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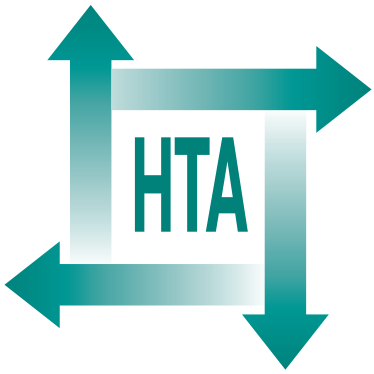

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Abstract

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Objectives: To assess the clinical effectiveness and cost-effectiveness of buprenorphine maintenance therapy (BMT) and methadone maintenance therapy (MMT) for the management of opioid-dependent individuals.

Data sources: Major electronic databases were searched from inception to August 2005. Industry submissions to the National Institute for Health and Clinical Excellence were accessed.

Review methods: The assessment of clinical effectiveness was based on a review of existing reviews plus an updated search for randomised controlled trials (RCTs). A decision tree with Monte Carlo simulation model was developed to assess the cost-effectiveness of BMT and MMT. Retention in treatment and opiate abuse parameters were sourced from the meta-analysis of RCTs directly comparing flexible MMT with flexible dose BMT. Utilities were derived from a panel representing a societal perspective.

Results: Most of the included systematic reviews and RCTs were of moderate to good quality, and 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). 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 criteria as opiate-dependent or heroin-dependent users, without significant co-morbidities. RCT meta-analyses have shown that a fixed dose of MMT or BMT has superior levels of retention in treatment and opiate use than placebo or no treatment, with higher fixed doses being more effective than lower fixed doses. There was evidence, primarily from non-randomised observational studies, that fixed-dose MMT reduces mortality, HIV risk behaviour and levels of crime compared with no therapy and one small RCT has shown the level of mortality with fixed-dose BMT to be significantly less than with placebo. Flexible dosing (i.e. individualised doses) of MMT and BMT is more reflective of real-world practice. Retention in treatment was superior for flexible MMT than flexible BMT dosing but there was no significant difference in opiate use. Indirect comparison of data from population cross-sectional studies suggests that mortality with BMT may be lower than that with MMT. A pooled RCT analysis showed no significant difference in serious adverse events with MMT compared with BMT. Although treatment modifier evidence 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 a primary care or outpatient clinic setting. Although most of the included economic evaluations 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. One company (Schering-Plough) submitted cost-effectiveness evidence based on an economic model that had a 1-year time horizon and sourced data from a single RCT of flexible-dose MMT compared with flexible-dose BMT and utility values obtained from the literature; the results showed that for MMT vs no drug therapy, the incremental cost-effectiveness ratio (ICER) was £12,584/quality-adjusted life-year (QALY), for BMT versus no drug therapy, the ICER was £30,048/QALY and in a direct comparison, MMT was found to be

slightly more effective and less costly than BMT. The assessment group model found for MMT versus no drug therapy that the ICER was £13,697/QALY, for BMT versus no drug therapy that the ICER was £26,429/QALY and, as with the industry model, in direct comparison, MMT was slightly more effective and less costly than BMT. 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.
Conclusions: Both flexible-dose MMT and BMT are more clinically effective and more cost-effective than no drug therapy in dependent opiate users. In direct comparison, a flexible dosing strategy with MMT was found be somewhat more effective in maintaining individuals in treatment than flexible-dose BMT 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-dependent users' preferences. Future research should be directed towards the safety and effectiveness of MMT and BMT; 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); and uncertainties in cost-effectiveness identified by current economic models.

Contents

Glossary and list of abbreviations

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

Glossary

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

Maintenance A process whereby an individual who is physically dependent on a drug is taken off that drug and a substitute drug is prescribed instead.

Modelling Modelling involves simplifying reality to a level that describes the essential consequences and complications of different options for decision-making.

Quality-adjusted life-year Based on the number of years of life that would be added by the intervention. Each year in perfect health is assigned the value of 1.0 down to a value of 0 for death. If the extra years would not be lived in full health, for example if the patient were to lose a limb, or be blind or be confined to a wheelchair, then the extra life-years are given a value between 0 and 1 to account for this.

