♦ per QALY gained	£3,114-£4,140 per QALY gained	Dynamic model incorporating population effects associated with an infectious diseases and therefore not appropriate for direct comparison with other static models.

♣ Dependent on the prevalence rate assumed within the population

♦ These results were also reported in the previously published paper Zaric et al. 2000a

Table 10 Summary of published economic analyses reporting cost per life year saved/gained or cost per QALY

Drug regimen	Comparator	Study	Date	Time Horizon	ICER	Converted costs to UK£ 2005	Comment
Buprenorphine (BMT) maintenance therapy	Conventional' treatment (i.e. MMT)•	Barnett et al.	2001	10 years	5% HIV prevalence US$14,000 - $84,700* cost per QALY gained 40% HIV prevalence US$10,800 - $66,700* cost per QALY gained	£5,317-£32,169 per QALY gained £4,102-£25,332 per QALY gained	Dynamic model incorporating population effects associated with an infectious diseases and therefore not appropriate for direct comparison with other static models. Favourable results are reported for BMT but their comparison was not with MMT directly. The examines the effect of adding buprenorphine maintenance therapy to the US health care system in addition to individuals already receiving MMT maintenance therapy, therefore the apparent cost-effectiveness of BMT n this case applies to the additional individuals who receive it, for whom MMT maintenance is unsuccessful or not appropriate.
	MMT	Doran et al.	2003	1 year	Cost per heroin free day MMT dominated BPN ICER MMT versus BMT (95%CI) -$201 per heroin free day (-$2069 to $1809)	-£93.94 per heroin free day	Use same RCT data (Mattick et al, 2003) as Schering-Plough economic submission. Sensitivity analysis indicates that costs of BMT and MMT could be equivalent

	MMT	Harris et al.	2005	1 year	Cost per heroin free day (HFD): Excluding costs attributed to crime MMT dominated BPN Including costs attributed to crime BMT had lower costs and less HFD compared to MMT Cost per QALY: Excluding costs attributed to crime: ICER for BMT vs MMT AUS$39,404 Including costs attributed to crime: BPN dominated MMT	Excluding costs attributed to crime: £17,326 per QALY gained	Authors conclude that data do not provide support for significant difference between BMT and MMT outcomes and costs.

♣ Dependent on the prevalence rate assumed within the population ♦ These results were also reported in the previously published paper Zaric et al. 2000a

Table 11 Summary of published economic analyses reporting 'alternative' outcome measures

Drug	Comparator	Study	Date	Time Horizon	ICER	Comment
Methadone maintenance therapy (MMT)	Therapeutic Community Programmes	Goldschmidt	1976	NA	Cost per normabider criterion ('successful') patient: MMT US$147, TCP US$243 Cost per heroin-free patient: MMT US$61, TCP US$122	Study considered too old to be useful or relevant to current treatment regimens
	Cumulative dollar-benefit to society as a result of 285 patients treated in five modalities of care: a facility offering hospital follow-up services, i.e., short term counselling; a drug free residential facility; a residential halfway house; a 14-day in-patient detoxifcation programme; and, an outpatient MMT programme.	Sirotnik & Bailey	1975	NA	Total dollar-benefit to society of US$3.4 million	Study considered too old to be useful or relevant to current treatment regimens
	Comparison of MMT costs, criminal activity costs, earnings and healthcare use costs within a simulated population of 1 million	Zarkin et al.	2005	Lifetime	Benefit-cost ratio (i.e. MMT treatment compared to No MMT treatment) over a lifetime was 37.72.	Dynamic model incorporating population effects associated with an infectious diseases and therefore not appropriate for direct comparison with other static models.

NA: not applicable

Treatment Comparators

The three studies that reported BMT as the primary intervention all used MMT as the comparator. [137,138,141] The remaining studies used a variety of comparators: Sheerin et al. (2004)[142] and Sirotnik & Bailey (1975)[136] compared five treatment modalities, including MMT as an option; Barnett (1999)[141] compared MMT to a drug-free treatment regime; Dijkgraaf et al. (2005)[86] compared MMT to MMT plus heroin; Goldschmidt (1976)[143] compared MMT to a therapeutic community program; Zarkin et al. (2005)[144] compared the cost of MMT among a simulated population of 1 million; Zaric et al. (2000a)[139] compared the cost effectiveness and cost utility of MMT within four different populations with a high or low prevalence of HIV; and, Zaric et al. (2000b)[140] compared the cost effectiveness and cost utility of the expansion of a MMT programme within the same HIV prevalent populations.

Barnett et al. (2001)[145] report a favourable scenario in their evaluation of BMT but their comparison was not with MMT directly. The authors developed a dynamic model to determine the effect of adding buprenorphine maintenance therapy to the US health care system in addition to individuals already receiving MMT maintenance therapy, therefore the apparent cost-effectiveness of BMT in this case applies to the additional individuals who receive it, for whom MMT maintenance is unsuccessful or not appropriate The model and results are based on the assumption that MMT is the treatment of choice for the majority of individuals.

In the studies comparing BMT to MMT, the study by Doran et al produced results that were favourable to MMT in the base case results in which the full costs of BMT had been used, but the sensitivity analysis found that any of the differences between BMT and MMT disappeared when the price of BMT and the time taken to dose a patient with BMT are reduced. They argued that such reductions are increasingly likely to be observed as BMT maintenance treatment becomes more widely used. Harris et al. (2005)[138] showed BMT was dominated by MMT for both the outcome of cost per heroin free day and for cost per QALY. When the perspective was widened to include the cost of crime, BMT dominated MMT, but the authors had expressed serious concern about the quality of the crime data.

Economic Models

Six of these studies developed an economic model: Barnett (1999),[141] Barnett et al. (2001);[145] Sheerin et al. (2004);[142] Zaric et al. (2000a & 2000b);[139,140] and, Zarkin et al. (2005).[144]Barnett (1999)[141] and Sheerin et al. (2004)[142] developed Markov models with a time horizon of a lifetime and 10 years, respectively. Zarkin et al. (2005)[144] developed a Monte Carlo simulation with a lifetime time horizon. Published papers by Barnett et al. (2001)[145] and Zaric et al. (2000a & 2000b)[139,140] were based on a single dynamic model, with a time horizon of 10 years and which included wider population effects associated with infectious diseases which might result from needle sharing. Direct comparison between the ICERs of these different studies is difficult as the analyses are very different in terms of treatment comparators, time horizons, outcome measures, and modelling scenarios.

Of the studies of both MMT and BMT that reported a cost per QALY all were within the threshold of £30,000 per QALY[147] with one exception; Barnett et al. (2001)[145] reported the results of modelled scenarios in which the prevalence of HIV was either low (5%) or high (40%) and the price per BMT dose was varied between $5 and $30. Under the ‘worse case’ scenario, i.e. high prevalence community at $30 per BMT dose, the cost per QALY of BMT compared to MMT was reported to be $84,700 (UK £ 32,169 (2005)). These results were based upon a Dynamic model in order to include the wider population effects associated with

infectious diseases and this model was also used in the studies by Zaric et al. (2000a & 2000b).[139,140] All three studies took the perspective of the US healthcare system, and all used a time horizon of 10 years. Barnett et al. (2001)[145] used BMT as the primary intervention and Zaric and colleagues used MMT. All three papers report results in terms of cost per QALY, and in the case of Zaric et al. (2000a)[139] cost per life year gained, within HIV prevalent populations. Barnett et al. (2001)[145] and Zaric et al. (2000b)[140] use two populations: either with a high (40%) or low (10%) HIV prevalence. Zaric et al. (2000a)[139] use an additional two populations, reporting results in terms of a prevalence of HIV of 5%, 10%, 20% and 40%. The results reported by Zaric and colleagues in this latter paper include the same results reported in their paper reference (2000b).[140]

6.1.3 Overview of findings

Overall, the 11 included economic evaluations were judged to be of high quality. However, as is so often the case for systematic reviews of economics studies, synthesising the results in a form of a meta analysis is impossible because of the heterogeneity between studies and therefore an attempt is made to further reduce the discussion to the few high quality studies that are likely to provide the most relevant comparison to the policy questions of the current report.

To this end, the studies summarised in Table 9, which report the results in outcomes other than cost per life year gained/saved or cost per QALY are not considered useful comparators for the current report. The studies by both Goldschmit (1976)[143] and Sirotnik & Bailey (1975)[136] are both now some years old and therefore some of the treatment regimens considered are rather dated. The latter study, although satisfying the quality criteria, appears to be a rather crude cost benefit analysis with the data reported in cumulative drug costs, drug free weeks and 'anticipated drug costs' for five different treatment modalities with insufficient detail about how some of these data are derived. In contrast, one of the most recent papers in our review, Zarkin et al (2005), [144] used a transmission dynamic model, with a lifetime time horizon with respect to heroin use, treatment for heroin criminal behaviour, employment and health care use. The use of a dynamic model in this case is wholly appropriate when trying to estimate the population effect of transmission of HIV and other drug related infectious diseases over time, but it is beyond the remit and the modelling deemed appropriate for use in the current report. Infectious diseases have population effects relating to the spread of disease that can only be properly incorporated into a transmission dynamic model. However, these models have been shown to produce results that are different to standard static models, such as decision trees or Markov models when evaluating infectious diseases.[148,149] We were aware of these types of models at the outset of this report and specifically clarified in the protocol that the construction of this type of model for the current report would not be feasible. As result of the available evidence on the different results produced by static and dynamic models, and the unpredictable nature of the direction of the results, it is inappropriate to compare the results of the evaluations that have used dynamic models which include the wider population effects associated with the spread of infectious diseases such as HIV, with the results of appropriately conducted static models that have not included these wider effects. Thus in summary none of these studies are considered to provide appropriate comparisons for the current report.Table 9 and Table 10 present a summary of all the included studies that reported cost per life year saved/gained or cost per QALY, which should provide a more appropriate comparison for the policy purposes of this report. However, only five of the included studies presented results in terms of cost per QALY. Three of these studies, Barnett et al,[145] and two studies Zaric et al (2000a)[139] and

(2000b)[140] (both these latter studies included Barnett as a co-author), used quality of life data from the literature which were appropriate for '*other conditions that limit activities such as moderate angina, ulcer and severe angina'*. These were then specifically adjusted for HIV and AIDS according to literature based estimates. It was difficult to validate or critically appraise whether the resultant estimates are truly appropriate. Furthermore, the relevance of these quality of life data which are more specifically directed at HIV and AIDS for use in the current evaluation in the current report is more questionable. Two other more recent studies had used new data collected alongside trials. Harris et al (2005)[138] calculated heroin free days from self reported heroin use using the Australian Quality of Life instrument and weighted utility was calculated using weights derived from an Australian time trade off exercise. Dijkgraaf et al. (2005)[86]used EuroQol EQ-5D questionnaire responses completed by participants as a basis for calculated QALYs. Responses were given at 6, 10 and 12 months. The quality of life estimates used in these latter two, more recent studies were considered more relevant and appropriate to the current study.

Three studies, Zaric et al (2000a[139] & 2000b[140]) and Barnett et al (2001)[145] all used transmission dynamic models and considered the wider population effects of HIV transmission as a result of drug abuse and therefore, as explained above, direct comparisons may be misleading. The study by Sheerin et al. (2004)[142] report a study based in New Zealand which compared Maori to non-Maori drug users (distinguishing between male & female) and compared MMT alone with five different 'treatment options' for hepatitis C (HCV) infection. Given the focus of this study was the difference between treating Maori and non-Maori populations, the results are not deemed relevant to the context of the current report.

The recent study Dijkgraaf et al. (2005)[86]report a cost-utility analysis of MMT combined with heroin compared to MMT alone. This study, based on two Dutch RCTs, which recruited from existing MMT programmes across six cities compared patients randomised to MMT plus heroin or MMT alone. EQ-5D data were collected at baseline, 6, 10 and 12 months and primary cost data was also collected alongside the trial. The results showed that MMT plus heroin dominated MMT alone. The focus of the author's conclusion was that, although the treatment cost of MMT plus heroin was more expensive than MMT alone, the higher costs were offset by the savings in criminal activity. Although this study appears to be clear and well reported, it is not certain how these findings can be generalised for comparison with the current report.

The remaining three studies by Doran et al (2003)[137] Harris et al (2005)[138] and Barnett et al (1999)[141] appear to provide the most relevant comparison to the current TAR. The study by Doran et al (2003)[137] found MMT to be both more effective and less expensive than BMT in their base case ICER which was presented as cost per heroin free day. The most recent study by Harris et al. (2005),[138] reports a randomised trial of the relative cost effectiveness of BMT compared to MMT, and was deemed to be of high quality although the study is restricted to a primary care setting which may reduce its relevance to the current TAR.. Thus focussing on the results that exclude the cost of crime, in the case of the first outcome (cost per heroin free day) MMT dominated BMT, which is a result which concurs with that of Doran et al (2003).[137] For the second outcome (cost per QALY) the cost of treating with BMT was AUS$39,404 (£17,326 in 2005 UK Sterling). If the costs of crime are included in the analysis BMT dominates MMT. However, the authors argue that the cost data were highly skewed because of the high costs of crime committed by a small number of people. Furthermore, in their discussion the authors explain that: *"The point estimates of costs and outcomes suggest that BMT may have an advantage in those initiating therapy although the confidence*

intervals are wide. The uncertainty analysis of one therapy being better value for money compared with the other is close to 50%. In other words the data could not discriminate between the two treatments in terms of the expected net benefits."

Finally, Barnett et al (1999)[141] reports the results of an evaluation which compared MMT to drug-free treatment in terms of cost per life year gained and is a study that is deemed the most relevant to the current TAR. The effectiveness parameters are populated by literature review and cost parameters sourced by previously published paper by the same author. The authors used a Markov model to simulate a cohort of 1000, 25 year old opioid dependents individuals, over a lifetime time horizon. The study reports that the average 25 year old would receive additional 14.6 years of life at an additional cost of $75,372. Thus, the cost per additional life year was reported to be $5,250 (UK£3,904).

6.1.4 Summary

- Twenty-eight potentially relevant includable economic evaluations were identified. Of these, eleven met the inclusion criteria and were included for full review and quality assessment.
- Eight studies assessed the cost effectiveness of methadone and two assessed buprenorphine for opiate abuse. Five studies were cost-utility analyses, with the cost-effectiveness ratio (ICER) reported as a cost per quality adjusted life year (QALY) gained. There were three cost effectiveness analyses and two cost benefit analyses used. Six papers reported use of an economic model: two used Markov models, one used a Monte Carlo simulation and three papers reported using a dynamic model. Direct comparisons of the ICERs between the studies is not possible because of their different approaches to modelling, different time horizons, comparators and perspective, country of origin, source of preference weights and effectiveness data used.
- Although most of the included papers were considered to be of high quality, none used all of the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS and PSS context.
- Only one study, by Barnett et al (1999) compared the cost effectiveness of methadone maintenance therapy (MMT) with drug free treatment and this study found MMT to be a cost effective treatment.
- There were two studies that compared the cost effectiveness of buprenorphine maintenance therapy (BMT) directly with MMT that were appropriate for policy questions of thie current report, namely Doran et al (2003) and Harris et al (2005). The latter study by Harris et al. (2005) presented base case results in favour of BMT but its sensitivity analysis undermined confidence in the result. The independence of this study was also of concern. An independent analysis by of Doran et al (2003) found MMT to dominate BMT i.e. MMT was more effective and less costly.
- No studies assessing the cost effectiveness of BMT compared to no drug therapy were found.
- One study, by Masson et al (2004) showed MMT to be more costly than methadone detoxification but to be more effective in preventing opiate abuse

6.2 Review of industry cost-effectiveness submissions

Two industry submissions were received – Schering Plough for buprenorphine and Cardinal Health for methadone. The remainder of this section undertakes a commentary on the Schering-Plough submission, the only one of the two submissions that included a cost effectiveness analysis.

6.2.1 Schering-Plough (Buprenorphine) submission

Overview of Model

A decision tree based model with Monte-Carlo simulation was developed to assess the cost-effectiveness of BMT compared with MMT for opioid dependent patients over a one-year time horizon. The model was structured to consider: overall maintenance therapy vs. no drug treatment; BMT vs. no drug treatment; and BMT vs. .MMT. Cost effectiveness was assessed as the incremental cost per QALY. Costs were calculated from an NHS/PSS perspective. Both simple one-way and probabilistic sensitivity analyses were undertaken.

The active treatment arm of model was split into two main parts – those 20% of patients who were deemed unable to take methadone for "*clinical reasons*" and instead were given BMT and the remaining 80%, who could receive MMT. The model therefore allowed the assessment of cost effectiveness at 3-levels (1) the cost effectiveness of BMT versus no treatment in the 20% of patients deemed unsuitable for MMT; (2) For the remaining 80% of patients, the cost effectiveness of BMT versus MMT and (3) for the overall patient group, the cost effectiveness of maintenance therapy versus no drug treatment.

Critique of model

1. Patient subgroup

The model assumes that two groups of patients contribute to the 20% unable to take methadone: drug misusers taking medications (i.e. antipsychotics, benzodiazepines) contributing to a potential increased risk of Q-T interval prolongation with co-administration of methadone and those with HIV or HCV as there are "potential drug interactions with HIV/HCV medications". CiC removed.

Furthermore, we were unable to find published evidence available to suggest such a high proportion of patients are unable to take methadone. Usually, patients who are HIV positive or taking certain medications instead require careful dose adjustment.

To test this issue in clinical practice an opportunistic survey of addiction specialist working in the UK and Ireland was conducted through the Specialist Clinical Addiction Network (SCAN). SCAN is a national network of consultant psychiatrists who work in the field of addiction, and at the time of the survey it had a membership of 200. An e-mail was sent to all members in December 2005 asking the following questions:

1. In your opinion, what percentage of clients attending your service(s)for treatment for opioid dependence have absolute medical contraindications to receiving methadone (and so would have to have buprenorphine)?
2. In your opinion, what percentage of clients attending your service(s) for treatment for opioid dependence do not wish to receive methadone (and so would have to have buprenorphine)?

The survey was open for 7 days, and 58 responses (29%) were received. Thirty two of the respondents felt that there were no medical contraindications to methadone, and the mean rate was 0.6% (range 0 to 5). The mean response to question 2 was 20.4% (range 5-50). Therefore, it would appear that the Schering Plough model overestimates the number of patients that cannot take methadone for medical reasons, although this figure may be more reflective of patient preference.

2. Selection of effectiveness data from a single RCT

The model considers the proportion of patients retained in treatment after induction (2 weeks), 6 weeks, 13 weeks and 6 months, and then follows those retained in treatment at 6 months for a further 6 months. For each period of time, a utility value and cost is attached to each arm of the tree. Data on retention in treatment and dosing is from one trial alone namely Mattick et al (2003).[106] Mattick et al (2003) details the initial 13 weeks of a randomised double blind controlled trial comparing flexible dose BMT and MMT. The open-label stages of the same trial were reported separately in Doran et al (2003),[137] providing data for retention in treatment at 6 months. Retention rate data was presented with mean and standard deviations and alpha and beta distributions (Table 12). We note that the economic model is based on data on one specific RCT whereas an updated systematic review identifies a total of 7 RCTs comparing flexible dose MMT with BMT.

The Schering-Plough submission highlighted two data limitations - comparability due to the different modalities and doses of treatment resulting in highly individualised treatment and that induction dosing schedule used in Mattick (2003) may be suboptimal, leading to lower treatment retention rates for BMT.

Table 12 Probability of retention in treatment (adapted from appendix 1 Schering Plough submission)

Probability	Mean	SD	Distribution	
			Alpha	Beta
Methadone				
2 weeks	0.87	0.06	26.00	3.99
6 weeks	0.73	0.05	54.83	20.80
13 weeks	0.59	0.04	82.23	57.14
6 months	0.44	0.03	112.68	143.41
Buprenorphine				
2 weeks	0.80	0.06	38.18	9.72
6 weeks	0.63	0.05	70.41	41.35
13 weeks	0.50	0.04	95.50	95.50
6 months	0.36	0.03	122.52	217.81

3. Alternate day dosing

The trial used a flexible dosing regimen, and patients were dosed daily through weeks 1-6, with weeks 1-2 for induction and the following 4 weeks for treatment stabilisation. Although patients within the trial were able to have alternate day BMT dosing after 6 weeks, the model assumed daily dosing throughout the whole 12 months as alternate-day dosing "*is not a recognised practice in the UK"*. Therefore the retention rates used by the model are for alternate day dosing, prompting the Scering-Plough submission to state that "*the model may underestimate the proportion of patients that would be retained on buprenorphine with this daily dosing regimen, since daily buprenorphine may improve retention rates*". However, we are concerned about this assumption as there is no published evidence that alternate day dosing results in worse retention in treatment on a BMT programme. Indeed as shown by the recent RCT of Marsch in 2005 [98], there is evidence showing no difference in retention in treatment and level of opiate abuse with dose frequency.

The probabilities used by the model were the absolute probabilities for each point in time. However, using absolute probabilities is incorrect as the package used (TreeAge) assumes that these imputed probabilities are conditional. For example, if 80% of patients were retained in buprenorphine maintenance treatment at 2 weeks, and 63% of patients were retained in treatment at 6 weeks, the conditional probability of being in treatment at 6 weeks is 79%. It is unclear therefore, what effect using the absolute instead of the conditional probabilities will have on the final results. The model we have developed uses conditional probabilities, and the calculation of these and their confidence intervals will be explained in detail later.

4. Utility values

Due to the lack of utility data, values in the Schering-Plough submission were based on those from the Harris et al (2005)[138] paper, and an adjustment factor assumed by Barnett (2001)[145] was then applied to these values 'for not being in treatment'. This latter study used adjustments of 0.9 for quality of life in maintenance therapy and 0.8 for an injecting drug user, therefore a reduction of 0.1 in injecting drug users not in treatment was assumed in the model. However, there is no indication in the model write-up about the patient group in terms of their status as injecting or non-injecting drug users. Therefore it is uncertain whether the 0.1 reduction is feasible as it only refers to injecting drug users in the Barnett study.

5. Resource utilisation & costs

Resource use and costs in the Schering-Plough submission were derived from several studies. Mattick et al (2003)[106] provided the data for the number of counselling sessions per week (one session a week) and number of urine tests conducted (every fortnight). A time in motion study reported in the paper by Doran et al (2003)[137] provided data for the time taken to dispense and supervise patients taking methadone or buprenorphine. Rates of health care usage were taken from the NTORS reported in Gossop et al (2001).[29] Rates differed for patients in treatment and not in treatment. The use of health care resources were assumed to be the same for both methadone and buprenorphine users. Controlled drug fees and prescription fees were not included and the authors stated inclusion would have increased the relative costs for each treatment and reduced the difference between buprenorphine and methadone. Unit costs were obtained from
AiC removed, the British National Formulary and Curtis and Netten (2004).[151] Due to the

model representing one year, discounting was not applied. The cost data used in this model appears to be entirely reasonable and the correct methodology has been applied.

Model results

1. BMT vs. no drug treatment
The results of Schering-Plough model for buprenorphine versus no treatment for 20% patients who could not have MMT for "*clinical reasons*" showed BMT to be more expensive and slightly more effective in terms of QALYs. The ICER was £30,048 per QALY. For patients who could be treated with either therapy, BMT was slightly more expensive than methadone and yielded marginally less QALYs, resulting in methadone dominating. As the difference in QALYs is so small (0.00055) and given the parameter uncertainty in the model, the difference in efficacy is in reality highly uncertain.

2. MMT vs. BMT
For those (80%) patients who were deemed suitable for MMT, MMT was found to be dominant (i.e. less costly and more effective) compared to BMT.

3. Maintenance therapy vs. no drug treatment
Running the Schering-Plough model for maintenance treatment versus no treatment gave an ICER of £12,584 per QALY. This result was obtained by using the results of comparison 1 and 2 above within their decision tree in the "roll-back" calculation. The TreeAge package requires a threshold to be set, however the point here is that by setting a threshold of £30,000 per QALY gained, the model ignores the treatment that is not cost-effective. In this case, BMT is not cost-effective when compared with no treatment. As a result of this, the treatment versus no treatment results do not include BMT (as the ICER is over £30,000). Therefore it is difficult to interpret the meaning of this ICER as maintenance therapy actually represents a mixture of methadone (80%) and 'no treatment' (20%). Therefore this is not a true comparison of maintenance therapy versus no treatment, because by setting the threshold, the relevant comparator has been ignored.

Deterministic sensitivity analysis was performed on the different decisions. For maintenance treatment versus no drug treatment, the main parameter affecting the model ICERs were the choice of utility values. In the comparison of buprenorphine with methadone, rates of retention in treatment and utility values at 12 months were the most sensitive. Probabilistic sensitivity analysis was also performed to explore parameter uncertainty, and scatter plots were presented.

Conclusions
In the discussion of the Schering-Plough submission economic analysis section, the authors state that "*conclusions based with much emphasis on the model should be discouraged*". Their reasoning behind this statement is the very small incremental improvement in QALYs on MMT which they state to be unreliable as the modelling was imprecise and there was a lack of data conditional on patient preferences and retention rates. We entirely agree with their concerns. As a result of their own concerns, Schering-Plough emphasise the patient preference argument, and state that both treatments should be available for patients. In the model they use the assumption that 20% of patients cannot take methadone for medical reasons, an assumption about which we have already expressed our concern above. Perhaps a

more feasible option would be to consider different proportions of patients who are unwilling to take methadone for reasons of preference and carry out the same analysis of BMT versus no treatment. The authors also state that societal costs, i.e. the effects on crime, productivity etc were not included in the model, therefore the "*potential additional benefits of the medication have not been captured"*.

The submission concludes that there "*are several factors favouring treatment with buprenorphine over methadone which could not be addressed in the economic analysis*". These factors include methadone related problems and retention in treatment affected by patient preferences. Schering-Plough stated that buprenorphine should therefore be made available as an alternative to methadone, and if it is not available, there may be patients who have no other treatment option available.

6.3 Assessment Group economic model

6.3.1 Introduction

This section provides details of a model developed by the assessment team and used to evaluate the cost-effectiveness of BMT compared to the current standard treatment, which is typically MMT. BMT and MMT are also individually compared to no treatment for maintenance therapy of patients with opioid dependence over a 12-month period.

6.3.2 Methods

A decision tree with Monte Carlo simulation was used to assess the cost-effectiveness of BMT compared with MMT or 'no treatment'. The model was designed to estimate costs, from the perspective of the UK NHS and PSS and outcomes in terms of QALYs for 12-months for the three strategies. The model also attempts to incorporate uncertainty in probabilities, resource use and utilities by incorporating the input parameters of the model as probability distributions. These distributions were used in a Monte Carlo simulation in order for uncertainty in the results of the model to be presented. The model was developed in TreeAge Pro 2005. All costs are presented in 2004 UK pounds and costs and benefits are not discounted due to the model assessing only 12 months.

Description of the model

The model follows patients for one-year and the main parameter of interest is retention in treatment. The model considers the proportion of patients retained in treatment at 2 weeks, 6 weeks, 13 weeks, 25 weeks and finally at 12 months. Follow up is more frequent in the early stages of treatment because at this stage the drop out rate is higher and the drop out stabilises around the 6-month stage. For each period of time, a utility value and cost is attached to each arm of the tree Figure 8.

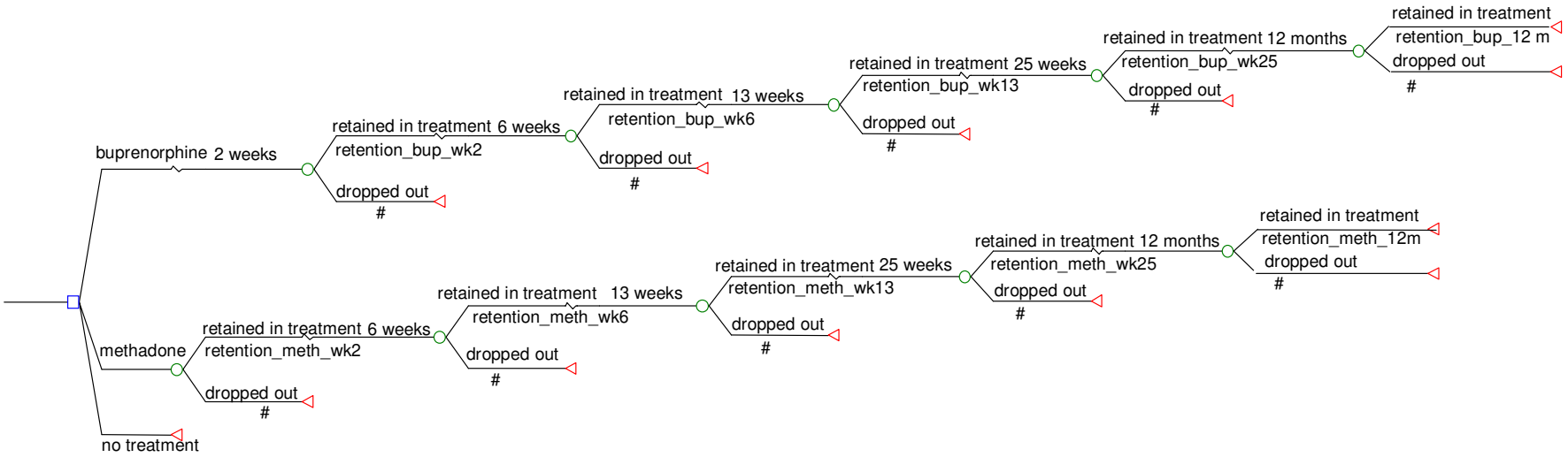


Figure 8 Decision tree for maintenance treatment with buprenorphine or methadone

In addition to buprenorphine and methadone arms, an arm representing 'no treatment' was also included for this analysis. The purpose of this arm was to allow the comparison of buprenorphine with no treatment to assess the cost-effectiveness for patients who do not take methadone. The reasons for not taking methadone may be attributable to patient preference (see section 6.2.1).

Estimation of model parameters

Retention in treatment
Data for a flexible dose regimen for both BMT and MMT was used rather than a fixed dose regimen (see section 5.2.6). The recent updated Cochrane systematic review by Mattick (2005)[66] identified seven trials (including Mattick 2003)[106] that compared methadone and buprenorphine in flexible dosing. The obtained pooled hazard ratio of 1.40 (95% CI: 1.69 to 1.15) was used to estimate the relative risk of dropping out from the treatment. A Weibull distribution (shape parameter = 0.7215, scale parameter = 0.0893) (Figure 9) was fit to the buprenorphine data (Table 13) to allow for extrapolation beyond 24 weeks. Weibull was superior to an exponential fit. To derive the comparative retention in treatment curve for methadone we applied the pooled hazard ratio derived from the seven studies of flexible dosing (Hazard Ratio methadone vs. buprenorphine = 1/ 1.396 = 0.716).

Table 13 Retention in treatment with BMT

Week	Retained	95% LCI	95% UCI	SE (Retained)
1	0.924	0.896	0.944	0.012
2	0.857	0.823	0.886	0.016
3	0.816	0.779	0.848	0.018
4	0.785	0.746	0.819	0.019
5	0.750	0.709	0.786	0.020
6	0.725	0.683	0.763	0.020
7	0.698	0.655	0.737	0.021
8	0.669	0.626	0.709	0.021
9	0.647	0.602	0.687	0.022
10	0.616	0.571	0.657	0.022
11	0.581	0.535	0.623	0.022
12	0.564	0.519	0.607	0.023
13	0.549	0.503	0.592	0.023
14	0.531	0.484	0.575	0.023
15	0.516	0.468	0.561	0.024
16	0.504	0.455	0.550	0.024
17	0.496	0.447	0.543	0.024
18	0.478	0.424	0.529	0.027
19	0.478	0.424	0.529	0.027
20	0.469	0.413	0.522	0.028
21	0.469	0.413	0.522	0.029
22	0.459	0.402	0.515	0.029
23	0.459	0.402	0.515	0.029
24	0.448	0.387	0.506	0.030

LCI: lower confidence interval; UCI: upper confidence interval

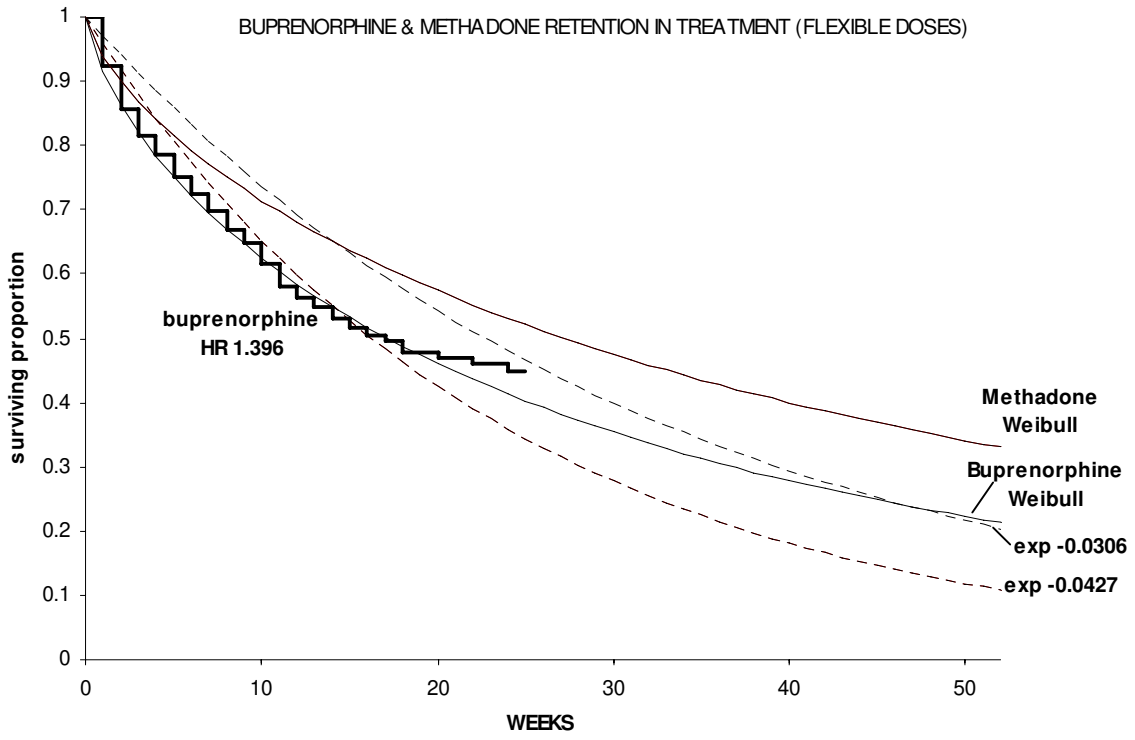


Figure 9 Weibull fit to buprenorphine retention in treatment and derived methadone curve.

Level and nature of drug misuse

As some patients retained within a maintenance therapy program will still misuse drugs, data on the proportion of patients misusing drugs is required. In addition, the nature of their drug misuse, specifically if they are injecting drug users is also important. Both parameters are required by the model in order to assign appropriate use of health care resources and utility values. The method of assigning resource use and utilities to different patient groups will be described in the relevant sub-sections.

Opioid positive or negative urine data was reported in six of seven RCT studies of MMT versus BMT in flexible dosage (Strain 1994a,[110] Strain 1994b,[111] Petitjean 2001, [112] Fischer 1999,[108] Johnson 2000,[109] and Mattick 2003[106]). Weekly data for those retained in treatment through time was only available from Mattick 2003 and Johnson 2000. Weekly, biweekly or tri-weekly data was reported for completers only (those still in treatment at end of follow up) in several studies (Strain 1994, Petitjean 2001 and Fischer, 1999) and Strain 1994 reported overall data for periods of different dosage regimen. The urine analysis results from Mattick 2003 and Johnson 2000 were combined (weighted according to study size in each arm) and are shown in Table 14. The analysis assumes that the percentage of negative urines is equivalent to the percentage of the retained patients at each time point that are drug free at that time.

Table 14 Proportion of patients free of opioids

Week	% who are opioid free and retained in buprenorphine treatment	% who are opioid free and retained in methadone treatment
1	14.22	12.07
2	27.16	27.13
3	34.48	30.17
4	38.74	37.25
5	31.03	37.93
6	43.98	37.99
7	37.07	42.67
8	44.51	42.28
9	36.21	42.24
10	42.45	44.17
11	37.50	44.83
12	41.19	45.28
13	38.79	38.79
14	42.82	45.80
15	43.10	43.97
16	52.16	37.93
17	49.14	43.97
Mean over 17 week period	38.50	38.50

For those not retained in treatment it was assumed that patients return to their pre-treatment habits irrespective of their period of MMT or BMT. At entry into treatment in the Mattick (2003)[106] study 15.7% of urines were opioid-free and 84.3% positive. This is close to the 89% reported to be heroin abusers at entry into MMT by Gossop et al 2001[152] in a UK cohort study. Because the Mattick study concerned Australian patients, we have used 89% (from the UK study) as representing the proportion using opioids amongst those not retained in treatment and assumed that this does not change significantly through time.

The estimates for the number of individuals injecting and not injecting was taken from the NTORS study (Gossop 2003).[29] The proportion of individuals who are injecting while not in treatment was estimated to be 61% (39% of those not in treatment were not injecting). The proportion of individuals injecting while in treatment was estimated to be 44% (56% of those in treatment were not injecting).

Resource use and costs

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

NHS/PSS perspective (Reference case)

Maintenance therapy included both pharmacological treatment and counselling. In this model, maintenance therapy for both BMT and MMT assumed a flexible dosing regimen and uses data on mean dose from the Mattick trial (Mattick et al 2003)[106] shown in Table 15. Where no published standard deviations (SD) were available, the SDs for the probabilities were based on: SD = rate/√(N). In the maintenance period, N=202 and 192 for patients treated with methadone and buprenorphine respectively (Mattick et al 2003).[106] Mean daily dose was assumed to be the same as week 13 from that week onwards. This approach is the same as that used in the Schering-Plough model. It was assumed patients in treatment attended one counselling session per week and had one urine test per fortnight to monitor treatment success (Table 16). When patients dropped out of treatment, counselling and urine testing did not occur. Data was obtained from the Mattick (2003) trial, and the same approach described above used for calculation of standard deviations. Unit cost information used in the industry submission was also used here.

Table 15 Maintenance therapy doses (mg) per day

	Buprenorphine				Methadone			
			Range				Range	
Period	Mean	SD	Lower limit	Upper limit	Mean	SD	Lower limit	Upper Limit
Week 1	5.20	0.36	1	16	34.40	1.17	20	70
Week 2	8.00	0.53	2	24	43.10	1.41	20	80
Week 3	9.10	0.63	2	28	47.50	2.11	20	110
Week 4	9.80	0.63	2	28	50.10	2.11	20	110
Week 5	10.30	0.63	2	28	51.30	3.05	20	150
Week 6	10.90	0.63	2	28	52.60	3.28	10	150
Weeks 7&8	10.80	0.72	2	32	53.60	3.28	10	150
Weeks 8&9	10.90	0.67	4	32	54.10	3.28	10	150
Weeks 9&10	11.20	0.67	4	32	54.40	3.28	10	150
Weeks 10&11	11.00	0.72	2	32	55.20	3.28	10	150
Weeks 11&12	11.10	0.72	2	32	56.40	3.28	10	150
Weeks 12&13	11.20	0.72	2	32	57.30	3.28	10	150
Week 13	11.20	0.72	2	32	57.30	3.28	10	150

(From Mattick *et al* 2003)

Table 16 Maintenance therapy resource use

	Mean	SD	Unit cost (£)**
Counselling sessions per week	1	0.050	8.54
Urine tests in maintenance period per week	0.5	0.025	1.12

(From Mattick *et al* 2003)[106] ** As used in the industry submission

Data on resource use for the reference cases, required for the model, was extracted using data supplied by 'problem drug-users' within NTORS that covered health care services, the criminal justice system and employment. This study, described in detail in Gossop et al 1998,[13] is the largest prospective longitudinal cohort study of treatment outcome for drug misusers conducted to date in the UK. The study collected data on drug-taking behaviour, health, criminal activity and service use before and after entry to a treatment programme. The model assumes that drug misusers not on treatment have experiences similar to that

reported by the NTORS participants in the twelve months prior to entering treatment and that drug misusers in treatment have consequences experienced from the treatment programmes described in the NTORS study. The NTORS study recorded resource use of substance misusers and found higher rates of GP contacts and inpatients stays amongst those in short term treatment. These items are presented in Table 17. Where published standard deviations were not available, the same approach as detailed in the industry submission 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 2004.[151] The unit cost for an A&E visit and for inpatient hospital stays have been calculated using estimates provided by Godfrey et al (2002)[153] and updated to 2004 figures using the Hospital and Community Health Services (HCHS) pay and prices index. Based on Godfrey et al (2002),[153] the A&E cost assumes that many of these visits would be serious and therefore would involve an overnight stay. Godfrey et al notes that the unit cost for community health visits may be an underestimate as it does not take into account expensive outpatient visits to a psychiatrist.

Drug costs are taken from the British National Formulary (No. 50, September 2005) with methadone costing £0.0135 per mg and buprenorphine £0.48 per mg. The latter uses the cost of 2mg tablets rather than 8mg tablets as the model assumes a flexible dosing regimen which requires smaller tablets. The average cost for dispensing methadone and buprenorphine were taken from the Seven Borough Buprenorphine Study.[150] The model uses the average fees charged by pharmacies presented in Table 18. The frequency and type of dispensing for a patient entering maintenance treatment for 12 months was based on the following assumptions:

- First three months: supervised dispensing, 6 days a week (as per DoH guidelines)
- Second trimester: unsupervised dispensing, 6 days a week
- Months 6 to 12: three times a week unsupervised dispensing

Table 17 NHS/PSS perspective resource use and costs[c]

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

Gossop et al 2001[154]; Godfrey et al 2002[153]; Curtis and Netten 2004[151].

Table 18 Dispensing Fees

Fee	**Value for Methadone (£)**	**Value for Buprenorphine (£)**	**Comments**
Prescription Fee	0.95	0.95	Paid for each occasion treatment is dispensed
Controlled Drug Fee	1.28	2.23	Paid for each occasion treatment is dispensed
Supervised Dispensing	1.80	2.42	

Source: Seven Borough Study[150]

[c] $SD=rate/\sqrt{(N^{\text{opioid dependent}} * P^{tx})}$ or $SD=rate/\sqrt{(N^{\text{opioid dependent}} * (1-P^{tx}))}$

Societal Perspective (Non-reference Case)

The NTORS study provides the most detailed source of information of criminal consequences associated with drug misuse. The study asked clients to recall experiences related to criminal behaviour and thus covered the following: drug arrests; arrests for acquisitive crimes; stays in police custody; appearances in court; and stays in prison. As before the data from the NTORS study is combined with unit cost information to estimate the total social costs associated with drug misuse. It is assumed that information supplied by clients prior to treatment will be similar to users not on treatment. The model also assumes that drug misusers in either treatment have consequences experienced from the treatment programmes described in the NTORS study. Godfrey et al, 2002a, [153] 2002b[155] provides the unit cost information for drug arrests (assuming no victim costs are included), police detention costs, court appearances, prison and victim costs. Surprisingly, the level of arrests for drug offences and acquisitive crime were higher for users in treatment in the first year than those not in treatment. The report containing this data highlights this unexpected result but does not give any further explanation, and states that additional analysis of the data was not possible within the project. However a subsequent paper[156] (Healey, 2003) conducted a re-analysis on the same NTORS data and found a higher rate of crimes reported at entry (before treatment) than at follow-up (on treatment). Therefore, further analysis to find the reason for this apparent contradiction is required. In addition, the data should be viewed with some caution as it is self-report data which has not been validated by official crime data.

For the police detention costs the NTORS study estimated that users are held in police custody on average for 2 nights, 1.2 nights and 0.8 nights for no treatment, treatment < 1 year and treatment > 1 year respectively. The cost of an overnight stay is estimated at £69 per stay. Godfrey et al, 2002a[153] used estimates provided by Brand and Price (2000)[157] 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 19.

Estimation of QALYs

Early in the literature review process for the current TAR, there appeared to be very limited published data available on the quality of life associated with drug abuse. Many of the available data appeared not to be appropriate for the purpose of the current evaluation because it specifically related to quality of life for patients suffering some of the potential consequences of drug abuse such as HIV or AIDS.[139,140,145] At that point it was considered appropriate to seek some entirely new data from the experimental health utilities panel co-ordinated by the Peninsula Technology Assessment Group (PenTAG). This would allow specific data to be collected relevant to the specific health states that were considered most relevant to the evaluation and modelling process of the current TAR. We use the results of our own utility exercise co-ordinated by PenTAG in the reference case analysis of the current TAR. We use the utility values estimated by the two most recently published studies, Dijkgraaf et al. (2005)[86] and Harris et al. (2005)[138] in our sensitivity analysis to the reference case and the results compared with our base case. The utility values estimated by Harris et al (2005)[138] were also used in the modelling exercise of industry submission from Schering-Plough.

The PenTAG panel is funded jointly by the UK Department of Health, NHS Quality Improvement Scotland and NICE. The panel uses a randomly selected group of individuals who are members of the public who have given their consent to involvement in this process. These individuals make valuations on given health states via the Value of Health Panel Website using the standard gamble method.

Table 19 Societal perspective resource use and costs

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

CJS = Criminal Justice System; Harries, 1999[158]; Godfrey 2002a[153]; Godfrey 2002b[155]

A total of 10 health states were defined to describe a range of alternative health states that could be experienced by individuals abusing drugs. The health states were defined by the team and involved considerable input from one clinician (ED) with expertise in this area. An iterative process followed this first stage with further advice from PenTAG. The health states were then provided to the panel and the QALYs derived from PenTAG based on the results of this panel are presented in Appendix 12.

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 use reduction (injecting drug misusers)'; 'On treatment with drug use reduction (non- injectors)'; 'Not on treatment and injecting drug misusers'; and 'Not on treatment but non –injecting drug misusers'.

Patients retained in treatment were assigned an average weighted QALY obtained from the utilities provided by using the average proportion of patients in treatment consuming drugs for both injectors and non-injectors and the proportion of patients who were drugs free while on treatment. Data were used to estimate the average proportion of drugs free patients for the first 2 weeks (referred to as the 'induction phase' [Mattick, 2003]) and the average proportion of patients who were drugs free while on treatment for the rest of the period (showing a clear stabilisation after week 2). We used these weights to estimate a QALY for on treatment first two weeks and on treatment for weeks 3 to 52. The weights for injector and non-injectors were taken from NTORS (Gossop 2003)[29] assuming that 44% of those abusing drugs are injectors. The mean weighted QALYs are presented in Table 20.

For those not retained in treatment we assumed that patients returned to their pre-treatment habits irrespective of their period of MMT or BMT for which the same QALY was used in both cases. We obtained an average weighted QALY from the results obtained by the health panel by considering the average proportion consuming drugs that are injectors and the average proportion consuming drugs that are non-injectors. The weighted QALY obtained had a mean value of 0.62 (SD 0.21). In order to obtain a beta distribution for QALYs we used the method of moments methodology.

Table 20 Estimated QALYs for patients in treatment

Period	**Methadone** Mean (SD)	**Buprenorphine** Mean (SD)
First 2 weeks	0.7017 (0.1950)	0.7039 (0.1944)
Weeks 3 to 52	0.7458 (0.1836)	0.7455 (0.1837)

Assessment of cost-effectiveness

Data on the incremental cost per QALY are presented in two ways. Firstly, mean costs and QALYs for the alternative interventions are presented and the incremental cost per QALY calculated where appropriate. The second mode of presentation uses the results of the probabilistic sensitivity analysis and shows cost-effectiveness acceptability curves (CEACs) and 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 a strategy is cost-effective at different threshold values of willingness to pay for an additional QALY. The probabilistic sensitivity analysis was undertaken using appropriate distributions for all model variables, shown in Table 21. A normal distribution was used for the doses of methadone and buprenorphine, and means and standard deviations are shown in table Table 15. The model was run for 10,000 simulations.

Three separate incremental analyses were conducted -MMT vs. no therapy; BMT vs. BMT and BMT vs. MMT.

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

Table 21 Distribution and parameter values used in probabilistic sensitivity analysis

Normal distributions		
Parameter	**Mean**	**SD**
Survival analysis		
log of hazard ratio for methadone-buprenorphine	0.336	0.096
log of lambda (λ) for buprenorphine	-2.516	0.033
gamma (γ) for buprenorphine	0.721	0.014
Resource use (per patient per year)		
A&E visits (in treatment)	0.8	0.003
A&E visits (not in treatment)	0.7	0.002
Outpatient mental health services (in treatment)	0.8	0.003
Outpatient mental health services (not in treatment)	1.3	0.004
GP visits (in treatment)	5.6	0.022
GP visits (not in treatment)	3.6	0.010
Inpatient mental health services (in treatment)	0.4	0.002
Inpatient mental health services (not in treatment)	1.5	0.004
Inpatient stay (in treatment)	2.8	0.011
Inpatient stay (not in treatment)	1.75	0.005
Counselling sessions (per week)	1.0	1
Number of urine tests (per week)	0.5	0.025

Beta distributions			
Parameter	**Expected value**	**α**	**β**
QALY value not on treatment	0.623	2.704	1.636
QALY value on methadone (weeks 1 & 2)	0.702	3.161	1.343
QALY value on methadone (3 weeks & over)	0.746	3.448	1.175
QALY value on buprenorphine (weeks 1 & 2)	0.704	3.177	1.336
QALY value on buprenorphine (3 weeks & over)	0.746	3.445	1.175

Deterministic sensitivity analysis for reference case

The sensitivity analysis focussed on varying the assumptions and parameters. Further details and justification are provided below.

Dispensing of buprenorphine

One of the main arguments made for buprenorphine treatment is that it is a safer drug and requires less frequent dispensing than methadone. In countries such as France and USA buprenorphine has been introduced without a need for regular or supervised dispensing. We explore the model sensitivity to changes in buprenorphine dispensing assuming from week 1 to 13 alternate day (three days a week) supervised dispensing and from week 14 to 52 alternate day unsupervised dispensing.

Utility score using utility values from Harris (2005)

A sensitivity analysis was performed using the utility values from Harris (2005)[138] as these were the values used in the industry submission model. However, instead of using a value for a specific point in time (the approach of the industry model), the overall QALY value for both strategies (while on treatment) has been used (methadone = 0.59 and buprenorphine = 0.62). This approach was taken because the model should reflect expected values of health states during a specific period of time x. This was assumed more appropriate than assuming, as the industry model does, a single measure for a specific health state at a particular point in time, and then using the same value for the rest of the time spent in that health state. The paper reported the small difference in the QALYs was statistically insignificant.

For the utility values for the 'no treatment' health states and the 'drop-out from treatment' health states we used a utility value of 0.505. This value was obtained by reducing the average value while on treatment for methadone and buprenorphine (0.605) by 0.1 following the methodology used in the industry submission, based on the paper of Barnett et al (2001).[145]

Table 22 Utility values used in the sensitivity analysis

	Buprenorphine	Methadone
Harris	0.62	0.59
Dijkgraaf	0.73	0.73

Original Source: Harris 2005[138]; Dijkgraaf (2005)[86]

Utility score using utility values from Dijkgraaf (2005)

A further analysis was performed using the utility values from Dijkgraaf (2005). This study compared maintenance methadone therapy with methadone plus heroin. Utility values were obtained utility values from patients using the EQ-5D questionnaire at baseline, 6, 10, 12 months and an overall QALY values for the 12 months was calculated. This paper did not report values for buprenorphine, therefore we used the values for methadone therapy alone for both therapies. The utilities obtained from the PenTAG data were from a small sample size (n=22) and the values from this paper were obtained from 237 patients. Therefore, due to the much larger number of respondents we felt it was important to use these values in the model, even though they are patient values rather than population values.

As above, instead of using a value for a specific point in time (the approach of the industry model), the overall QALY value has been used. For the utility values for the 'no treatment' health states and the 'drop-out from treatment' health states we used a utility value of 0.63. As before, this value was obtained by reducing the utility value while on treatment for methadone and buprenorphine (0.73) by 0.1.

Societal costs

The victim costs of crime differ greatly between patients in a treatment programme and those not in treatment or who have dropped out of treatment. Therefore the impact of the inclusion of these costs was assessed by conducting the societal perspective evaluation with costs to the criminal justice system only.

6.3.3 Results

Reference case- NHS/PSS perspective

Table 23 and Table 24 present the results of the deterministic analysis. MMT is more expensive but more effective than being on no treatment at all, giving an ICER of £13,697 per QALY gained. BMT is more expensive and marginally less effective than MMT therefore by definition, is dominated by methadone. When considering BMT versus no treatment, buprenorphine is more expensive and more effective and has an ICER of £26,429 per QALY gained.

Table 23 Cost-effectiveness results of all strategies

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
No treatment	1053.25		0.6230		
Methadone	1970.97	917.72	0.6900	0.0670	13,697
Buprenorphine	2490.97	520.00	0.6774	-0.0126	(Dominated)

Table 24 Cost-effectiveness results of BMT versus no treatment

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
No treatment	1053.25		0.6230		
Buprenorphine	2490.97	1437.72	0.6774	0.0544	26,429

Non-reference case: Societal perspective

Costs to the criminal justice system and victim of crime costs were included in the analysis to assess the cost-effectiveness of MMT and BMT from a wider societal perspective. The results for all strategies are presented in Table 25 and for buprenorphine versus no treatment in Table 26. All strategies are dominated by MMT, and BMT is dominant over no treatment. Again the QALY difference between MMT and BMT is very small.

Table 25 Non-reference case: Cost-effectiveness results of all strategies from a societal perspective

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Methadone	28344.81		0.6900		-
Buprenorphine	30991.91	2647.105	0.6774	-0.0126	(Dominated)
No treatment	38917.25	10572.44	0.6230	-0.0670	(Dominated)

Table 26 Non-reference case: Cost-effectiveness results of BMT versus no treatment from a societal perspective

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Buprenorphine	30991.91		0.6774	-	-
No treatment	38917.25	7925.34	0.6230	-0.0544	(Dominated)

Sensitivity analysis

Reference case probabilistic sensitivity analysis

The incremental cost-effectiveness plane for BMT versus MMT is shown in Figure 10 and demonstrates that BMT always has a higher cost than MMT, however there is a great deal of variability in the QALY difference. The CEAC in Figure 11 shows that compared with MMT, BMT is unlikely to be cost effective at any threshold.

The incremental cost-effectiveness plane for buprenorphine versus no treatment is shown in Figure 12 and demonstrates that buprenorphine always has a higher cost than no treatment, however the difference in QALYs is unclear. The CEACs for both MMT and MMT versus no treatment in Figure 13 show that MMT has a higher probability of being cost effective at any threshold. However by comparing Figure 11 and Figure 13, BMT is more likely to be cost-effective when compared with no treatment than when compared with MMT.

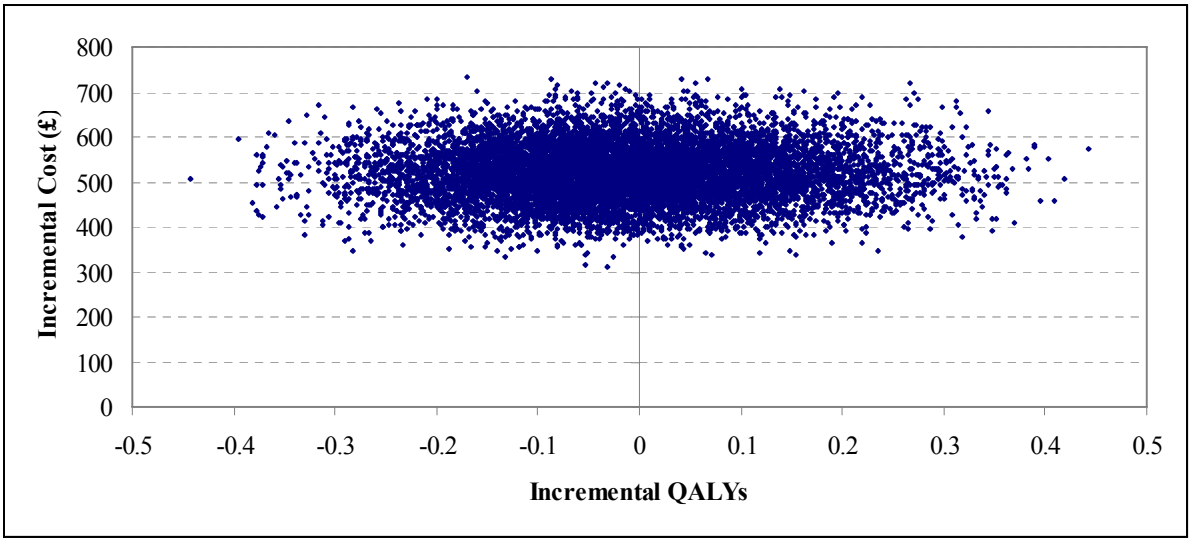


Figure 10 Incremental cost effectiveness plane for BMT compared with MMT

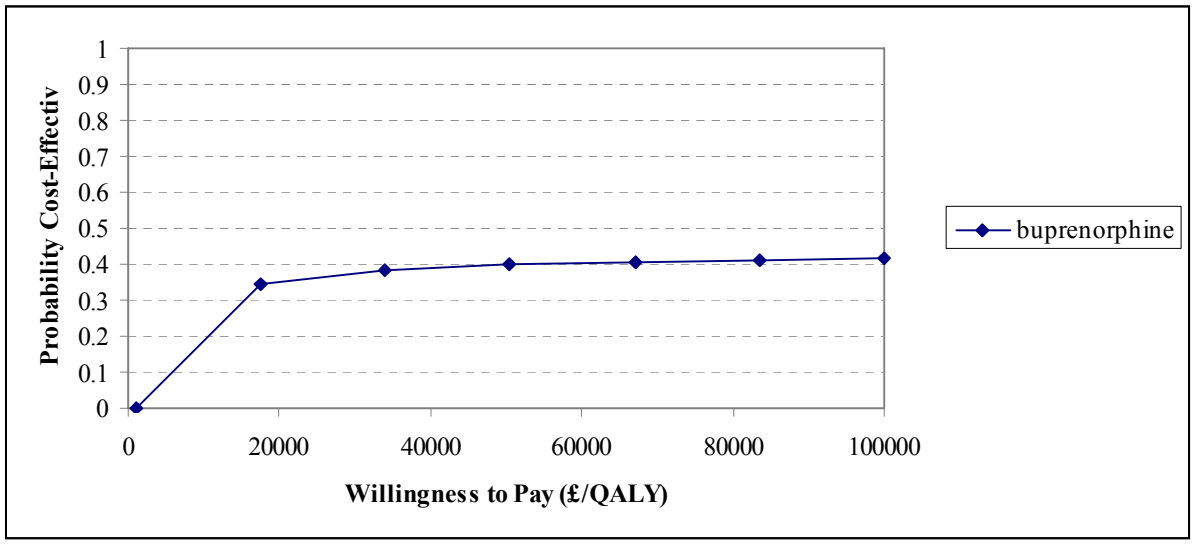


Figure 11 Cost-effectveness acceptability curve for BMT compared with MMT

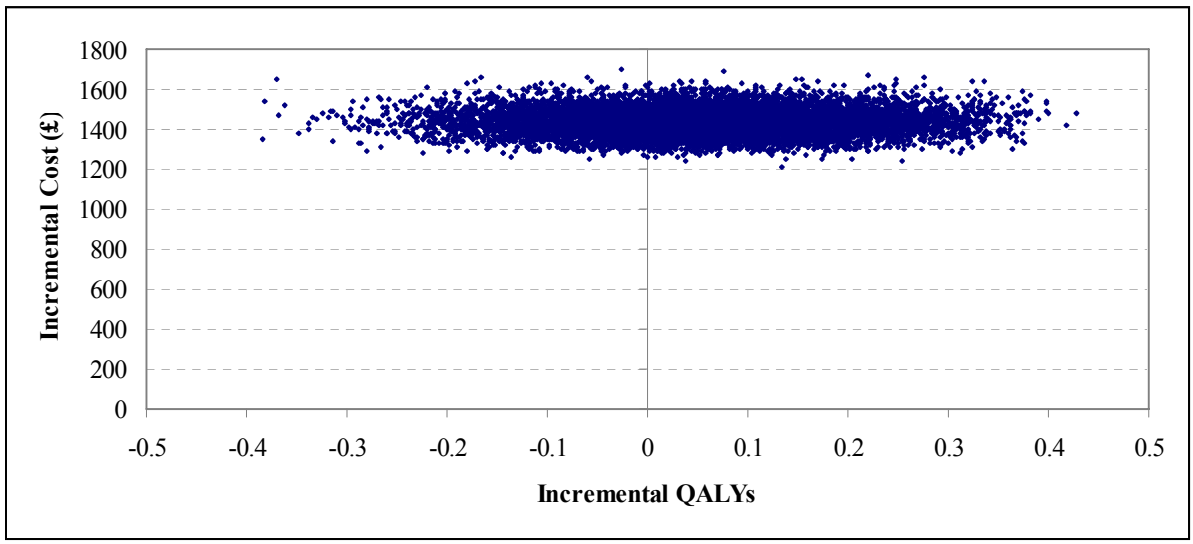


Figure 12 Incremental cost-effectiveness plane for BMT compared to no treatment

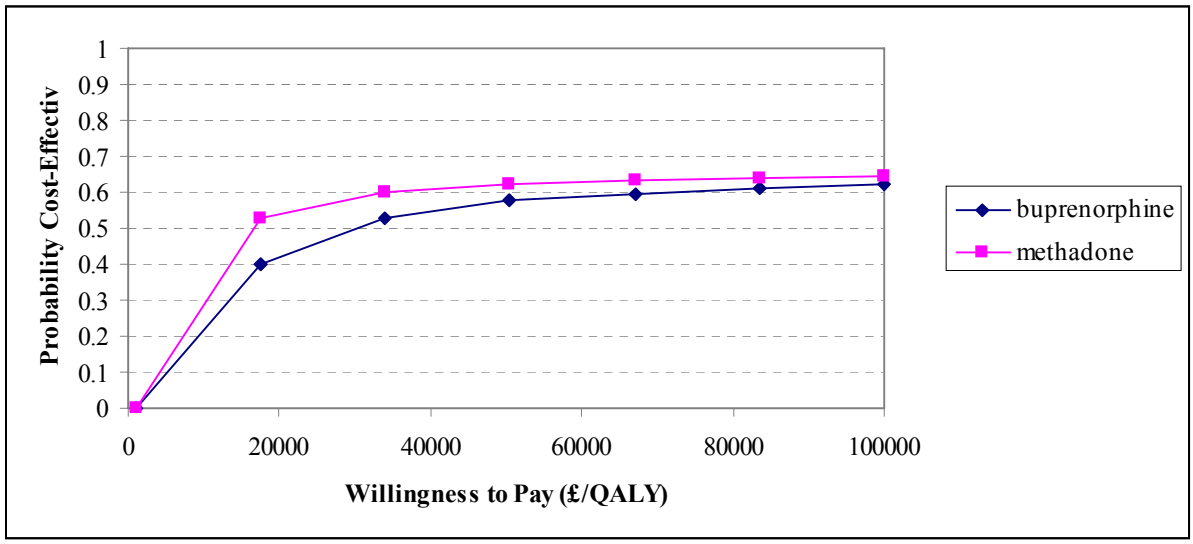


Figure 13 Cost effectiveness acceptability curves for BMT and MMT compared with no treatment

Deterministic sensitivity analysis

Dispensing of buprenorphine

By assuming less frequent dispensing (alternate day) and unsupervised dispensing of buprenorphine in weeks 14 to 52, BMT is still dominated by MMT, however the ICER for BMT versus no treatment is reduced to £24,074 per QALY gained. The results for all strategies are presented in Table 27 and for BMT versus no treatment in Table 28.

Utility scores

Using the utilities from the industry submission (i.e. Harris) in the model has resulted in BMT no longer being dominated by MMT. However, the ICER is £108,333 per QALY gained, due to the very small positive difference in QALYs. Using the Dijkgraaf utilities, the ICER for MMT versus no treatment is slightly higher than the reference case, and BMT is still dominated by MMT.

Comparing BMT to no treatment, the values used by the industry submission give a very similar result to the reference case. However, the Dijkgraaf values give a higher ICER of £31,598 per QALY gained.

Societal costs

When victim costs of crime were excluded, methadone was no longer dominant over no treatment and instead had an ICER of £25,033 per QALY gained. Buprenorphine was dominated by methadone. Comparing buprenorphine with no treatment, buprenorphine was no longer dominiant, and had an ICER of £37,806 per QALY gained. Both demonstrate the considerable impact the inclusion of victim costs has on the results.

Table 27 Sensitivity analysis: Cost-effectiveness results for all strategies

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Alternative buprenorphine dispensing					
No treatment	1053.25		0.6230		
Methadone	1949.53	896.28	0.6900	0.0670	13,377
Buprenorphine	2362.86	413.33	0.6774	-0.0126	(Dominated)
Using alternative utilities					
Harris					
No treatment	1053.25		0.5050		
Methadone	1970.97	917.72	0.5525	0.0475	19,320
Buprenorphine	2490.97	520.00	0.5573	0.0048	108,333
Dijkgraaf					
No treatment	1053.25		0.6300		
Methadone	1970.97	917.72	0.6858	0.0558	16,447
Buprenorphine	2490.97	520.00	0.6755	-0.0103	(Dominated)
Exclusion of victim costs from societal perspective					
No treatment	8090.25		0.6230		
Methadone	9767.50	1677.25	0.6900	0.0670	25,033
Buprenorphine	10146.90	379.40	0.6774	-0.0126	(Dominated)

Table 28 Sensitivity analysis: Cost-effectiveness results of BMT versus no treatment

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Alternative buprenorphine dispensing					
No treatment	1053.25		0.6230		
Buprenorphine	2362.86	1309.61	0.6774	0.0544	24,074
Using alternative utilities					
Harris					
No treatment	1053.25		0.5050		
Buprenorphine	2490.97	1437.72	0.5573	0.0523	27,490
Dijkgraaf					
No treatment	1053.25		0.6300		
Buprenorphine	2490.97	1437.72	0.6755	0.0455	31,598
Exclusion of victim costs from societal perspective					
No treatment	8090.25		0.6230		
Buprenorphine	10146.90	2056.65	0.6774	0.0544	37,806

Summary

- The assessment group developed a decision tree with Monte Carlo simulation model to assess the cost-effectiveness of BMT and MMT compared to no drug therapy and BMT compared to MMT. The model was designed to estimate costs, from the perspective of the UK National Health Service and Personal Social Services and outcomes in terms of QALYs for 12-months for the three strategies.
- According to this model both MMT and BMT are cost effective strategies compared to no drug therapy. These findings were robust to sensitivity analysis.
- Although MMT was dominant in comparison to BMT from the perspectives of both the NHS/PSS and society (inclusion of the criminal justice system costs) the difference in QALYs was very small. These findings of the assessment group model are broadly consistent with the results of the Schering-Plough model and the review of previous economic evaluations.
- The strengths of the assessment group economic model include the integration of data on retention in treatment and level of opiate abuse whilst on treatment, whereas the Scering-Plough model has only used data on retention in treatment. In addition we have formally modelled the time related nature of the data on retention in treatment. Also, as very limited data on utilities associated with drug abuse was found in the published literature, our model has used entirely new and unique data on utilities derived specifically for this project. The industry submission has used utility data elicited from patients. In contrast, we have used utilities derived from a panel representing a wider societal perspective. Finally, unlike the Schering-Plough submission that used data from only one trial, the clinical data in this model has been derived from a systematic review and meta-analysis of all the available published evidence.
- A limitation of the assessment group model was use of the utility data collected from a very limited section of the population. Furthermore, by taking a one-year time horizon, both the economic models of the assessment group and Schering-Plough did not take into account any differences between methadone and buprenorphine maintenance therapy in mortality.

7 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Compared to no drug therapy, both buprenorphine and methadone maintenance are associated with small gains in health-related quality of life gains in of opioid abusers. By keeping opioid abusers in drug therapy, both buprenorphine and methadone are not associated with cost savings to the NHS. However, from a wider societal perspective, both drugs, by reducing the level of crime, and thereby costs, may offset NHS costs and result in a potentially substantial cost saving to society.

Methadone has been in use in treatment services for over 30 years, and most clinicians (and many patients) have a good understanding of how to use it safely and effectively. Buprenorphine has only been available in the UK for 5 years, and so clinicians are only starting to develop the most effective induction and maintenance regimes. Equivalence tables comparing methadone and buprenorphine are still in evolution, and there is some acceptance that the initial induction doses included in the UK licence were too low for effective treatment. Buprenorphine induction can be made easier with adequate dose flexibility and clinical monitoring, but these factors are not always present in UK drug treatment services.

8 DISCUSSION

8.1 Clinical effectiveness

31 systematic reviews (including either RCT & non RCT evidence) met the inclusion criteria of this report. Many of the studies included in these reviews overlap. In addition, we identified an additional 28 RCTs published more recently (since 2001). The majority of systematic reviews and RCTs were of moderate to good quality, focused on short-term (up to 1-year follow up) outcomes of retention in treatment and the level of opiate use (self-report or urinalysis) in those individuals retained in treatment. Most studies employed a trial design that compared a fixed dose strategy (i.e. all individuals received a standard dose) of MMT or BMT and were conducted in predominantly young men who fulfilled DSM-IV criteria as opiate abusers or heroin dependent, without significant co-morbidities. However, flexible dosing (i.e. individualised doses) of MMT and BMT is more reflective of real world practice and was therefore focused on this report.

MMT vs. no drug therapy/placebo: A number of RCT meta-analyses have consistently shown that fixed dose MMT has superior levels of retention (e.g. 20-97mg vs. placebo: pooled relative risk [RR] - 3.91, 95% CI: 1.17 to 13.2) in treatment and opiate use (e.g. 35-97mg vs. no treatment: pooled effect size - 0.65, 0.41 to 0.89) than placebo or no treatment, with higher fixed doses of MMT being more effective than lower fixed doses (retention in treatment e.g. ≥50 mg vs. <50mg: pooled RR - 1.25, 0.94 to 1.67). There was evidence, primarily from non-randomised observational studies, that fixed dose MMT reduces mortality, HIV risk behaviour and levels of crime compared to no therapy.

BMT vs. no drug therapy/placebo: Two RCT meta-analyses show that fixed dose BMT has superior levels of retention in treatment (e.g. 6-12mg vs. placebo: pooled RR- 1.74, 1.06 to 2.87) and opiate use (6-16mg vs. placebo: pooled RR - 1.74, 1.06 to 2.87) than placebo or no therapy, with higher fixed doses of BMT being more effective than lower fixed doses (e.g. retention in treatment 8-16mg vs. 1-4mg: effect size - 0.21, 0.12 to 0.31. One small RCT has shown that the level of mortality with fixed dose BMT to be significantly less than placebo.

BMT vs. MMT: A number of RCT meta-analyses have consistently shown that fixed doses of MMT had superior retention in treatment and opiate than comparable fixed doses of BMT. A recently updated and unpublished Cochrane systematic review of 7 RCTs directly compared flexible dosing MMT to flexible dosing BMT in 976 opiate dependent individuals. Amongst RCTs employing flexible dose regimens the allowable daily equivalent dose commonly ranged from 20 or 30mg to 60 or 120mg for methadone and 2 or 4mg to 8 or 16 mg for buprenorphine. No further RCTs comparing flexible MMT and BMT were identified through our searches. Retention in treatment was superior for flexible MMT than flexible BMT dosing (pooled hazard ratio: 1.40, 95% CI: 1.15 to 1.69) although there was no significant difference in opiate use (standardised mean difference: 0.12, 95% CI: -0.02 to 0.26). Indirect comparison of data from population cross sectional studies, suggest that the level of mortality with BMT may be lower than that of MMT. A pooled RCT analysis showed no significant difference in the rate serious adverse events with MMT compared to BMT.

Treatment modifiers: - Although the amount of evidence on treatment modifiers was limited, adjunct psychosocial and contingency interventions (e.g. financial incentives for opiate free urine samples) appeared to enhance the effects of both MMT and BMT. Also, MMT and BMT appear to be similarly effective whether delivered in primary care or outpatient clinic setting.

MMT vs. MDT and BMT vs. BDT:
Two RCTs demonstrated MMT to have superior retention in treatment and opiate use than MDT. One RCT has shown BMT to be superior to BDT.

8.2 Cost effectiveness

11 economic evaluations met the inclusion criteria of this report. Eight studies assessed the cost effectiveness of MMT and two BMT for opiate abuse. Direct comparisons of the results between the studies is not readily possible because of their different approaches to modelling, different time horizons, comparators and perspective, country of origin, source of preference weights and effectiveness data used. Although most of the included papers were considered to be of high quality, none used all of the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context.

Industry economic evidence
One company (Schering-Plough) submitted cost effectiveness evidence. This submission was based on an economic model that had a 1-year time horizon and sourced data from a single RCT of flexible dose MMT compared to flexible BMT and utility values obtained from the literature.
MMT vs. no drug therapy: Incremental cost effectiveness (ICER) £12,584/quality adjusted life year (QALY) and

BMT vs. no drug therapy: £30,048/QALY respectively. In a direct comparison,
MMT vs. BMT: MMT was found to be slightly more effective (QALY difference of 0.00055) and less costly than BMT.

Assessment group model
MMT vs. no drug therapy: ICER £13,697/QALY
BMT vs. no drug therapy: £26,429/QALY.
MMT vs. BMT: As with the industry model, in direct comparison, MMT was slightly more effective (QALY difference 0.0126) and less costly than BMT (-£520).
When considering social costs, both MMT and BMT gave more health gain and were less costly than no drug treatment. These findings were robust to deterministic and probabilistic sensitivity analyses.

Neither the assessment group nor industry model assessed the cost effectiveness of MMT compared to MDT or BMT compared to BDT.

8.3 Strengths, limitations and uncertainties of assessment

The main strengths of this report are that its economic analysis are based on:

- Retention in treatment and opioid use parameters sourced from the pooled analysis of a systematic review of RCT evidence of flexible dose MMT vs. BMT.
- This pooling was based on a meta-analysis using the time-dependent nature (i.e. hazard ratios) of the outcomes.
- Given the limited data on appropriate utilities associated with drug use in the published literature, we derived utility values from a panel of members of the general public. The advantage of this process was the ability to derive utility values for specific health states appropriate for our model outcomes. In addition, the values had the advantage of being population-based estimates rather than being patient specific values and using the latter is a common criticism of QALY estimates.
- Inclusion of wide societal costs including the criminal justice system.

Potential limitations and uncertainties of this report are:

- Most of clinical effectiveness evidence comparing MMT and BMT was based on a trial fixed dose strategy design (i.e. all individuals received a standard dose) conducted in predominantly young men who fulfilled DSM-IV criteria as opiate abusers or heroin dependent, without significant co-morbidities. There was a limited evidence base for MMT and BMT in the primary care and criminal justice settings or in particular opiate abusers such as drug injectors and the HIV-infected. This potentially limited the applicability of the evidence base to real world practice. However, where possible, this report focused on flexible dose design data. In addition limited data in abuser subgroups (e.g. injectors vs. non injectors) and treatment settings (e.g. criminal justice vs. health care setting) suggested equivalent MMT and effectiveness of methadone and buprenorphine maintenance.
- The relatively short-time horizon of the assessment group model (i.e. 1-year) - Longer term modelling would have meant the inclusion of outcomes such as mortality and HIV related behaviours. From our review of systematic reviews and recent RCTs, we concluded that there was some evidence that compared to no therapy, BMT and MMT may improve mortality. However, that there was difference in mortality between MMT and BMT remains uncertain. However, a recent BMJ editorial has suggested that mortality on buprenorphine was five times lower than methadone.[159] Since the

completion of our main initial literature searches we undertook a further (non-systematic) search for observational data on this issue. Three additional studies were identified. Auriacombe et al 2005[113]made direct comparison of drug overdose deaths in methadone and buprenorphine users in France for the years 1994 to 1998. Numbers of patients in receipt of methadone and buprenorphine were calculated indirectly from sales records provided by manufacturers and estimates regarding average dose; drug associations were ascertained from local evidence rather than lab-based tests. Total deaths and person years at risk were: methadone 19 and 9360; buprenorphine 27 and 132900. Unfortunately unknown proportions of these deaths occurred during buprenorphine treatment as distinct from deaths associated with drug diversion and the data is old and probably not safely generalizable to the UK. Schifano et al 2005[160] reported that 43 deaths associated with buprenorphine had been recorded in the UK spanning the years 1980 to 2002. No correlation was found between buprenorphine associated mortality rate and buprenorphine prescription load, however authors argue this may merely reflect the predominant availability of only low dose formulations until recently. Information on whether the deaths were associated with buprenorphine diversion or treatment was not available nor data on person years at risk. In an Australian study Gibson and Degenhardt (2005)[161] have reported death rates in buprenorphine and methadone treatment in terms of deaths/episode of treatment. If we assume that episodes of treatment with methadone and buprenorphine are of similar average duration then these results indicate that risk of death may be 100 times greater for methadone treatment.

- Although new utility values for specific health states have been derived, the panel used to derive these estimates was relatively small.
- Some caution must be applied to the results from a societal perspective. The criminal justice system (CJS) costs alone were higher for patients in treatment than those out of treatment. Excluding victim costs of crime changed the societal perspective results: methadone maintenance treatment no longer was dominant over buprenorphine or no-treatment and had an ICER of at least £25,000; buprenorphine maintenance therapy also was no longer dominant over no-treatment and had an ICER of more than £37.000.
- There was insufficient clinical evidence in order to estimate the cost effectiveness of strategy of maintenance therapy with buprenorphine or methadone compared to a detoxification strategy.

9 CONCLUSIONS

9.1 Implications for service provision

Both flexible dose MMT and BMT appear to be more clinically effective and more cost effective than no drug therapy in opiate abusers. In direct comparison, flexible dose MMT (daily equivalent dose from 20 or 30mg to 60 or 120mg) was found be somewhat more effective in maintaining individuals in treatment than BMT (daily equivalent dose 2 or 4mg to 8 or 16 mg) and was therefore associated with a slightly higher health gain and lower costs. However, this needs to be balanced by the more recent experience of clinicians in the use of buprenorphine, the possible risk of higher mortality of MMT and individual opiate abuser's preferences.

9.2 Suggested research priorities

In general the quality of the clinical evidence base included in this report was good. However, the large majority of studies have been conducted in the US and focused on short-term changes in retention in treatment and opioid use outcomes as assessed by urinalysis. The health effects of various substances of abuse seem to be strongly dependent on social context, with strong emphasis on regulatory policies, including prohibition and level of law enforcement. Therefore, the transferability of results from other countries to the UK may be limited. UK ongoing trials that we identified from searches are listed in Appendix 13.

The body of evidence of the cost-effectiveness of methadone and buprenorphine in opioid abusers is limited and conditional on the quality of clinical evidence. Future research should focus on the majority uncertainties in cost effectiveness identified by current economic models, particularly the utility data in opioid abusers and how this relates to treatment success. Economic models need to be updated on the availability of such future data.

Future research should be directed toward the following:

- Safety & effectiveness of methadone and buprenorphine as it is delivered in the UK. Specifically, the key differences between UK & the conditions of previous RCTs is the issue of unsupervised dispensing. Current UK guidelines (Orange Guidelines, DOH 1999) suggest treatment with methadone and buprenorphine should be initiated under conditions of supervised dispensing, and that 'stable' patients can then move to having unsupervised doses. In practice, there are many sites across England and Wales which do not have the capacity for supervised buprenorphine (and to a lesser extent methadone) dispensing, and medications are dispensed to patients without supervision. The safety and effectiveness of unsupervised substitution methadone versus buprenorphine treatment has not been adequately examined in RCTs.

- Potential safety concerns regarding methadone and buprenorphine. Specifically:

- Mortality risks with methadone and buprenorphine treatment. There is some literature suggesting that buprenorphine treatment may be associated with an overall lower mortality risk than methadone (see section 5.2.6). However, these limited comparative accounts of methadone- and buprenorphine-related mortality rates have considerable limitations. Further research examining comparative mortality rates of methadone and buprenorphine related treatment in UK settings is required.
- Drug interactions. The key drug interactions for the opioids methadone and buprenorphine concern the concomitant use of other sedatives, especially benzodiazepines, alcohol and (tricyclic) antidepressants. These sedative drugs are routinely identified in the vast majority of methadone and buprenorphine related deaths. The relative safety of methadone and buprenorphine in combination with such sedatives has not been widely researched. Other drug interactions of particular clinical relevance include the anti-retroviral medications used for the treatment of HIV and HCV viral conditions.

- Substitution/withdrawal: Whilst the findings regarding substitution treatment are fairly robust, there continue to be uncertainties regarding the safety and efficacy of substitution medications in particular patient subgroups, such as within the criminal justice system, or within young people (below aged 21). These aspects of treatment may benefit from further research.

- Cost effectiveness: The body of evidence of the cost-effectiveness of methadone and buprenorphine in opioid abusers is limited and conditional on the quality of clinical evidence. Future research should focus on the majority uncertainties in cost effectiveness identified by current economic models, particularly the utility data in opioid abusers and how this relates to treatment success. Economic models need to be updated on the availability of such future data.