List of abbreviations

A&E	Accident and Emergency
AIDS	acquired immunodeficiency syndrome
ARIF	Aggressive Research Intelligence Facility
BCS	British Crime Survey
BDT	buprenorphine detoxification therapy
BMT	buprenorphine maintenance therapy
BNF	British National Formulary
CCT	comparative controlled trial
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CJS	criminal justice system
CRA	community reinforcement approach
DoH	Department of Health
DSM	*Diagnostic and Statistical Manual of Mental Disorder*
EQ-5D	EuroQuol questionnaire
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus

continued

List of abbreviations *continued*

HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IDU	injecting drug user
ITT	intention-to-treat
LAAM	*levo*-α-acetylmethadol
MD	mean difference
MDT	methadone detoxification therapy
MMT	methadone maintenance therapy
MT	maintenance therapy
NDTMS	National Drug Treatment Monitoring System
NEPOD	National Evaluation of Pharmacotherapies for Opioid Dependence
NICE	National Institute for Health and Clinical Excellence
NTA	National Treatment Agency for Substance Misuse
NTORS	National Treatment Outcome Research Study
OR	odds ratio
PenTAG	Peninsular Technology Assessment Group
PSS	Personal Social Services
QA	quality assessment
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SCAN	Specialist Clinical Addiction Network
SD	standard deviation
SMD	standardised mean difference
SPC	summary product characteristics
TES	Treatment Effectiveness Score
WMD	weighted mean difference

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

Executive summary

Background

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 NHS and Personal Social Services (PSS).

Although methadone is the mainstay drug used in current practice, for the purposes of this report we sought to address three specific questions:

- Is MMT effective and cost-effective compared with no drug therapy?
- Is BMT effective and cost-effective compared with 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 across drug doses, patient subgroups and treatment settings; assess the cost-effectiveness of BMT and MMT from a wider societal perspective; and compare the effectiveness of BMT with buprenorphine detoxification therapy (BDT) and MMT with methadone detoxification therapy (MDT).

Methods

Comprehensive bibliographic searches were undertaken, from 1996 or the year of database inception to August 2005, so as to identify clinical effectiveness 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 effectiveness and cost-effectiveness evidence. A decision tree was developed with a 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 NHS and PSS and outcomes in terms of quality-adjusted life-years (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-dose MMT with flexible-dose BMT. Utilities were derived from a panel representing a wider societal perspective.

Results

Clinical effectiveness

Thirty-one systematic reviews (including either RCT or non-RCT evidence) met the inclusion criteria of this report. Many of the studies included in these reviews overlap. In addition, 28 RCTs published more recently (since 2001) were identified. 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 the *Diagnostic and Statistical Manual of Mental Disorder* IV criteria as opiate-dependent or heroin-dependent users, 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 versus no drug therapy/placebo

A number of RCT meta-analyses have consistently shown that fixed-dose MMT has superior levels of retention [e.g. 20–97 mg versus placebo: pooled relative risk (RR) 3.91, 95% confidence interval

(CI) 1.17 to 13.2] in treatment and opiate use (e.g. 35–97 mg versus no treatment: pooled effect size 0.65, 95% CI 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 versus <50 mg: pooled RR 1.25, 95% CI 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 with no therapy.

BMT versus no drug therapy/placebo
Two RCT meta-analyses show that fixed-dose BMT has superior levels of retention in treatment (e.g. 6–12 mg versus placebo: pooled RR 1.74, 95% CI 1.06 to 2.87) and opiate use (6–16 mg versus placebo: pooled RR 1.74, 95% CI 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 8–16 mg versus 1–4 mg: effect size pooled RR 0.21, 95% CI 0.12 to 0.31). One small RCT has shown that the level of mortality with fixed-dose BMT is significantly less than with placebo.

BMT versus MMT
A number of RCT meta-analyses have consistently shown that fixed doses of MMT had superior retention in treatment of opiate abuse than comparable fixed doses of BMT. A recently updated and unpublished Cochrane systematic review of seven RCTs directly compared flexible-dose MMT with flexible-dose BMT in 976 opiate-dependent individuals. Amongst RCTs employing flexible-dose regimens, the allowable daily equivalent dose commonly ranged from 20 or 30 to 60 or 120 mg for methadone and 2 or 4 to 8 or 16 mg for buprenorphine. No further RCTs comparing flexible-dose MMT and BMT were identified through our searches. Retention in treatment was superior for flexible-dose MMT than flexible-dose BMT dosing (pooled hazard ratio 1.40, 95% CI 1.15 to 1.69), but 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 suggests that the level of mortality with BMT may be lower than that with MMT. A pooled RCT analysis showed no significant difference in the rate of serious adverse events with MMT compared with 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 a primary care or an outpatient clinic setting.

Cost-effectiveness

Previous economic evaluations

Eleven economic evaluations met the inclusion criteria of this report. Eight studies assessed the cost-effectiveness of MMT and two BMT for opiate abuse. Direct comparison 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 with flexible-dose BMT and utility values obtained from the literature.