10 APPENDICES

Appendix 1 Literature search strategies

SYSTEMATIC REVIEWS

Source – Cochrane Library (CDSR, DARE, HTA database) (Wiley internet interface) 2005 Issue 3

#1 methadone OR methadone OR buprenorphine OR subutex in All Fields in all products
1681
#2 MeSH descriptor Methadone explode all trees in MeSH products
546
#3 MeSH descriptor Buprenorphine explode all trees in MeSH products
383
#4 (#1 OR #2 OR #3)
1687

Source - Ovid MEDLINE(R) 1966 to August Week 1 2005

1 (methadone or buprenorphine or methadose or subutex).mp. (10103)
2 exp opioid related disorders/ (12317)
3 substance withdrawal syndrome/ (14177)
4 substance related disorders/ (52782)
5 heroin dependence/ (5893)
6 (substance abuse or substance misuse or substance dependen$).mp. (22005)
7 (opioid abuse or opioid misuse or opioid dependen$).mp. (973)
8 (heroin abuse or heroin misuse or heroin dependen$).mp. (6084)
9 (opiate abuse or opiate misuse or opiate dependen$).mp. (1044)
10 or/2-9 (84788)
11 1 and 10 (6434)
12 (systematic adj review$).mp. (7138)
13 (data adj synthesis).mp. (3532)
14 (published adj studies).ab. (5008)
15 (data adj extraction).ab. (3349)
16 meta-analysis/ (6098)
17 meta-analysis.ti. (5681)
18 comment.pt. (276647)
19 letter.pt. (533452)
20 editorial.pt. (175896)
21 editorial.pt. (175896)
22 animals/ (3775268)
23 human/ (8914050)
24 22 not (22 and 23) (2893184)
25 11 not (18 or 19 or 20 or 24) (5875)
26 or/12-17 (24830)
27 25 and 26 (49)
28 from 27 keep 1-49 (49)

Source - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 12, 2005

1 (methadone or buprenorphine or methadose or subutex).mp. [mp=title, original title, abstract, name of substance word] (166)
2 (substance abuse or substance misuse or substance dependen$).mp. (258)
3 (opioid abuse or opioid misuse or opioid dependen$).mp. (45)
4 (heroin abuse or heroin misuse or heroin dependen$).mp. (21)
5 (opiate abuse or opiate misuse or opiate dependen$).mp. (45)
6 (substance withdrawal or opioid withdrawal or opiate withdrawal or heroin withdrawal).mp. (26)
7 or/2-6 (344)
8 1 and 7 (37)
9 from 8 keep 1-37 (37)

Source - EMBASE (Ovid)1980 to 2005 Week 33

1 (methadone or buprenorphine or methadose or subutex).mp. (14929)
2 (substance abuse or substance misuse or substance dependen$).mp. (17119)
3 (opioid abuse or opioid misuse or opioid dependen$).mp. (1002)
4 (heroin abuse or heroin misuse or heroin dependen$).mp. (2476)
5 (opiate abuse or opiate misuse or opiate dependen$).mp. (1058)
6 heroin dependence/ or opiate addiction/ (5197)
7 WITHDRAWAL SYNDROME/ (8466)
8 SUBSTANCE ABUSE/ (13158)
9 or/2-8 (29623)
10 1 and 9 (3802)
11 "systematic review"/ (5606)
12 (systematic adj review$).tw. (6471)
13 (data adj synthesis).tw. (3206)
14 (published adj studies).ab. (4854)
15 (data adj extraction).ab. (2931)
16 Meta Analysis/ (22406)
17 meta-analysis.ti. (5388)
18 or/11-17 (37978)
19 10 and 18 (61)
20 from 19 keep 1-61 (61)

CLINICAL EFFECTIVENESS - RANDOMISED CONTOLLED TRIALS

Source – Cochrane Library (CENTRAL) (Wiley internet interface) 2005 Issue 3

#1 methadone OR methadose OR buprenorphine OR subutex in All Fields in all products 1681
#2 MeSH descriptor Methadone explode all trees in MeSH products 546
#3 MeSH descriptor Buprenorphine explode all trees in MeSH products 383
#4 (#1 OR #2 OR #3)1687
#5 MeSH descriptor Substance Withdrawal Syndrome explode all trees in MeSH products 1191
#6 MeSH descriptor Heroin Dependence explode all trees in MeSH products 294
#7 (substance abuse OR substance misuse OR substance dependen*) in All Fields in all products 2405
#8 (opioid abuse OR opioid misuse OR opioid dependen*) in All Fields in all products 577
#9 (heroin abuse OR heroin misuse OR heroin dependen*) in All Fields in all products 649
#10 (opiate abuse OR opiate misuse OR opiate dependen*) in All Fields in all products 721
#11 (#5 OR #6 OR #7 OR #8 OR #9 OR #10) 3917
#12 (#4 AND #11) 850
#13 (#4 AND #11), from 2001 to 2005 305

Source - Ovid MEDLINE(R) 1999 to August Week 1 2005

1 (methadone or buprenorphine or methadose or subutex).mp. (2585)
2 exp opioid related disorders/ (3172)
3 substance withdrawal syndrome/ (3066)
4 substance related disorders/ (11455)
5 heroin dependence/ (1264)
6 (substance abuse or substance misuse or substance dependen$).mp. (9517)
7 (opioid abuse or opioid misuse or opioid dependen$).mp. (558)
8 (heroin abuse or heroin misuse or heroin dependen$).mp. (1337)
9 (opiate abuse or opiate misuse or opiate dependen$).mp. (570)
10 or/2-9 (22157)
11 1 and 10 (1772)
12 randomized controlled trial.pt. (77138)
13 controlled clinical trial.pt. (14355)
14 randomized controlled trials.sh. (25065)
15 random allocation.sh. (14027)
16 double blind method.sh. (26619)
17 single blind method.sh. (4790)
18 or/12-17 (132130)
19 (animals not human).sh. (858647)
20 18 not 19 (118597)
21 clinical trial.pt. (146258)
22 exp clinical trials/ (59324)
23 (clin$ adj25 trial$).ti,ab. (53914)
24 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (26524)
25 placebo$.ti,ab. (33401)
26 random$.ti,ab. (141076)
27 placebos.sh. (4730)

28 research design.sh. (14772)
29 or/21-28 (304643)
30 29 not 19 (266803)
31 30 not 20 (151695)
32 20 or 31 (270292)
33 11 and 32 (453)
34 limit 33 to yr="2001 - 2005" (339)
35 from 34 keep 1-339 (339)

Source - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 12, 2005

1 (methadone or buprenorphine or methadose or subutex).mp. [mp=title, original title, abstract, name of substance word] (166)
2 (substance abuse or substance misuse or substance dependen$).mp. (258)
3 (opioid abuse or opioid misuse or opioid dependen$).mp. (45)
4 (heroin abuse or heroin misuse or heroin dependen$).mp. (21)
5 (opiate abuse or opiate misuse or opiate dependen$).mp. (45)
6 (substance withdrawal or opioid withdrawal or opiate withdrawal or heroin withdrawal).mp. (26)
7 or/2-6 (344)
8 1 and 7 (37)
9 from 8 keep 1-37 (37)

Source - EMBASE (Ovid) 1996 to 2005 Week 33

1 (methadone or buprenorphine or methadose or subutex).mp. (7457)
2 (substance abuse or substance misuse or substance dependen$).mp. (12801)
3 (opioid abuse or opioid misuse or opioid dependen$).mp. (733)
4 (heroin abuse or heroin misuse or heroin dependen$).mp. (1603)
5 (opiate abuse or opiate misuse or opiate dependen$).mp. (751)
6 heroin dependence/ or opiate addiction/ (3621)
7 WITHDRAWAL SYNDROME/ (4563)
8 SUBSTANCE ABUSE/ (10844)
9 or/2-8 (19913)
10 1 and 9 (2544)
11 randomized controlled trial/ (83862)
12 exp clinical trial/ (278742)
13 exp controlled study/ (1442477)
14 double blind procedure/ (37680)
15 randomization/ (13701)
16 placebo/ (40769)
17 single blind procedure/ (4489)
18 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (1461304)
19 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (50581)
20 (placebo$ or matched communities or matched schools or matched populations).mp. (64814)
21 (comparison group$ or control group$).mp. (73516)
22 (clinical trial$ or random$).mp. (396288)

23 (quasiexperimental or quasi experimental or pseudo experimental).mp. (870)
24 matched pairs.mp. (1071)
25 or/11-24 (1663543)
26 10 and 25 (1090)
27 limit 26 to yr="2001 - 2005" (722)
28 from 27 keep 1-722 (722)
29 from 28 keep 1-722 (722)

Source - PsycINFO (Ovid) 2000 to August Week 1 2005

1 (methadone or buprenorphine or methadose or subutex).mp. (1250)
2 exp methadone maintenance/ (607)
3 drug abuse/ or drug dependency/ (8880)
4 exp HEROIN ADDICTION/ (435)
5 exp DRUG WITHDRAWAL/ (1620)
6 drug rehabilitation/ (3236)
7 (substance abuse or substance misuse or substance dependen$).mp. (6796)
8 (opioid abuse or opioid misuse or opioid dependen$).mp. (376)
9 (heroin abuse or heroin misuse or heroin dependen$).mp. (216)
10 (opiate abuse or opiate misuse or opioid dependen$).mp. (384)
11 or/2-10 (14662)
12 1 and 11 (1003)
13 clinical trials/ (388)
14 clinical trial.mp. (1364)
15 controlled trial.mp. (1954)
16 or/13-15 (3470)
17 12 and 16 (55)
18 from 17 keep 1-55 (55)
19 limit 18 to yr="2001 - 2005" (48)
20 from 19 keep 1-48 (48)

Source – Sociological Abstracts (CSA Illumina) 2001 – Aug 2005

Last Search Query: (methadone or methadose or subutex) or buprenorphine

Source – International Bibliography of the Social Sciences (BIDS) 2001 – Aug 2005

methadone or methadose or subutex or buprenorphine

ONGOING TRIALS

Source – National Research Register 2005 Issue 3

#1. (buprenorphine or methadone or methadose or subutex)191

#2. METHADONE explode all trees (MeSH)89
#3. BUPRENORPHINE single term (MeSH)14
#4. (#1 or #2 or #3)191
#5. ((substance next abuse) or (substance next misuse) or (substance next dependen*))656
#6. ((opioid next abuse) or (opioid next misuse) or (opioid next dependen*))23
#7. ((heroin next abuse) or (heroin next misuse) or (heroin next dependen*))32
#8. ((opiate next abuse) or (opiate next misuse) or (opiate next dependen*))77
#9. (#5 or #6 or #7 or #8)756
#10. (#4 and #9)89

Sources – Current Controlled Trials and Clinical Trials.gov

buprenorphine or methadone or methadose or subutex

QUALITY OF LIFE

Source - Ovid MEDLINE(R) 1966 to July Week 4 2005

1 substance abuse$.mp. or exp Substance-Related Disorders/ (150166)
2 exp Opioid-Related Disorders/ or opioid$ abuse$.mp. (12376)
3 opioid$ dependence.mp. (511)
4 opioid addict$.mp. (333)
5 opioid abuse$.mp. (156)
6 exp Heroin Dependence/ or heroin addict$.mp. (6366)
7 quality of life/ (47551)
8 life style/ (21846)
9 health status/ (26839)
10 health status indicators/ (9303)
11 or/7-10 (96714)
12 or/1-6 (150406)
13 11 and 12 (2097)
14 limit 13 to yr="2004 - 2005" (253)
15 from 14 keep 1-253 (253)

ECONOMIC EVALUATION

Source – Cochrane Library (DARE, NHSEED) (Wiley internet interface) 2005 Issue 3

Source - Ovid MEDLINE(R) 1966 to August Week 1 2005

1 (methadone or buprenorphine or methadose or subutex).mp. (10103)
2 exp opioid related disorders/ (12317)
3 substance withdrawal syndrome/ (14177)
4 substance related disorders/ (52782)
5 heroin dependence/ (5893)
6 (substance abuse or substance misuse or substance dependen$).mp. (22005)
7 (opioid abuse or opioid misuse or opioid dependen$).mp. (973)
8 (heroin abuse or heroin misuse or heroin dependen$).mp. (6084)
9 (opiate abuse or opiate misuse or opiate dependen$).mp. (1044)
10 or/2-9 (84788)
11 1 and 10 (6434)
12 economics/ (23981)
13 exp "costs and cost analysis"/ (117204)
14 cost of illness/ (7215)
15 exp health care costs/ (24676)
16 economic value of life/ (4499)
17 exp economics medical/ (9672)
18 exp economics hospital/ (13430)
19 economics pharmaceutical/ (1505)
20 exp "fees and charges"/ (21731)
21 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (209242)
22 or/12-21 (306036)
23 11 and 22 (274)
24 from 23 keep 1-274 (274)

Source - EMBASE (Ovid) 1980 to 2005 Week 33

1 (methadone or buprenorphine or methadose or subutex).mp. (14929)
2 (substance abuse or substance misuse or substance dependen$).mp. (17119)
3 (opioid abuse or opioid misuse or opioid dependen$).mp. (1002)
4 (heroin abuse or heroin misuse or heroin dependen$).mp. (2476)
5 (opiate abuse or opiate misuse or opiate dependen$).mp. (1058)
6 heroin dependence/ or opiate addiction/ (5197)
7 WITHDRAWAL SYNDROME/ (8466)
8 SUBSTANCE ABUSE/ (13158)
9 or/2-8 (29623)
10 1 and 9 (3802)
11 cost benefit analysis/ (21209)
12 cost effectiveness analysis/ (39107)
13 cost minimization analysis/ (844)
14 cost utility analysis/ (1376)
15 economic evaluation/ (2586)
16 (cost or costs or costed or costly or costing).tw. (124174)
17 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (59100)
18 (technology adj assessment$).tw. (1187)
19 or/11-18 (187759)
20 10 and 19 (193)

21 from 20 keep 1-193 (193)

Source – Cochrane Library (NHSEED) (Wiley internet interface) 2005 Issue 3

See systematic reviews strategy

Source - HEED August 2005

Methadone OR methadose OR subutex OR buprenorphine

SEARCHES FOR EXISTING MODELS

Source - Ovid MEDLINE(R) 1966 to August Week 1 2005

1 (methadone or buprenorphine or methadose or subutex).mp. (10103)
2 exp opioid related disorders/ (12317)
3 substance withdrawal syndrome/ (14177)
4 substance related disorders/ (52782)
5 heroin dependence/ (5893)
6 (substance abuse or substance misuse or substance dependen$).mp. (22005)
7 (opioid abuse or opioid misuse or opioid dependen$).mp. (973)
8 (heroin abuse or heroin misuse or heroin dependen$).mp. (6084)
9 (opiate abuse or opiate misuse or opiate dependen$).mp. (1044)
10 or/2-9 (84788)
11 1 and 10 (6434)
12 decision support techniques/ (5142)
13 markov.mp. (4231)
14 exp models economic/ (4314)
15 decision analysis.mp. (2060)
16 cost benefit analysis/ (35727)
17 or/12-16 (46850)
18 11 and 17 (60)
19 from 18 keep 1-60 (60)

Source – EMBASE (Ovid)1980 to 2005 Week 33

1 (methadone or buprenorphine or methadose or subutex).mp. (14929)
2 (substance abuse or substance misuse or substance dependen$).mp. (17119)
3 (opioid abuse or opioid misuse or opioid dependen$).mp. (1002)
4 (heroin abuse or heroin misuse or heroin dependen$).mp. (2476)
5 (opiate abuse or opiate misuse or opiate dependen$).mp. (1058)
6 heroin dependence/ or opiate addiction/ (5197)
7 WITHDRAWAL SYNDROME/ (8466)
8 SUBSTANCE ABUSE/ (13158)
9 or/2-8 (29623)
10 1 and 9 (3802)
11 decision support techniques/ (479)
12 markov.mp. (2733)
13 exp models economic/ (11849)
14 decision analysis.mp. (1889)
15 cost benefit analysis/ (21209)
16 or/11-15 (37099)
17 10 and 16 (40)
18 from 17 keep 1-40 (40)

Appendix 2 Methodological issues pertaining to assessment of urine samples for drug abuse.

Assessment of opioid use

Opioid use can include either the use of heroin or methadone. It is difficult to summarise the available data on opioid use. Opioid use was reported in a variety of ways by systematic reviews. Several different metrics were used (e.g. proportion of individuals taking opioids, the mean level of heroin) coupled to self-report methods and/or objective testing (i.e. urinalysis) making an overall meta-analysis difficult. The two most frequently reported measures of substance use were proportion of individuals who self-report opioid use (see Table 37) and urine confirmed opioid use (Table 38) and for conciseness these are reported here. A particular difficulty with urinalysis is that the results of the tests done in each patient are not independent. Another difficulty that applies to both opioid use outcomes is that such outcomes are often only available in patients retained in treatment. Both self-report opioid use and urine opioid analysis results are reported here. The results from other opioid substance use outcomes are listed in Table 57 (Appendix 9).

A further difficulty of assessment of substance use, particularly when assessed by urinalysis, is that outcomes are usually only available in those who are retained in treatment. Historically, most RCTs only ever included data on subjects followed up (i.e. usually still in treatment). Such analysis violates the principle of intention to treat. More recent trials have attempted to deal with this problem using the Treatment Effectiveness Score (TES) as proposed by Ling (1998).[162] According to TES, each patient is given a score of 0 to 100% calculated as number of negative (or positive) urines divided by the total number of possible urines that could have been given. Missing urines (whether from patients retained in treatment or not retained in treatment) are assumed to be positive. An alternative method is to impute that individuals who drop out revert to baseline levels of use (e.g. Mattick et al, 2003[106]). Abstinence rates for those who remain in treatment might therefore be regarded, as a best-case scenario while the all-case analysis is a worst-case.

Appendix 3 Characteristics of Systematic Reviews.

Table 29. Systematic reviews with studies addressing effectiveness of methadone at different doses or versus placebo / no treatment in maintenance therapy

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients) *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Caplehorn 1995 [49]	Journal	1966 to 1995	5 (24,219 patient yrs) *5 relevant*	Cohort	MA	Heroin depend't	1] MMT	1] Discharged from MMT	Mortality
Faggiano 2003 [52]	Cochrane	1947 to 2001	21 (5984) *19 relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid depend't	1] MMT	1] M different doses	Illicit drug use. Trt retention. Abstinence. Mortality.
Farre 2002 [53]	Journal	1966 to 1999 (Dec)	13 (1944) *10 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] MMT	1] M different doses 2] Placebo	Illicit drug use. Trt retention.
Glanz 1997 [56]	Journal	1966 to 1996	12 (1362) *2 relevant*	RCTs	MA	Opioid depend't	1] MMT	1] M different doses	Illicit drug use. Trt retention. Side effects.
Gowing 2004 [57]	Cochrane	Data-base origins to 2003 (July)	28 (7900) *21 relevant*	RCTs, Cohort, Ca-Co, Descriptive.	Narrative	Opioid depend't	1] MMT	1] No MMT *(1 RCT, 2 Cohort, 2 Ca-Co, 4 descriptive studies)* Time points *(12 single-group descriptive studies)*	HIV-risk behaviours.
Hopfer 2002 [59]	Journal	Not reported	14 (6263) *3 relevant (methadone)*	Non-randomised studies. Surveys & descriptive studies.	Narrative	Heroin-using youth	1] MMT	Time points *(3 single group studies)*	Illicit drug use. Trt retention.

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients) *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Hulse 1998 [43]	Journal	1966 to 1996	7 (not reported) *5 relevant*	Ca-Co	MA	Opiate-using pregnant women	1] MMT no heroin 2] MMT + heroin 3] MMT ± any opiate 4] Heroin no meth: 5] Any opiate	1] No opiates	Neonatal mortality. Birth weight.
Johansson 2003 [60]	Book chapter	1966 to 2000	69 (7881) *17 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] MMT	1] Placebo 2] No treatment 3] MMT different doses	Illicit drug use. Trt retention.
Layson-Wolf 2002[62]	Journal	1996 to 2001 (May)	Unclear (Unclear) *5 relevant*	RCTs + unclear	Narrative	Opioid depend't	1] MTT	1] Placebo 2] No treatment 3] MMT different doses	Illicit drug use. Trt retention.
Marsch 1998 [64]	Journal	Not reported *end not later than 1997*	30 (7980) *30 relevant*	Controlled studies (≥ 2 groups) & pre-post- studies	MA	Opioid abusers.	1] MMT	1] No trt: 2] Interrupted trt 3] Single group time points	Opioid use. HIV-risk behaviours. Criminality.
Mattick 2003 [65]	Cochrane	1966 to 2001	6 (954) *4 relevant*	Controlled clinical trials (RCTs)	MA	Opioid depend't	1] MMT	1] No treatment 2] Drug-free trt: 3] Placebo 4] MMT different doses	Illicit drug use. Trt retention. Criminality. Mortality.
Mattick 2005 [66]	Cochrane	1996 to 2005	13 (2560) *4 relevant*	RCTs	MA	Opioid depend't	1] MMT	1] MMT different doses	Illicit drug use. Trt retention.
Prendergast 2002 [68]	Journal	Not reported *(studies from 1965 to 1996)*	78 (12,168) *? relevant* *(8 methadone)*	Controlled studies (≥ 2 groups) & single group pre- post-studies.	MA	Drug abusers	1] Methadone programmes	1] No or minimal trt	Illicit opiate use. Crime.

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients) *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Prendergast 2000 [67]	Journal	Not reported *(studies from 1965 to 1996)*	143 (35,879) *38 relevant*	Controlled studies (≥ 2 groups) & single group pre- post- studies.	MA	Drug abusers	1] Methadone programmes	1] No or minimal trt	Illicit opiate use. Crime.
Simoens 2005 [71]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *No. Relevant -unclear*	RCTs	Narrative	‡ Opioid depend't	1] MMT	1] Unspecified / unclear	Abstinence. Illicit drug use. Trt retention.
Simoens 2002 [72]	HTA	1990 to 2002	92 (not reported) *8 RCT & 6 other relevant*	RCTs, single group pre- post-, &, quasi-exp'l studies	Narrative	‡‡ Opioid depend't	1] MMT	1] Placebo 2] MMT different doses. 3] Single group time points	Abstinence. Illicit drug use. Trt retention. Criminality Others
Sorensen 2000 [73]	Journal	1988 to 1998	33 (17,771) *16 longitudinal & 7 cross sectional relevant*	Longitudinal& cross sectional	Narrative	Drug abusers	1] MMT	1] Single group time points 2] No MMT *(cross sectional studies)*	HIV-risk behaviours
Van Beusekom 2001 [75]	HTA	Not reported *(studies up to 2000)*	222 (not reported) *unclear*	RCTs, cohort, cross sectional, guidelines & others	Narrative	Opioid depend't	1] MMT	1] MMT different doses 2] No trt: 3] Not clearly determinable	Illicit drug use. Trt retention. Mortality.
West 2000 [76]	Journal	Not reported to 2000	9 (995) *4 relevant*	Controlled comparative studies	MA	Opioid depend't	1] MMT	1] MMT different doses.	Illicit drug use.

†: All reviews contain narrative elements therefore "narrative" refers to reviews restricted to narrative methods and lacking meta-analysis. ‡: in MTT community programmes. ‡‡: involved in community maintenance or detoxification, or residential rehabilitation treatment. **MMT**: methadone maintenance therapy. **Trt**: treatment. exp'l: experimental. **HTA**: Health technology assessment.

Table 30. Systematic reviews with studies addressing the effectiveness of methadone v. buprenorphine in maintenance therapy

Author & Year	Data sources	Search Start & End Date	No. primary Studies (Total No. patients) *No. relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Barnett 2001 [48]	Journal	Not clear to 1998	5 (540) *5 relevant*	RCTs *(Double Blind)*	MA	Opioid depend't	1] MMT	1] Bup: MT	Illicit drug use. Trt retention.
Davids 2004 [51]	Journal	not reported	Unclear (not reported) *13 relevant*	Exp'l & observational follow up	Narrative	Opioid depend't	1] MMT	1] Bup: MT	Selective.
Faggiano 2003 [52]	Cochrane	1947 to 2001	21 (5984) 4 *relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid depend't	1] MMT	1] Bup: MT	Illicit drug use. Trt retention. Abstinence. Side effects.
Farre 2002 [53]	Journal	1996 to 1999 (Dec)	13 (1944) *6 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] MMT	1] Bup: MT	Illicit drug use. Trt retention.
Johansson 2003 [60]	Book chapter	1966 to 2000	69 (7881) *8 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] MTT	1] Bup: MT	Illicit drug use. Trt retention.
Layson-Wolf 2002 [62]	Journal	1996 to 2001 (May)	Unclear (Unclear) *3 relevant*	RCTs + unclear	Narrative	Opioid depend't	1] MTT	1] Bup: MT	Illicit drug use. Trt retention.
Lintzeris 2003 [63]	Un-publishe d	Not clear to 2003	24 (>4400) *17 relevant*	RCTs (14) + population studies (3)	Narrative	Opioid depend't	1] MMT	1] Bup: MT	Illicit drug use. Trt retention. Mortality
Mattick 2003 [66]	Cochrane	1966 to 2001	13 (2560) *10 relevant*	RCTs	MA	Opioid depend't	1] MTT	2] Bup: MT	Illicit drug use. Trt retention.
Raisch 2002 [69]	Journal	1966 to 2000 (Nov)	Unclear (not reported) *3 relevant*	Unclear, review articles also used	Narrative	Opioid depend't	1] MTT	1] Bup: MT	Selective
Simoens 2005 [71]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *14 relevant*	RCTs	Narrative	‡ Opioid depend't	1] MMT	1] Bup: MT	Abstinence. Illicit drug use. Trt retention.
Simoens 2002 [43]	HTA	1990 to 2002	92 (not reported) *13 RCTs*	RCTs, single group pre- post-, & quasi-exp'l studies	Narrative	‡‡ Opioid depend't	1] MMT	1] Bup: MT	Abstinence. Illicit drug use. Trt retention. Criminality. Etc

Author & Year	Data sources	Search Start & End Date	No. primary Studies (Total No. patients) *No. relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
West 2000 [76]	Journal	Not reported to 2000	9 (995) *9 relevant*	Controlled comparative studies	MA	Opioid depend't	1] MMT	2] Bup: MT	Illicit drug use.

†: All reviews contain narrative elements therefore "narrative" refers to reviews restricted to narrative methods and lacking meta-analysis. ‡: in MTT community programmes. ‡‡: involved in community maintenance or detoxification, or residential rehabilitation treatment. **MMT**: methadone maintenance therapy. **BMT**: buprenorphine maintenance therapy. **Trt**: treatment. **exp'l**: experimental. **HTA**: Health technology assessment.

Table 31 Systematic reviews with studies of methadone effectiveness v. other treatments (except buprenorphine), or with methadone + a potential modifier of effectiveness.

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients) *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Amato 2004 [47]	Cochrane	1985 (Jan) to 2003 (April)	12 (981) *12 relevant*	RCTs	MA	Opioid depend't	1] Psycho-social (8 types).	1] Psycho-social + pharmacotherapy (MMT)	Illicit drug use. Trt retention.
Clark 2002 [50]	Cochrane	1966 (Jan) to 2000 (Aug)	18 (3766) *18 relevant*	RCTs (15) Controlled prospective (3)	MA	Heroin depend't	1] MMT	1] LAAM MT	Illicit drug use *(heroin).* Trt retention. Side effects. Mortality.
Faggiano 2003 [52]	Cochrane	1947 to 2001	21 (5984) 3 *relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid depend't	1] MMT	1] LAAM MT 2] MMT + CRA	Illicit drug use. Trt retention. Side effects. Criminality.
Farre 2002 [53]	Journal	1966 to 1999 (Dec)	13(1944) *2 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] MMT	1] LAAM MT	Illicitt drug use. Trt: retention.
Ferri 2005 [54]	Cochrane	1966 to 2005	4 (577) *4 relevant*	RCTs	Narrative	Opioid depend't	1] MMT	1] MMT + Heroin	Illicit drug use. Trt retention. Crime. Social functioning.
Fridell 2003 [55]	Book chapter	unclear to 1999 (March)	Unclear (not reported) *unclear 27? relevant*	RCTs	MA	Drug depend't	1] M	1] M + Psycho-social	Illicit drug use *(heroin).* Trt retention.

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients) *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Glanz 1997 [56]	Journal	1966 to 1996	12 (1362) *12 relevant*	RCTs	MA	Opioid depend't	1] MMT	1] LAAM MT	Illicitt drug use. Trt retention. Side effects.
Gowing 2004 [57]	Cochrane	Data-base origins to 2003 (July)	28 (7900) *5 relevant*	RCTs 2 Cohort 3 Ca- Co 2 Other 21	Narrative	Opioid depend't *injecting*	1] MMT	1] MMT + other 2] Injected MMT *(Time points in 1 cohort & 4 descriptive studies)*	HIV-risk behaviours.
Griffith 2000 [58]	Journal	Not reported	30 (1613) *30 relevant*	Randomised & non-randomised pre- post-studies	MA	Single or poly-drug depend't	1] MMT	1] MMT + CRA 2] MTT + other	Illicit drug use.
Johansson 2003 [60]	Other (book (chapter)	1966 to 2000	69 (7881) *20 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] MMT	1] LMT 2] Heroin MT 3] MMT + CRA 4] MMT + antidepressants	Illicit drug use. Trt retention.
Kirchmayer 2003 [61], & 2002 [163]	Cochrane	1973 to 2003 (Feb)	11 (707) *1 relevant*	Controlled clinical trials	MA	Opioid depend't	1] MMT	1] Naltrexone MT	Illicit drug use. Trt retention.
Layson-Wolf 2002 [62]	Journal	1996 to 2001 (May)	Unclear (Unclear) *2 relevant*	RCTs + unclear	Narrative	Opioid depend't	1] MMT	1] LMT 2] Slow provision of MMT	Illicit drug use. Trt retention.
Prendergast 2002 [68]	Journal	Not reported *(studies 1965 to 1996)*	78 (12,168) *No: relevant unclear (8 methadone)*	Controlled studies (≥ 2 groups) & single group pre- post-studies.	MA	Drug abusers	1] Methadone programmes	1] No or minimal trt	Illicitt drug use. Crime.
Roozen 2004 [70]	Journal	Start date database to 2002 (March)	11 (812) *1 relevant*	RCTs	MA	Drug abusers *addicted*	1] MMT + usual care	1] MMT + CoRA 2] MMT + CRA +relapse prevention	Illicit drug use. Time to relapse.

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients) *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Simoens 2005 [71]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *No: Relevant -unclear*	RCTs	Narrative	‡ Opioid depd't	1] MMT	1] Unspecified / unclear	Abstinence. Illicit drug use. Trt retention.
Simoens 2002 [72]	HTA	1990 to 2002	92 (not reported) *12 RCTs & 1other Relevant*	RCTs, single group pre-post-, &, quasi-exp'l studies	Narrative	‡‡ Opioid depend't	1] MMT	1] L MT 2] Counselling 3] MMT + CoRA 4] MMT + fluoxetine 5] MMT + Yoga 6] Frequent contact 7] MMT heroin *(injected or inhaled)*	Abstinence. Illicit drug use. Trt retention. Criminality. Etc
Stanton 1997 [74]	Journal	Not reported	15 (not reported) *2 relevant*	RCTs	MA	Illicit drug users	1] MMT	1] MMT + Family-couples	Illicitt drug use.
Van Beusekom 2001 [75]	HTA	Not reported *(studies up to 2000)*	222 (not reported) *unclear*	RCTs, cohort, cross sectional, guidelines & others	Narrative	Opioid depend't	1] MMT	1] MMT + various other (e.g psychosocial) 2] MMT different dose 3] Not clear	Illicit drug use. Trt retention. Mortality.

†: All reviews contain narrative elements therefore "narrative" refers to reviews restricted to narrative methods and lacking meta-analysis. ‡: in MTT community programmes. ‡‡: involved in community maintenance or detoxification, or residential rehabilitation treatment. **MMT**: methadone maintenance therapy. **LMT**: *l* - acetyl methadol maintenance therapy. Trt: treatment. **exp'l**: experimental. **CRA**: contingency reinforcement approach. **CoRa**: community reinforcement approach. **HTA**: Health technology assessment.

Table 32 Systematic reviews with studies addressing effectiveness of buprenorphine at different doses or v. placebo / no treatment

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients) *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Davids 2004 [51]	Journal	not reported	Unclear (not reported) *2 relevant*	Experimental & observational follow up	Narrative	Opioid depend't	1] BMT	1] Placebo	Selective§
Faggiano 2003 [52]	Cochrane	1947 to 2001	21 (5984) 2 *relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid depend't	1] BMT	1] BMT different doses	Illicit drug use. Trt retention. Abstinence.
Farre 2002 [53]	Journal	1966 to 1999 (Dec)	13 (1944) *2 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] BMT	1] BMT different doses	Illicit drug use. Trt retention.
Johansson 2003 [60]	Book chapter	1966 to 2000	69 (7881) *6 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] BMT	1] Placebo 2] BMT different doses	Illicitt drug use. Trt retention.
Layson-Wolf 2002 [62]	Journal	1996 to 2001 (May)	Unclear (Unclear) *1 relevant*	RCTs + unclear	Narrative	Opioid depend't	1] BMT	1] BMT different doses	Illicit drug use. Trt retention.
Lintzeris 2003 [63]	Un-publishe d	Not clear to 2003	24 (>4400) *6 relevant*	RCTs	Narrative	Opioid depend't	1] BMT	1] Placebo 2] BMT different doses	Illicitt drug use. Trt retention.
Mattick 2005 [66]	Cochrane	1966 to 2005	13 (2560) *4 relevant*	RCTs	MA	Opioid depend't	1] BMT	1] BMT different doses	Illicit drug use. Trt retention.
Raisch 2002 [69]	Journal	1966 to 2000 (Nov)	Unclear (not reported) *2 relevant*	Unclear, review articles also used	Narrative	Opioid depend't	1] BMT	1] Placebo 2] BMT different doses	Selective§
Simoens 2005 [71]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *No. Relevant - unclear*	RCTs	Narrative	‡ Opioid depend't	1] BMT	1] Unspecified / unclear	Abstinence. Illicit drug use. Trt retention.
Simoens 2002 [72]	HTA	1990 to 2002	92 (not reported) *13 relevant*	RCTs, single group pre- post-, & quasi-exp'l studies	Narrative	‡‡ Opioid depend't	1] BMT	1] BMT different doses	Abstinence. Illicit drug use. Trt retention. Criminality. etc
West 2000 [76]	Journal	Not reported to 2000	9 (995) *3 relevant*	Controlled comparative studies	MA	Opioid depend't	1] BMT	1] BMT different doses	Illicit drug use.

†: All reviews contain narrative elements therefore "narrative" refers to reviews restricted to narrative methods and lacking meta-analysis. ‡: in MTT community programmes.
‡‡: involved in community maintenance or detoxification, or residential rehabilitation treatment. § : Selective = outcomes selected inconsistently across primary studies.
BMT: buprenorphine maintenance therapy. **Trt**: treatment**. exp'l**: experimental. **HTA**: Health technology assessment.

Table 33. Systematic reviews with studies addressing effectiveness of buprenorphine maintenance therapy v. other treatments (except methadone) or buprnorphine + a potential moderator of effectiveness.

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients) *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Davids 2004 [51]	Journal	not reported	Unclear (not reported) *2 relevant*	Exp'l & observational follow up	Narrative	Opioid depend't	1] BMT	1] BMT +psycho-social 2] LMT	Selective§
Faggiano 2003 [52]	Cochrane	1947 to 2001	21 (5984) 1 *relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid depend't	1] BMT	1] LMT	Illicit drug use. Trt retention. Abstinence. Side effects.
Johansson 2003 [60]	Book cchapter	1966 to 2000	69 (7881) *1 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] BMT *(outpatient)*	1] BMT *(special clinic)*	Illicit drug use. Trt retention.
Layson-Wolf 2002 [62]	Journal	1996 to 2001 (May)	Unclear (unclear) *1 relevant*	RCTs + unclear	Narrative	Opioid depend't	1] BMT	1] LMT	Illicit drug use. Trt retention.
Lintzeris 2003 [63]	Un-publishe d	Not clear to 2003	24 (>4400) *15 relevant*	RCTs + quasi-RCT (1)	Narrative	Opioid depend't	1] BMT	1] BMT in different setting 2] BMT dose regimens	
Mattick 2005 [66]	Cochrane	1996 to 2005	13 (2560) *1 relevant*	RCTs	MA	Opioid depend't	1] BMT	1] LMT	Illicit drug use. Trt retention.
Raisch 2002 [69]	Journal	1966 to 2000 (Nov)	Unclear (not reported) *5 relevant*	Unclear, review articles also used	Narrative	Opioid depend't	1] BMT	1] LMT 2] Dose regimens 3] Subcutaneous administration	Selective§
Simoens 2005 [71]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *No. Relevant -unclear*	RCTs	Narrative	‡ Opioid depend't	1] BMT	1] Unspecified / unclear	Abstinence. Illicit drug use. Trt retention.
Simoens 2002 [72]	HTA	1990 to 2002	92 (not reported) *12 RCTs relevant*	RCTs, case-control, quasi-experimental	Narrative	‡‡ Opioid depend't	1] BMT	1] BMT at different dose times 2] BMT + hydromorphine MT 3] LMT 4] Reducing Bup: doses	Abstinence. Illicit drug use. Trt retention. Criminality. Etc

†: All reviews contain narrative elements therefore "narrative" refers to reviews restricted to narrative methods and lacking meta-analysis. ‡: in MTT community programmes. ‡‡: involved in community maintenance or detoxification, or residential rehabilitation treatment. §: Selective = outcomes selected inconsistently across primary studies. **BMT**: buprenorphine maintenance therapy. **LMT**: *l* -acetymethadol maintenance therapy. **Trt**: treatment. **exp'l**: experimental. **HTA**: Health technology assessment.

Table 34. Systematic reviews with studies that compare methadone maintenance therapy with methadone withdrawal therapy.

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Faggiano 2003 [52]	Cochrane	1947 to 2001	21 (5984) 1 *relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid depend't	1] MMT *(RCT at different doses)*	1] M detoxification (RCT ; zero dose following stable doses)	Illicit drug use. Trt retention.
Gowing 2004 [57]	Cochrane	Data-base origins to 2003 (July)	28 (7900) *1 relevant*	RCTs, Cohort, Ca-Co, Descriptive.	MA	Opioid depend't *injecting*	1] MMT *(RCT prison setting)*	1] M withdrawal *(RCT prison setting)*	HIV-risk behaviours.
Hopfer 2002 [59]	Journal	Not reported	14 (6263) *3 relevant (methadone)*	Non-randomised: surveys, case-control, descriptive.	Narrative	Heroin-using youth	1] MMT	1] M detox	Illicit drug use. Trt retention. Detoxification duration.
Johansson 2003 [60]	Book chapter	2000	69 (7881) *2 relevant*	RCTs (Double Blind)	MA	Opioid depend't	1] MMT	1] M detox	Illicit drug use. Trt retention.
Mattick 2003 [65]	Cochrane	1966 to 2001	6 (954) *3 relevant*	Controlled clinical trials (RCTs)	MA	Opioid depend't	1] MMT	1] M detox	Illicit drug use. Trt retention. Criminality. Mortality.
Raisch 2002 [69]	Journal	1966 to 2000 (Nov)	Unclear (not reported) *1 relevant*	Unclear, review articles also used	Narrative	Opioid depend't	1] MMT	1] M detox	Selective
Simoens 2002 [72]	HTA	1990 to 2002	92 (not reported) *1 RCTrelevant*	RCTs, single group pre- post-, &, quasi-exp'l studies	Narrative	‡‡ Opioid depend't	1] MMT	1] M withdrawal	Abstinence. Illicit drug use. Trt retention. Withdrawal severity. Criminality. HIV-risk behaviour

Author & Year	Data sources	Search Start & End Date	No. Primary Studies (Total No. Patients *No. Relevant Studies*	Primary Study Designs Included	Meta-Analysis† / Narrative	Target Popul'n	Interventions Included	Comparators	Outcomes
Van Beusekom 2001 [75]	HTA	Not reported *(studies up to 2000)*	222 (not reported) *2 relevant*	RCTs, cohort, cross sectional, guidelines & others	Narrative	Opioid depend't	1] MMT	1] M withdrawal	Illicitt drug use. Trt: retention. Mortality.

MA: meta-analysis. **M**: methadone. **MMT**: methadone maintenance therapy. **M deto**: Methadone detoxification.

Appendix 4 Characteristics of included RCTs and key results reported

Table 35. Details of included randomised controlled trials

Author	Country / Trial Year /Setting	N *(N / Group)*	Population	Intervention / Comparator	Jadad Score	Follow Up	Main Findings
Ahmadi 2003a[77]	Iran 2002 Outpatient clinic	N=108 (3x36)	IV Buprenorphine abusers DSM –IV Mean 29.4 yrs 100% male Mean buprenorphine abuse 1.8 yrs	Group 1: Methadone 50 mg /day Group 2: Buprenorphine 5 mg /day Group 3: Clonidine 0.4 mg /day All offered weekly counselling	2	12-weeks	Retention in treatment: Group 1 30/36 (83%) Group 2 21/36 (58%) Group 3 4/36 (11%) P=0.02 Group 1 v 2, P < 0.0001 Group 3 v 1 or 2.
Ahmadi 2003b[78]	Iran 2000-2001 Outpatient clinic	N=420 (3 groups not reported)	Opioid dependent DSM –IV consecutive admissions Mean 36.3 yrs 97% male Daily drug abuse for at least 6 mos.	Group 1: Buprenorphine 1 mg /day Group 2: Buprenorphine 2 mg /day Group 3: Buprenorphine 4 mg /day All offered weekly counselling	2	24-weeks	Retention in treatment: Group 1 45.7% Group 2 55.7% Group 3 62.9%. P < 0.05 Group 3 v 2, P<0.001 Group 3 v 1.
Ahmadi 2003c[79]	Iran 2000-2001 Outpatient clinic	N=123 (3x41)	Heroin dependent DSM –IV Mean 31.4 yrs 100 % male. Heroin abuse for at least 6 mos.	Group 1: Buprenorphine 1 mg /day Group 2: Buprenorphine 3 mg /day Group 3: Buprenorphine 8 mg /day All offered weekly counselling	3	12-months	Retention in treatment: Group 1 7/41 (17%) Group 2 16/41 (39%) Group 3 26/41 (63%) P=0.00002 Group 1 v 3, P= 0.027 Group 2 v 1, P= 0.027 Group 3 v 2. No significant adverse events recorded.

Author	Country / Trial Year /Setting	N *(N / Group)*	Population	Intervention / Comparator	Jadad Score	Follow Up	Main Findings
Avants 2004[80]	USA 2000-2001 Community based programme	N=220 (112/108)	Opoid dependent DSM IV Mean 37 yrs 68% male All entering new methadone treatment	Group 1: Methadone 85mg/day + harm reduction programme Group 2: Methadone 85mg/day alone Both groups received counselling	2	12-weeks	Retention in treatment – Group 1 97/112 (87%) Group 2 93/108 (86%) NS Illicit opoid abuse [opiate free urine 3 weeks] - Group 1: 47% Group 2: 53% P=0.41 Sexual behaviour [weeks of safe sex] – Group 1 Mean 3.7 SD (3.9) Group 2 2.4 (3.4) P=0.01
Blanken 2005[¥81] Outcomes & prognostic analysis based on RCTs of van den Brink 2003[103]	The Netherlands 1998-2001 Treatment Centres	N=430 (193/237)	Heroin dependent Mean 39 yrs 80% male	Group 1: Methadone up to 150mg/day alone Group 2: Methadone 150mg/day + heroin up to 1g/day (injected or inhaled) Patients already in methadone treatment	2	12-months	'Treatment effectiveness' [combined outcome of health improvement+no serious deterioration+no substantial increase in cocaine or amphetamine use] Group 1 28.7% Group 2 51.8% P=0.0001 Patinets who had attempted detox previously were more likely to respond to heroin + methadone than others.
Brooner 2004 [82]	USA Not reported Outpatient clinic	N=127 (65,62)	Opioid dependent. DSM –III new admissions Mean 38.2 yrs 46% male 49% cocaine abusers	Group 1: Methadone (flexible dose) + Standard Stepped Care. Group 2: Methadone (flexible dose) + Stepped Care Contingency Enhanced (= Motivated Stepped Care)	2	90-days	Opiod positive urines: Group 1 30% Group 2 20% P=0.046 Any-drug positive urines Group 1 58% Group 2 44% P=0.029 Counselling attendance rate: Group 1 44% Group 2 83% P <0.001
Chutuape 2001[83]	USA 1994-1996 Home and clinic	N=55 (16/18/19)	Opoid dependent Mean 38 yrs 60% male Compliant in methadone treatment for 5 weeks	Group 1: Methadone 60mg 3 days/week + contingency weekly urine testing Group 2: Methadone 60mg 3 days/week + contingency monthly urine testing Group 3: Methadone 60mg 3 days/week + random urine testing	1	6-months	Retention in treatment – Group 1 10/16 (63%) Group 2 15/18 (83%) Group 3 18/19 (95%) P<0.05 Illicit opiate abuse [urinalysis] – NS Sustained opiate & cocaine abstinence – Group 1 56.6 Group 2 38.9% Group 3 10.5% P<0.002

Author	Country / Trial Year /Setting	N *(N / Group)*	Population	Intervention / Comparator	Jadad Score	Follow Up	Main Findings
Cornish 2002[84]	USA Not reported Inpatients	N=15 (10/5)	Opoid dependent DSM-IV Mean 44 yrs 100% male Standardised in methadone for 10 days before study	Group 1: Methadone 5-70mg/day + dextromethorphan (120-240 mg/day) Group 2: Methadone 5-70mg/day + placebo)	3	14-days	Adverse events - Group 1 174 events Group 2 21 events
Dean 2002 [85]	Australia Not reported Not reported	N=29 (25/24)	Opoid dependent Mean 35 yrs 67% male Beck Depression Inventory score >21 In methadone treatment ≥ 3-months	Group 1: Methadone (dose not reported) + fluoxetine 20mg/day Group 2: Methadone (dose not reported) + placebo	3	12-weeks	Retention in treatment – Group 1 15/25 (60%) Group 2 19/24 (79%) P=0.14 Depression [number of depression scales] – Group 1 better than 2 [no data reported] P<0.0001
Dijkgraaf 2005[¥] [86] Economic study based on van den Brink 2003 [103]	Holland 1998-2000 Not reported	430 (237,193)	Heroin inhalers and injectors; DSM –IV Compliant in Methadone treatment for at least 4 weeks.	Group 1: Methadone 12 mos. Group 2: Methadone + Heroin 12 months (Methadone mean range: 57- 67 mg / day Heroin mean range 548 mg / day)	3	12-months	Economic study from societal perspective. Methadone + heroin dominant to methadone alone. QALY gain 0.0588 (0.016 – 0.099) P=0.01. Cost savings Euros: 12,793 (1,083 – 25,229) P=0.032 Main driver of cost savings was less damage to crime victims which more than offset the extra cost of treatment for Group 2.
Dolan 2003[87]	Australia 1997-1998 Prison	382 (191/191)	Heroin dependent Mean 27 yrs 100% male	Group 1: wait list Group 2: methadone 30-60mg/day	3	16-weeks	Retention in treatment – Group 2 130/191 (68%) Illicit opiate abuse [self reported or analysis] Group 1 67% Group 2 25% P<0.001 Syringe sharing - Group 1 75/124 (60%) Group 2 34/129 (26%) P<0.001 Hepatitis C - Group 1 31.7 per 100 py 24.3 NS HIV – Both group 0%

Author	Country / Trial Year /Setting	N *(N / Group)*	Population	Intervention / Comparator	Jadad Score	Follow Up	Main Findings
Eder 2005[88]	Austria 1999-2001 Addiction clinic	N=64 (32,32)	Opiate dependent DSM –IV Mean 28-29 yrs 87% male	Group 1: Slow release morphine (mean 620 mg/day) 7 wks then methadone (mean 89mg/day) 7 wks. Group 2: Methadone (mean 80mg/day)) 7 wks then slow release morphine (mean 709 mg/day) 7 wks. Both groups received psychosocial counselling.	5	14-weeks	Retention in treatment: morphine (84%) methadone (76%) – NS Drug positive urines 80-90% opioids, 30-60% cocaine. – NS between drugs. Depressive symptoms: decrease in favour of morphine in second period P < 0.0001 Side effects similar between drugs.
Giacomuzzi 2001 [89]	Austria Not reported Outpatients University Clinic	N=60 (30,30)	Heroin dependent ICD-10 Mean 31 yrs 9-12 yrs morphine / methadone dependence	Group 1: Methadone roup 2: Morphine sulphate Both groups received conselling, doses not reported.	1	6-months	QoL (German version of Lancashire instrument: subjective and objectyive domains) Group 1 superior to group 2 in 9/10 subjective domains P <0.05, and overall for subjective domains P=0.012. Group 1 superior to group2 in 6/20 objective domains P<0.05. Group 1experienced fewer adverse side effects and used illicit drugs less than group 2.
Grabowski 2004ii[90]	USA Not reported Research clinic	N=96 (33/32/31)	Cociane and Heroin dependent DSM-IV Mean 37 yrs 59% male	Group 1: Methadone 1.1mg/kg/day alone Group 2: Methadone 1.1mg//kg/day+Risperidone 2mg/day Group 3: Methadone 1.1mg/kg/day+Risperidone 4mg/day Both groups received psychosocial therapy	4	24-weeks	Retention in treatment - Group 1 7/33 (21%); Group 2 11/32 (32%); Group 3 14/31 (45%). No significant different between groups (P=0.120) Illicit opiate use [urine analysis] - NS (P>0.90) HIV - no conversions during the study Depression [Beck depression inventory] - No significant difference between groups (P>0.24)
Grabowski 2004i[90]	USA Not reported Research clinic	N=96 (40/30/28)	Cocaine and Heroin dependent DSM-IV Mean 37 yrs 67% male No previous methadone treatment	Group 1: Methadone 1.1mg/kg/day alone Group 2: Methadone 1.1mg//kg/day+d-Amphetamine 30mg/day Group 3: Methadone 1.1mg/kg/day+d-Amphetamine 60mg/day All patients received psychosocial therapy	4	24-weeks	Retention in treatment - Group 1 10/40 (25%); Group 2 14/28 50%); Group 3 11/28 (39%). (P=0.107) Illicit opiate use [urinalysis]- Trend for lowest for group 3 (P=0.07) HIV - no conversions during the study Depression [Beck depression inventory] - NS (P>0.68)

Author	Country / Trial Year /Setting	N *(N / Group)*	Population	Intervention / Comparator	Jadad Score	Follow Up	Main Findings
Jones 2001 [91]	USA 1996-1997 Residential followed by outpatient	N=70 (44,36)	Opiate dependent pregnant women DSM –III with cocaine abuse Mean 28 yrs	Group 1: Methadone (mean 42 mg /day) + Standard Care. Group 2: Methadone (mean 42 mg /day) + Standard Care with Incentives (escalating voucher schedule) Both groups 7 days residential then 7 days outpatient.	3	14-days	Withdrawal: Group 1 2/36 Group 2 3/44 NS Attendance in first 7 days: Group 1 mean 6.6 days Group 2 mean 6.9 days P=0.05 Attendance in second 7 days: Group 1 mean 4.1 days Group 2 mean 5.2 days P<0.05 % Opiate positive urines in second 7 days: Group 1 18% Group 2 7% P<0.05 % Cocaine positive urines in second 7 days: Group 1 14% Group 2 12% P<0.05
King 2002 [92]	USA Not reported Community treatment clinic	N=78 (25/27/26)	Opoid dependent Mean 45yrs 67% male 12-months of successful prior methadone treatment	Group 1: Methadone (dose not reported) delivered in physician office + monthly reported schedule Group 2: Methadone (dose not reported) delivered in treatment clinic + monthly reported schedule Group 1: Methadone (dose not reported) delivered in physician office + monthly reported schedule	2	6-months	Retention in treatment - Group 1 23/25 (29%), Group 2 24/27 (89%) 23/25 (92%) NS Illicit drug use [urinalysis] – Group 1 2/21 Group 2 1/19 Group 3 1/25 NS New employment or social commitments – Group 1 96% Group 71% Group 33% P<0.001
Kosten 2003 [93]	USA Not reported Outpatient facility	N=160 (40/40/40/40)	Opoid and cocaine dependent DSM-IV Mean 36-38 yrs 66% male	Group 1: Buprenorphine 16mg/day + Desipramine 150mg/day + contingency management (financial vouchers) Group 2: Buprenorphine 16mg/day + Placebo + contingency management (financial vouchers) Group 3: Buprenorphine 16mg/day + Desipramine Group 4: Buprenorphine 16mg/day + Placebo	4	13-weeks	Retention in treatment – NS (data not reported) Illicit drug use [opiate and cocaine free urines] – Group1 50% Group2 25% Group 3 29% Group 4 29% P=0.05 Illicit drug use [opiate free urines] – Group1 65% Group2 49% Group 3 43% Group 4 54% P=0.10 Depression [number of depression inventories] – NS (data not reported)
Kristensen 2000 [94]	Norway Not reported Not reported	N=50 (25/25)	Opoid dependent ICD-10 Mean 36 yrs 75% male >10 yrs drug treatment experience	Group 1: Buprenorphine 16mg/day [fixed] Group 2: Methadone mean 106/day [individually adjusted] All patients received rehabilitation input	2	24-weeks	Retention in treatment – Group 1 21/25 (85%) Group 2 2/25 (36%) P<0.0005 Illicit drug use [positive opiate urinalysis] – Group 1 20% Group 2 25% P<0.01

Author	Country / Trial Year /Setting	N *(N / Group)*	Population	Intervention / Comparator	Jadad Score	Follow Up	Main Findings
Lidz 2004 [95]	USA 1995-1998		in MMT	Group 1: Methadone + Vocational Problem Solving (VPS) Group 2: Methadone + Job Seekers Workshop (JSW) Group 3: Methadone + both VPS & JSW	2	12-months	No interventions produced greater employment or better overall rehabilitation.
Loftwall 2005 [96] [Update of Strain, 1996]	USA Not reported University research unit	N=164 (80/84)	Opoid dependent DSM-IIIR Mean 32.5 yrs 71% male Patients not in treatment	Group 1: Methadone 50mg/day Group 2: Buprenorphine 8mg/day	3	16-weeks	Safety [liver function tests] – NS Side effects [self report] – NS
Margolin 2003 [97]	USA	N=18 (2x9)	Opiate abusers DSM –IV Mean 38.8 yrs 47% male In methadone treatment (mean 5 months)	Group 1: Methadone + placebo Group 2: Methadone + magnesium aspartate (732 mg /day) (Methadone assumed mean ~ 95 mg / day) All were offered counselling.	5	12-weeks	Retention in treatment (weeks): Group 1 8.9 (SD 4.0) Group 2 10.9 (SD 2.5) P >0.05 % Opiate positive urines: Group 1 22.6% (SD 22.7) Group 2 46.4% (SD 21.8) P=0.04 % Cocaine positive urines: No Significant difference between groups
Marsch 2005 [98]	USA Not reported Outpatient clinic	134 (44,44,45)	Opioid dependent DSM –IV Mean 33 yrs 64% male	Group 1: Buprenorphine received daily Group 2: Buprenorphine received three times / week Group 3: Buprenorphine received two times / week Maintenance doses were equivalent to 4, 8, 10 or 12 mg / day.	4	24-weeks	Retention in treatment: Group 1 69% Group 2 73% Group 3 64% P=0.70; log rank 0.58 P=0.74 % opioid negative urines: Group 1 73% Group 2 70% Group 3 73% –NS Cocaine abstinence: Group 1 8.5 weeks Group 2 8.9 weeks Group 3 7.0 weeks P=0.71
Pollack 2002[99]	USA Not reported Outpatient clinic	23 (11,12)	Opioid dependent DSM –III Mean 39.5 yrs 43% male In Methadone treatment. Mean of 20 yrs drug use.	Group: 1 Methadone (mean in range 56-75 mg/day) + enhanced counselling Group 2: Methadone (mean in range 56-75 mg/day) + cognitive-behavioural therapy. Both groups monetary reinforcement.	2	6-months	Post hoc secondary analyses only: First 8 weeks % urine negative for illicit drugs. Groups 1 & 2 < 11% (P>0.37).

Author	Country / Trial Year /Setting	N *(N / Group)*	Population	Intervention / Comparator	Jadad Score	Follow Up	Main Findings
Ritter 2003 [100]	Australia 1999-2001 Primary care	101 (52,49)	Opioid dependent Mean 33 yrs 69% male In Methadone treatment > 8 weeks	Group 1: Flexible Methadone (mean 65 mg/day) Group 2: Flexible LAAM (mean 232 to 249 mg/day depending on follow up time)	3	12-months	Retention in treatment: At 3 months Group 1 45/49 (92%) Group 2 42/44 (95%); 6 months Group 1 42/49 (86%) Group 2 41/44 (93%); 12 months Group 1 35/49 (71%) Group 2 37/44 (84%). Log rank 1.07, P=0.3. Self reported heroin use (Q score): 3 months Group 1 0.29 Group 2 0.20 P=0.59; 6 months Group 1 0.23 Group 2 0.41 P=0.37; 12 months Group 1 0.25 Group 2: 0.46 P=0.34.
Sigmon 2004 [101]	USA 2000-2001 University research unit	46 (14,16,16)	Cocaine abusers using opiates and cocaine Mean 42.4 yrs 57% male In Methadone treatment average 3 months	Group 1: Methadone Group 2: Methadone + quantitative reinforcement (voucher dependent on drug concentration in urine) Group 3: Methadone+ qualitative reinforcement (voucher dependent on % fall in drug concentration in urine) (Methadone dose 100 mg/day).	3	24 wks	Cocaine abstinence (% cocaine-negative urines). No Significant difference between groups.
† van den Brink 2003i [103]	Holland 1998-2000 Not reported	375 (139,117, 119)	Heroin inhalers DSM –IV Mean 40 yrs 79% male Compliant in Methadone treatment for at least 4 weeks.	Group 1: Methadone 12 mos. Group 2: Methadone + Heroin 12 months Group 3: Methadone 6 months then 6 months Methadone + Heroin. (Methadone mean range: 57- 67 mg / day Heroin mean range 548 mg / day)	3	12-months	Completed treatment: Group 1: 121/139 (87%) Group 2: 80/117 (80%) Group 3: not reported. Responders (dichotomous composite outcome measure *physical, mental & social*): Group 1: 37/139 (27%) Group 2: 58/117 (50%) Group 3: not reported. Difference P < 0.05 Serious Adverse Events related to Heroin: Group 1: NA Group 2: 5/117 Group 3: 1/119
† van den Brink 2003ii [103]	Holland 1998-2000 Not reported	174 (98,76)	Heroin injectors DSM –IV Mean 40 yrs 82% male Compliant in Methadone treatment for at least 4 weeks.	Group 1: Methadone 12 mos. Group 2: Methadone + Heroin 12 months (Methadone mean range: 60- 71 mg / day Heroin mean range 548 mg / day)	3	12-months	Completed treatment: Group 1: 83/98 (85%) Group 2: 55/76 (72%) Responders (dichotomous composite outcome measure *physical, mental & social*): Group 1: 31/98 (31%) Group 2: 42/76 (56%) Difference P < 0.05 Serious Adverse Events related to Heroin: Group 1: NA Group 2: 4/76

Author	Country / Trial Year /Setting	N *(N / Group)*	Population	Intervention / Comparator	Jadad Score	Follow Up	Main Findings
Zanis 2001[102]	USA Not reported Community based programme	109 (62,47)	Mean 43.5 yrs 61% male Compliant in Methadone treatment at least 3 months Unemployed.	Group 1: Methadone (dose not reported) + cognitive VPS (vocational problem solving skills). Group 2: Methadone (dose not reported) + counselling IPS (interpersonal problem solving)	2	12 wks	Achieved employment within 6 months follow up: Group 1: 43/58 (58.6%) Group 2: 16/43 (37%) P < 0.05

† Included in the systematic review by Ferri (2005) and discussed in the review of reviews and source for ¥ Blanken 2005[81] and Dijkgraaf 2005[86]. ASI = addiction severity index. * IR = incentive reinforcement depending on results of urine analysis for cocaine derivative.

Appendix 5 Quality assessment instruments

Systematic reviews

A modified version of the Oxman & Guyatt[45] assessment tool and scale was used to assess the quality of reviews. This consists of 9 quality interrogations each answerable as "yes", or "no", or "partially / cant tell" carrying scores of 2, 0 and 1 respectively. The 9 questions are listed below.

1. Were the search methods used to find evidence on the primary question(s) stated?
    - ***Yes***, description of databases searched, search strategy, and years reviewed. ***2 points***
    - ***Partially***, description of methods not complete. ***1 point***
    - ***No***, no description of search methods. ***0 points***
2. Was the search for evidence reasonably comprehensive?
    - ***Yes***, at least one computerized database searched as well as a search of unpublished or non-indexed literature. ***2 points***
    - ***Can't tell***, search strategy partially comprehensive, at least one of the strategies were performed. ***1 point***
    - ***No***, search not comprehensive or not described well. ***0 points***
3. Were the criteria used for deciding which studies to include in the review reported?
    - ***Yes*****,** in- and exclusion criteria clearly defined. ***2 points***
    - ***Partially***, reference to in- and exclusion criteria can be found but are not defined clearly enough**.** ***1 point***
    - ***No***, no criteria defined. ***0 points***
4. Was bias in the selection of articles avoided?
    - ***Yes*****,** issues influencing selection bias were covered. Two of three of the following bias avoiding strategies were used: two or more assessors independently judged study relevance and selection using predetermined criteria, reviewers were blinded to identifying features of the study, and assessors were blinded to treatment outcome. ***2 points***
    - ***Can't tell***, only one of the strategies used. ***1 point***
    - ***No***, selection bias was not avoided or was not discussed. ***0 points***
5. Were the criteria used for assessing the validity for the studies that were reviewed reported?
    - ***Yes***, criteria defined. ***2 points***
    - ***Partially***, some discussion or reference to criteria. ***1 point***

- ***No*****,** validity or methodological quality criteria not used or not described. ***0 points***

6. Was the validity for each study cited assessed using appropriate criteria?
    - ***Yes*****,** criteria used addressed the major factors influencing bias. ***2 points***
    - ***Partially*****,** some discussion, but not clearly described predetermined criteria. ***1 point***
    - ***No*****,** criteria not used or not described. ***0 points***
7. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?
    - ***Yes*****,** qualitative and quantitative methods are acceptable. ***2 points***
    - ***Partially***, partial description of methods to combine and tabulate; not sufficient to duplicate. ***1 point***
    - ***No***, methods not stated or described. ***0 points***
8. Were findings of the relevant studies combined appropriately relative to the primary question of the overview?
    - ***Yes***, combining of studies appears acceptable. ***2 points***
    - ***Can't tell***, should be marked if in doubt. ***1 point***
    - ***No***, no attempt was made to combine findings, and no statement was made regarding the inappropriateness of combining findings**.** ***0 points***
9. Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?
    - ***Yes***, data were reported that support the main conclusions regarding the primary question(s) that the overview addresses. ***2 points***
    - ***Partially, 1 point***
    - ***No***, conclusions not supported or unclear. ***0 points***

RCTs

An adapted Jadad scale was used to assess quality of RCTs. The three questions and scoring system employed are listed below:

1. Was the study described as randomised (this includes the use of words such as randomly, random, and randomisation)?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring the items:
A score of 1 point for each 'yes' and 0 points for each 'no'.

1 additional point was given if:

For question 1, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated, etc.)
And:
If for question 2 the method of double blinding was well described and it was appropriate (identical placebo, active placebo, dummy, etc.)

The following guidelines were used for assessment:

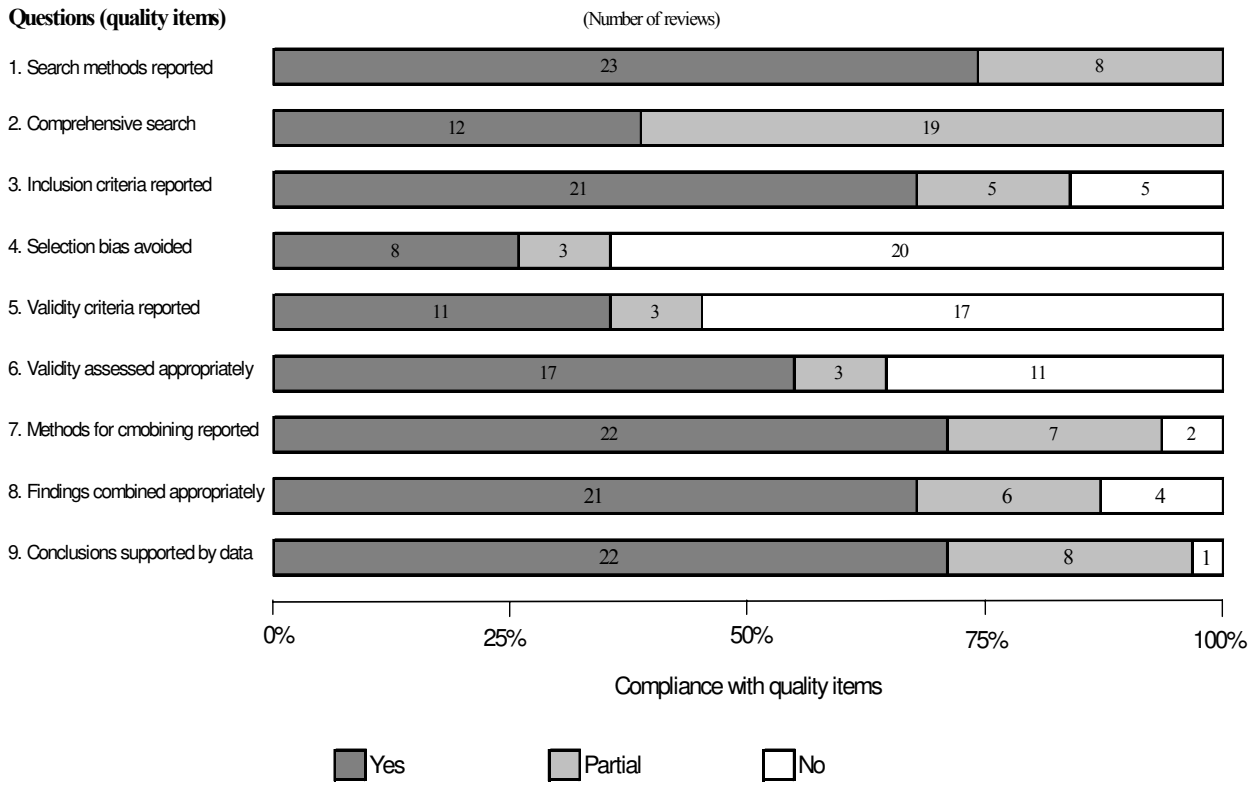
1. Randomisation
   A Method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigator could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.
2. Double blinding
   A study must be regarded as double blind if the word 'double blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned and well described.
3. Withdrawals and dropouts
   Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points. An exception is made, if the presented data clearly describes that there have been no withdrawals.

Appendix 6 Quality assessment of Systematic reviews

Summary of quality scores for included systematic reviews

	Score on question									
Review	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total
Amato 2004 [47]	2	2	2	1	2	2	2	2	2	17
Barnett et al 2001[48]	1	1	0	0	0	0	2	2	2	8
Caplehorn 1995[49]	2	2	1	0	0	0	2	2	2	11
Clark N et al 2002[50]	2	2	2	1	2	2	2	1	2	16
Davids & Gastpar 2004[51]	1	1	1	0	0	0	2	2	1	8
Faggiano et al 2003[52]	2	2	2	1	2	2	2	1	2	16
Farre et al 2002[53]	2	1	1	0	2	0	2	2	2	12
Ferri et al 2005[54]	2	2	2	0	2	2	2	2	2	16
Fridell 2003[55]	2	1	1	0	1	0	1	0	1	7
Glanz et al 1997[56]	1	1	0	0	2	1	2	2	2	11
Gowing et al 2004[57]	2	2	2	1	2	2	2	2	2	17
Griffith et al 2000[58]	1	1	2	0	0	0	1	1	2	8
Hopfer et al 2002[59]	2	1	2	0	0	0	2	2	2	11
Hulse 1998[43]	2	1	2	0	1	0	2	2	2	12
Johansson 2003[60]	2	1	0	0	0	0	2	2	2	9
Kirchmayer et al 2003[61]	2	2	2	1	2	2	2	2	2	17
Layson-Wolf et al 2002[62]	2	1	0	0	0	0	0	1	0	4
Lintzeris 2004[63]	1	1	0	0	0	0	0	0	1	3
Marsch 1998[64]	1	1	2	0	0	0	2	2	2	10
Mattick et al 2003[65]	2	1	2	1	2	2	2	2	2	16
Mattick et al 2005[66]	2	2	2	1	2	2	2	2	2	17
Mayet et al 2005[164]	2	2	2	1	2	2	2	2	2	17
Prendergast et al 2000[67]	2	2	2	0	1	1	2	2	1	13
Prendergast et al 2002[68]	2	1	2	0	0	0	2	2	2	11
Raisch et al 2002[69]	1	1	2	0	0	0	1	0	1	6
Roozen et al 2004[70]	2	1	2	1	2	2	2	2	2	16
Simoens et al 2005[71]	2	1	2	0	2	0	2	2	2	13
Simoens 2002[43]	2	2	2	1	2	1	1	1	2	14
Sorensen & Copeland 2000[73]	2	1	1	0	0	0	2	2	1	9
Stanton & Shadish 1997[74]	1	1	2	0	2	2	1	0	1	10
van Beusekom, et al 2001[75]	2	2	2	0	2	0	1	1	1	11
West et al 2000[76]	2	1	2	0	0	0	1	2	2	10

Score 2: fully matched the criteria.
Score 1: partially matched the criteria.
Score 0: no mach for the criteria.


Questions (quality items)
(Number of reviews)
1. Search methods reported
23
8
2. Comprehensive search
12
19
3. Inclusion criteria reported
21
5
5
4. Selection bias avoided
8
3
20
5. Validity criteria reported
11
3
17
6. Validity assessed appropriately
17
3
11
7. Methods for cmobining reported
22
7
2
8. Findings combined appropriately
21
6
4
9. Conclusions supported by data
22
8
1
0%
25%
50%
75%
100%
Compliance with quality items
Yes
Partial
No

Reviews are listed in alphabetical order by first author.

The quality assessment of the systematic reviews

Questions	Score	Amato, 2004[47]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 2	Sources: 1. Electronic: MEDLINE (Jan 1966-April 2003), PsycINFO (1887-Aug 2000), EMBASE (Jan 1980-April 2003), and Cochrane Controlled Trials Register (issue 3 2003), etc. 2. Reference lists of articles and hand-searched reviews and conference abstracts.
Inclusion criteria reported (Q3)	2	Clearly defined types of studies RCTs, participants (opiate addicts), intervention and control (agonist + psychosocial v. agonist), and outcomes (IDU and treatment retention etc).
Selection bias avoided (Q4)	1	Three reviewers independently selected studies. It was not reported whether the reviewers were blinded to the identifying feature and the treatment outcome of the studies.
Validity criteria reported (Q5)	2	Used the quality criteria identified in the Cochrane Reviewers Handbook 4.2. The quality assessment items (e.g. allocation concealment, blinding, etc.) were defined.
Validity for each study assessed appropriately (Q6)	2	Studies were assessed according to described criteria.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Meta-analysis methods described for dichotomous and continuous outcomes, statistical heterogeneity amongst study effect sizes was estimated; combining of findings appears appropriate.
Conclusions supported by data (Q9)	2	This review examined whether addition of psychosocial approaches to agonist maintenance treatment improved patient outcome measures (treatment retention, illicit drug use, and improved social and health status). Eight different psychosocial approaches were identified each added to methadone maintenance treatment. Eleven RCTs were included. Authors concluded that addition of psychosocial interventions to MMT: 1. significantly improves heroin abuse during treatment. 2. improves treatment retention, but not to statistical significance. Further they concluded there was insufficient evidence to determine an effect for other outcomes (e.g. QoL), and that studies were heterogeneous. Sensitivity analysis was done to determine impact of low quality studies. The meta-analysis supports the first conclusion. The evidence that treatment retention is improved is very weak; eight studies (none in themselves reaching statistical significance) were combined in a meta-analysis with an summary RR of only 0.94 (*CI 0.85 to 1.02*); thus an effect, if it exists, may be of little clinical significance given the fact that a single time point only contributed to the analysis and retention in treatment drops greatly and continuously during study periods.

The quality assessment of the systematic reviews

Questions	Score	Barnett, 2001[48]
Search methods reported and comprehensive search (Q1 & Q2)	1 &1	Searched Medline (before 1998) only. Restricted to papers in English language. Search strategy was not reported.
Inclusion criteria reported (Q3)	1	Limited to 2ble-blind RCTs and methadone vs buprenorphine comparisons
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Meta-analysis undertaken . Where statistical significant heterogeneity not detected.
Conclusions supported by data (Q9)	2	1. This review examines the question of effectiveness of buprenorphine relative to methadone and included 5 RCTs. 2. Conclusion stated: 1). The variation between trials may be due to differences in dose levels, patient exclusion criteria and provision of psychosocial treatment. 2). The difference in the effectiveness of buprenorphine and methadone may by statistically significant, but the differences are small compared to the wide variance in outcomes achieved in different methadone treatment programs. 3). Further research is needed to determine if buprenorphine treatment is more effective than methadone in particular settings or in particular subgroups of patients. 3. Are these conclusions supported by data? 1). Tested heterogeneity existed in effect of the studies, the treatment dose was varied, but the variation of patient exclusion criteria and provision of psychosocial treatment for the studies were not reported. 2). Data showed that buprenorphine generally tended to be more effective in the included studies, but not in all the studies the difference was significant. Effect size for the studies varied widely. 3). Effectiveness of buprenorphine comparing methadone was derived from the 5 included trials and was not strongly concluded.

The quality assessment of the systematic reviews

Questions	Score	Caplehorn 1995 [49]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 2	Searched Medline (1966 to 1995) only. Search strategy was reported. Any language restriction unclear.
Inclusion criteria reported (Q3)	1	Studies looking at risk of mortality with methadone treatment for heroin addiction
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Meta-analysis methods described for combining relative rates of mortality per person year (fixed effects model). Absolute risk differences were not combined because of the evidence of statistical heterogeneity. The combining of findings appears appropriate.
Conclusions supported by data (Q9)	2	This meta-analysis examined whether methadone maintenance reduced the risk of death amongst opioid addicts. The relative mortality rates were combined from five cohort studies that compared addicts in treatment with those not in, or no longer in, methadone treatment. Authors concluded that MMT: 1. significantly reduces mortality; the combined relative rate from five studies = 0.25 (*CI 0.19 to 0.33).* The meta-analysis supports the conclusion that MMT patients are about ¼ as likely to die as those not in MTT.

The quality assessment of the systematic reviews

Questions	Score	Clark, 2002[50]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 2	Sources: 1. Electronic: MEDLINE (Jan 1996-Aug 2000), PsycINFO (1887-Aug 2000), EMBASE (Jan 1985-Aug 2000), and Cochrane Controlled Trials Register (issue 2 2000), etc. 2. Reference lists of articles and bibliography. 3. CPDD abstracts and NIDA monographs 4. Pharmaceutical industry: BI 5. Personal contact MEDLINE (Ovid) search strategy was used.
Inclusion criteria reported (Q3)	2	Clearly defined types of studies, participants (heroin dependent), intervention (LAAM) and control (methadone), and outcome measures.
Selection bias avoided (Q4)	1	Selected independently by two reviewers using the criteria. It is not reported whether the reviewers were blinded to the identifying feature and the treatment outcome of the studies.
Validity criteria reported (Q5)	2	Used the quality scales developed by the drug and alcohol Cochrane review group for experimental studies and controlled prospective studies. The quality assessment items (e.g. allocation concealment, blinding, etc.) were defined.
Validity for each study assessed appropriately (Q6)	2	Each included study was assessed using the quality items of the quality criteria.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 1	15 studies were included for meta-analyses, which were conducted for the suitable outcome measures (retention, heroin use and mortality) RCTs. Fixed effects meta-analysis undertaken throughout regardless of levels of heterogeneity.
Conclusions supported by data (Q9)	2	1. The review examined the question of the efficacy and acceptability of LAAM maintenance with methadone maintenance in the treatment of heroin dependence. It included 15 RCTs and 3 controlled prospective studies. 2. Conclusion stated: LAAM appears more effective than methadone at reducing heroin use. More LAAM patients than methadone ceased their allocated medication during the studies, but many transferred to methadone and so the significance of this is unclear. There was no difference in safety observed, although there was not enough evidence to comment on uncommon adverse events. 3. Is it supported by data? Estimated effect size on both non-abstinence and percentage of urine tests negative for opiates of those collected (per person per week) was in favour of LAAM with statistical significance (RR 0.81, 95%CI 0.72-0.91; WMD -10.0, 95%CI -11.5 to -8.5, $p<0.00001$, respectively). Cessation of allocated medication at the end of the study period: RR 1.36, 95% CI 1.07 to 1.73, p=0.001. All cause mortality: RR 2.28, 95% CI 0.59 to 8.9, p=0.2

The quality assessment of the systematic reviews

Questions	Score	Davids, 2004[51]
Search methods reported and comprehensive search (Q1 & Q2)	1 & 1	Searches: MEDLINE and PSYNDEXplus from their earliest entries (end data was not reported). No search strategy was reported. Language restriction was not reported.
Inclusion criteria reported (Q3)	1	No criteria reported, but some known as observational and experimental studies were reviewed.
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Narrative analysis without a quantitative summary.
Conclusions supported by data (Q9)	1	1. This review examines the question of the current status of what is known about the pharmacology of buprenorphine, with a particular emphasis on the issues of maintenance therapy in heroin addiction. It did not clearly state the number of studies included. 2. Conclusion stated: Buprenorphine appears to be a well-tolerated drug, with a benign overall side effect. Buprenorphine is an additional treatment option for heroin dependent patients, especially for those who do no wish to start or continue with methadone or for those who do not seem to benefit from adequate dosages of methadone. 3. Is it supported by data? The authors reported result in a narrative account without a quantitative data. It is difficult to determine if conclusions are justifiable without accessing the primary studies.

The quality assessment of the systematic reviews

Questions	Score	Faggiano, 2003[52]
Search methods reported and comprehensive search (Q1 and Q2)	2 & 2	Sources: 1. Electronic: MEDLINE (OVID 1996-2001), EMBASE (1988-2001), ERIC (1988-2001), Psychinfo (1974-2001), etc. 2. Further studies searched through letters to the authors and check of references. The CDAG (Cochrane Drugs and Alcohol Group) search strategy was applied together with a specific MESH strategy. Unpublished literature was also searched. No language restriction.
Inclusion criteria reported (Q3)	2	Clearly defined the types of studies (RCTs, CCTs, etc), participants (opoid addicted patients), intervention (comparison between two or more different dosages of MMT, etc), and outcome measures.
Selection bias avoided (Q4)	1	Each potentially relevant study not excluded in the previous steps of selection (e.g. sifting by reading the abstract by two reviewers) was obtained and was independently assessed by two reviewers. It was not reported whether the reviewers were blinded to the study identifying features.
Validity criteria reported (Q5)	2	Quality assessment used the CDAG's checklist, and the quality items were defined.
Validity for each study assessed appropriately (Q6)	2	Each of the included studies was assessed using the quality assessment items.
Methods for combining reported and findings combined appropriately (Q7 and Q8)	2 & 1	Meta-analysis was conducted for the RCTs, which were classified according to the used range of dose, and for 3 prospective studies (CPSs) of which the data was useful for a meta-analysis. Others were descriptively analysed. Fixed effects meta-analysis undertaken throughout regardless of levels of heterogeneity
Conclusions supported by data (Q9)	2	1. The review examined the question of the efficacy of different dosages of MMT in modifying health and social outcomes and in promoting opiod dependents' family, occupational and relational functioning. It included 11 RCTs and 10 Controlled Prospective Studies. 2. Conclusion stated: methadone dosages ranging from 60 to 100 mg/day are more effective than lower dosages in retaining patients and in reducing use of heroin and cocaine during treatment. 3. Is it supported by data? Estimated effect size from the RCTs: 1). Retention rates: high (60mg to 109 mg/day) vs low doses (1-39 mg/day) at short follow-ups: RR=1.36[1.13, 1.63] 2). Opioid use: high vs middle doses (40-59 mg/day): WMD=-1.89[-3.43, -0.35] 3). Opioid abstinence (urine based) at >3-4w: high vs low doses: RR=1.59[1.16, 2.18, high vs middle doses: RR=1.51[0.63, 3.61]; 4). Cocaine abstinence (urine based) at >3-4w: high vs low doses: RR=1.81[1.15, 2.85]

The quality assessment of the systematic reviews

Questions	Score	Farre, 2002 [53]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: 1. Electronic: PubMed database from 1996 to Dec 1999, Cochrane Library (1999 issue 4) using the major medical subject headings and key words. 2. References lists of retrieved articles. Manual review of the tables of contents of journals on drug of abuse included in the psychiatry and substance abuse subject category listing 1997 of the Journal Citation Reports®, etc. No searches of unpublished sources were reported. All languages were included.
Inclusion criteria reported (Q3)	1	Study design (double blinded RCTs), intervention (methadone maintenance), and outcome measure were defined. Details of participants (patients of opioid addiction) were not defined in the criteria but can be seen from the text of the review.
Selection bias avoided (Q4)	0	Selection process was not reported.
Validity criteria reported (Q5)	2	Used Jadad criteria and the criteria were defined.
Validity for each study assessed appropriately (Q6)	0	No description
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Meta-analysis was used for pooling both the outcomes of illicit drug use and failure in retention, using random effect model where there was heterogeneity.
Conclusions supported by data (Q9)	2	1. This review examined the question of the effect of methadone maintenance strategies on the endpoints of retention rate and reduction of illicit opioid use. It included 13 studies 2. Conclusion stated: agonist-maintenance programmes, oral methadone at doses of 50mg/day or higher is the drug of choice for opioid dependence. 3. Is it supported by the data: 1). High doses vs low doses of methadone in the reduction of illicit opioid use: OR=1.92, 95% CI 1.32-2.78. 2). It concluded that "High doses of methadone were significantly more effective than low doses of buprenorphine (< 8mg/day) for retention rates and illicit opioid use, but similar to high doses of buprenorphine (>=8mg/day) for both parameters". The estimated effectiveness of high dose methadone) for retention rates and illicit drug use is OR 1.25 (95% CI 0.94 –1.67) and OR 1.72 (95% CI 1.26–2.36), respectively. The estimated effectiveness of low dose buprenorphine for retention rates and illicit drug use is OR 2.72 (95% CI 1.12- 6.58) and OR 3.39 (95% CI 1.87- 6.16), respectively. The estimated effectiveness of high dose buprenorphine for retention rates and illicit drug use is OR 1.14 (95% CI 0.83-1.59) and OR 1.08 (95% CI 0.75-1.57) respectively. 3). Patients treated with LAAM had more risk of failure of retention than those receiving high doses of methadone (OR 1.92, 95%CI 1.32-2.78).