MMT versus no drug therapy
The incremental cost-effectiveness ratio (ICER) was £12,584/QALY.

BMT versus no drug therapy
The ICER was £30,048/QALY.

MMT versus BMT
In a direct comparison, MMT was found to be slightly more effective (QALY difference of 0.00055) and less costly than BMT.

Assessment group model

MMT versus no drug therapy
The ICER was £13,697/QALY.

BMT versus no drug therapy
The ICER was £26,429/QALY.

MMT versus BMT
As with the industry model, in a 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.

Discussion

Strengths, limitations and uncertainties

The principal strengths of this report are that its cost-effectiveness analyses 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 with BMT (more reflective of real-world clinical practice than fixed-dose design trials); 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 the 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-dependent user subgroups and treatment settings.

Conclusions

Implications for service provision

Both flexible-dose MMT and BMT are more clinically effective and more cost-effective than no drug therapy in dependent opiate users. In direct comparison, a flexible dosing strategy with MMT (daily dose equivalent 20–120 mg) was found to be somewhat more effective in maintaining individuals in treatment than flexible-dose BMT (daily dose equivalent 4–16 mg) 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-dependent users' 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) and uncertainties in cost-effectiveness identified by current economic models.

Chapter 1
Background

Description of health problem

Heroin and other opioids are powerful drugs that can induce a sense of well-being, deliver a boost to self-esteem and increase tolerance to pain. People taking opioids, whether for recreational use or for a medical condition, may become dependent on these drugs. 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] the most commonly used drugs being cannabis and ecstasy. Opioid-dependent users constitute a small proportion of the world population (less than 1% of those aged 15 years 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 include opium, morphine and codeine. The term 'opiate' is also used for the semi-synthetic drug heroin that is produced from poppy compounds. The term 'opioids' refers to opiates and other semi-synthetic and synthetic compounds with similar properties.[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.

Diagnosis

The diagnosis of dependence has been operationalised in the *Diagnostic and Statistical Manual of Mental Disorder* (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) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   (b) markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
   (a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for withdrawal from the specific substances)
   (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance (e.g. visiting

multiple doctors or driving long distances), use the substance (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).

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 years. 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 opioid misuse means that they will have extensive treatment histories. Treatment for people with established opioid-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 10–20 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]

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 16–59-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, such 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 15–64 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] This high contact for opioid problems may reflect the availability of substitutes, which do not exist for other drugs of abuse.

Impact of health problem

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

Increased mortality

Addiction-related deaths, including unintentional overdose, drug-related injuries and many illnesses directly attributable to chronic drug dependence, explain one-quarter to one-third of the mortality in an opioid-addicted population.[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 with the general population;[11] however, more recent cohort studies have shown that mortality rates in drug users have 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 healthcare.[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 (IDUs) may be exposed to blood-borne infections through the sharing of infected needles, syringes or other injecting paraphernalia. The prevalence of HIV infection among IDUs in the UK has increased in recent years, but 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 HCV. Interaction with alcohol consumption would exacerbate the problem. One-third of patients in the NTORS sample were heavy drinkers and drinking did not diminish during treatment. In England and Wales, HCV 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 injection sites prior to injecting.[14]

Mental illness

The Epidemiological Catchment Area study reported a 47% lifetime prevalence rate of substance abuse among patients with schizophrenia compared with 16% in the general population,[15] and these figures are confirmed in UK studies.[16,17] 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. Opioid dependence is less associated with severe mental illness such as schizophrenia or bipolar disorder than stimulant drugs or alcohol. Psychosis is not a typical feature of the opioid withdrawal syndrome, but it has been reported in some cases after stopping methadone.[18] Bloom and colleagues have proposed that an excess of endogenous opioids may have a role in the pathogenesis of schizophrenia,[19] 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.

However, other psychiatric co-morbidity is common in opioid-dependent populations, with anxiety, affective, antisocial and other personality disorders particularly common.[15,20] Recent psychiatric treatment was reported by one in five of the 1075 subjects recruited to NTORS, and psychiatric symptom levels were high.[21] Clinical studies suggest that half of opioid-dependent individuals have a lifetime depressive episode, and one-third have depressed mood at intake to addiction treatment.[7]

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.[22] It is estimated that 2–3% of all children under the age of 16 years have parents with drug problems, but 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.[23] 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.[23]