The quality assessment of the systematic reviews

Questions	Score	Ferri M, 2005[54]
Search methods reported and comprehensive search (Q1 and Q2)	2 & 2	Sources: 1). Electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) issue 1, 2005. MEDLINE (1996 to 2005), EMBASE (1980 to 2005), and CINAHL (until 2005 on OVID) 2). Relative websites, trial registers, and ongoing trials. No language and publication year restriction. Search strategy with filter was reported.
Inclusion criteria reported (Q3)	2	Clearly defined the types of study (RCT), participants (adults aged 18 or older and were chronic heroin dependents), intervention (heroin alone or combination with methadone), control treatment (no intervention, methadone maintenance, waiting list for conventional treatments, and any other treatments which are compared against heroin), and outcome measure (retention in treatment, relapse to street heroin use, etc).
Selection bias avoided (Q4)	0	Not reported.
Validity criteria reported (Q5)	2	Defined randomisation method, allocation concealment, and follow-up.
Validity for each study assessed appropriately (Q6)	2	Assessed all the include studies for each of the aspect of the quality criteria.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Narrative analysis of the data. No meta-analysis was performed because of heterogeneity of interventions for the included studies.
Conclusions supported by data (Q9)	2	1. The review aimed to assess the efficacy and acceptability of heroin maintenance treatment versus methadone or other substitution treatments for opioid dependence; it included 4 studies of which one study meets our review question. 2. Conclusion stated: No definitive conclusion about the overall effectives of heroin prescription is possible. Results favouring heroin treatment come from studies conducted in countries where easily accessible MMT at effective dosages is available. In those studies heroin prescription was addressed to patients who had failed previous methadone treatments. 3. Is it supported by data? Non-comparability of the experimental studies was available, the authors therefore just analysed the primary results without drawing a definitive conclusion on the effectiveness.

The quality assessment of the systematic reviews

Questions	Score	Fridell, 2003[55]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: MEDLINE, Alconline, and Cochrane Library. Years searched were the earliest studies from the late 1970s to June 1999. No unpublished and grey literature searches were reported. Search strategy was to use terms e.g. substance abuse disorders, substance abuse, etc. Unknown whether there was a language restriction.
Inclusion criteria reported (Q3)	1	Studies looking at the effect of psychosocial interventions on opiate dependence. Details not reported
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	1	All initially classified RCTs were assessed for quality based on a manual developed by SBU. But criteria were not defined.
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	1 & 0	Effect size (d) calculated and meta-analyses were conducted. Details of heterogeneity assessment not given.
Conclusions supported by data (Q9)	1	1. The review examined the question of the effect of pyschosoial interventions (with or without drug therapy) for opiate abuse The review concluded that re-educative interventons and psychotherapies have significant effects on relapse compared to treated control groups. The effect sizes are moderate. Difficult to assess how much the conclusions are attributable to non-drug vs drug therapy

The quality assessment of the systematic reviews

Questions	Score	Glanz, 1997 [56]
Search methods reported and comprehensive search (Q1 & Q2)	1 & 1	Sources: MEDLINE Years of the database searched: 1966-1996 No other sources were searched. Search used keywords e.g. heroin addiction, methadone, etc. Unknown whether there was a language restriction.
Inclusion criteria reported (Q3)	0	RCTs of methadone vs. LAAM in the management of heroin addiction. No formal inclusion/exclusion criteria.
Selection bias avoided (Q4)	0	Not mentioned.
Validity criteria reported (Q5)	2	Used a formal quality scoring according to the method of Chalmers and indicated the quality aspects.
Validity for each study assessed appropriately (Q6)	1	Reported the quality assessment aspect of blinding for each study, and scored quality for each study.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Calculated mean risk difference for the dichotomous variables. Meta-analysis was conducted using both fixed-effect model and random-effect model but where there was heterogeneity the random effects result was considered.
Conclusions supported by data (Q9)	2	1. The review examined the question of the efficacy of LAAM relative to methadone in the treatment of opiate addiction. It included 14 RCTs comparing methadone with LAAM in treatment of heroin addiction. 2. Conclusion stated: Given the potential practical and operational benefits of LAAM therapy over methadone in certain situations, it would seem reasonable at this point to support and encourage LAAM therapy as an important alternative to methadone. 3. Is it supported by data? Pooled data of LAAM vs methadone: 1). Illicit drug use (heterogeneity detected, considering random-effect model) mean risk difference = -0.01 (95%CI: -0.07 to 0.04). 2). Patient retention in treatment program: (heterogeneity detected, considering random-effect model) mean risk difference = -0.13 (95%CI: -0.21 to -0.04). 3). Compliance: (no heterogeneity, fixed-effect model used) mean risk difference= 0.04 (95%CI: 0.02 to 0.05)

The quality assessment of the systematic reviews

Questions	Score	Gowing, 2004[57]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 2	Sources: 1. Electronic: MEDLINE, EMBASE , PsycINFO, CINAHL. (Searched from commencement to July 2003). Reference lists of articles and hand-searched and conference abstracts. No specific action for retrieval of unpublished material.
Inclusion criteria reported (Q3)	2	Clearly defined types of studies (controlled before after, interrupted time and descriptive studies, participants (opiate injecting), intervention (substitution using agonists), and outcomes (HIV risk behaviours etc).
Selection bias avoided (Q4)	1	Two reviewers independently selected studies. It was not reported whether the reviewers were blinded to the identifying feature and the treatment outcome of the studies.
Validity criteria reported (Q5)	2	Used a formal quality assessment and scoring system steered by guidelines developed by the Cochrane Drugs and Alcohol Group and made appropriate for various study designs.
Validity for each study assessed appropriately (Q6)	2	Reported the quality assessment for each study addressing potential sources of bias and confounding likely in non-randomised study designs.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Data-analysis described for dichotomous and continuous outcomes in individual studies. Statistical heterogeneity amongst study effect sizes was not reported; considerable clinical heterogeneity amongst studies was remarked upon and no combined summary effect sizes were calculated. Not combining findings may appear over cautious in view of the fact that overall conclusions have been drawn from the ***"consistency"*** of the individual study estimates.
Conclusions supported by data (Q9)	2	This review examined if substitution treatment for injecting opioid addicts using an agonist reduced behaviours conducive to HIV infection (opioid injecting & needle sharing, multiplicity of sexual partners, condom use) and rate of seroconversion. Twenty-seven studies were classified as: RCTs (2), cohort (3), case-control (2) or descriptive (20) studies. In all studies methadone was used as the agonist substitute. Authors concluded that oral substitution (i.e. methadone) treatment: 1. significantly reduces injecting and needle sharing. 2. is associated with reduced multiplicity of sexual partners amongst injecting drug users and reduced exchange of drugs for money. 3. has little impact on condom use. 4. is associated with reduced seroconversion (HIV infection). The consistency of the individual study effect sizes supports the authors' conclusions. Meta-analysis with a random effects model would have been informative.

The quality assessment of the systematic reviews

Questions	Score	Griffith, 2000[58]
Search methods reported and comprehensive search (Q1 & Q2)	1 & 2	1. Electronic database: Search in subject indexes: MEDLINE, PSYCLIT, and PSYCINFO. Citation searches: Science Citation Index and Social Sciences Citation Index. 2. Footnote chasing 3. Hand searching journals 4. Consultation (networking with researchers) Language not mentioned. Years searched and search strategy were not clearly reported. Whether there was a language restriction was not reported.
Inclusion criteria reported (Q3)	2	Defined population (patients were receiving treatment in OMT (outpatient methadone treatment)), data type (outcome measure and statistics of outcomes), and study comparison (contingency management (CM) vs control groups, and pre- vs post-measures of CM group)
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	1 & 1	Effect size calculated and meta-analysis was conducted using a fixed-effects model, but heterogeneity existed.
Conclusions supported by data (Q9)	2	1. This review examines the question of the effectiveness of CM in outpatient methadone treatment (OMT). It included 30 studies. 2. Conclusion: contingency management is effective in reducing supplemental drug use for these patients. Significant moderators of outcomes included type of reinforcement provided, time to reinforcement delivery, the drug targeted for behavioural change, number of urine specimens collected per week, and type of subject assignment. These factors represent important considerations for reducing drug use during treatment. 3. Is the conclusion supported by data?

The quality assessment of the systematic reviews

Questions	Score	Hopfer CJ, 2002[59]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: 1. Electronic databases: MEDLINE, and Psych/INFO. 2. Reference lists. Years searched: not reported. Search strategy: using key words. Limited to English language.
Inclusion criteria reported (Q3)	2	Defined the types of the articles: reported on treatment studies or clinical characteristics of opiate-using adolescents or young adults, sample size (>20), etc.
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	No controlled trials were found by the review. The authors conducted narrative analysis of the descriptive studies and treatment studies without quantitatively pooling the results for those treatment studies where spare quantitative data was available. For the treatment studies, treatment and outcome measure differed from study to study.
Conclusions supported by data (Q9)	2	1. The review examines the question of clinical characteristics or treatments focussed on heroin-using youth. It included 9 treatment studies (reporting on treatment of heroin-using youth) and 5 descriptive studies. Of the 9 treatment studies, 6 reported methadone maintenance. 2. Conclusion stated: Descriptive studies of heroin-using youth demonstrate substantial poly-substance use and psychiatric co-morbidity. The largest treatment trial found that, of 4 different treatment modalities, methadone maintenance had the highest retention rate. For youth who stayed in treatment for at least 6 months, therapeutic communities or drug-free treatment resulted in better outcomes compared with methadone maintenance. Length of time in treatment, regardless of modality, was the best predictor of outcome. The rise of heroin among adolescents and young adults calls for descriptive studies as well as controlled treatment studies. 3. Is it supported by data? Due to no controlled trials being found in the review the authors made no definitive conclusion on effectiveness.

The quality assessment of the systematic reviews

Questions	Score	Hulse, 1998[43]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: Electronic: MEDLINE (1966-June 1996). Reference lists of obtained article. English language only.
Inclusion criteria reported (Q3)	2	Authors sought all published data on neonatal mortality associated with women using opiates. Only *post hoc* reasons for study exclusion described.
Selection bias avoided (Q4)	0	No information reported.
Validity criteria reported (Q5)	1	No clear criteria identified however authors remark that none of the primary studies had adjusted for confounding.
Validity for each study assessed appropriately (Q6)	0	Studies were not assessed according to described criteria.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Meta-analysis methods described for dichotomous outcomes in case control studies (odds ratio using Mantel Haenszel for 5 of 6 meta-analyses and random effects for one) performed in statistical package Egret. Statistical heterogeneity amongst study effect sizes was estimated; Combining of findings appears appropriate.
Conclusions supported by data (Q9)	2	This review examined whether heroin use and methadone maintenance, either singly or in combination, influenced neonatal mortality amongst pregnant opiate users. Seven case control studies were identified and used in meta-analyses. Authors concluded that the increased risk of neonate mortality seen in women using methadone and heroin (RR = 6.37 *CI 2.6 to 14.7*) relative to those using methadone alone (RR = 1.75 *CI 0.6 to 4.6*) is probably due to "*chaotic life style*" associated with illicit drug use rather than use of heroin *per se. (life style factors: poor nutrition, STDs & other illness etc)* This appears an unsupported conclusion since no data about life style was taken into account in the analyses.

The quality assessment of the systematic reviews

Questions	Score	Johansson, 2003[60]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: 1. Electronic: (1). Searched MEDLINE year 1966 through 2000 using search terms 'alcohol', 'substance use', and 'RCT'. (2). The Cochrane Library. 2. Reference lists in published articles and reviews. Unknown whether grey literatures were searched. In the 'included studies' but not the 'search strategy and method' section, it indicated that a compilation of unpublished articles were also included. Unknown whether there was a language restriction.
Inclusion criteria reported (Q3)	0	Included trials examining drug therapy for opioid dependence. Formal criteria not reported.
Selection bias avoided (Q4)	0	Not reported.
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Meta-analysis for primary outcome measures of abuse and retention was conducted and where heterogeneity tested was positive random model was used.
Conclusions supported by data (Q9)	2	1. The review attempted to answer the question whether maintenance treatment has an effect on opioid dependence. It included 69 RCTs, 3 meta-analyses, 5 reviews, 2 non-randomised studies, and a compilation of unpublished articles. Of the 69 RCTs, 1 was in buprenorphine vs placebo and 2 were in methadone vs placebo, 9 were in methadone vs LAAM, 6 in methadone vs buprenorphine. 2. Conclusion stated, and is it supported by data? 1). Buprenorphine is superior to placebo in reducing abuse (d = 0.44, CI: 0.00, 0.89) but has little effect on retention (d = 0.13, CI: - 0.31, 0.57). 2). Maintenance treatment with agonists (including partial) is effective. Compiling the studies of both buprenorphine and methadone vs placebo: in reducing abuse: d =0.55 (CI 0.44, 0.67), d = 0.62 (CI 0.40, 0.84); retention: d =0.75 (CI 0.63, 0.87), d (random model) = 0.81 (CI 0.45, 1.17). 3). Methadone has the same effect as LAAM on abuse (d = -0.06, CI: -0.19, 0.06), but is superior on retention (d = 0.34, CI: 0.22, 0.46). 4). There were no differences between methadone and buprenorphine in terms of primary outcome measures (on abuse d = 0.13, CI: – 0.33, 0.28; on retention d = 0.00, CI: -0.15, 0.16). 5). Methadone at higher dose was superior on abuse and retention: 80-100mg vs 50mg on abuse d =0.28 (0.10, 0.46), on retention d =0.25 (0.07, 0.43); 50-80mg vs 20-45 mg on abuse d=0.36 (0.23, 0.49), on retention d= 0.30 (0.17, 0.43). Buprenorphine 16mg v. 8mg per day had no difference on primary outcome measures but 8-16mg is superior to 1-4 mg on abuse (d=0.25, CI: 0.15, 0.35) and retention (d= 0.21, CI: 0.12, 0.31).

The quality assessment of the systematic reviews

Questions	Score	Kirchmayer, 2003[61]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 2	Sources: 1. Electronic: MEDLINE (1973-first year of naltrexone use in humans-July 2000), EMBASE (1974-July 2000), Cochrane Controlled Trials Register (Cochrane Library issue 2001. 4). 2. Hand search, personal contact, pharmaceutical industry contact, etc. Drugs and alcohol Group search strategy was used and presented. Clear from included studies, but not stated. There was little / no language restriction.
Inclusion criteria reported (Q3)	2	Clearly defined types of studies (RCTs and CCTs), participants (patients dependent on heroin, or former heroin addicts dependent on methadone and participating in a naltrexone treatment programme), intervention (oral naltrexone alone or together with other pharmacological or behavioural treatments), control (placebo, or pharmacological treatments except naltrexone, etc.), and outcome measures.
Selection bias avoided (Q4)	1	Two reviewers independently assessed each potentially relevant study. Not stated if reviewers were blinded to the identifying features and the treatment outcome of the studies.
Validity criteria reported (Q5)	2	Quality criteria were reported and the quality items were identified.
Validity for each study assessed appropriately (Q6)	2	Each included study was assessed using the quality items from the criteria.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Meta-analysis (OR & WMD) was restricted to 2 or 3 of 11 included studies because of heterogeneity. Descriptive analysis was used for the remaining studies and outcomes.
Conclusions supported by data (Q9)	2	The review examined the question of the effects of naltrexone maintenance treatment in prevention relapse in opioid addicts after detoxification. It included 11 studies of which only one study was relevant to our review. The conclusion of this was that methadone retained patients in treatment significantly better than did naltrexone. Authors concluded that evidence did not allow final evaluation of naltrexone and there was a trend in favour of naltrexone for certain groups of patients. These conclusions appear to be supported by the data.

The quality assessment of the systematic reviews

Questions	Score	Layson-Wolf, 2002[62]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: 1. Electronic: MEDLINE (Jan 1966 [1996 presumed misprint] to May 2001). Reference lists of articles. Search terms defined.
Inclusion criteria reported (Q3)	0	Not clearly defined (i.e. "*studies relevant to the topic"*).
Selection bias avoided (Q4)	0	No information provided.
Validity criteria reported (Q5)	0	No formal criteria were defined.
Validity for each study assessed appropriately (Q6)	0	Individual studies described but studies were not assessed for their validity.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	0 & 1	Narrative methods were used but were not described. Meta-analysis methods for combining findings were not considered.
Conclusions supported by data (Q9)	0	This review summarised the methadone literature on many fronts including analgesia, opiate dependence, and pharmacokinetics. With regard to methadone maintenance therapy for opioid dependent patients the authors do not arrive at clearly articulated concrete conclusions other than that individualised dosing and evaluation would be the best way to ensure safe use. The data presented do not directly bear on this.

The quality assessment of the systematic reviews

Questions	Score	Lintzeris N, 2004 [63]
Search methods reported and comprehensive search (Q1 & Q2)	1 & 1	Sources: "two Cochrane reviews facilitated the process of identifying relevant research regarding the efficacy of BPN for maintenance and detoxification treatment, respectively. A systematic literature search was conducted using PubMed to identify key papers published. Literature searches were also conducted using keywords relevant to specific topics."
Inclusion criteria reported (Q3)	0	Not reported
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	0 & 0	For the part of the paper which is relevant to our review, the results were descriptively reporte. It was not mentioned why the results were not quantitatively pooled.
Conclusions supported by data (Q9)	1	1. The paper aimed to review the evidence regarding the use of BPN in the management of opioid dependence, in the target audiences of commissioners and clinicians working in the field; in critical deficiencies or 'gaps' in the available evidence; and in the key clinical recommendations arising from the evidence review. It consists of 3 parts: evidence base regarding the use of BPN, recommendations regarding clinical practice, and issues regarding treatment dissemination and uptake. Only the use of BPN for maintenance in the first part of this paper is relevant to our review question, and it had 5 RCTs in BPN versus placebo, and 11 RCTs in BPN versus methadone. 2. Conclusion stated and relevant to our review: 1). BPN maintenance significantly is more effective than placebo therapy, and at high doses it is more effective than at lower doses. 2). High dose methadone is more effective than 'medium' or 'low' dose BPN, while methadone and BPN are comparable at 'medium' dose and 'low' dose. 3. Is it supported by data? 1). BPN groups had statistically superior outcomes in retention rate, heroin or other drug use, improvements in well-being and life satisfaction, and opiate free urines (with quantitative data and p values given for most of these). With regard to different doses of BPN, there were no quantitative data given. 2). -- The findings of flexible dose studies: treatment retention for methadone vs BPN: RR= 0.82, 95% CI 0.69 -0.96, p=0.01. --- The retention for 50 mg methadone vs 5 mg BPN: 59% vs 84%, p=0.001. --- With regard to that methadone and BPN are comparable at both 'medium' dose and 'low' dose, no quantitative data but only p values were given.

The quality assessment of the systematic reviews

Questions	Score	Marsch, 1998 [64]
Search methods reported and comprehensive search (Q1 & Q2)	1 & 1	Sources: MEDLINE, PSYCLIT and PSYCINFO databases; and cross-referencing procedures. Published in English language from 1965. (The end date was not reported). Search strategy was not reported.
Inclusion criteria reported (Q3)	2	Including studies published in English language from 1965. Described population (heroin dependents), intervention (MMT), and comparator (not in treatment).
Selection bias avoided (Q4)	0	Apparently one reviewer selected studies, but performed the procedure twice.
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported. How study design might influence study effect sizes, thereby revealing potential biases, was explored statistically.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Extensive description of meta-analytic procedures was provided. Summary estimates by outcome appear acceptable when viewed in the context of the review questions. Heterogeneity of studies was statistically significant for all summary estimates and a random effects model may have been more appropriate than the fixed inverse variance method used. Data from studies with both a comparator and time series design types were included in the meta-analysis. Some might consider that the combination of clinical heterogeneity and statistical heterogeneity amongst the combined studies was such as to preclude sensible combination of results.
Conclusions supported by data (Q9)	2	1. This review did not clearly report the number of studies included, but described that 11, 8, and 24 studies investigated the effect of MMT on illicit opiate use, HIV risk behavior and criminal activities, respectively (some of studies were identical). Of the included studies, some were comparing MMT with a no treatment comparator and some of them compared pre- and post treatment. 2. Conclusion: The treatment effectiveness of MMT is evident among opiate-dependent individuals across a variety of contexts, cultural and ethnic groups, and study designs. 2. Evidence: Estimated summary effect size of MMT in reducing IDU : r = 0.351 *(d = 0.75)* (mean); 0.185 *(d = 0.38)* (weighted FE) Estimated summary effect size of MMT in reducing HIV risk behaviours: r = 0.217 *(d = 0.44)* (mean); r = 0.18 *(d = 0.37)* Estimated summary effect size of MMT in reducing criminal behaviours: r = 0.25 *(d = 0.52)* (mean); r = 0.16 *(d = 0.33)*. *Recalculating summary effect sizes using random effects model (MetaWin software) yields: IDU r = 0.29 (95% CI 0.17 to 0.40); HIV risk r = 0.18 (0.12 to 0.24); crime r = 0.21 (0.15 to 0.27)*

The quality assessment of the systematic reviews

Questions	Score	Mattick RP, 2003[65]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: 1. Electronic databases: Cochrane Drugs and Alcohol Review Group Register, the Cochrane Controlled Trials Register, MEDLINE, MEBASE, Current contents, Psychlit, CORK, etc. 2. Proceedings and reference lists 3. Unpublished RCTs. Years searched: up to 2001. Search strategy with filters was clearly defined. Did not report whether there was a language restriction.
Inclusion criteria reported (Q3)	2	Clearly defined the study design, population (opioid dependent), intervention (MMT) and outcome measures.
Selection bias avoided (Q4)	1	Two reviewers independently assessed the studies for inclusion. Blinding to selection was not reported.
Validity criteria reported (Q5)	2	Criteria of methodological quality assessment for randomisation procedure and the likelihood that randomisation was not biased was defined.
Validity for each study assessed appropriately (Q6)	2	Aspects of blinding, concealment of allocation, and sample sizes were considered for each of the studies.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Standardised effect size (relative risk) was calculated for each study. Meta-analysis was performed. A random effects model was used for meta-analysis where the test for heterogeneity was significant.
Conclusions supported by data (Q9)	2	1. The review examined the question of the effects of methadone maintenance treatment (MMT) compared with treatments that did not involve opioid replacement therapy for opioid dependence. It included 6 studies. 2. Authors' conclusion: Methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy. It does not show a statistically significant superior effect for criminal activity. The overall estimate of effect sizes were in favour of methadone: patient retention in the treatment from 3 RCTs for MMT compared with non-pharmacological approaches: RR = 3.05; 95% CI: 1.75-5.35. In suppression of heroin use from 3 RCTs: RR = 0.32; 95% CI: 0.23-0.44. In criminal activity from 3 RCTs: RR=0.39; 95% CI: 0.12-1.25. Therefore data supports the conclusions.

The quality assessment of the systematic reviews

Questions	Score	Mattick RP, 2003 updated 2005[66]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 2	Sources: 1. Electronic: Cochran Library, MEDLINE, EMBASE, , Current Contents. Psychlit, CORK, ADCA, ADF-VIC, CEIDA, ABN, etc., including proceedings. 2. Reference lists of all identified studies and published reviews. 3. Unpublished relevant RCT Databases searched up to 2001, inclusive. Relevant search strategy and terms and filters were described. It was not stated whether there was a language restriction or not.
Inclusion criteria reported (Q3)	2	Identified the types of studies, participants (dependent on heroin or other opioids), intervention (Buprenorphine maintenance therapy compared with methadone maintenance therapy or placebo), and types of outcome measures.
Selection bias avoided (Q4)	1	Three reviewers independently assessed each potentially relevant study for inclusion. Reviewers were not blinded to identifying features and the treatment outcome of the studies.
Validity criteria reported (Q5)	2	Criteria were reported with identified quality items.
Validity for each study assessed appropriately (Q6)	2	Each study was assessed using the quality items.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	A standard effect size by outcome was calculated for each study. For dichotomous outcomes (retention data) RR and 95% CI were calculated and combined through a random effect model. Standardised mean difference was calculated for continuous outcomes and combined using fixed or random effects model as appropriate.
Conclusions supported by data (Q9)	2	1. The review examined the question of the effects of buprenorphine maintenance against placebo or methadone maintenance in retaining patients and in suppressing illicit drug use. 2. Conclusion stated: Buprenophine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is not more effective than methadone at adequate dosages. Only high and very high doses of buprenorphine suppressed heroin use more than placebo. 3. Is it supported by data? 1). Buprenorphine given in flexible doses vs methadone in retaining patient in treatment: RR= 0.82; 95% CI: 0.69-0.96. 2). High dose buprenorphine vs high dose methadone in retention: RR= 0.79; 95% CI: 0.62-1.01. 3). Buprenorphine vs placebo in patients in treatment at low doses: RR=1.24; 95% CI=1.065-1.45, high doses: RR=1.21; 95% CI=1.02-1.44, and very high doses: RR=1.52; 95% CI=1.23-1.88.

The quality assessment of the systematic reviews

Questions	Score	Prendergast, 2000[67]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 2	Many databases searched 1965-1996 (MEDLINE, Current Contents, PsycINFO and others.) Bibliographies were searched, researchers contacted, grey literature & unpublished literature sought. Search strategy stated. Studies restricted to North American in English.
Inclusion criteria reported (Q3)	2	Extensive criteria clearly defined.
Selection bias avoided (Q4)	0	Not mentioned or discussed.
Validity criteria reported (Q5)	1	No formal quality assessment tool described. Studies were explicitly separated according to study design (comparative or single group studies) and their relative robustness considered.
Validity for each study assessed appropriately (Q6)	1	No validity criteria described. Statistical analysis of the potential influence of "*investigator allegiance*" leading to bias in effect size estimates.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Extensive description of meta-analytic procedures provided. Summary estimates by outcome (drug abuse and crime) appear acceptable when viewed in the context of the review questions. Heterogeneity of study effect sizes was statistically significant and a random effects model (as well as fixed effects) was used. *[Combined Studies exhibited considerable heterogeneity both statistical and clinical (different interventions, populations and outcome measures); several methadone studies (6) were omitted because drug abuse measures did not include opiates].*
Conclusions supported by data (Q9)	1	1. The review attempted to identify elements of drug dependence treatment programmes that were associated with larger effect size (ES) for prevention of illicit drug abuse and of criminality. One hundred and forty three studies of various interventions and study designs were included. 2. ES (SMD) for methadone studies was provided but no confidence intervals or ***p*** values given & no results statistical test for heterogeneity were reported. SMD for methadone studies were: *Comparator group design.Single group design* *Drug abuse0.49 (8 studies)1.48 (22 studies)* *Criminal activity0.17 (3 studies)0.8 (16 studies)* SMD as the outcome parameter is difficult to interpret in terms of a real effect. With regard to methadone studies the authors concluded from weighted correlation analysis that ES correlated with: decade of study (older studies larger ES), methadone dose (bigger dose larger ES), strength of implementation (stronger implementation smaller ES), and treatment retention (longer treatment larger ES). These conclusions are compromised because correlations were all weak (p values usually > 0.05), often contradictory in direction according to study design, and because of missing data (a considerable proportion of studies lacked usable data, a situation likely to result in bias in estimate of correlation). The transferability to UK programmes is likely limited as all studied programmes operated in a North American setting.

The quality assessment of the systematic reviews

Questions	Score	Prendergast, 2002[68]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: 1. Search online bibliographic database: Current Contents (Social and Behavioural Sciences), Dissertation Abstracts, ETOH (Alcohol and Alcohol Problems Science database), GPO Monthly Catalog, Magazine and Newspaper Index, MEDLINE, NTIS, PsychINFO, PAIS, Sociological Abstracts, and Social Work Abstracts. 2. Checking printed sources. 3. Requests to colleagues and organizations. 4. Unpublished papers. An initial search and two update searches 12 and 18 months later were conducted. Years of the database searched were not reported. Search strategy was not reported.
Inclusion criteria reported (Q3)	2	Defined intervention (which was directed toward changing the drug use and /or related behaviours or attitudes of illicit drug users population (18 or older)), the condition of intervention, comparison condition, setting (US or Canada), outcome data (quantitative outcome variables), and study type (e.g. design). Data of the document reporting the study was between 1965 and 1996 (inclusive); English language only; including grey literature *(these were not stated in the search but in the selection criteria).*
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Effect sizes from each individual study werepresented in a stem-and leaf plot. Meta-analysis was conducted for drug use and crime using both fixed and random-effect model. Heterogeneity was tested.
Conclusions supported by data (Q9)	2	1. The aim of this review was to determine the effectiveness of drug abuse treatment programmes and what programme elements modify effect size. The number of studies included in the review was not clear (78 studies in drug use and 25 studies in crime, but it is not clear whether the numbers overlapped). It does not answer the question of the effectiveness of either methadone maintenance alone or buprenorphine maintenance alone. 2. Conclusion stated: Drug abuse treatment is effective in reducing drug use and crime in the US. Effect sizes were associated with the moderating and mediating variables reported in the original studies. 3. Is it supported by data? The fixed effects weighted mean (95% CI): for drug use 0.30 (0.25, 0.35), for crime 0.13 (0.04, 0.21). The random effects weighted mean (95% CI): for drug use 0.33 (0.25, 0.42), for crime 0.13 (-0.004, 0.27).

The quality assessment of the systematic reviews

Questions	Score	Raisch, 2002[69]
Search methods reported and comprehensive search (Q1 & Q2)	1 & 1	1. Electronic database: MEDLINE and HEALTHSTAR (1966 to Nov 2000). 2. 'Secondary' and 'Tertiary' sources were also searched, but it is not clear what do the authors refer to by these. No search strategy reported. Whether there was a language restriction was not reported.
Inclusion criteria reported (Q3)	2	There were no formal criteria. According to the abstract, the selection of studies was restricted to published ones only. Defined the treatment (buprenorphine/naloxone), population (patients with opioid dependence (OD)), study design (RCT involving head-to head comparisons of active treatments or active/placebo comparisons), and pharmacisits' activities in the treatment and prevention of OD.
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 and Q8)	1 & 0	Narrative analysis of the results without a combination of quantitative data. The was quantitative data for a few of the studies described in the review, but it is not clear whether these studies were those included by the review's search, or just cited by the review in the text.
Conclusions supported by data (Q9)	1	1. This review aimed to investigate opioid dependence (OD), its treatment, and the use of buprenorphine with naloxone as a treatment alternative for OD. But it is not clear how many studies were included by the review. 2. Conclusion stated: OD is a critical unmet health problem in the US. Buprenophine combined with naloxone represents an innovative treatment for OD in outpatient settings. This new treatment has advantages over MMT. 3. Is conclusion supported by data? The results of clinical effectiveness were reported in a narrative account of several studies without a quantitative synthesis. It is difficult to determine if conclusions are justifiable.

The quality assessment of the systematic reviews

Questions	Score	Roozen, 2004[70]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: 1. Electronic databases: Biological Abstracts, ERIC, LISA, OSH, Periodical Abstracts, PsycINFO, SERFILE and Sociological Abstracts; EMBSE, MEDLINE and CINAHL. Screening the Cochrane Library, 2002, issue 1. 2. Screening of reference lists. 3. No grey literature searches were reported. Years of the databases searched were from the date of commencement. Search strategy was of the UK Cochrane Centre, run in conjunction with a specific search that included combinations of the key words. Searches were restricted to RCTs published in English language only.
Inclusion criteria reported (Q3)	2	Clearly defied the study design (RCT), participants (alcohol, cocaine and opiate abuse or dependence aged 18-65 years, etc), interventions (community reinforcement approach (CRA) with pharmacological maintenance treatment, e.g. methadone; etc.), and outcome measures.
Selection bias avoided (Q4)	1	Two reviewers independently selected the trials to be included without blinding to the identification of the studies.
Validity criteria reported (Q5)	2	The criteria used (issued by the Cochrane Back Review Group) and modification to the criteria was described.
Validity for each study assessed appropriately (Q6)	2	The criteria were applied to each study and the result was presented.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	A meta-analysis of the same variables and separate meta-analyses for the effects of different treatment durations were performed using random effects model. A qualitative analysis was also performed using a four-level rating system for strength of the scientific evidence.
Conclusions supported by data (Q9)	2 & 2	1. The review examined the question of the effectiveness of community reinforcement approach (CRA) compared with usual care and CRA versus CRA plus contingency management. It included 11 studies of which two were opioid studies; of these two studies, only one study which compared CRA with usual care in a methadone maintenance program was relevant to our review question. 2. Conclusion stated (relevant to our review topic): There is limited evidence that community reinforcement approach is more effective in a methadone maintenance program. 3. Is it supported by data? In the study compared of single CRA versus usual care in a methadone maintenance program, in the long term (>16 weeks) CRA was significantly more effective than the usual care, based on the consecutive (3 weeks) opiate-negative urine analysis (84% vs 78%) and the 6-month ASI composite scores; but no confidence intervals and p value were given.

The quality assessment of the systematic reviews

Questions	Score	Simoens, 2005[71]
Search methods reported and comprehensive search (Q1 & Q2)	2 &1	Sources: 1. Electronic database: MEDLINE, PsycINFO, CINAHL, SSCI, the Lindesmith Library database, the controlled Trials Register of the Cochrane Library, ASSIA, EBSCO, and the British Library Catalogue. 2. Grey literature. Years searched were from 1990 to 2002. Search strategy was reported. English language only.
Inclusion criteria reported (Q3)	2	Defined study design, intervention (administration of methadone or buprenorphine maintenance treatment, etc.) and its setting, control (pharmacological treatment, placebo, or have no treatment), population (opioid dependence, not clearly defined in the criteria but can be seen from the text of the review), and the outcome measure.
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	2	Criteria outlined by Cochrane Collaboration. The quality items were defined.
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Because of the heterogeneity of primary studies as evidenced by the lack of uniformity in study design, participants, administered doses of methadone or buprenorphine, duration of maintenance treatment, and methods of reporting outcomes, a meta-analytic approach was abandoned in favour of a descriptive review.
Conclusions supported by data (Q9)	2	1. This review examines the question of the effectiveness of community maintenance programmes with methadone or buprenorphine in treating opiate dependence. 2. Conclusion stated: The literature supports the effectiveness of substitute prescribing with methadone or buprenorphine in treating opiate dependence. Provision of methadone or buprenorphine by primary care physicians is feasible and may be effective. 3. Is the conclusion supported by the data? Data from the studies showed a tendency that higher doses of methadone and buprenorphine are associated with better treatment outcomes. Low-dose methadone is less effective than buprenorphine. Higher doses of methadone are slightly more effective than buprenorphine. There was some evidence that primary care could be an effective setting to provide this treatment, but such evidence was sparse. These differences were not statistically proven.

The quality assessment of the systematic reviews

Questions	Score	Simoens, 2002[43]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 2	Sources: 1. Electronic database: MEDLINE, PsycINFO, CINAHL, SSCI, the Lindesmith Library database, the controlled Trials Register of the Cochrane Library, ASSIA, EBSCO, and the British Library Catalogue. 2. Grey literature. Years searched were from 1990 to 2002. Search strategy was reported. English language only.
Inclusion criteria reported (Q3)	2	Defined study design (controlled & before-after studies etc), intervention (community maintenance or detoxification and residential rehabilitation programmes), population (opioid dependence), and outcome measures illicit drug use, retention in treatment and others). Reviews also included.
Selection bias avoided (Q4)	1	Two reviewers independently applied inclusion criteria.
Validity criteria reported (Q5)	2	Criteria outlined by Cochrane Collaboration and CASP guidelines. The quality items were defined.
Validity for each study assessed appropriately (Q6)	1	A summary of quality of included studies provided rather than individual analysis study by study.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	1 & 1	Method for narrative combination of study results sketchy, there was a lack of use of quantitative data in drawing conclusions (although quantitative data was presented in extensive appendices).
Conclusions supported by data (Q9)	2	This review aimed to identify and appraise the strength and direction of evidence about the effectiveness of treatment programmes for opioid dependent patients and to identify programme factors that influence outcomes. One hundred and forty one studies were included. The authors concluded the effectiveness of methadone, buprenorphine (& LAAM) were well established but transferability to a UK setting requires caution. Some evidence supported the proposition that higher doses of methadone & buprenorphine were associated with better treatment outcomes, and that provision of methadone in primary care (as distinct from specialist clinics) was effective. Although the data may well support these conclusions the link between quantitative data and the conclusions drawn by the authors was not clear from their narrative treatment of the evidence

The quality assessment of the systematic reviews

Questions	Score	Sorensen JL, 2000[73]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: 1. Electronic databases: MEDLINE, and Psych/INFO, 2. Reference lists. Years searched: 1988-1998. Search strategy: using key words. Restricted to English language only.
Inclusion criteria reported (Q3)	1	No formal inclusion/exclusion criteria. Defined type of study (studies published and describing empirical research) and type of publication (peer reviewed journals).
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported
Methods for combining reported and findings combined appropriately (Q7 & Q8)	2 & 2	Narrative analysis. There is no quantitative data for all the studies except two.
Conclusions supported by data (Q9)	1	1. This review examines the question of drug abuse treatment as a means of preventing infection with HIV and included 33 studies. 20 of these studies included MMT, and 11 of them focused solely on MMT. 2. Conclusion stated: the accumulated research provides sufficient evidence to conclude that MMT is a powerful tool to protect IDUs against HIV seroconversion. 3. Is it supported by data? The authors reported results mostly in a narrative account. It is difficult to determine if conclusion is justifiable without accessing the primary data.

The quality assessment of the systematic reviews

Questions	Score	Stanton, 1997[74]
Search methods reported and comprehensive search (Q1 & Q2)	1 & 1	Sources: 1. Three earlier reviews. 2. The database compiled by William R. Shadish who had devoted considerable resources to locating the published and unpublished family-couples outcome studies. Included a computer scan of the bibliography from the search plus an update of the computerized searches of *Dissertation Abstracts International and Psychological Abstracts.* 3. Ongoing communications over the past 25 years between the first author of this review and colleagues. Unknown the years of the database searched. No search strategy was reported. Unknown whether there was a language restriction.
Inclusion criteria reported (Q3)	2	Defined the symptom of primary interest (use-abuse of, or addiction to, one or more illicit drugs), study type (two or more comparison-control conditions, at least one of which involved some form of family or couples-marital therapy), and study design (– random assignment of participants.)
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	2	Used a rating system and a revised design quality scale. The quality items defined were: whether the therapists in all conditions are of equal experience and are competent to deliver the treatment; whether the compared treatments are equivalent in terms of their length and the extent to which they are valued, whether the researcher is also a therapist within the study, etc)
Validity for each study assessed appropriately (Q6)	2	Assessed the studies using the above quality criteria.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	1 & 0	A meta-analysis of substance abuse outcomes was conducted. Details of the methods were not reported.
Conclusions supported by data (Q9)	1	1. The review synthesized drug abuse outcome studies that included a family-couple therapy treatment condition. It included 15 studies of which 4 studies had methadone maintenance treatment. 2. Conclusion stated (and relevant to our review): family therapy is as effective for adults as for adolescents and appears to be a cost-effective adjunct to methadone maintenance. 3. Is it supported by data? Drugs use: family-couple therapy vs non-family therapy or alternative interventions: self reported d=0.48, Dod=0.43, Tad=0.43. With adults: family-couple therapy vs another form of treatment or intervention: self reported d=0.42, DOd=0.50, Tad=0.48. With adolescents: family-couple therapy vs another form of treatment or intervention: self reported d=0.39, DOd=0.39, Tad=0.40.

The quality assessment of the systematic reviews

Questions	Score	West SL, 2000[76]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 1	Sources: 1. Electronic databases: MEDLINE and PsychInfo. 2. Reference lists. It is not reported whether unpublished and grey literatures were searched. No time limit was constrained on the search. Searches used subject headings e.g. buprenorphine, opiate, etc. It was not reported whether there was a language restriction.
Inclusion criteria reported (Q3)	2	Formal criteria were reported. Defined comparison and participants (buprenorphine vs methadone in treatment of opiate addiction), etc.
Selection bias avoided (Q4)	0	Not reported
Validity criteria reported (Q5)	0	Not reported
Validity for each study assessed appropriately (Q6)	0	Not reported. Assessed effect size of the studies.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	1 & 2	A meta-analysis was conducted. An effect size based on the number of individuals who had and had not tested positive for illicit use was calculated. It did not report whether random model or fixed model was used.
Conclusions supported by data (Q9)	2	1. This review's aim was to quantitatively compare the effectiveness of buprenorphine and methadone. It included 9 studies. 2. Conclusion stated: Findings suggest a relative equality in the efficacy of buprenorphine and methadone, although patients receiving methadone were less likely to test positive for illicit opiate use. Past experience with methadone maintenance acted as a moderation variable, however, such that those receiving buprenorphine were more likely to stay drug-free in studies that included patients with prior methadone experience. 3. Is it supported by data? The average un-weighted mean effect size across all studies was r= -0.0460 (d= -0.0921) (methadone vs buprenorphine). A test of heterogeneity indicates that the effect sizes are not homogenous across studies ($p<0.001$). Four of the studies were available for focused tests to assess whether individual study characteristics were acting as moderating variables and contributing to the differentiation across studies, and the results were significant ($Z=3.99$, $p<0.01$).

The quality assessment of the systematic reviews

Questions	Score	Van Beusekom 2001[75]
Search methods reported and comprehensive search (Q1 & Q2)	2 & 2	Sources: Cochrane Library, MEDLINE, EMBASE, Psychinfo, Socialscisearch and others. Searched from 1995 to 2001. Few language restrictions.
Inclusion criteria reported (Q3)	2	Broad inclusion criteria for the literature about methadone
Selection bias avoided (Q4)	0	Methods to avoid bias not mentioned.
Validity criteria reported (Q5)	2	Criteria for RCT quality clearly defined.
Validity for each study assessed appropriately (Q6)	0	There was little or no reference to study quality in the narrative text of this TAR and no appendix provided that might contain such information.
Methods for combining reported and findings combined appropriately (Q7 & Q8)	1 & 1	Narrative methods used. The authors state "*Priority is given to studies of higher study quality; these studies are described more elaborately and have received more weight in the concluding chapter*". However unfortunately the text does not allow the unequivocal identification of these studies and no formal quality assessment of studies appears to have been carried out despite the provision of the quality assessment criteria to be used.
Conclusions supported by data (Q9)	1	The review examined many aspects of methadone treatment and focussed on: adequate dosing; efficacy as a substitution drug, and the role of additional psychosocial treatments and the optimum duration of treatment. The authors reviewed a large number of primary studies and several systematic reviews however the link between quantitative data in these studies and the conclusions drawn is not clearly delineated.

Appendix 7 Quality assessment of RCTs

Author	*Ahmadi 2003b*[77]	*Ahmadi 2003c*[78]	*Ahmadi 2003*[79]	*Brooner 2004*[82]	*Jones 2001*[91]	*Pollack 2002*[99]
	Jadad score	**Jadad score**	**Jadad score**	**Jadad score**	**Jadad score**	**Jadad score**
Was assignment of treatment described as random?	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**
Was method of randomisation well described & appropriate?	No**0**	No**0**	No**0**	No **0**	Yes**1**	No**0**
Was the method really random?	Unlikely. No method described arm balance too even.	Unlikely. No method described.	Unlikely. No method described arm balance too even.	Can't tell no method described	Possible; "selection of one of two colour chips from a hat with replacement".	Block randomisation was done but no methods described.
Was allocation concealed & concealment method described?	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Was study described as double blind?	No**0**	No**0**	Yes**1**	No**0**	No **0**	No**0**
Who was blinded?	NA	NA	NA	NA	NA	NA
Was method of blinding adequately described?	NA**0**	NA**0**	No**0** Blinding method not described	NA**0**	NA **0**	NA**0**
Were withdrawals stated?	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**
SCORE on Jadad sale	**2**	**2**	**3**	**2**	**3**	**2**
Comments	Like other trials by authors no randomisation method reported but perfect number balance between trial arms.	Like other trials by authors no randomisation method reported; number in trial arms was not reported. Neither were available after contact with author.	Like other trials reported by authors no randomisation method reported but perfect number balance between trial arms.	Not possible to blind contingency enhancement. Withdrawals considered to be accounted for here by reported counselling attendance analysis	Not possible to blind incentive treatment.	Small numbers resulted in imbalance after randomisation and led authors to many post hoc analyses.

Author	*Ritter 2003*[100]	*Marsch 2005*[98]	*Eder 2005* [88]	*Margolin 2003* [97]	*Lidz 2004* [95]	*Avants 2000*[80]
	Jadad score	**Jadad score**	**Jadad score**	**Jadad score**	**Jadad score**	**Jadad score**
Was assignment of treatment described as random?	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**
Was method of randomisation well described & appropriate?	Yes **1** Independent randomisation telephone service using dynamic balancing method.	No**0**	Yes **1** computer generated randomisation	Yes 1	No**0**	No**0**
Was the method really random?	Yes	Cant tell	Yes	Cant tell	Unlikely	Unlikely
Was allocation concealed & concealment method described?	Yes	No	Yes	No	No	Not stated
Was study described as double blind?	No**0**	Yes**1**	Yes **1**	Yes 1	No**0**	No**1**
Who was blinded?	NA	Patients, clinicians.	Patients, clinicians and assessors	Patients, clinicians.	Not applicable	Not applicable
Was method of blinding adequately described?	NA**0**	Yes **1** Placebo methods described	Yes **1** Placebo matched to treatments	Yes 1 Placebo matched pills	Not applicable**0**	Not applicable **0**
Were withdrawals stated?	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**
SCORE on Jadad sale	**3**	**4**	**5**	**5**	**2**	**2**
Comments	Open label trial.	*Not possible to blind contingency management Baseline characteristics of groups balanced	Double dummy cross-over RCT.	Data reported indicates blinding of patients was reasonably successful.	Baseline characteristics of groups balanced	Baseline characteristics of groups balanced

Author	*Van den Brink 2003*[103]	*Dijkgraff 2005* [86]	*Blanken 2004* [81]	*Sigmon 2004*[101]	*Zanis 2001*[102]	*Giacomuzzi 2001* [89]
	Jadad score			**Jadad score**	**Jadad score**	**Jadad score**
Was assignment of treatment described as random?	Yes**1**	This was an economic study based on the RCT of Van Den Brink 2003 The quality of this study is dealt with in the economics section of the report.	This was a prognostic study based on combination of data from the two trials reported by van den Brink 2003	Yes **1**	Yes **1**	Yes**1**
Was method of randomisation well described & appropriate?	Yes**1**			Yes **1**	**No 0**	No**0**
Was the method really random?	Probably			Probably	Cant tell	Cant tell
Was allocation concealed & concealment method described?	Not stated			Not stated	Not stated	Not stated
Was study described as double blind?	No **0**			No **0**	No **0**	No **0**
Who was blinded?	Not applicable			Not applicable	Not applicable	Not applicable
Was method of blinding adequately described?	Not applicable **0**			Not applicable **0**	Not applicable **0**	No **0**
Were withdrawals stated?	Yes **1**			Yes **1**	Yes **1**	No**0**
SCORE on Jadad sale	**3**			**3**	**2**	**1**
Comments	Randomisation stratified and performed by independent organisation.			Not possible to blind reinforcement interventions.	Baseline characteristics of groups balanced	Baseline characteristics of groups not adequately described, outcome measures only made at end of follow up not at baseline.

Author	*Chutuape 2001*[83]	*Cornish 2001*[84]	*Dean 2001*[85]	*Loftwall 2005*[96]
	Jadad score	**Jadad score**	**Jadad score**	**Jadad score**
Was assignment of treatment described as random?	Yes**1**	Yes**1**	Yes**1**	Yes**1**
Was method of randomisation well described & appropriate?	No**0**	No**0**	No**0**	No**0**
Was the method really random?	Unlikely	Unlikely	Unlikely	Unlikely
Was allocation concealed & concealment method described?	Not stated	Not stated	Not stated	Not stated
Was study described as double blind?	No **0**	Yes**1**	Yes***1**	Yes***1**
Who was blinded?	Open label	Patients, clinicians and assessors	Patients, clinicians and assessors	Patients, clinicians and assessors
Was method of blinding adequately described?	**0**	Yes – **1** identical placebo	Yes –**1** placebo identical	Yes – **1** identical method of administration
Were withdrawals stated?	No**0**	No**0**	No**0**	No**0**
SCORE on Jadad sale	**1**	**3**	**3**	**3**
Comments	Baseline characteristics of groups balanced		Baseline characteristics of groups balanced *Not described as 'double blind'	Baseline characteristics of groups balanced *Not described as 'double blind'

Author	*Dolan 2003*[165]	*Grabowski 2004*[90]	*Kosten 2003*[93]	*King 2003*[92]	*Kristensen 2005*[94]
	Jadad score	**Jadad score**	**Jadad score**	**Jadad score**	**Jadad score**
Was assignment of treatment described as random?	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**
Was method of randomisation well described & appropriate?	Yes – random draw from envelopes**1**	No**0**	No**0**	No**0**	No**0**
Was the method really random?	Yes	Unlikely.	Probably	Cant tell	Cant tell
Was allocation concealed & concealment method described?	No	No	No	No	No
Was study described as double blind?	No**0**	Yes**1**	Yes*__1__	No**0**	No**0**
Who was blinded?	Not applicable	Patients, clinicians and assessors	Patients, clinicians and assessors	Not applicable	Not applicable
Was method of blinding adequately described?	Not applica**0**	Yes **1** identical placebo	Yes – placebo **1**	Not applicable**0**	Not applicable**0**
Were withdrawals stated?	Yes**1**	Yes**1**	Yes**1**	Yes**1**	Yes**1**
SCORE on Jadad sale	**3**	**4**	**4**	**2**	**2**
Comments	Baseline characteristics of groups balanced	Authors combined 2 separately randomised control groups for analysis, may introduce bias.	*Not possible to blind contingency management Baseline characteristics of groups balanced		Baseline characteristics of groups balanced

Appendix 8 Quality assessment of economic studies

	Phillips Criteria	Barnett 1999	Zaric 2000a & 2000b	Zaric (2001)	Barnett (2001)	Zaric 2000&2005	Masson (2005)	Sheerin (2004)
	STRUCTURE							
1.	Is there a clear statement of the decision problem?	Y	Y	Y	Y	Y	Y	Y
2.	Is the objective of the model specified and consistent with the stated decision problem?	Y	Y	Y	Y	Y	Y	Y
3.	Is the primary decision maker specified?	Y	Y	Y	Y	Y	UC	Y
4.	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y	Y
5.	Are the model inputs consistent with the stated perspective?	Y	Y	Y	Y	Y	Y	Y
6.	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y	UC	Y	UC	Y
7.	Are the sources of the data used to develop the structure of the model specified?	Y	Y	Y	Y	Y	Y	Y
8.	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	Y	Y	Y	Y	Y
9.	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y	Y
10.	Have all feasible and practical options been evaluated?	Y	Y	Y	Y	Y	Y	Y
11.	Is there justification for the exclusion of feasible options?	Y	NA	NA	Y	NA	N	Y
12.	Is the chosen model type appropriate given the	Y	Y	Y	Y	Y	Y	Y

	Phillips Criteria	Barnett 1999	Zaric 2000a & 2000b	Zaric (2001)	Barnett (2001)	Zaric 2000&2005	Masson (2005)	Sheerin (2004)
	decision problem and specified casual relationships within the model?							
13.	Is the time horizon of the model sufficient to reflect all important differences between the options?	Y	Y	Y	Y	Y	Y	Y
14.	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	NA	Y	Y	NA	Y	NA (Markov model)	Y
15.	Is the cycle length define and justified in terms of the natural history of disease?	NA	NA	NA	NA (Time horizon has been justified)	NA	Y	UC
16.	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	Y	Y	Y (technical appendix is referred to)	Y	Y	Y
17.	Where choices have been made between data sources are these justified appropriately?	Y	Y	Y	Y	Y	Y	Y
18.	Where expert opinion has been used are the methods described and justified?	NA	NA	NA	Y (briefly)	NA	NA	NA
19.	Is the choice of baseline data described and justified?	Y	Y	Y	Y	Y	Y	Y
20.	Are transition probabilities calculated appropriately?	Y	Y	Y	Y	Y	UC?	UC
21.	Has a half-cycle correction been applied to both costs and outcomes?	Y	N	N	N	N	Y	N
22.	If not, has the omission been justified?	N	N	N	N	N	NA	
23.	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	NA	NA	NA	NA	NA	Y	N

	Phillips Criteria	Barnett 1999	Zaric 2000a & 2000b	Zaric (2001)	Barnett (2001)	Zaric 2000&2005	Masson (2005)	Sheerin (2004)
24.	Are the costs incorporated into the model justified?	Y	Y	Y	Y	Y	Y	N (Not fully justified)
25.	Has the source for all costs been described?	Y	Y	Y	Y	Y	Y	N (In part)
26.	Have discount rates been described and justified given the target decision maker?	Y	Y	Y	Y	Y	Y	Y
27.	Are the utilities incorporated into the model appropriate?	NA	Y	Y	Y	Y	Y	NA
28.	Is the source of utility weights referenced?	NA	Y	Y	N	Y	N	NA
29.	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	NA	NA	NA	NA	NA	NA	NA
30.	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	Y	Y	Y	Y	Y	NA
31.	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Y	Y	Y	Y	Y	Y	Y
32.	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	Y	N (reference has been made to previous publications)	Y	Y	N

	Drummond Adapted Criteria (Healey 2003)	S&B (1975)	Goldschmidt (1976)	Strang (2000)	M&Z (2003)	Doran (2003)	Doran (2004)	Harris (2005)
1.	Was a well-defined question posed in an answerable form?	Y	Y	N	Y	Y	Y	Y

2.	Was a comprehensive description of the competing alternatives given?	Y	Y	UC	Y	Y	Y	Y
3.	Was there evidence that the programmes effectiveness was established?	UC	Y	UC	Y	Y	Y	Y
4.	Were all the important and relevant costs and consequences for each alternative identified?	UC	Y	UC	Y	Y	Y	Y
5.	Were costs and consequences measured accurately in appropriate physical units?	UC	UC	Costs Y	Y	Y	Y	Y
6.	Were costs and consequences valued credibly?	UC	UC	Costs Y	Y	Y	Y	Y
7.	Were costs and consequences adjusted for differential timing?	N	N	N	Y	N	N	Y
8.	Was an incremental analysis of costs and consequences of alternatives performed?	N	Y	N	Y	Y	Y	Y
9.	Was allowance made for uncertainty in the estimates of costs and consequences?	N	N	N	Y	Y	N	Y
10.	Did the presentation and discussion of study results include all issues of concern to users?	N	N		Y	Y	Y	Y

Appendix 9 Treatment outcomes from overview of systematic reviews

Table 36 Proportion of individuals retained in treatment

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treat-ment (%)	Comp-arator (%)	Duration of follow up (weeks)	Relative risk (95% CI) (unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone vs. placebo/no therapy									
20-50mg vs. no therapy	Mattick (2003)[65]	3	505	RCT	68%	25%	26	3.05 (1.75 to 5.35) [R]	0.02
20-97mg vs. placebo	Farre (2002)[53]	2	348	RCT	54%	17%	15-32	3.91 (1.17 to 13.2) [R]*	0.001
35-97mg vs. no therapy&	Johansson (2003)[60]	6	1013	RCT/CCT	NR	NR	6-152	d:0.92 (0.54 to 1.29 [R]	<0.05
Buprenorphine vs. placebo/no therapy									
≤5mg	Mattick (2005)[66]	5	1131	RCT	60%	39%	16-24	1.50 (1.19 to 1.88) [R]	0.007
6-12mg	Mattick (2005)	4	887	RCT	65%	38%	17-52	1.74 (1.06 to 2.87) [R]	<0.0001
18mg	Mattick (2005)	4	728	RCT	63%	41%	4-52	1.74 (1.02 to 2.96) [R]	0.0001
Methadone dosages									
60-109mg vs. 1-39mg	Faggiano (2003)[52]	5	496	RCT	56%	41%	17-26	1.36 (1.13 to 1.63) [F]	0.0002
60-109mg vs. 1-39mg	Faggiano (2003)	1	140	RCT	35%	21%	52	1.63 (0.95 to 2.77)	NA
60-109mg vs. 40-59mg	Faggiano (2003)	2	347	RCT	80%	79%	7-13	1.01 (0.91 to 1.12) [F]	0.14
60-109mg vs. 40-59mg	Faggiano (2003)	3	560	RCT	57%	46%	27-40	1.23 (1.05 to 1.45)	0.19
40-57mg vs. 1-39mg	Faggiano (2003)	1	166	RCT	52%	41%	20	1.26 (0.91 to 1.75) [F]	NA
>110mg vs. 40-59mg	Faggiano (2003)	1	80	RCT	63%	38%	27	1.67 (1.05 to 2.66) [F]	NA
>110mg vs. 60-109mg	Faggiano (2003)	1	80	RCT	63%	65%	27	0.96 (0.69 to 1.34)	NA
High (≥50 mg) vs. low (<50mg)	Farre (2002)[53]	8	1041	RCT	55%	44%	15-40	OR 1.25 (0.94 to 1.67) [R]	0.13
80-100mg vs. 50mg	Johansson (2003)[60]	3	478	RCT/CCT	NR	NR	24-40	d 0.25 (0.07 to 0.43) [F]	>0.05
50-80mg vs. 20-45mg	Johansson (2003)	8	892	RCT/CCT	NR	NR	14-52	d 0.30 (0.17 to 0.43) [F]	>0.05

[F]: fixed effects meta-analysis [R]: random effects meta-analysis; **: analysis by this report authors; &: includes studies that provided of psychosocial treatment; d effect size; OR: odds ratio; NR: not reported; CCT comparative controlled trial..

Table 36 cont. Proportion of individuals retained in treatment

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow up (weeks)	Relative risk (95% CI) (unless otherwise indicated)	Hetero-geneity test (P-value)
Buprenorphine doses									
16 mg. vs. 8mg	Johansson (2003) [60]	1	370	RCT	NR	NR	16	d 0.18 (-0.03 to 0.38)	NA
8-16mg vs. 1-4mg	Johansson (2003)	6	1620	RCT	NR	NR	2-24	d 0.21 (0.12 to 0.31) [F]	>0.05
Methadone vs. buprenorphine									
50-80mg vs 6-12mg	Barnett (2001)[48]	5	540	RCT	NR	NR	16-26	HR 1.26 (1.01 to 1.57) [F]	0.088
20-100mg vs. 2-16mg	Davids (2004)[51]	4	NR	RCT/ CCT	NR	NR	NR	2/6 favoured B 1/6 favoured low dose M 2/6 M=B	NA
≥50mg vs. <8mg	Farre (2002)[53]	1	57	RCT	NR	NR	24	RR 2.72 (1.12 to 6.58)	NA
≥50mg vs. ≥8mg	Farre (2002)	5	529	RCT	NR	NR	17-24	RR 1.14 (0.83 to 1.59)	NR
<50mg vs. ≥8mg	Simeons (2005)[71]	4	NR	RCT	NR	NR	NR	3/4 M=B, 1/4 B>M	NA
<50mg vs. <8mg	Simeons (2005)	4	NR	RCT	NR	NR	NR	4/4 M>B	NA
≥50mg vs. ≥8mg	Simeons (2005)	4	NR	RCT	NR	NR	NR	1/4 M>B, 1/4 B=M	NA
≥50mg vs. <8mg	Simeons (2005)	3	NR	RCT	NR	NR	NR	2/3 M>B, 1/4 B=M	NA
flexible vs. flexible	Simeons (2005)	2	NR	RCT/	NR	NR	NR	1/2 M>B, 1/4 B=M	NA
20-100mg vs. 2-12mg	Johansson (2003)[60]	6	648	CCT	NR	NR	NR	d 0.00 (-0.15 to 0.16) [F]	>0.05
flexible vs. flexible	Mattick (2005)[66]	7	976	RCT	63%	53%	17-26	1.19 (1.07 to 1.33) [F]	0.23
≤35mg vs. ≤5mg	Mattick (2005)	3	211	RCT	58%	39%	18-24	1.47 (1.10 to 2.00) [F]	0.62
50-80mg vs. ≤5mg	Mattick (2005)	3	263	RCT	73%	47%	18-24	1.54 (1.23 to 1.89) [F]	0.62
≤35mg vs. 6-16mg	Mattick (2005)	6	469	RCT	44%	43%	16-24	1.01 (0.66 to 1.54) [R]	0.003
50-80mg vs. 6-16mg	Mattick (2005)	7	708	RCT	56%	44%	13-24	1.26 (1.01 to 1.56) [R]	0.04

[F]: fixed effects meta-analysis [R]: random effects meta-analysis; NR: not reported CCT comparative controlled trial.

Table 36 cont. Proportion of individuals retained in treatment

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow up, weeks	Relative risk (95% CI) (unless otherwise indicated)	Heterogeneity test (P-value)
Methadone vs LAAM									
NR vs NR	Clark (2002)[50]	4	464	RCT/CCT	73%	56%	12	1.64 (1.28 to 2.11) [R]	0.69
NR vs. NR	Clark (2002)	6	543	RCT/CCT	54%	36%	24-48	1.25 (0.91 to 1.73) [R]	<0.0001
≥50mg vs. 65-80(x3/wk)	Farre (2002)[53]	3	524	RCT	49%	39%	15-40	OR 1.92 (1.31 to 2.81)	0.0008
50-100mg vs. 30-80mg	Glanz et al (1997)[56]	11	1442	RCT	NR	NR	3-52	RD 0.11 (0.03 to 0.19) [R]	<0.05
26-100mg vs.36-115mg (x3/wk)	Johansson (2003)[60]	9	1043	RCT/CCT	NR	NR	3-52	d 0.34 (0.22 to 0.46) [F]	>0.05
NR vs. 2x1mg/mg methadone or 3x2.2 mg/mg methadone	Layson-Wolf (2002)[62]	1	NR	CCT	NR	NR	NR	M=L	NA
Buprenorphine vs. LAAM 16-32 mg vs. 75-115mg	Raisch (2002)[69]	1	110	RCT	NR	NR	17	B=L	NA
Methadone vs. Naltrexone									NA
	Kirchmayer (2002)[61]	1	60	RCT	NR	NR	NR	M>N	
	Johansson (2003)[60]	1	60	CCT	87%	27%	12	M>N	NA
	Mattick (2005)[66]	1	204	RCT	84%	21%	24	RR 4.0 P<0.0001	NA
Methadone vs. heroin 10-120mg vs 30-120mg	Ferri (2005)[54]	1	96	RCT	25%	70%	52	0.35 (0.21 to 0.59)**	NA
Methadone alone vs. Methadone+heroin (oral+inhaled) NR vs NR	Ferri (2005) [54]	2	428	RCT	87%	70%	24-52	0.24 (1.11 to 1.38) [F]**	0.35
Methadone alone vs. methadone+ psychosocial therapy	Fridell (2003)[55]	6	739	RCT	NR	NR	12-52	d 0.13 (-0.24 to 0.51) [R]*	0.009
	Amato (2004)[47]	8	510	RCT	79%	77%	NR	1.06 (0.98 to 1.18)	0.11

*meta-analysis undertaken by report authors; [F]: fixed effects meta-analysis [R]: random effects meta-analysis; &: includes studies that provided of psychosocial treatment; RD: risk difference; NR: not reported; CCT comparative controlled trial.

Table 36 cont. Proportion of individuals retained in treatments

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow up (weeks)	Relative risk (95% CI) (unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone fast induction (1-day) vs. methadone slow induction (14-day)	Layson-Wolf (2002)[62]	1	NR	CCT	43%	39%	52	Non statistically significant difference	NR
Methadone outpatient vs. specialist clinic	Johansson (2003)[60]	2	119	RCT/ CCT	NR	NR	26-52	OP=S	NR
Buprenorphine vs. naltrexone	Mattick (2005)[66]	1	204	RCT	59%	21%	24	RR: 2.81 P<0.0001	NA

OP=S opiate abuse in 2 groups was the same; NR: not reported; CCT comparative controlled trial.

Table 37 Self-reported opioid use

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treat-ment (%)	Comp-arator (%)	Duration of follow up (weeks)	Relative risk (95% CI) (unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone vs. placebo/no treatment									
60mg vs. no therapy	Gowing (2004)[57]	1	256	RCT	25%	81%	16	0.31 (0.23 to 0.42)	NA
40-80mg vs. no therapy	Gowing (2204)	7	1746	BA			8-24	0.31 to 0.60**	NA
	Sorensen & Copeland	3	3236	BA			3-12	3/3 positive	NA
NR	(2000)[73]			RCT/	NR	NR	NR	Mean effect size 0.78++	NR
	Prendergast (2000)[+67]	11	NR	CCT/BA					
≥50mg	Farre (2002)[53]	2	347	RCT	61%	74%	15	0.82 (0.69 to 0.98)*	NA
35-97mg vs. no treatment	Johansson (2003)[60]	7	1046	RCT/CCT	NR	NR	6-152	d 0.65 (0.41 to 0.89) [R]**	<0.05
Methadone dosages									
High (≥50 mg) vs. low (<50mg)	Farre (2002)[53]	5	942	RCT	50%	64%	15-40	0.82 (078 to 0.95) [R]*	0.765*
80-100mg vs. 50mg.	Johansson (2003)[60]	3	478	RCT/CCT	NR	NR	24-40	d 0.28 (0.10 to 0.46) [F] **	>0.05
5-80mg vs. 20-45mg.	Johansson (2003)	8	892	RCT/CCT	NR	NR	15-52	d 0.36 (0.23 to 0.49) [F] **	>0.05
Buprenorphine doses									
16 mg. vs. 8mg	Johansson (2003)[60]	1	370	RCT	NR	NR	16	d 0.10 (-0.10 to 0.30)++	NA
8-16mg vs. 1-4mg	Johansson (2003)	6	1559	RCT	NR	NR	2-24	d 0.25 (0.15 to 0.35) [F]++	>0.05

**Pooling not performed due to observational nature of evidence; +: included self-reported and measured opoid use; ++ effect size: hedges g or d; *: calculated by this report authors; &: includes studies that provided of psychosocial treatment; NR: not reported [F]: fixed effects meta-analysis [R]: random effects meta-analysis; CCT comparative controlled trial; BA before & after.

Table 37 cont. Self-reported opioid use

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treat-ment (%)	Comp-arator (%)	Duration of follow up (weeks)	Relative risk (95% CI) (unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone vs. buprenorphine									
20-100mg vs. 8-32mg	Raisch (2000)[69]	3	NR	RCT	NR	NR	NR	2 studies M=B 1 study M>B	NA
≥50mg vs. <8mg	Farre (2002)[53]	2	148	RCT	NR	NR	24	0.29 (0.16 to 0.53)	NR
≥50mg vs. ≥8mg	Farre (2002)	4	335	RCT	NR	NR	17-24	0.93 (0.63 to 1.33)	NR
<50mg vs. ≥8mg	Simeons (2005)[71]	4	NR	RCT	NR	NR	NR	1 M>B 1 M=B 2 B>M	NR
<50mg vs. <8mg	Simeons (2005)	3	NR	RCT	NR	NR	NR	2/3M>B 1/3 M=B	NR
≥50mg vs. ≥8mg	Simeons (2005)	3	NR	RCT	NR	NR	NR	1 M>B 2 M=B	NR
≥50mg vs. <8mg	Simeons (2005)	3	NR	RCT	NR	NR	NR	3/3 M>B	NR
flexible vs. flexible	Simeons (2005)	1	NR	RCT	NR	NR	NR	1/1 M=B	NR
20-100mg vs. 2-12mg	Johansson (2003)[60]	6	648	RCT/CCT	NR	NR	NR	0.13 (-0.03 to 0.28)[F]	>0.05
Methadone vs. LAAM									
≥50mg vs. 65-80 (x3)	Farre (2002)[53]	2	464	RCT	26%	23%	15-40	1.38 (0.91 to 2.17)	NR
50-100mg vs.30-90mg	Glanz (1997)[56]	10	1382	RCT			3-52	RD 0.02 (-0.03 to 0.08) [R]	<0.05
26-100mg vs.36-115mg (x3/wk)	Johansson (2003)[60]	9	996	RCT/CCT	NR	NR	3-52	d -0.06 (-0.19 to 0.06) [F]	>0.05
Buprenorphine vs. LAAM									
16-32 mg vs, 75-115mg	Raisch (2002)[69]	1	110	RCT	NR	NR	17	B=L	NA

++ effect size: d; *: calculated by this report authors; RD risk difference; B=L opiate abuse in the 2 groups the same; M>B level of opiate abuse in methadone group lower than buprenorphine group; B>M level of opiate abuse in buprenorphine group lower than methadone group; NR: not reported; [F] fixed effects meta-ana;ysis; CCT comparative controlled trial.

Table 37 cont. Self reported opioid use

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treat-ment (%)	Comp-arator (%)	Duration of follow up (weeks)	Relative risk (95% CI) (unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone vs. heroin 60mg vs. 60mg	Johnasson (2003)[60]	1	52	RCT/ CCT	59%	64%	52	M=N	NA
Methadone vs. Naltrexone NR vs NR NR vs NR	 Kirchmayer (2002)[61] Johansson (2003)[60]	 1 1	 60 60	 RCT CCT	 NR 50%	 NR 50%	 NR 12	 1/1 M=N M=N	 NA NA
Contingency management + methadone vs. methadone alone	Johansson (2003) [60]	4	239	RCT/CCT	NR	NR	8-52	3/4 CM>M 1/4 CM=M	NA
Methadone + psychosocial therapy& vs. methadone alone	Fridell (2003)[55]	9	1227	RCT	NR	NR	12-52	d 0.21 (0.08 to 0.35)*	0.095

CM=M or M=N or M=H: opiate abuse levels of two groups are similar; CM>M: contingency management opiate abuse levels lower than methadone alone; * meta-analysis carried out by report authors; NR: not reported; CCT comparative controlled trial.

Table 38 Urine confirmed opioid abstinence.

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Duration of follow up (months)	Mean difference (95% CI) (Unless otherwise indicated)	Heterogeneity test (P-value)
Methadone dosages							
60-109mg vs. 1-39mg	Faggiano (2003)[52]	3	237	RCT	At > 3~4 weeks	RR 1.59 (1.16 to 2.18-2.00)[F]	P=0.001
60-109mg vs. 40-59mg	Faggiano (2003)	1	59	RCT	At > 3~4 weeks	RR 1.51 (0.63 to 3.61)[F]	NA
Methadone vs. burprenorphine							
50-80mg vs. 8-12mg	Barnett (2001)[48]	4	488	RCT	NR	0.083 (0.027 to 0.140) [F]	0.074
20-80mg vs 2-8mg	West (2003)[76]	9	995	RCT/CCT	1.5-12	d=-0.0921++ NS	<0.001
35-65mg vs. 2-6mg	Layson-Wolf (2002)[62]	1	NR	CCT	6	M>B P<0.0003	NR
20mg vs. 16-48mg	Layson-Wolf (2002)	1	220	RCT	4	B>M P<0.005	NR
60-100mg vs. 16-48mg	Layson-Wolf (2002)	1	220	RCT	4	M=B	NR
Methadone vs. LAAM							
20mg vs. 16-48mg	Layson-Wolf (2002)[62]	1	220	RCT	4	L>M P<0.005	NA
60-100mg vs. 16-48mg	Layson-Wolf (2002)	1	220	RCT	4	M=L	NA
Methadone vs.Methadone + reinforecement strategies*	Griffiths (2000)[58]	30	NR	RCT/CCT	NR	Weighted Z 0.25 (0.20 to 0.30)** P<0.001	<0.001
Methadone + psychosocial therapy& vs. methadone alone	Amato (2004)[47]	5	388	RCT	NR	RR 1.45 (1.10 to 1.88)	0.18

+: proportion of urinalyses that test positive; ++: very small effect size; *: includes changes in methadone dose, methadone take homes, vouchers; **: positive vs. MMT+R > MMT alone; M>B: methadone better than burprenorphine; LAAM better than methadone; NR: not reported [F] fixed effects meta-analysis CCT comparative controlled trial;.

Table 39 All cause mortality

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treat-ment (%)	Comp-arator (%)	Duration of follow up (months)	Relative risk (95% CI)	Hetero-geneity test (P-value)
Methadone vs. placebo NR NR	 Mattick (2003)[65] Caplehorn (1995)[49]	 3 5	 435 3618+	 RCT CCT	 1.4% NA	 3.2% NA	 12.5 6-252	 0.49 (0.06 to 4.23) [R]* Rate ratio++ 0.25 (0.19 to 0.33) [R]*	 0.14 >0.75
Burprenorphine vs.placebo 16 mg	Linzeris & Ford (2004)[63]	1	40	RCT	0%	20%	12	0.05 (0 to 0.79)*	NA
Burprenorphine vs. methadone NR	Linzeris & Ford (2004) [63]	2	NR	CS	NR	NR	3-5yrs	B<M	NR
Methadone vs. LAAM ??mg vs. ??mg	Clark (2002)[50]	4	1008	RCT/CCT	0.2%	0.9%	10-12	0.43 (0.11 to 1.69) [F]	0.61
Methadone vs. heroin 20-120mg vs. 30-120mg	Ferri (2005)[54]	1	96	RCT	1.9%	4.5%	12	0.42 (0.04 to 4.51)*	NA
Methadone vs. methadone+heroin NR vs. NR	Ferri (2005) [54]	1	174	RCT	1.3%	1.0%	12	1.2 (0.1 to 20.2)*	NA

*meta-analysis undertaken by report authors; [F]: fixed effects meta-analysis [R]: random effects meta-analysis; ++: based on person years of exposure; B<M statistically less deaths in buprenorphine treated individuals than methadone; CS cross sectional studies; CCT comparative controlled trial NA not applicable

Table 40 Overdose mortality

Comparison Daily dose Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment deaths (%)	Control deaths (%)	Duration of follow up (months)	Relative risk (95% CI) Unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone dosages									
>75mg vs. 5-55mg	Faggiano (2003)[52]	1	1138	CCT	0%	5%	72	0.29 (0.02 to 5.34)	NA
>75mg vs. 55-70mg	Faggiano (2003)	1	678	CCT	0%	3%	72	0.38 (0.02 to 9.34)	NA
55-70mg vs. 5-55mg	Faggiano (2003)	1	1184	CCT	3%	5%	72	0.57 (0.06 to 5.06)	NA

CCT comparative controlled trial;

Table 41 Discontinuation due to side effects

Comparison Daily dose Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treat-ment (%)	Comp-arator (%)	Duration of follow up (months)	Relative risk (95% CI) (Unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone vs. LAAM	Glanz (1998)[56]	4	1160	RCT	NR	NR	8-10	RD 0.04 (0.02 to 0.05) [F]	>0.05

[F]: fixed effects meta-analysis CCT comparative controlled trial; RD risk difference

Table 42 Serious adverse events+

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow up (months)	Relative risk (95% CI)	Hetero-geneity test (P-value)
Methadone vs. placebo	Mattick (2003)[65]	2	335	RCT	7.6%	13.0%	6-12	0.59 (0.33 to 1.04) [F]*	0.24

+: self-reported adverse events during course of study;
*meta-analysis undertaken by report authors; [F]: fixed effects meta-analysis

Table 43 Suicide attempts

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment deaths (%)	Comparator (%)	Duration of follow up (months)	Relative risk (95% CI)	Hetero-geneity test (P-value)
Methadone vs. heroin 60mg vs. 60-480mg (oral/iv)	Johnansson (2003)[60]	1	51	RCT/ CCT	19%	4%	26	M>M	NA

M>H: more suicide attempts with methadone than methadone; CCT comparative controlled trial

Table 44 Opioid poisonings

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow up (months)	Relative risk (95% CI)	Hetero-geneity test (P-value)
Buprenorphine vs. methadone NR vs. NR	Linzeris & Ford (2004)[63]	1	NR	CS	NR	NR	5 yrs	B>M	NA

B>M: more poisoning with buprenorphine than morphine: CS cross sectional studies;

Table 45 NEPOD Adverse events (per 100-patient years) – pooled RCT

	Methadone (420 individuals)	**Buprenorphine** (492 individuals)	**LAAM** (124 individuals)	**Naltrexone** (380 individuals)
Total number of individual days of treatment	48,565	34,756	14,493	16,409
Heroin overdose	0	5	0	11
Other overdose	0	2	3	2
Psychiatric mood/suicide	2	1	0	4
All other SAEs	8	13	8	36
Total SAEs	**10**	**20**	**10**	**56**

Based on the NEPOD[104] report reviewd by Linzeris and Ford 2004[63]; SAEs: serious adverse events.

Table 46 Criminal activity – mean number of crimes per week

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Mean difference (95% CI) (Weighted mean difference unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone dosages 60-109mg vs. 40-59mg	Faggiano (2003)[52]	1	59	RCT	0.05 (-0.03 to 0.13)	NA

Table 47 Self-reported or objective measures of crime

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of stud-ies	No. of patients	Type of studies	Treatment (%) or Mean (SD)	Comparato r (%) or Mean (SD)	Duratio n of follow up (weeks)	Effect size (95% CI) Relative risk (Unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone vs. placebo/no treatment									
	Mattick (2003)[65]	3	363	RCT	3%	12%	50	0.39 (0.12 to 1.25) [R]	0.28
	Prendergast (2000)[67]	11	NR	RCT/ CCT/BA	NR	NR	NR	Mean effect size: 0.54++	NR
	Marsch (1998)[64]	24	6994	CCT/BA	NR	NR	1-624	0.70 (“large effect”)**	0.001
Methadone vs. heroin 10-120mg vs. 30-120mg	Ferri (2005)[54]	1	88	RCT	65%	43%	52	1.01 (0.74 to 1.38)*	NA
Methadone vs. buprenorphine flexible vs. flexible	Mattick (2005)[66]	1	212	RCT	0.6 (1.3)	0.5 (1.0)	13	SMD 0.14 (-0.14 to 0.41)	NA

[R]: random effects meta-analysis; ++: hedges g; *: analysis by this report authors; **: effect size: r-value CCT comparative controlled trial; BA before & after.

Table 48 HIV risk behaviours / risk score

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Duration of follow up (mo)	Effect size [r-value] Mean (P-value)	Hetero-geneity test (P-value)
Methadone vs. placebo /no treatment	Marsch (1998)[64]	8	1756	CCT or BA or ITS	1-232	0.21 ("small to moderate effect")	0.78
	Gowing (2004)[57]	4		BA	2-9	All studies show reduction in HIV risk score (P<0.01)	NA
	Sorensen & Copeland (2000)[73]	20	14780	BA/CS	3-103	20/20 M>no Rx	NA

M>no Rx: methadone better outcome than no treatment CS cross sectional studies; CCT comparative controlled trial; ITS interrupted time series; BA Before & after

Table 49 Multiple sex partners (self report)

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Duration of follow up (mo)	Relative risk Mean range	Heterogeneity test (P-value)
Methadone vs. placebo/no treatment	Gowing (2004)[57]	4	1029	BA	6-124	0.39 to 1.40	NA

BA Before &after

Table 50 Unprotected sex (self report)

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Duration of follow up (mo)	Relative risk Mean range	Heterogeneity test (P-value)
Methadone vs. placebo/no treatment	Gowing (2004)[57]	6	1544	BA	6-124	0.46 to 1.05	NA

BA Before &after

Table 51 HIV seroconversion

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Duration of follow up (mo)	Seroconversion rate++	Hetero-geneity test (P-value)
Methadone vs. placebo /no treatment	Sorensen & Copeland (2000)[73]	5	17984	BA/CS	12-53	12-53	NA
	Gowing (2004) [57]	5	1029	BA or CC or CCT	6-124	3/100 vs 5/1000 py 1.4% vs 3.1% ppy 0.7 vs 4.3 py	NA

++individual study results (MMT vs control reported) py (per year) ppy (per patient year); CCT comparative controlled trial; BA before & after CC case control CS cross sectional

Table 52 Employment

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treat-ment (%)	Comp-arator (%)	Duration of follow up (months)	Relative risk (95% CI)	Hetero-geneity test (P-value)
Methadone vs. heroin									
NR vs. NR	Ferri (2005)[54]	1	88	RCT	50%	43%	1	1.22 (0.77 to 1.93)* M=H	NA
NR vs. 480mg iv	Johansson (2003)[60]	1	51	RCT/CCT	14%	22%	6		NA

*: calculation by this report authors; CCT comparative controlled trial

Table 53 Neonatal mortality

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparato r (%)	Duration of follow up (months)	Relative risk (95% CI)	Hetero-geneity test (P-value)
Methadone* vs. no therapy	Hulse (1998)[43]	3	1983	NR	3.3%	1.7%	NR	1.75 (0.60 to 4.59)	>0.05

*during pregnancy

Table 54 Retention in treatment: Number of weeks

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Mean difference (95% CI) (Unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone dosages						
60-109mg vs. 1-39mg	Faggiano (2003)[52]	3	237	RCT	3.54 (2.19 to 4.89) [F]	0.0005
60-109mg vs. 40-59mg	Faggiano (2003)	1	59	RCT	-0.30 (-0.77 to 0.17) [F]	NA
Methadone vs. buprenorphine						
35-60mg vs. 2-6mg	Layson-Wolf (2002)[62]	1	NR	CCT	4 (NR) P<0.005	NA

[F]: fixed effects meta-analysis CCT comparative controlled trial;

Table 55 Opioid use (self-reported – times/week)

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Mean difference (95% CI) (Unless otherwise indicated)	Heterogeneity test (P-value)
Methadone dosages						
60-109mg vs. 1-39mg	Faggiano (2003)[52]	1	110	RCT	-2.00 (-4.77 to 0.77)	NA
60-109mg vs. 40-59mg	Faggiano (2003)	1	59	RCT	-1.89 (-3.43 to -0.35)	NA

Table 56 Opioid use (self-reported –mg/week)

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Mean difference (95% CI) (Unless otherwise indicated)	Heterogeneity test (P-value)
Methadone dosages						
60-109mg vs. 40-59mg	Faggiano (2003) [52]	1	59	RCT	-0.31 (-0.70 to 0.08)	NA

Table 57 Opioid abstinence score

Comparison	Author (year)	No. of	No. of	Type of	Duration of	Mean difference	Heterogeneity test (P-

Daily dose (unless otherwise indicated)		studies	patients	studies	follow up (wks)	(95% CI) (Unless otherwise indicated)	value)
Methadone dosages							
60-109mg vs. 1-39mg	Faggiano (2003) [52]	3	337	RCT	>3-4	1.59 (1.16 to 2.18) [F]	0.001
60-109mg vs. 40-59mg	Faggiano (2003)	1	59	RCT	>3-4	1.51 (0.63 to 3.61)	NA

[F]: fixed effects meta-analysis

Table 58 Illicit drug use (self-reported & objective)

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Duration of follow up (weeks)	Mean difference (Unless otherwise indicated)	Heterogeneity test (P-value)
Methadone vs. placebo/no treatment							
NR mg/day	Marsch (1998)[64]	11	1930	CCT/BA	1-624	r: 0.35 (“moderate effect”)	0.53

CCT comparative controlled trial; BA before & after

Table 59 Injecting use (self-reported)

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treat-ment (%)	Comp-arator (%)	Duration of follow up (weeks)	Relative risk (95% CI) (Unless otherwise indicated)	Hetero-geneity test (P-value)
Methadone vs. placebo/no treatment									
	Gowing (2004)[57]	1	253	RCT	20%	54%	16	0.37 (0.26 to 0.55)	NA
	Gowing (2004)	7	1700	BA	NR	NR	16-56	0.25 to 0.78**	NA
	Soresen & Copeland (2000)[73]	9	14780	BA/CS	NR	NR	3-108	8/9 positive studies	NA

**Pooling not performed due to observational nature of evidence; BA before & after CC case control CS cross sectional; NR not reported

Table 60 Sharing injecting equipment

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Duration of follow up (weeks)	Relative risk (95% CI) (Unless otherwise indicated)	Heterogeneity test (P-value)
Methadone vs. placebo/no treatment	Gowing (2004) [57] Gowing (2004)	1 7	253 1491	RCT BA	16 16-56	0.45 (0.35 to 0.59) range 0.39 to 0.75**	NA NA

**Pooling not performed due to observational nature of evidence BA before & aftrer

Table 61 Morphine positive urines

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment positive patients (%) or Mean (SD)	Control positive patients (%) or Mean (SD)	Duration of follow up (weeks)	Relative risk (95% CI) (Unless otherwise indicated)	Hetero-geneity test (P-value)
Buprenorphine vs. placebo/no therapy									
≤5mg	Mattick (2005)[66]	2	487	RCT	NA	NA	2-16	SMD 0.10 (-0.80 to 1.01) [R]	<0.0001
6-12mg	Mattick (2005)	2	463	RCT	NA	NA	2-16	SMD –0.28 (-0.47 to –0.10) [R]	0.004
8mg	Mattick (2005)	3	620	RCT	NA	NA	4-52	SMD –1.23 (-1.95 to –0.51)	<0.0001
Methadone vs. placebo/no treatment# NR mg/day	Mattick (2003)[65]	1	169	RCT	29%	60%	NR	0.59 (0.39 to 0.87)*	NA
Methadone vs. buprenorphine									
flexible vs. flexible	Mattick (2005) [66]	6	837	RCT	NA	NA	6-24	SMD 0.12 (-0.02 to 0.26) [F]	0.66
≤35mg vs. ≤5mg	Mattick (2005)	1	59	RCT	34 (15)	29 (13)	24	SMD 0.35 (-0.16 to 0.87)	NA
50-80mg vs. ≤5mg	Mattick (2005)	1	57	RCT	19 (9)	25 (13)	24	SMD –0.88 (-1.42 to –	NA

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment positive patients (%) or Mean (SD)	Control positive patients (%) or Mean (SD)	Duration of follow up (weeks)	Relative risk (95% CI) (Unless otherwise indicated)	Hetero-geneity test (P-value)
≤35mg vs. 6-16mg	Mattick (2005)	3	317	RCT	NA	NA	17-52	0.33) SMD 0.31 (-0.11 to 0.72) [R]	0.04
50-80mg vs. 6-16mg	Mattick (2005)	3	314	RCT	NA	NA	17-52	SMD –0.25 (-0.75 to 0.25)	0.01

*meta-analysis undertaken by report authors [F]: fixed effects meta-analysis; [R]: random effects meta-analysis; NA not applicable

Table 62 Heroin positive urines

Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of patients	Type of studies	Treatment positive patients (%)	Control positive patients (%)	Duration of follow up (weeks)	Relative risk (95% CI) (Unless otherwise indicated)	Heterogeneity test (P-value)
Methadone vs. LAAM NR vs. NR	Clark (2002)[50]	8	262	RCT/ CCT	24%	21%	13-52	1.14 (0.95 to 1.38) [F]	0.34

CCT comparative controlled trial; [F} fixed effects meta-analysis

Table 63 Self-reported heroin use

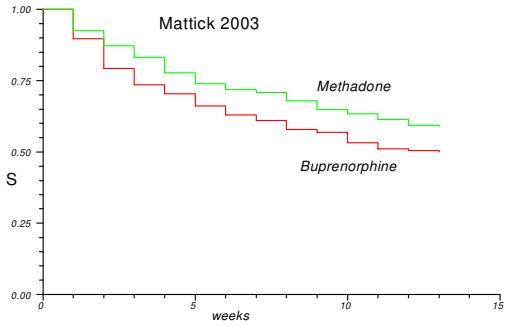
Comparison Daily dose (unless otherwise indicated)	Author (year)	No. of studies	No. of individuals	Type of studies	Treatment (%)	Comparator (%)	Duration of follow up (weeks)	Relative risk (95% CI) (Unless otherwise indicated)	Heterogeneity test (P-value)
Methadone vs. buprenorphine									
flexible vs. flexible	Mattick (2005) [66]	3	420	RCT	NA	NA	13-26	SMD 0.12 (-0.07 to 0.31) [F]	0.76
≤35mg vs. ≤5mg	Mattick (2005)	1	37	RCT	6.8 (4.3)	8.1 (4.5)	24	SMD -0.29 (-0.96 to 0.38)	NA
50-80mg vs. ≤5mg	Mattick (2005)	1	35	RCT	8.4 (4.6)	8.1 (4.5)	24	SMD –0.06 (-0.61 to 0.74)	NA
≤35mg vs. 6-16mg	Mattick (2005)	1	34	RCT	6.8 (4.3)	9.9 (5.0)	24	SMD -0.67 (-1.41 to 0.07)	NA
50-80mg vs. 6-16mg	Mattick (2005)	2	72	RCT	NA	NA	24	SMD 0.03 (-0.45 to 0.50)	0.24
Methadone vs. heroin									
10-120mg vs. 30-120mg	Ferri (2005)	1	88	RCT	58%	64%	52	0.91 (0.66 to 1.27)*	NA
NR vs. 480mg (iv)	Johnansson (2003)	1	51	RCT/ CCT	2%	48%	26	H>M	NR

[F]: fixed effects meta-analysis; *: analysis by this report authors; H>M: heroin better than methadone CCT comparative controlled trial NA not applicable

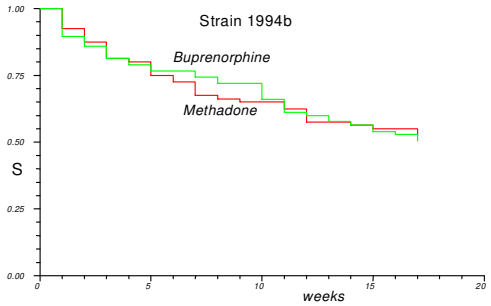
Appendix 10 Retention in treatment (individual studies, flexible dosing)

Proportions retained in treatment were estimated from graphs or tables published in 7 studies comparing flexible dosing of buprenorphine and methadone. Kaplan Meier plots were constructed and hazard ratios estimated by log rank test using Stats Direct software. Details of proportions retained in treatment at different times of treatment are shown in the following tables.

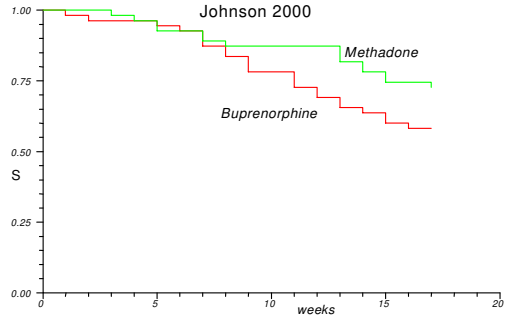
bup vs. meth HR 1.326722 (0.989092 to 1.779603)



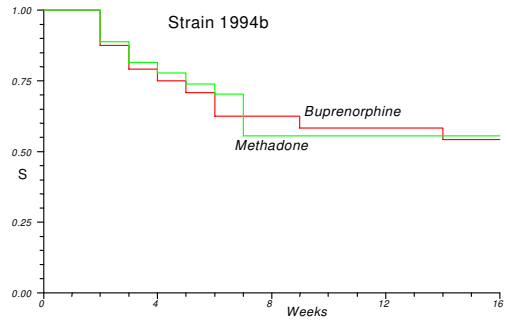
bup vs. meth HR = 1.03208 (0.6657 to 1.1600)



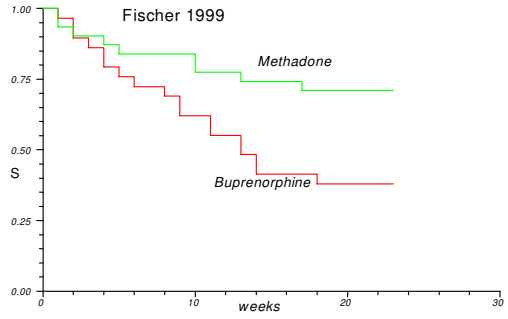
bup vs. meth HR = 1.705964 (0.902424 to 3.224996)



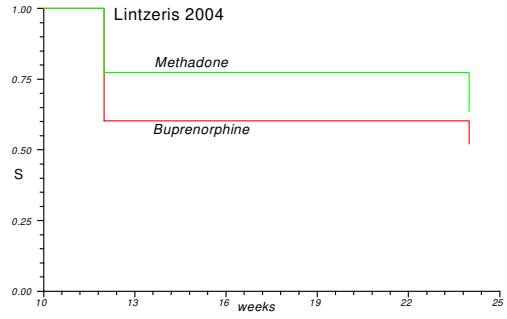
bup vs. meth HR = 1.06003 (0.467095 to 2.405641)



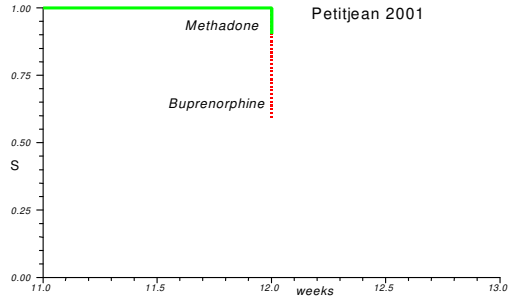
bup vs. meth HR = 2.559714 (1.196926 to 5.474138)



bup vs. meth HR = 1.404447 (0.843009 to 2.339799)



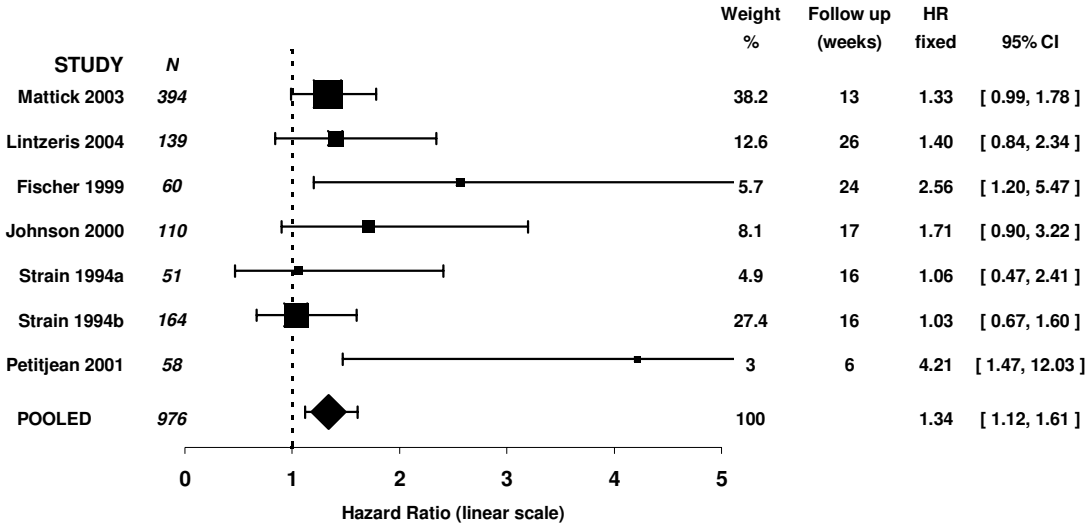
bup vs. meth HR = 4.209877 (1.472981 to 12.032105)



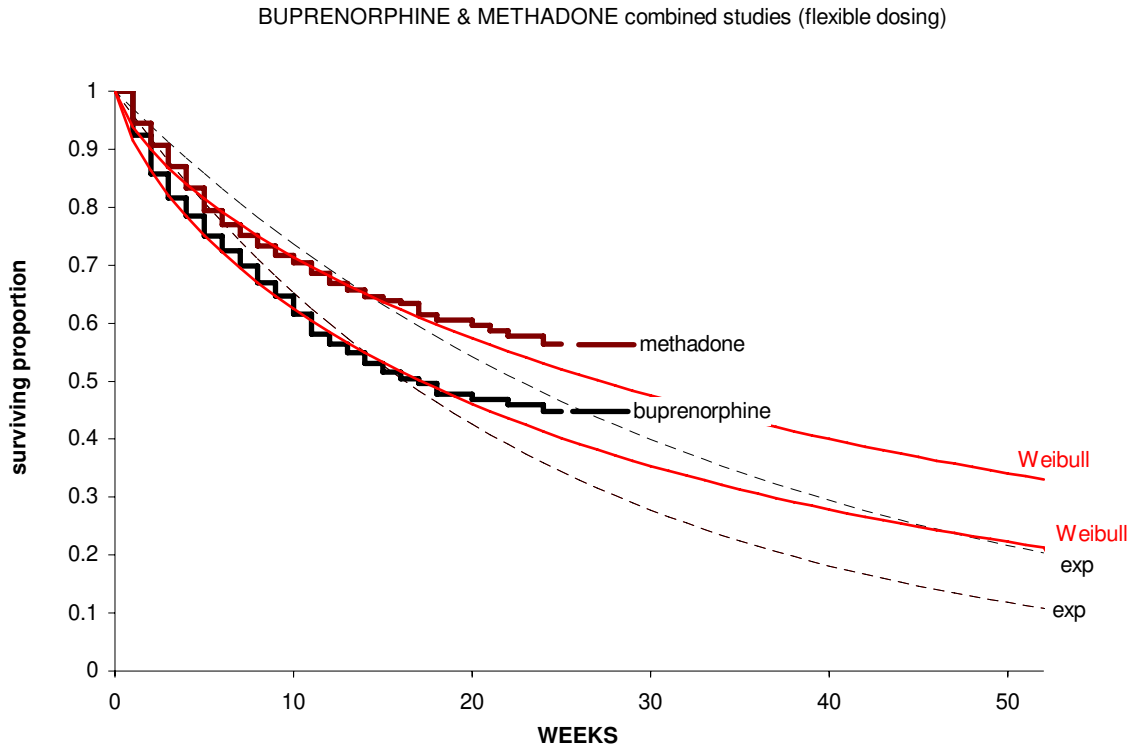
	buprenorphine group					methadone group			
Mattick 2003									
Time	At risk	Dead	Censored	S		At risk	Dead	Censored	S
1	192	20	0	0.895833		202	15	0	0.925743
2	172	20	0	0.791667		187	11	0	0.871287
3	152	11	0	0.734375		176	8	0	0.831683
4	141	6	0	0.703125		168	11	0	0.777228
5	135	8	0	0.661458		157	8	0	0.737624
6	127	6	0	0.630208		149	4	0	0.717822
7	121	4	0	0.609375		145	2	0	0.707921
8	117	6	0	0.578125		143	6	0	0.678218
9	111	2	0	0.567708		137	6	0	0.648515
10	109	7	0	0.53125		131	3	0	0.633663
11	102	4	0	0.510417		128	4	0	0.613861
12	98	1	0	0.505208		124	4	0	0.594059
13	97	1	96	0.5		120	1	119	0.589109
Strain 1994b									
Time	At risk	Dead	Censored	S		At risk	Dead	Censored	S
1	84	9	0	0.892857		80	6	0	0.925
2	75	3	0	0.857143		74	4	0	0.875
3	72	4	0	0.809524		70	5	0	0.8125
4	68	2	0	0.785714		65	1	0	0.8
5	66	2	0	0.761905		64	4	0	0.75
6	64	0	0	0.761905		60	2	0	0.725
7	64	2	0	0.738095		58	4	0	0.675
8	62	2	0	0.714286		54	1	0	0.6625
9	60	0	0	0.714286		53	1	0	0.65
10	60	5	0	0.654762		52	0	0	0.65
11	55	4	0	0.607143		52	2	0	0.625
12	51	1	0	0.595238		50	4	0	0.575
13	50	2	0	0.571429		46	0	0	0.575
14	48	1	0	0.559524		46	1	0	0.5625
15	47	2	0	0.535714		45	1	0	0.55
16	45	1	0	0.52381		44	0	0	0.55
17	44	2	42	0.5		44	2	42	0.525

Strain 1994a									
Time	At risk	Dead	Censored	S		At risk	Dead	Censored	S
2	24	3	0	0.875		27	3	0	0.888889
3	21	2	0	0.791667		24	2	0	0.814815
4	19	1	0	0.75		22	1	0	0.777778
5	18	1	0	0.708333		21	1	0	0.740741
6	17	2	0	0.625		20	1	0	0.703704
7	15	0	0	0.625		19	4	0	0.555556
9	15	1	0	0.583333		15	0	0	0.555556
14	14	1	0	0.541667		15	0	0	0.555556
16	13	0	13	0.541667		15	0	15	0.555556

	buprenorphine group					methadone group			
Fischer 1999									
Time	At risk	Dead	Censored	S		At risk	Dead	Censored	S
1	29	1	0	0.965517		31	2	0	0.935484
2	28	2	0	0.896552		29	1	0	0.903226
3	26	1	0	0.862069		28	0	0	0.903226
4	25	2	0	0.793103		28	1	0	0.870968
5	23	1	0	0.758621		27	1	0	0.83871
6	22	1	0	0.724138		26	0	0	0.83871
8	21	1	0	0.689655		26	0	0	0.83871
9	20	2	0	0.62069		26	0	0	0.83871
10	18	0	0	0.62069		26	2	0	0.774194
11	18	2	0	0.551724		24	0	0	0.774194
13	16	2	0	0.482759		24	1	0	0.741935
14	14	2	0	0.413793		23	0	0	0.741935
17	12	0	0	0.413793		23	1	0	0.709677
18	12	1	0	0.37931		22	0	0	0.709677
23	11	0	11	0.37931		22	0	22	0.709677
Johnson 2000									
Time	At risk	Dead	Censored	S		At risk	Dead	Censored	S
1	55	1	0	0.981818		55	0	0	1
2	54	1	0	0.963636		55	0	0	1
3	53	0	0	0.963636		55	0	0	0.981818
4	53	0	0	0.963636		54	1	0	0.963636
5	53	1	0	0.945455		53	2	0	0.927273
6	52	1	0	0.927273		51	0	0	0.927273
7	51	3	0	0.872727		51	2	0	0.890909
8	48	2	0	0.836364		49	1	0	0.872727
9	46	3	0	0.781818		48	0	0	0.872727
11	43	3	0	0.727273		48	0	0	0.872727
12	40	2	0	0.690909		48	0	0	0.872727
13	38	2	0	0.654545		48	3	0	0.818182
14	36	1	0	0.636364		45	2	0	0.781818
15	35	2	0	0.6		43	2	0	0.745455
16	33	1	0	0.581818		41	0	0	0.745455
17	32	0	32	0.581818		41	1	40	0.727273
Lintzeris 2004									
Time	At risk	Dead	Censored	S		At risk	Dead	Censored	S
12	73	29	0	0.60274		66	15	0	0.772727
24	44	6	38	0.520548		51	9	42	0.636364
Petitjean 2001									
Time	At risk	Dead	Censored	S		At risk	Dead	Censored	S
12	27	11	16	0.592593		31	3	28	0.903226



The figure below shows Kaplan Meier plots for treatment retention obtained by combining results from the seven studies of methadone vs buprenorphine in flexible dosing; also shown is the Weibull fit for buprenorphine and the Weibull fit for methadone derived from this using the pooled hazard ratio of 1.396. In addition indicated is the exponential fit to buprenorphine data and the methadone exponential fit derived from this using the pooled hazard ratio.


BUPRENORPHINE & METHADONE combined studies (flexible dosing)
surviving proportion
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
10
20
30
40
50
WEEKS
methadone
buprenorphine
Weibull
Weibull
exp
exp

Appendix 11 Table of excluded studies with rationale

Table 64 List of studies excluded from review of systematic reviews

	Citation	COMMENT / REASON FOR EXCLUSION
1	Aavitsland P. 1998[166]	No search strategy
2	Anonymous, 1990. Office-of-Technology-Assessment. [167]	No search strategy
3	Anonymous. *Prescrire International 1996; 5(23):66-70.* [168]	No search strategy
4	Boyarsky BK, et al 2000[169]	No search strategy
5	Brewer DD, et al 1998[170]	No description of intervention and comparator
6	Chapleo CB. 1997[171]	No search strategy
7	Doran C, et al 2005[172]	No search strategy. *Review of reviews.*
8	Fischer B, et al 2005[173]	No search strategy. *Review of reviews*
9	Gruen RL, et al 2003[174]	No appropriate population
10	Hermstad R, et al 1998[175]	Foreign language
11	Johnson RE. 1997[176]	No search strategy
12	Kreek MJ. 1997[177]	No search strategy
13	Maddux JF, et al 1980[178]	Primary study
14	Perry AE, et al 2005 [179]	Protocol only
15	Prendergast ML, et al 2001[180]	No intervention
16	Rayburn WF & Bogenschutz MP. 2004[181]	No search strategy
17	Van Den BW & Van Ree JM. 2003[182]	No search strategy
18	Walter DS. 1997[183]	No search strategy
19	Weinmann S, et al 2004[184]	Foreign language
20	Wingood GM, & DiClemente RJ. 1996[185]	No intervention
1	Medical-Technology-Unit-Federal-Social-Insurance-Office-Switzerland. 2000[186]	Full text not obtainable

Table 65 Excluded studies from potential RCTs.

	Citation	**Reason for exclusion**
1	Ahmadi,J. and Ahmadi,K., 2003. Controlled trial of maintenance treatment of intravenous buprenorphine dependence. *Irish Journal of Medical Science*, **172**, 171-173.	Already in SR (Mattick 2005)
2	Ahmadi,J., Ahmadi,K., and Ohaeri,J., 2003. Controlled, randomized trial in maintenance treatment of intravenous buprenorphine dependence with naltrexone, methadone or buprenorphine: a novel study. *European Journal of Clinical Investigation*, **33**, 824-829.	Superceded by Ahmadi,J. *Irish Journal of Medical Science*, **172**, 171-173.
3	Ahmadi,J. and Ahmadi,M., 2004. Twelve-month maintenance treatment of heroin-dependent outpatients with buprenorphine. *Journal of Substance Use*, **8**, 39-41.	Already in SR (Mattick 2005)
4	Ahmadi,J. and Bahrami,N., 2002. Buprenorphine treatment of opium-dependent outpatients seeking treatment in Iran. *Journal of Substance Abuse Treatment*, **23**, 415-417.	Already in SR (Mattick)
5	Ahmadi,J., 2002. Buprenorphine maintenance treatment of heroin dependence: the first experience from Iran. *Journal of Substance Abuse Treatment*, **22**, 157-159.	Already in SR (Mattick 2005)
6	Ahmadi,J., 2003. A randomized, clinical trial of buprenophine maintenance treatment for Iranian patients with opioid dependency. . *Addictive Disorders & Their Treatment*, **1**, 2002-2027.	Already in SR (Mattick 2005)
7	Ahmadi,J., 2003. Methadone versus buprenorphine maintenance for the treatment of heroin-dependent outpatients. *Journal of Substance Abuse Treatment*, **24**, 217-220.	Not randomised

8	Amass,L., Kamien,J.B., and Mikulich,S.K., 2001. Thrice-weekly supervised dosing with the combination buprenorphine-naloxone tablet is preferred to daily supervised dosing by opioid-dependent humans. *Drug & Alcohol Dependence*, **61**, 173-181.	Not randomised
9	Annon,J., Longshore,R., Rawson,R., and Anglin,M.D., 2001. Methadone and LAAM maintenance treatment: effects on HIV risk behaviors. *Drug and Alcohol Dependence*, **63 Suppl 1**, 8.	Abstract
10	Batki,S.L., Gruber,V.A., Bradley,J.M., Bradley,M., and Delucchi,K., 2002. A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. *Drug & Alcohol Dependence*, **66**, 283-293.	Inappropriate outcomes
11	Buydens-Branch, Branchey,M., and Reel-Brander,C., 2005. Efficacy of buspirone in the treatment of opioid withdrawal. *Journal of Clinical Psychopharmacology*, **25**, 230-236.	Not maintenance
12	Carpenter,K.M., Brooks,A.C., Vosburg,S.K., and Nunes,E.V., 2004. The effect of sertraline and environmental context on treating depression and illicit substance use among methadone maintained opiate dependent patients: a controlled clinical trial. *Drug & Alcohol Dependence*, **74**, 123-134.	Abstract
13	Carpenter,K.M., Nunes,E.V., and Vosburg,S., 2002. Does reinforcement density moderate the effects of pharmacotherapy for depresssion in methadone-maintained opiate-dependent patients? *Drug and Alcohol Dependence*, **66 Suppl 1**, 27.	Mixed population, alcohol or illicit drug users.
14	Clark,N., Khoo,K., Lintzeris,N., Ritter,A., and Whelan,G., 2002. A randomized trial of once-daily slow-release oral morphine versus methadone for heroin dependence. *Drug and Alcohol Dependence*, **66 Suppl 1**, 33.	Abstract
15	Clark,N., Ritter,A., Lintzeris,N., Kutin,J., and Bammer,G., 2001. Office-based LAAM maintenance for opioid dependence: a randomized comparison with methadone. *Drug and Alcohol Dependence*, **63 Suppl 1**, S29.	Abstract
16	Coviello,D.M., Zanis,D.A., and Lynch,K., 2004. Effectiveness of vocational problem-solving skills on motivation and job-seeking action steps. Substance Use & Misuse, 39, 2309-2324.	Report duplicate of Zanis 2001 297
17	Cunningham,R.J., Miotto,K., Donovick,R., Charuvastra,C., Fraddis,J., Ho,W., Samiy,T., and Ling,W., 2001. Setting affect the treatment of opiate dependence using buprenorphine/naloxone. *Drug and Alcohol Dependence*, **63 Suppl 1**, S36.	Abstract
18	Curran,H.V., Kleckham,J., Bearn,J., Strang,J., and Wanigaratne,S., 2001. Effects of methadone on cognition, mood and craving in detoxifying opiate addicts: a dose-response study. *Psychopharmacology*, **154**, 153-160.	Not maintenance
19	Dawe,S., 2001. Multisystemic family therapy in methadone maintained families: preliminary results from a randomized controlled trial. *Drug and Alcohol Dependence Sixty.Third.Annual Scientific Meeting., Scottsdale., Arizona.*, **63 Suppl 1**, S37-S38.	Abstract
20	Dean,A.J., Bell,J., Christie,M.J., and Mattick,R.P., 2004. Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence. *European Psychiatry: the Journal of the Association of European Psychiatrists*, 19, 510-513.	Not HRQOL, secondary analysis of old study
21	Doran,C.M., Shanahan,M., Bell,J., and Gibson,A., 2004. A cost-effectiveness analysis of buprenorphine-assisted heroin withdrawal. *Drug & Alcohol Review*, **23**, 171-175.	Economic study
22	Dürsteler-Mac-Farland,K.M., Strasse,H., Meier,N., Kuntze,M., and Ladewig,D., 2002. Effects of a single 50% increase in daily methadone dose on heroin craving and mood in low- versus high-dose methadone patients. *Drug and Alcohol Dependence*, **66 Suppl 1**, 48-49.	Abstract
23	Eder,H., Kraigher,D., Peternell,A., Schinler,S., Jagsch,R., Kasper,S., and Fischer,G., 2002. Delayed-release morphine and methadone for maintenance therapy in opioid dependence. *Drug and Alcohol Dependence*, **66 Suppl 1**, 50.	Abstract
24	Epstein,D.H., Schmittner,J., Schroeder,J.R., and Preston,K.L., 2003. Promoting simultaneous abstinence from cocaine and heroin with a methadone dose incease and a novel contingency. *65th.Annual Scientific Meeting.of the College.on Problems of Drug Dependence*, 45.	Abstract
25	Fiellin,D.A., O'Connor,P.G., Chawarski,M., Pakes,J.P., Pantalon,M.V., and Schottenfeld,R.S., 2001. Methadone maintenance in primary care: a randomized controlled trial. *JAMA*, 286, 1724-1731.	Already in SR (Simoens)
26	Fudala,P.J., Bridge,T.P., Herbert,S., Williford,W.O., Chiang,C.N., Jones,K., Collins,J., Raisch,D., Casadonte,P., Goldsmith,R.J., Ling,W., Malkerneker,U., McNicholas,L., Renner,J., Stine,S., Tusel,D., and Buprenorphine/Naloxone Collaborative Study Group., 2003. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone.[see comment]. *New England Journal of Medicine*, **349**, 949-958.	Already in SR (Mattick 2005)
27	Galanter,M., Dermatis,H., Glickman,L., Maslansky,R., Sellers,M.B., Neumann,E., and Rahman-Dujarric,C., 2004. Network therapy: decreased secondary opioid use during buprenorphine maintenance. *Journal of Substance Abuse Treatment*, **26**, 313-318.	Not maintenance
28	Galanter,M., Dermatis,H., Glickman-l, Maslansky,R., Brealyn,S.M., and Rahman,D.C., 2004. Network therapy and buprenorphine maintenance for the treatment of heroin addiction. *66th.Annual Scientific Meeting.of the College.on Problems of Drug Dependence*.	Duplicate report of ID 87, not maintenance
29	Gonzalez,G., Feingold,A., Oliveto,A., Gonsai,K., and Kosten,T.R., 2003. Comorbid major depressive disorder as a prognostic factor in cocaine-abusing buprenorphine-maintained patients treated with desipramine and contingency management. *American Journal of Drug & Alcohol Abuse*, **29**, 497-514.	Study of prognostic factors
30	Greenwald,M.K., 2002. Maximizing Suppression of Heroin Craving: A Randomized-Group, Double-Blind Comparison of Two Methadone Induction Schedules. *Drug and Alcohol Dependence*, **66 Suppl 1**, 68-69.	Abstract

31	Gross,A., Jacobs,E.A., Petry,N.M., Badger,G.J., and Bickel,W.K., 2001. Limits to buprenorphine dosing: a comparison between quintuple and sextuple the maintenance dose every 5 days. *Drug & Alcohol Dependence*, **64**, 111-116.	Not maintenance; Not randomised
32	Jiang,T.P., Li,L.Y., Liu,Y.H., and Wu,S.Q., 2003. Clinical control study on methadone and buprenorphine for heroin dependence. *Chinese Journal of Drug Dependence*, **12**, 119-122.	Not randomised, abstract inconsistent with text; not maintenance.
33	Jones,H., Johnson,R.E., Jasinski,D.R., O'Grady,K., Chisholm,C., Choo,R., Crocetti,M., Dudas,R., Harrow,C., Huestis,M., Jansson,L., Lantz,M., Lester,B., and Milio,L., 2004. A randomized controlled study of buprenorphine and methadone in pregnant opioid-dependent patients: Their effect on the neonatal abstinence syndrome. *Sixty.Sixth.Annual Scientific Meeting.of the College.on Problems of Drug Dependence*.	Inappropriate outcomes; neonate abstinence syndrome
34	Jones,H.E., Johnson,R.E., Jasinski,D.R., and Milio,L., 2005a. Randomized controlled study transitioning opioid-dependent pregnant women from short-acting morphine to buprenorphine or methadone. *Drug & Alcohol Dependence*, **78**, 33-38.	Switch pharmacotherapy and doubts about randomisation
35	Jones,H.E., Johnson,R.E., Jasinski,D.R., O'Grady,K.E., Chisholm,C.A., Choo,R.E., Crocetti,M., Dudas,R., Harrow,C., Huestis,M.A., Jansson,L.M., Lantz,M., Lester,B.M., and Milio,L., 2005b. Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug & Alcohol Dependence*, **79**, 1-10.	Inappropriate outcomes
36	Kakko,J., Svanborg,K.D., Kreek,M.J., and Heilig,M., 2003. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial.[see comment]. *Lancet*, **361**, 662-668.	In Mattick review
37	King,V., Brooner,R., Kidorf,M., Stoller,K., Carter,J., and Schwartz,R., 2002a. A controlled trial of methadone medical maintenance: 12-month results. *Drug and Alcohol Dependence*, **66 Suppl 1**.	Abstract only
38	Kosten,T., Oliveto,A., Feingold,A., Poling,J., Sevarino,K., Cance-Katz,E., Stine,S., Gonzalez,G., and Gonsai,K., 2003. Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. *Drug & Alcohol Dependence*, **70**, 315-325.	Secondary analysis of old study
39	Krook,A.L., Brors,O., Dahlberg,J., Grouff,K., Magnus,P., Roysamb,E., and Waal,H., 2002. A placebo-controlled study of high dose buprenorphine in opiate dependents waiting for medication-assisted rehabilitation in Oslo, Norway.[see comment]. *Addiction*, **97**, 533-542.	Already in SR (Mattick 2005)
40	Lintzeris,N., Ritter,A., Panjari,M., Clark,N., Kutin,J., and Bammer,G., 2004. Implementing buprenorphine treatment in community settings in Australia: experiences from the Buprenorphine Implementation Trial. American Journal of Addictions, 13 Suppl 1, S29	Already in SR (Mattick 2005)
41	Lofwall,M.R., Strain,E.C., Stitzer,M.L., and Bigelow,G.E., 2004. Comparative safety and side-effect profiles of buprenorphine vs. methadone in the outpatient treatment of opioid dependence. *Sixty.Sixth.Annual Scientific Meeting.of College.on Problems of Drug Dependence*.	Superseded by Loftwall 2005 ref 391
42	Mattick,R.P., Ali,R., White,J.M., O'Brien,S., Wolk,S., and Danz,C., 2003. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction, 98, 441-452.	Already in SR (Mattick 2005)
43	Maxwell,S. and Shinderman,M.S., 2002. Optimizing long-term response to methadone maintenance treatment: A 152-week follow-up using higher-dose methadone. *Journal of Addictive Diseases*, **21**, 1-12.	Not randomised
44	Mitchell,T.B., White,J.M., Somogyi,A.A., and Bochner,F., 2002. Slow release oral morphine as a maintenance pharmacotherapy for opioid dependence. *Drug and Alcohol Dependence*, **66 Suppl 1**.	Abstract
45	Mitchell,T.B., White,J.M., Somogyi,A.A., and Bochner,F., 2004. Slow-release oral morphine versus methadone: a crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapies for opioid dependence. *Addiction*, **99**, 940-945.	Switch prior to randomisation
46	Montoya,I.D., Gorelick,D.A., Preston,K.L., Schroeder,J.R., Umbricht,A., Cheskin,L.J., Lange,W.R., Contoreggi,C., Johnson,R.E., and Fudala,P.J., 2004. Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. *Clinical Pharmacology & Therapeutics*, **75**, 34-48.	Already in SR (Lintzeris 2003)
47	Neri,S., Bruno,C.M., Pulvirenti,D., Malaguarnera,M., Italiano,C., Mauceri,B., Abate,G., Cilio,D., Calvagno,S., Tsami,A., Ignaccolo,L., Interlandi,D., Prestianni,L., Ricchena,M., and Noto,R., 2005. Randomized clinical trial to compare the effects of methadone and buprenorphine on the immune system in drug abusers. *Psychopharmacolgy,***179,** 700-704	Inappropriate outcomes; immune system measures
48	Newcombe,D.A., Bochner,F., White,J.M., and Somogyi,A.A., 2004. Evaluation of levo-alpha-acetylmethdol (LAAM) as an alternative treatment for methadone maintenance patients who regularly experience withdrawal: a pharmacokinetic and pharmacodynamic analysis. *Drug & Alcohol Dependence*, **76**, 63-72.	Inappropriate outcomes
49	Petitjean,S., Stohler,R., Deglon,J.J., Livoti,S., Waldvogel,D., Uehlinger,C., and Ladewig,D., 2001. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug & Alcohol Dependence*, **62**, 97-104.	Already in SR (Mattick 2005)
50	Petry,N. and Martin,B., 2001. Prize reinforcement contingency management for cocaine-abusing methadone patients. *Drug and Alcohol Dependence*, **63 Suppl 1**, 122.	Abstract

51	Petry,N.M. and Martin,B., 2002. Low-cost contingency management for treating cocaine- and opioid-abusing methadone patients. *Journal of Consulting & Clinical Psychology*, **70**, 398-405.	Already in SR (Simoens)
52	Petry,N.M., Bickel,W.K., and Badger,G.J., 2001. Examining the limits of the buprenorphine interdosing interval: daily, every-third-day and every-fifth-day dosing regimens.[see comment]. *Addiction*, **96**, 823-834.	Already in SR (Simoens)
53	Pollack,M.H., Otto,M.W., Kaufman,M.J., Penava,S.J., Lanka,G.D., Yurgelun-Todd,D.A., and Renshaw,P.F., 2001. Renshaw cognitive-behavioral therapy for illicit drug use during methadone maintenance: treatment outcomes and MR spectroscopy findings. *Drug and Alcohol Dependence*, **63 Suppl 1**, 124.	Abstract
54	Preston,K.L., Umbricht,A., and Epstein,D.H., 2002. Abstinence reinforcement maintenance contingency and one-year follow-up. *Drug & Alcohol Dependence*, **67**, 125-137.	Already in SR (Simoens)
55	Primorac,A., Ortner,R., Jagsch,R., Rohrmeister,K., Langer,M., and Fischer,G., 2004. Double-dummy, double-blind comparison of buprenorphine and methadone in pregnant opioid-dependent women. *Sixty.Sixth.Annual Scientific Meeting.of the College.on Problems of Drug Dependence*.	Abstract
56	Ritter,A., Lintzeris,N., Clark,N., Kutin,J., and Bammer,G., 2001. A randomised trial of buprenorphine maintenance in primary case office-based settings: clinical guidelines, training programs and efficacy. *Drug and Alcohol Dependence*, **63 Suppl 1**, 131.	Abstract
57	Ritter,A., Lintzeris,N., Clark,N., Panjari,M., Harris,A., Godspodarevskaja,E., Kutin,J., and Bammer,G., 2002. A randomized trial of buprenorphine maintenance compared to methadone maintenance: Psycho-social outcomes. *Drug and Alcohol Dependence*, **66 Suppl 1**.	Abstract
58	Schottenfeld,R.S., Chawarski,M.C., Pakes,J.R., Pantalon,M.V., Carroll,K.M., and Kosten,T.R., 2005. Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *American Journal of Psychiatry*, **162**, 340-349.	Study of prognostic factors
59	Schwartz,R.P., Highfield,D., Battjes,R.J., Callaman,J.M., Butler,C., Rouse,C., Jaffe,J.H., and Brady,J.V., 2003. Interim methadone maintenance: preliminary findings. *65th.Annual Scientific Meeting.of the College.on Problems of Drug Dependence*, 593.	Abstract
60	Suchman,N.E., McMahon,T.J., and Luthar,S.S., 2004. Interpersonal maladjustment as predictor of mothers' response to a relational parenting intervention. *Journal of Substance Abuse Treatment*, **27**, 135-143.	Inappropriate outcomes; Study of prognostic factors
61	Silverman,K., Robles,E., Mudric,T., Bigelow,G.E., and Stitzer,M.L., 2004. A randomized trial of long-term reinforcement of cocaine abstinence in methadone-maintained patients who inject drugs. *Journal of Consulting & Clinical Psychology*, **72**, 839-854.	Mixed population, emphasis on cocaine abusers.
62	Sullivan,L.E., Chawarski,M., O'Connor,P.G., Schottenfeld,R.S., and Fiellin,D.A., 2005. The practice of office-based buprenorphine treatment of opioid dependence: is it associated with new patients entering into treatment? *Drug & Alcohol Dependence*, **79**, 113-116.	Not randomised
63	Triffleman,E., 2001. Sdpt vs Cbcst: a randomized controlled trial among ptsd + opiate dependent subjects. *Drug and Alcohol Dependence*, **63 Suppl 1**, 159.	Abstract
64	Van Den,B.W., Hendriks,V.M., Blanken,P., Koeter,M.W., van Zwieten,B.J., and Van Ree,J.M., 2003. Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials.[see comment][erratum appears in BMJ. 2003 Sep 27;3217(7417):724]. *BMJ*, **327**, 310.	In Ferri review
65	White,J.M., Danz,C., Kneebone,J., La-Vincente,S.F., Newcombe,D.A.L., and Ali,R.L., 2001. Relationship between Laam-methadone preference and treatment outcomes. *Drug and Alcohol Dependence*, **63 Suppl 1**, 168.	Abstract
66	Woody,G.E., McLellan,A.T., Bovasso,G., Kurtz,J., and O'Brien,C.P., 2001. Methadone maintenance and opioid positive urine: a test of 80 mg vs 120 mg and MET vs DC. *Drug and Alcohol Dependence*, **63 Suppl 1**, 173.	Abstract

Appendix 12 Health states and results from PenTAG

Table 66 Health states and utilities derived from the Value of Health Panel

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

Health state scenarios:

Assume on treatment:

1. Drugs free

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

2. Drugs reduction (injectors)

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

- You will have to collect medication from your community pharmacy at least once a week and possibly every day. You may accidentally overdose and require urgent medical attention.

3. Drugs reduction (non-injectors)

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

Assume not on treatment:

4. Drug misusers (injectors)

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

5. Drug misusers (non-injectors)

- You may experience moderate anxiety or low mood on most days. You may have difficulty getting to sleep.
- You may experience moderate pain or discomfort, sweats and shakes on most days. You may experience chest infections and shortness of breath

- You hardly ever feel tired
- You may find it difficult to obtain and hold down a job. You might incur debts that you find difficult to pay
- You may find it difficult to be punctual and reliable, leading to disagreements with family and friends
- You hardly ever have problems concentrating
- You may have reduced libido or an irregular menstrual cycle
- You may need to attend your GP or an A&E service to obtain emergency relief for your symptoms on a regular basis.

Appendix 13 Identified UK ongoing / unpublished RCTs.

Data base information lacked sufficient detail to be certain that trials were randomised and trials were not multiply registered. It was not easy to determine if listed trials registered as unpublished have in fact been published subsequent to registration.

Title	Trial status	Year	Country	Patients recruited	Designed number	Comparison
A pilot study of a motivational intervention to help opiate dependent patients on methadone who drink excessively	Complete	Jan 2001-Jan 2002	UK	Opiate dependent patients being treated with methadone who drink excessively.	NR	Unclear
Costing the "injectable clinic".	Complete	15/3/1998-14/6/1998	UK	N/A	NR	Unclear
Do serum methadone concentrations enable optimisation of maintenance doses in opiate dependent substance miss-users	Complete	1/9/2000-31/3/2001	UK	Methadone users	NR	Unclear
Functional magnetic resonance imaging study of cue induced craving in heroin addicts	Complete	1/1/1999-30/11/2001	UK	Methadone maintained males and healthy volunteer controls.	NR	Unclear
Methadone maintenance treatment for opiate addicts in shared care: is it effective in improving health outcomes and reducing criminal activity? A randomised controlled trial in a new primary care clinic.	Complete	1/2/1998-31/1/2003. Two-stage study, the 2nd stage is a RCT over 2yrs	UK	Opitae addicts	NR	Unclear
Phase III double -blind, double-dummy randomised controlled, single centre, parallel group study to compare the efficacy of buprenorphine/haloxone stabilisation and withdrawal with methadone stabilisationplus lofexidine-assissted withdrawal in addict	Complete	1/11/1997-31/10/1999	UK	Opiate-dependent addicts	NR	Unclear
Pilot study for a randomised control trial and patient preference trial of Subutex (Buprenorphine) versus Methadone maintenance treatment in the management of opiate dependent patients	Complete	12/5/2003-12/5/2004 (RCT and cohort study)	UK	Opiate dependent patients	NR	Unclear
Randomised controlled trial of Dihydrocodeine and methadone in the treatment of opiate dependence syndrome	Complete	28/8/2000 28/8/2004	UK	Opiate dependents	400	Dihydrocodeine v. methadone
Randomised Controlled Trial to assess the effectiveness of offering prescriptions of injectable opiates to opiate dependant drug users	Complete	1/1/1998-1/1/2000	UK	Opiate dependent drug users with inclusion criteria	Reported but not clear	Choice of treatment received v. no choice of treatment received

Title	Trial status	Year	Country	Patients recruited	Designed number	Comparison
The 2 year outcomes of Diamorphine versus methadone prescribing for long term heroin addiction.	Complete	1/3/1999-1/9/2000	UK	Heroin addicts	NR	Diamorphine v. methadone.
RCT of dihydrocodeine versus methadone treatment in opiate dependence syndrome	Complete	1/10/2000-30/9/2004	UK	Unclear	Unclear	Unclear
The effectiveness and cost effectiveness of cognitive behaviour therapy for opiate misusers in methadone maintenance treatment: a multicentre, randomised controlled trial	Complete	1/6/2000-30/6/2005	UK	Opiate miss-users.	220 opiate dependent patients	Unclear
The effectiveness and cost effectiveness of cognitive behaviour therapy for opiate miss-users in methadone maintenance treatment: a multi centre, randomised controlled trial (UKCBTMM).	Complete	1/8/2000-31/3/2004	UK	Opiate dependent patients	220 opiate dependent patients	Standard MMT plus CBT v. standard MMT alone.
The effectiveness and cost effectiveness of cognitive behaviour therapy for opiate miss-users in methadone maintenance treatment: A multi-centre, randomised controlled trial (UKCBTMM).	Complete	1/8/2000-1/2/2004	UK	Opiate dependent patients	220 opiate dependent patients	Standard MMT plus CBT v. standard MMT alone
The evaluation of Methadone Substitution Therapy and Its Impact on HIV Risk Behaviours	Complete	1/1/1993-3/3/1999	UK	Opiate dependents	NR	Unclear
Methadone maintenance treatment for opiate addicts in shared care: is it effective in improving health outcomes and reducing criminal activity? A randomised controlled trial in a new primary care clinic.	Closed to recruitment of pts.: follow-up continuing.	01 Feb 1998-31 Jan 2003 (2-stage study, the mainstage is a RCT over appro 2yrs.)	UK	Opiate addicts	NR	Unclear
Randomised controlled trial of Dihydrocodeine (DHC) and Methadone in the Treatment of Opiate dependence patients	Complete	01/09/2000 - 01/03/2005	UK	Opiate dependence patients	NR	Dihydrocodeine v. methadone
Methadone maintenance treatment for opiate addicts in shared care: is it effective in improving health outcomes and reducing criminal activity? A randomised controlled trial in a new primary care clinic.	Un-available	NR	UK	Opiate addicts	NR	Unclear
Evaluation of Liquid vs. Tablet Buprenorphine	Unclear	Start: Aug 1996.Record first received Sep 1999, last updated: June 2005	US	Opioid-related disorders	NR	Buprnorphine sublingual tablets v. sublingual solution.

Title	Trial status	Year	Country	Patients recruited	Designed number	Comparison
Buprenorphine / Naloxone Treatment for Opioid Dependence-Experinment III	Unclear	Start:July 1997.Record first received July 1997, last updated: July 2005	US	Heroin Dependence, Opioid-related disorders	NR	Buprenorphine/ naloxone combination tablet v. mathadone
Counselling conditions for Buprenorphine in a Primary	Unclear	Record first received Dec 2002, last updated: June 2005	US	Heroin Dependence, Opioid-related disorders/ Substance Abuse, Intravenous	NR	Standard Medical management (SMM) v. SMM education about addiction and recovery (Enhanced Medical Management, EMM)
Motivational Incentive for Enhanced Drug Abuse Recovery: Methadone Clinics.	Unclear	Star: Sep 2000, Data entry closure: Apr 2003	US	Substance-related Disorders	NR	Low v. typical incentive values of motivation

11 REFERENCES

1 Bearn J. Lofexidine for opiate detoxification. *Acta Neuropsychiatrica* 2004; **16**(5):239-245.

2 WHO/UNODC/UNAIDS Position Paper. Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention. Geneva: World Health Organisation; 2004.

3 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder. Washington: APA; 1994.

4 National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addiction. *JAMA* 1998; **280**(22):1936-1943.

5 Hser Y-I, Anglin MD, Powers K. A 24-year follow-up of California narcotics addicts. *Archives in General Psychiatry* 1993; **50**:577-584.

6 Joe GW, Chastain RL, Simpson DD. Length of careers. In: Simpson DD, Sells SB, editors. Opioid Addiction and Treatment: a 12-year follow-up. Malabar, FL: Keiger; 1990.

7 Marsden J, Strang J, Lavoie D, Abdulrahim D, Hickman M, Scott S. Drug Misuse. In: Stevens A, Raftery J, Mant J, Simpson S, editors. Health Care Needs Assessent: The Epidemiologically Based Needs Assessment Reviews. Abingdon: Radcliffe Medical Press; 2004. p. 367-450.

8 Biernacki P. Pathways From Heroin Addiction. Recovery Without Treatment. Philadelphia: Temple University Press; 1986.

9 Chivite-Matthews,N, Richardson,A, O'Shea,J, Becker,J, Owen,N, *et al.* Drug Misuse Declared: Findings from the 2003/4 British Crime Survey. London: Home Office; 2005.

10 National Treatment Agency for Substance Misuse. Statistical Release: Statistics for Drug Treatment Activity in England 2004/5 from the National Drug Treatment Monitoring System. London: National Treatment Agency; 2005.

11 Oppenheimer E, Tobbutt C, Taylor C, Andrew T. Death and survivial in a cohort of heroin addicts from London clinics. *Addiction* 1994; **89**:1299-1308.

12 Brugal MT, Domingo-Salvany A, Puig R, Barrio G, Garcia de OP, de la FL. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction* 2005; **100**(7):981-989.

13 Gossop M, Marsden J, Stewart D. NTORS at 1 year. The National Treatment Outcome Research Study: Changes in substance use, health and criminal behaviours at 1 year after intake. London: Department of Health; 1998.

14 Health Protection Agency. Infections Among Injecting Drug Users in the United Kingdom 2004. An Update. *Health Protection Scotland, National Public Health Servive for Wales, CDSC Northern Ireland, CRDHB,and the UASSG* 2005.

15 Regier CA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, *et al*. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the epidemiologic catchment area (ECA) study. *JAMA* 1990; **264**:2511-2518.

16 Regier DA, Rae DS, Narrow WE, Kaelber CT, Schatzberg AF. Prevalence of anxiety disorders and their comorbidity with mood and addictive disorders. *British Journal of Psychiatry* 1998; **173**(Suppl. 34):24-28.

17 Marsden J, Gossop M, Stewart D, Rolfe A, Farrell M. Psychiatric symptoms among clients seeking treatment for drug dependence. *British Journal of Psychiatry* 2000; **176**:285-289.
18 Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, *et al*. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990; **264**(19):2511-2518.
19 Menezes PR, Johnson S, Thornicroft G, Marshall J, Prosser D, Bebbington P, *et al*. Drug and alcohol problems among individuals with severe mental illness in south London. *Br J Psychiatry* 1996; **168**(5):612-619.
20 Graham HL, Maslin J, Copello A, Birchwood M, Mueser K, McGovern D, *et al*. Drug and alcohol problems amongst individuals with severe mental health problems in an inner city area of the UK. *Soc Psychiatry Psychiatr Epidemiol* 2001; **36**(9):448-455.
21 Levinson I, Galynker II, Rosenthal RN. Methadone withdrawal psychosis. *J Clin Psychiatry* 1995; **56**(2):73-76.
22 Bloom F, Segal D, Ling N, Guillemin R. Endorphins: profound behavioral effects in rats suggest new etiological factors in mental illness. *Science* 1976; **194**(4265):630-632.
23 Donovan SJ, Nunes EV. Treatment of comorbid affective and substance use disorders. Therapeutic potential of anticonvulsants. *Am J Addict* 1998; **7**(3):210-220.
24 Darke S, Ross J. Fatal heroin overdoses resulting from non-injecting routes of administration, NSW, Australia, 1992-1996. *Addiction* 2000; **95**(4):569-573.
25 Advisory Council on the Misuse of Drugs. Hidden Harm: Responding to the needs of children of Problem Drug Users. *Home Office: London* 2003.
26 Barnard M, McKeganey N. The impact of parental problem drug use on children: what is the problem and what can be done to help? *Addiction* 2004; **99**(5):552-559.
27 United Kingdom Anti-Drugs Coordinating Unit. Tackling Drugs to Build a Better Britain: The Government's ten-year strategy for tackling drug misuse. 1998. London, The Stationery Office.
28 Bennet Y, Holloway K, Williams T. Drug use and offending: Summary results of the First Year of the New-Adam Research Programme. *Home Office Research Findings no: 148 London: Home office* 2001.
29 Gossop M, Marsden J, Stewart D, Kidd T. The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. *Addiction* 2003; **98**:291-303.
30 Ward J, Mattick RP, Hall W. The Use of Methadone During Maintenance Treatment: Pharmacology, Dosage and Treatment Outcome. In: Ward J, Mattick RP, Hall W, editors. Methadone Maintenance Treatnment and Other Opioid Replacement Therapies. Amsterdam: Harwood Academic Publishers; 1998. p. 205-238.
31 Novick DM, Richman BL, Friedman JM, Friedman JE, Fried C, Wilson JP, *et al*. The medical status of methadone maintenance patients in treatment for 11-18 years. *Drug and Alcohol Dependence* 1993; **33**:235-245.
32 Caplehorn JR. Deaths in the first two weeks of maintenance treatment in NSW in 1994: identifying cases of iatrogenic methadone toxicity. *Drug Alcohol Rev* 1998; **17**(1):9-17.
33 Lintzeris,N, Clark,N, Muhleisen,P, Ritter,A. National Clinical Guidelines and Procedures for the use of Buprenorphine in the Treatment of Heroin Dependence. Canberra: Commonwealth of Australia; 2001.
34 Kleber HD. Opioids: Detoxification. In: Kleber HD, Galanter M, editors. Textbook of substance abuse treatment. Washington: American Psychiatric Press; 1999. p. 251-269.
35 Department of Health. Drug Misuse and Dependence - Guidelines on Clinical Management. London: Department of Health; 1999.

36 Payte JT, Zweben JE, Martin J. Opioid Maintenance Treatment. Principles of Addiction Medicine. Chevy Chase, MD: American Society of Addiction Medicine; 2003. p. 751-766.
37 Verster A, Buning E. Training Manual: Key Aspects of Substitution Treatment for Opiate Dependence. Amsterdam: Euro Methwork; 2003.
38 National Treatment Agency for Substance Misuse. Models of Care for the Treatment of Drug Misusers. London: National Treatment Agency for Substance Misuse; 2002.
39 UK Focal Point on Drugs. United Kingdom Drug Situation. Annul Report to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). London: Department of Health; 2004.
40 Lingford-Hughes AR, Welch S, Nutt DJ. Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association of Pharmacology. *Journal of Psychopharmacology* 2004; **18**(3):293-335.
41 Department of Health. Task Force to Review Services for Drug Misusers: Report of an Independent Review of Drug Treatment Services in England. London: Department of Health; 1996.
42 Hulse GK, Milne E, English DR, Holman CDJ. The relationship between maternal use of heroin and methadone and infant birth weight. *Addiction* 1997; **92**(11):1571-1579.
43 Hulse GK, Milne E, English DR, Holman CD. Assessing the relationship between maternal opiate use and antepartum haemorrhage. *Addiction* 1998; **93**(10):1553-1558.
44 Day E, George S. Management of drug misuse in pregnancy. *Advances in Psychiatric Treatment* 2005; **11**(4):253-261.
45 Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991; **44**(11):1271-1278.
46 Jadad A. *Randomised controlled trials* 1998; BMJ Books 1st edition.
47 Amato L, Minozzi S, Davoli M, Vecchi S, Ferri M, Mayet S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence [Cochrane review]. Cochrane Database of Systematic Reviews 2004 Issue 4. Chichester (UK): John Wiley & Sons, Ltd; 2004.
48 Barnett PG, Rodgers JH, Bloch DA. A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. *Addiction* 2001; **96**(5):683-690.
49 Caplehorn JR, Drummer OH. Mortality associated with New South Wales methadone programs in 1994: lives lost and saved. *Med J Aust* 1999; **170**(3):104-109.
50 Clark N, Lintzeris N, Gijsbers A, Whelan G, Dunlop A, Ritter A, *et al.* LAAM maintenance vs methadone maintenance for heroin dependence [Cochrane review]. Cochrane Database of Systematic Reviews 2002 Issue 2. Chichester (UK): John Wiley & Sons, Ltd; 2002.
51 Davids E, Gastpar M. Buprenorphine in the treatment of opioid dependence. *European Neuropsychopharmacology* 2004; **14**(3):209-216.
52 Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opiod dependence [Cochrane review]. Cochrane Database of Systematic Reviews 2003 Issue 3. Chichester (UK): John Wiley & Sons, Ltd; 2003.
53 Farre M, Mas A, Torrens M, Moreno V, Cami J. Retention rate and illicit opioid use during methadone maintenance interventions: A meta-analysis. *Drug & Alcohol Dependence* 2002; **65**(3):283-290.

54 Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin dependents [Cochrane review]. Cochrane Database of Systematic Reviews 2005 Issue 2. Chichester (UK): John Wiley & Sons, Ltd; 2005.
55 Fridell M. Psychosocial Treatment for Drug Dependence. In: Berglund M, Thelander S, Jonsson E, editors. Treating Alcohol and Drug Abuse; An Evidence based Review. Wiley; 2003. p. 325-413.
56 Glanz M, Klawansky S, McAullife W, Chalmers T. Methadone vs. L-alpha-acetylmethadol (LAAM) in the treatment of opiate addiction: A meta-analysis of the randomized, controlled trials. *American Journal on Addictions* 1997; **6**(4):339-349.
57 Gowing L, Farrell M, Bornemann R, Ali R. Substitution treatment of injecting opioid users for prevention of HIV infection [Cochrane review]. Cochrane Database of Systematic Reviews 2004 Issue 4. Chichester (UK): John Wiley & Sons, Ltd; 2004.
58 Griffith JD, Rowan-Szal GA, Roark RR, Simpson DD. Contingency management in outpatient methadone treatment: A meta-analysis. *Drug & Alcohol Dependence* 2000; **58**(1-2):55-66.
59 Hopfer CJ, Khuri, E, Crowley TJ, Hooks S. Adolescent heroin use: a review of the descriptive and treatment literature (DARE structured abstract). *Journal of Substance Abuse Treatment* 2002; **23**:231-237.
60 Johansson BA. Pharmacotherapy for Opioid Dependence. In: Berglund M, Thelander S, Jonsson E, editors. Treating Alcohol and Drud Abuse; An Evidence Based Review. Wiley; 2003. p. 465-531.
61 Kirchmayer U, Davoli M, Verster A. Naltrexone maintenance treatment for opioid dependence [Cochrane review]. Cochrane Database of Systematic Reviews 2003 Issue 2. Chichester (UK): John Wiley & Sons, Ltd; 2003.
62 Layson-Wolf C, Goode J-V, Small RE. Clinical use of methadone. *Journal of Pain & Palliative Care Pharmacotherapy* 2002; **16**(1):29-59.
63 Lintzeris N, Ford C. NTA: BPN Evidence to practice Briefing. *Unpublished* 2004;1-39.
64 Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: A meta-analysis. *Addiction* 1998; **93**(4):515-532.
65 Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence [Cochrane review]. Cochrane Database of Systematic Reviews 2003 Issue 2. Chichester (UK): John Wiley & Sons, Ltd; 2003.
66 Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence [Cochrane review]. Cochrane Database of Systematic Reviews unpublished. Chichester (UK): John Wiley & Sons, Ltd; 2005.
67 Prendergast ML, Podus D, Chang E. Program factors and treatment outcomes in drug dependence treatment: an examination using meta-analysis. *Substance Use & Misuse* 2000; **35**(12-14):1931-1965.
68 Prendergast ML, Podus D, Chang E, Urada D. The effectiveness of drug abuse treatment: A meta-analysis of comparison group studies. *Drug & Alcohol Dependence* 2002; **67**(1):53-72.
69 Raisch DW, Fye CL, Boardman KD, Sather MR. Opioid dependence treatment, including buprenorphine/naloxone. *Annals of Pharmacotherapy* 2002; **36**(2):312-321.

70 Roozen HG, Boulogne JJ, Van Tulder MW, Van Den BW, De Jong CAJ, Kerkhof AJ. A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. *Drug & Alcohol Dependence* 2004; **74**(1):1-13.
71 Simoens S, Matheson C, Bond C, Inkster K, Ludbrook A. The effectiveness of community maintenance with methadone or buprenorphine for treating opiate dependence. *British Journal of General Practice* 2005; **55**(511):139-146.
72 Simoens S, Matheson C, Inkster K, Ludbrook A, Bond C. The effectiveness of treatment for opiate dependent drug users. *https://scotland gov uk/library5/health/isrem-00 asp* 2002;1-190.
73 Sorensen JL, Copeland AL. Drug abuse treatment as an HIV prevention strategy: a review (DARE structured abstract). *Drug and Alcohol Dependence* 2000; **59**:17-31.
74 Stanton MD, Shadish WR. Outcome, attrition, and family-couples treatment for drug abuse: a meta-analysis and review of the controlled, comparative studies. *Psychological Bulletin* 1997; **122**(2):170-191.
75 Van Beusekom I, Iguchi M. A review of recent advances in knowledge about methadone maintenance treatment. *RAND Europe Report* 2001; http://www.rand.org/publications/MR/MR1396/:1-101.
76 West SL, O'Neal KK, Graham CW. A meta-analysis comparing the effectiveness of buprenorphine and methadone. *Journal of Substance Abuse* 2000; **12**(4):405-414.
77 Ahmadi J, Maany I, Ahmad M. Treatment of intravenous buprenorphine dependence: a randomized open clinical trial. *German Journal of Psychiatry* 2003; **6**:23-29.
78 Ahmadi J. A randomized, clinical trial of buprenophine maintenance treatment for Iranian patients with opioid dependency. *Addictive Disorders & Their Treatment* 2003; **1**(1):2002-2027.
79 Ahmadi J, Ahmadi M. Twelve-month maintenance treatment of heroin-dependent outpatients with buprenorphine. *Journal of Substance Use* 2003; **8**(1):39-41.
80 Avants SK, Margolin A, Usubiaga MH, Doebrick C. Targeting HIV-related outcomes with intravenous drug users maintained on methadone: a randomized clinical trial of a harm reduction group therapy. *Journal of Substance Abuse Treatment* 2004; **26**(2):67-78.
81 Blanken P, Hendriks VM, Koeter MW, Van Ree JM, Van Den BW. Matching of treatment-resistant heroin-dependent patients to medical prescription of heroin or oral methadone treatment: results from two randomized controlled trials. *Addiction* 2005; **100**(1):89-95.
82 Brooner RK, Kidorf MS, King VL, Stoller KB, Peirce JM, Bigelow GE, *et al*. Behavioral contingencies improve counseling attendance in an adaptive treatment model. *Journal of Substance Abuse Treatment* 2004; **27**(3):223-232.
83 Chutuape MA, Silverman K, Stitzer ML. Effects of urine testing frequency on outcome in a methadone take-home contingency program. *Drug & Alcohol Dependence* 2001; **62**(1):69-76.
84 Cornish JW, Herman BH, Ehrman RN, Robbins SJ, Childress AR, Bead V, *et al*. A randomized, double-blind, placebo-controlled safety study of high-dose dextromethorphan in methadone-maintained male inpatients. *Drug & Alcohol Dependence* 2002; **67**(2):177-183.
85 Dean AJ, Bell J, Mascord DJ, Parker G, Christie MJ. A randomised, controlled trial of fluoxetine in methadone maintenance patients with depressive symptoms. *Journal of Affective Disorders* 2002; **72**(1):85-90.

86 Dijkgraaf MGW, Van Der Zanden BP, De Borgie CAJM, Blanken P, Van Ree JM, Van Den Brink W. Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials. *British Medical Journal* 2005; **330**(7503):1297-1300.
87 Dolan KA, Shearer J, MacDonald M, Mattick RP, Hall W, Wodak AD. A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. *Drug & Alcohol Dependence* 2003; **72**(1):59-65.
88 Eder H, Jagsch R, Kraigher D, Primorac A, Ebner N, Fischer G. Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. *Addiction* 2005; **100**(8):1101-1109.
89 Giacomuzzi SM, Riemer Y, Ertl M, Kemmler G, Richter R, Rossler H, *et al*. Substitution treatment and quality of life: methadon vs. Retard morphine sulfate - a comparative study. *Suchtmedizin in Forschung und Praxis* 2001; **3**:89-96.
90 Grabowski J, Rhoades H, Stotts A, Cowan K, Kopecky C, Dougherty A, *et al*. Agonist-like or antagonist-like treatment for cocaine dependence with methadone for heroin dependence: two double-blind randomized clinical trials. *Neuropsychopharmacology* 2004; **29**(5):969-981.
91 Jones HE, Haug N, Silverman K, Stitzer M, Svikis D. The effectiveness of incentives in enhancing treatment attendance and drug abstinence in methadone-maintained pregnant women. *Drug & Alcohol Dependence* 2001; **61**(3):297-306.
92 King VL, Stoller KB, Hayes M, Umbricht A, Currens M, Kidorf MS, *et al*. A multicenter randomized evaluation of methadone medical maintenance. *Drug & Alcohol Dependence* 2002; **65**(2):137-148.
93 Kosten T, Oliveto A, Feingold A, Poling J, Sevarino K, Cance-Katz E, *et al*. Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. *Drug & Alcohol Dependence* 2003; **70**(3):315-325.
94 Kristensen O, Espegren O, Asland R, Jakobsen E, Lie O, Seiler S. Buprenorphine and methadone to opiate addicts--a randomized trial. *Tidsskrift for Den Norske Laegeforening* 2005; **125**(2):148-151.
95 Lidz V, Sorrentino DM, Robison L, Bunce S. Learning from disappointing outcomes: an evaluation of prevocational interventions for methadone maintenance patients. *Substance Use & Misuse* 2004; **39**(13-14):2287-2308.
96 Lofwall MR, Stitzer ML, Bigelow GE, Strain EC. Comparative safety and side effect profiles of buprenorphine and methadone in the outpatient treatment of opioid dependence. *Addictive Disorders & Their Treatment* 2005; **4**(2):49-64.
97 Margolin A, Kantak K, Copenhaver M, Avants SK. A preliminary, controlled investigation of magnesium L-aspartate hydrochloride for illicit cocaine and opiate use in methadone-maintained patients. *Journal of addictive diseases : the official journal of the ASAM , American Society of Addiction Medicine* 2003; **22**:49-61.
98 Marsch LA, Bickel WK, Badger GJ, Jacobs EA. Buprenorphine treatment for opioid dependence: the relative efficacy of daily, twice and thrice weekly dosing. *Drug and Alcohol Dependence* 2005; **77**:195-204.
99 Pollack MH, Penava SA, Bolton E, Worthington JJ, III, Allen GL, Farach FJ, Jr., *et al*. A novel cognitive-behavioral approach for treatment-resistant drug dependence. *Journal of Substance Abuse Treatment* 2002; **23**(4):335-342.
100 Ritter AJ, Lintzeris N, Clark N, Kutin JJ, Bammer G, Panjari M. A randomized trial comparing levo-alpha acetylmethadol with methadone maintenance for patients in primary care settings in Australia. *Addiction* 2003; **98**(11):1605-1613.

101 Sigmon SC, Correia CJ, Stitzer ML. Cocaine abstinence during methadone maintenance: effects of repeated brief exposure to voucher-based reinforcement. *Experimental & Clinical Psychopharmacology* 2004; **12**(4):269-275.
102 Zanis DA, Coviello D, Alterman AI, Appling SE. A community-based trial of vocational problem-solving to increase employment among methadone patients. *Journal of Substance Abuse Treatment* 2001; **21**(1):19-26.
103 Van Den Brink W, Hendriks VM, Blanken P, Koeter MW, van Zwieten BJ, Van Ree JM. Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials.*[erratum appears in BMJ. 2003 Sep 27;3217(7417):724]*. *BMJ* 2003; **327**(7410):310.
104 Mattick RP, Digiusto E, Doran C, O'Brien S, Shanahan M, Kimber J, *et al*. National Evaluation of Pharmacotherapies for Opioid Dependence: Report of results and recommendations. *National Drug and Alcohol Centre, Sydney* 2001;1-102.
105 Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. *Lancet* 2003; **361**(9358):662-668.
106 Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction* 2003; **98**(4):441-452.
107 Lintzeris N, Ritter A, Panjari M, Clark N, Kutin J, Bammer G. Implementing buprenorphine treatment in community settings in Australia: experiences from the Buprenorphine Implementation Trial. *American Journal on Addictions* 2004; **13 Suppl 1**:S29-S41.
108 Fischer G, Gombas W, Eder H, Jagsch R, Peternell A, Stuhlinger G, *et al*. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. *Addiction* 1999; **94**(9):1337-1347.
109 Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med* 2000; **343**(18):1290-1297.
110 Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Buprenorphine versus methadone in the treatment of opioid-dependent cocaine users. *Psychopharmacology (Berl)* 1994; **116**(4):401-406.
111 Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry* 1994; **151**(7):1025-1030.
112 Petitjean S, Stohler R, Deglon JJ, Livoti S, Waldvogel D, Uehlinger C, *et al*. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug & Alcohol Dependence* 2001; **62**(1):97-104.
113 Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in France. *JAMA* 2001; **285**(1):45.
114 Higgins ST, Stitzer ML, Bigelow GE, Liebson IA. Contingent methadone delivery: effects on illicit-opiate use. *Drug Alcohol Depend* 1986; **17**(4):311-322.
115 Stitzer ML, Iguchi MY, Felch LJ. Contingent take-home incentive: effects on drug use of methadone maintenance patients. *J Consult Clin Psychol* 1992; **60**(6):927-934.
116 Kidorf M, Stitzer ML, Brooner RK, Goldberg J. Contingent methadone take-home doses reinforce adjunct therapy attendance of methadone maintenance patients. *Drug Alcohol Depend* 1994; **36**(3):221-226.

117 Preston KL, Umbricht A, Epstein DH. Methadone dose increase and abstinence reinforcement for treatment of continued heroin use during methadone maintenance. *Arch Gen Psychiatry* 2000; **57**(4):395-404.
118 Gerra G, Borella F, Zaimovic A, Moi G, Bussandri M, Bubici C, *et al*. Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. *Drug Alcohol Depend* 2004; **75**(1):37-45.
119 Poirier MF, Laqueille X, Jalfre V, Willard D, Bourdel MC, Fermanian J, *et al*. Clinical profile of responders to buprenorphine as a substitution treatment in heroin addicts: results of a multicenter study of 73 patients. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2004; **28**(2):267-272.
120 Schottenfeld RS, Pakes JR, Kosten TR. Prognostic factors in Buprenorphine- versus methadone-maintained patients. *J Nerv Ment Dis* 1998; **186**(1):35-43.
121 Auriacombe M, Fatseas M, Franques-Reneric P, Daulouede JP, Tignol J. [Substitution therapy in drug addictions]. *Rev Prat* 2003; **53**(12):1327-1334.
122 Fudala PJ, Jaffe JH, Dax EM, Johnson RE. Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clin Pharmacol Ther* 1990; **47**(4):525-534.
123 Amass L, Bickel WK, Higgins ST, Badger GJ. Alternate-day dosing during buprenorphine treatment of opioid dependence. *Life Sci* 1994; **54**(17):1215-1228.
124 Amass L, Bickel WK, Crean JP, Blake J, Higgins ST. Alternate-day buprenorphine dosing is preferred to daily dosing by opioid-dependent humans. *Psychopharmacology (Berl)* 1998; **136**(3):217-225.
125 Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. Buprenorphine treatment of opioid dependence: clinical trial of daily versus alternate-day dosing. *Drug Alcohol Depend* 1995; **40**(1):27-35.
126 Bickel WK, Amass L, Crean JP, Badger GJ. Buprenorphine dosing every 1, 2, or 3 days in opioid-dependent patients. *Psychopharmacology (Berl)* 1999; **146**(2):111-118.
127 Schottenfeld RS, Pakes J, O'Connor P, Chawarski M, Oliveto A, Kosten TR. Thrice-weekly versus daily buprenorphine maintenance. *Biol Psychiatry* 2000; **47**(12):1072-1079.
128 O'Connor PG, Oliveto AH, Shi JM, Triffleman EG, Carroll KM, Kosten TR, *et al*. A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. *Am J Med* 1998; **105**(2):100-105.
129 Gibson AE, Doran CM, Bell JR, Ryan A, Lintzeris N. A comparison of buprenorphine treatment in clinic and primary care settings: a randomised trial. *Med J Aust* 2003; **179**(1):38-42.
130 Fiellin DA, O'Connor PG, Chawarski M, Pakes JP, Pantalon MV, Schottenfeld RS. Methadone maintenance in primary care: a randomized controlled trial. *JAMA* 2001; **286**(14):1724-1731.
131 Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, *et al*. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New England Journal of Medicine* 2003; **349**(10):949-958.
132 Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: Available evidence to inform clinical practice and research. *Journal of Substance Abuse Treatment* 2005; **28**(4):321-329.

133 Sees KL, Delucchi KL, Masson C, Rosen A, Clark HW, Robillard H, *et al*. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *JAMA* 2000; **283**(10):1303-1310.
134 Drummond MFJTO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996; **313**:275-283.
135 Phillips Z, Ginnelly L, Sculpher MS, Golder S, Riemsma R, Woolacott M, *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment* 2004; **8**(36):1-172.
136 Sirotnik KA, Bailey RC. A cost--benefit analysis for a multimodality heroin treatment project. *International Journal of the Addictions* 1975; **10**(3):443-451.
137 Doran CM, Shanahan M, Mattick RP, Ali R, White J, Bell J. Buprenorphine versus methadone maintenance: a cost-effectiveness analysis. *Drug & Alcohol Dependence* 2003; **71**(3):295-302.
138 Harris AH, Gospodarevskaya E, Ritter AJ. A randomised trial of the cost effectiveness of buprenorphine as an alternative to methadone maintenance treatment for heroin dependence in a primary care setting. *Pharmacoeconomics* 2005; **23**(1):77-91.
139 Zaric GS, Barnett PG, Brandeau ML. HIV transmission and the cost-effectiveness of methadone maintenance. *American Journal of Public Health* 2000; **90**(7):1100-1111.
140 Zaric GS, Brandeau ML, Barnett PG. Methadone maintanence and HIV prevention: a cost effectiveness analysis. *Manage Sci* 2000; **46**:1013-1031.
141 Barnett PG. The cost-effectiveness of methadone maintenance as a health care intervention. *Addiction* 1999; **94**(4):479-488.
142 Sheerin IG, Green FT, Sellman JD. What is the cost-effectiveness of hepatitis C treatment for injecting drug users on methadone maintenance in New Zealand? *Drug & Alcohol Review* 2004; **23**(3):261-272.
143 Goldschmidt PG. A cost-effectiveness model for evaluating health care programs: application to drug abuse treatment. *Inquiry* 1976; **13**(1):29-47.
144 Zarkin GA, Dunlap LJ, Hicks KA, Mamo D. Benefits and costs of methadone treatment: results from a lifetime simulation model. *Health Economics* 2005; **14**(11):1133-1150.
145 Barnett PG, Zaric GS, Brandeau ML. The cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States. 2001; **96**(9):1267-1278.
146 Masson CL, Barnett PG, Sees KL, Delucchi KL, Rosen A, Wong W, *et al*. Cost and cost-effectiveness of standard methadone maintenance treatment compared to enriched 180-day methadone detoxification. *Addiction* 2004; **99**(6):718-726.
147 Raftery J. NICE: Faster access to modern treatments? Analysis of guidance on health technologies. *BMJ* 2001;1300-1303.
148 Roberts T, Robinson S, Barton P, Bryan S, McCarthy A, MacLeod J, *et al*. The correct approach to modelling and evaluating Chlamydia screening. *Sexually Transmitted Infections* 2004; **80**:324-325.
149 Welte R PMLRKM. Costs and effects of Chlamydial screening: Dynamic versus static modelling. *Sexually Transmitted Diseases* 2005; **32**:474-483.
150 Ridge G, Lintzeris N, Gossop M, Witton J, Clark K, Strang J. The Seven Boroughs buprenorphine study. *National Addiction Centre 2004* 2004.
151 Curtis L, Netton A. Unit costs of health and social care. *Canterbury: PSSRU, University of Kent* 2004.
152 Gossop M, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: Two-year follow-up results from the National

Treatment Outcome Research Study. *Drug & Alcohol Dependence* 2001; **62**(3):255-264.
153 Godfrey C, Eaton G, McDougall C, Culyer A. The economic and social cost of Class A drug use in England and Wales. *Home Office Reaerch Report, Development and Statistics Directorate July 2002* 2002.
154 Gossop M, Marsden J, Stewart D. NTORS after five years: changes in substance use, health and criminal behaviour during the five years after intake. *Department of Health: London* 2001.
155 Godfrey C, Stewart S, Gossop M. National Treatment Outcome Research Study: Economic analysis of the Two Year Outcome Data. *Repor to the Department of Health 2002* 2002.
156 Healey A, Knapp M, Marsden J, Gossop M, Stewart D. Criminal outcomes and costs of treatment services for injecting and non-injecting heroin users: evidence from a national prospective cohort survey. *Journal of Health Services & Research Policy* 2003; **8**(3):134-141.
157 Brand S, Price R. The economic and Social costs of crime. *Home Office Research Study 217 Economic Resource Analysis, Research, Development and Statistics Directorate London Home Office* 2000.
158 Harries R. The costs of criminal justice. *Home Office Research, Development and Statistics Directorate Research Findings 103, London: Home Office* 1999.
159 Luty J, O'Gara C, Sessay M. Is methadone too dangerous for opiate addiction? *BMJ* 2005; **331**(7529):1352-1353.
160 Schifano F, Corkery J, Gilvarry E, Deluca P, Oyefeso A, Ghodse AH. Buprenorphine mortality, seizures and prescription data in the UK, 1980-2002. *Hum Psychopharmacol* 2005; **20**(5):343-348.
161 Gibson A, Degenhardt L. Mortality related to Maltrexone in the treatment of opiate dependence: A comparative analysis. *NDARC Technical Report No: 229* 2005.
162 Ling W, Shoptaw S, Wesson DR, Rawson R, Compton M, Klett CJ. Treatment effectiveness score as an utcome measure in clinical trials. *www drugabuse gov/pdf/monographs/monograph175/208-220_Lingpdf* 1998;208-220.
163 Kirchmayer U, Davoli M, Verster AD, Amato L, Ferri M, Perucci CA. A systematic review on the efficacy of naltrexone maintenance treatment in opioid dependence. *Addiction* 2002; **97**(10):1241-1249.
164 Mayet S, Farrell M, Ferri M, Amato L, Davoli M. Psychosocial treatment for opiate abuse and dependence. *Cochrane Database of Systematic Reviews* 2004;(1):CD004330.
165 Lele S, Hooper L. Pharmacological interventions for pain in patients with temporomandibular disorders (TMD) [protocol for a Cochrane review]. Cochrane Database of Systematic Reviews 2004 Issue 3. Chichester (UK): John Wiley & Sons, Ltd; 2004.
166 Aavitsland P. Is methadone efficient? Methadone therapy versus evidence-based medicine. *Tidsskrift for Den Norske Laegeforening* 1998; **118**(20):3105.
167 Office-of-Technology-Assessment. The effectiveness of drug abuse treatment: implications for controlling AIDS/HIV infection. 1990.
168 Buprenorphine: A valuable alternative to methadone for long-term heroin substitute. *Prescrire International* 1996; **5**(23):66-70.
169 Boyarsky BK, Cance-Katz EF. Improving the quality of substance dependency treatment with pharmacotherapy. *Substance Use & Misuse* 2000; **35**(12-14):2095-2125.

170 Brewer DD, Catalano RF, Haggerty K, Gainey RR, Fleming CB. A meta-analysis of predictors of continued drug use during and after treatment for opiate addiction. *Addiction* 1998; **93**(1):73-92.
171 Chapleo CB. European studies. *Research & Clinical Forums* 1997; **19**(2):51-53.
172 Doran C, Holmes J, Ladewig D, Ling W. Buprenorphine induction and stabilisation in the treatment of opiate dependence. *Heroin Addiction & Related Clinical Problems* 2005; **7**(1):7-18.
173 Fischer B, Rehm J, Kim G, Kirst M. Eyes wide shut? - A conceptual and empirical critique of methadone maintenance treatment. *European Addiction Research* 2005; **11**(1):1-9.
174 Gruen RL, Weeramanthri TS, Knight SE, Bailie RS. Specialist outreach clinics in primary care and rural hospital settings [Cochrane review]. Cochrane Database of Systematic Reviews 2003 Issue 4. Chichester (UK): John Wiley & Sons, Ltd; 2003.
175 Hermstad R, Johannessen G, Michelsen K. Hvilke effekter har vedlikeholdsbehandling med metadon pa rehabilitering av heroinavhengige? [What effects does methadone maintenance treatment have on the rehabilitation of heroin addicts?] (DARE provisional record). *Tidsskrift for Den Norske Laegeforening* 1998; **118**:3139-3141.
176 Johnson RE. Review of US clinical trials of buprenorphine. *Research & Clinical Forums* 1997; **19**(3):17-23.
177 Kreek MJ. Clinical update of opioid agonist and partial agonist medications for the maintenance treatment of opioid addiction. *Seminars in the Neurosciences* 1997; **9**(3-4):140-157.
178 Maddux JF, Desmond DP, Esquivel M. Outpatient methadone withdrawal for heroin dependence. *American Journal of Drug & Alcohol Abuse* 1980; **7**(3-4):323-333.
179 Perry AE, Ali RL, Coulton S, Glanville JM, Godfrey C, Lunn J, *et al.* Interventions for drug-using offenders in the courts, secure establishments and the community [protocol for a Cochrane review]. Cochrane Database of Systematic Reviews 2005 Issue 2. Chichester (UK): John Wiley & Sons, Ltd; 2005.
180 Prendergast ML, Urada D, Podus D. Meta-analysis of HIV risk-reduction interventions within drug abuse treatment programs. *Journal of Consulting & Clinical Psychology* 2001; **69**(3):389-405.
181 Rayburn WF, Bogenschutz MP. Pharmacotherapy for pregnant women with addictions. *American Journal of Obstetrics & Gynecology* 2004; **191**(6):1885-1897.
182 Van Den Brink W, Van Ree JM. Pharmacological treatments for heroin and cocaine addiction. *European Neuropsychopharmacology* 2003; **13**(6):476-487.
183 Walter DS. Clinical studies of buprenorphine in opioid dependence. *Research & Clinical Forums* 1997; **19**(2):29-33.
184 Weinmann S, Kunstmann W, Rheinberger P. Methadone substitution - A scientific review in the context of out-patient therapy in Germany. *Zeitschrift fur Arztliche Fortbildung und Qualitatssicherung* 2004; **98**(8):673-682.
185 Wingood GM, DiClemente RJ. HIV sexual risk reduction interventions for women: a review (DARE structured abstract). *American Journal of Preventive Medicine* 1996; **12**:209-217.
186 Medical-Technology-Unit-Federal-Social-Insurance-Office-Switzerland. Substitution treatment with buprenorphin in opioid dependency. 2000.