Health-related quality of life

There is little evidence about the health-related quality of life (HRQoL) 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 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.[24] 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 1435 arrestees drug-tested and interviewed by Bennett and colleagues,[25] 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. NTORS found that 61% of a drug misuse treatment sample reported committing crimes other than drug possession in the 3 months prior to starting treatment, with the most commonly reported offence being shoplifting.[20] Drug treatment led to significant reductions in offending levels.[26]

Management of opioid abuse

Methadone

Methadone is a synthetic μ-opioid receptor agonist with pharmacological activity similar to morphine. The summary product characteristics (SPC) for methadone state 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 10–40 mg daily, increased by 10–20 mg per week until no signs of withdrawal or intoxification; the usual dose range is 60–120 mg daily, but 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 gastrointestinal 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).[27] 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.[27]

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.[28] 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, 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 when other drugs are either introduced or withdrawn. Liver damage (for example following chronic alcohol use or HBV or HCV infection) may also impair the metabolism of methadone, leading to a lower dose requirement.

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 seven-fold greater than the risk of death prior to entering maintenance treatment.[29] 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 other trained health professional, 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 3 months may be useful to consider what has been achieved and to set new goals. Where possible, coexisting physical, emotional, social and legal problems should be addressed. UK guidelines for management are available.[30]

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.[31] The SPC for buprenorphine state 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 0.8–4 mg, adjusted according to response. In practice, a starting dose of over 4 mg/day is often used. The maximum daily dose is 32 mg.

Buprenorphine has a number of differences in its mode of action to methadone.[31] 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 lipophilicity 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 still unclear, with deaths having been reported.[31] UK guidelines for management are available.[30,32]

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.[33] 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 α_2-agonists (clonidine and lofexidine).

Maintenance (or substitution)

Whereas some patients can achieve abstinence from opioids rapidly, others require the support of prescribed medication for longer than a few months.[34] An alternative to attempting to stop opioid use altogether is the maintenance approach, which is the principal 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.[35] 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 and 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.[36]

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 (DoH) prescribing guidance recommends maintaining individuals on a daily dose of methadone between 60 and 120 mg.[34] 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 when initiating prescribing, the dose–consumption of opioids should usually be supervised.[34] 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; with increased prescribing, there has also been an expansion in prescribing by primary care practitioners. Access to prescribing has been increased since the advent of the National Treatment Agency for Substance Misuse (NTA), 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 must 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.

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 10-year national drug strategy, *Tackling Drugs to Build a Better Britain* (1998), identified treatment as one of the four key areas for action.[24] 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 and to

improve its quality and the retention of users in treatment. It is the responsibility of the 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.[37] The National Institute for Health and Clinical Excellence (NICE) is currently working on clinical guidelines for detoxification and psychological interventions for opiate misuse.[38]

The UK Government Spending Review 2004 saw agreement of a new Public Service Agreement 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 (CJS).
- 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 years, especially by the most vulnerable young people.

Direct expenditure for tackling drugs in the 2003–4 financial year was £1244 million, of which £503 million was spent on drug treatment.[39]

According to Models of Care, services for drug misusers can be grouped into four broad tiers:[37]

- 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. According to the updated 2005 version of Models of Care, all prescribing interventions are tier 3, and as such require comprehensive assessment, are driven by an individually tailored care plan and carry a high duty of care for the clinician prescribing the controlled drug. 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 coexisting physical and emotional, social and legal problems are addressed as far as possible.[37] Prescribing should be complemented by structured psychotherapy, in addition to other services such as welfare advice and 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 co-morbidity (e.g. mental illness), young 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 are at risk of developing them.[24] The strategy defines three groups: children (aged 12 years or less), young people (aged 13–17 years) and young adults (aged 18–24 years). There are significant challenges in designing appropriately matched treatments and support for young people, and 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]

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]

A recent audit[45] indicates that in England approximately 80% of those receiving substitute opioids are prescribed methadone, with three-quarters of these on a maintenance regime and one-quarter a reduction programme. The number of patients currently receiving buprenorphine was about one-fifth of those on methadone and, of these, the split between maintenance and reduction strategies was approximately 60:40.

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

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

Anticipated costs associated with intervention

The quarterly drug spend for buprenorphine in summer 2005 was around £3.8 million. Assuming a unit drug cost of £0.48/mg (BNF) and an average dose of 16 mg/day, this corresponds to approximately 0.495 million daily doses per quarter and 5400 patient days of drug treatment/day. If 47% of the cost per patient is estimated to be drug cost (*Table 1*), the total annual cost for the NHS is probably about £32 million. 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 £43 million.

TABLE 1 *Annual cost of buprenorphine treatment per patient*

Item	Cost (£)
Drug	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**

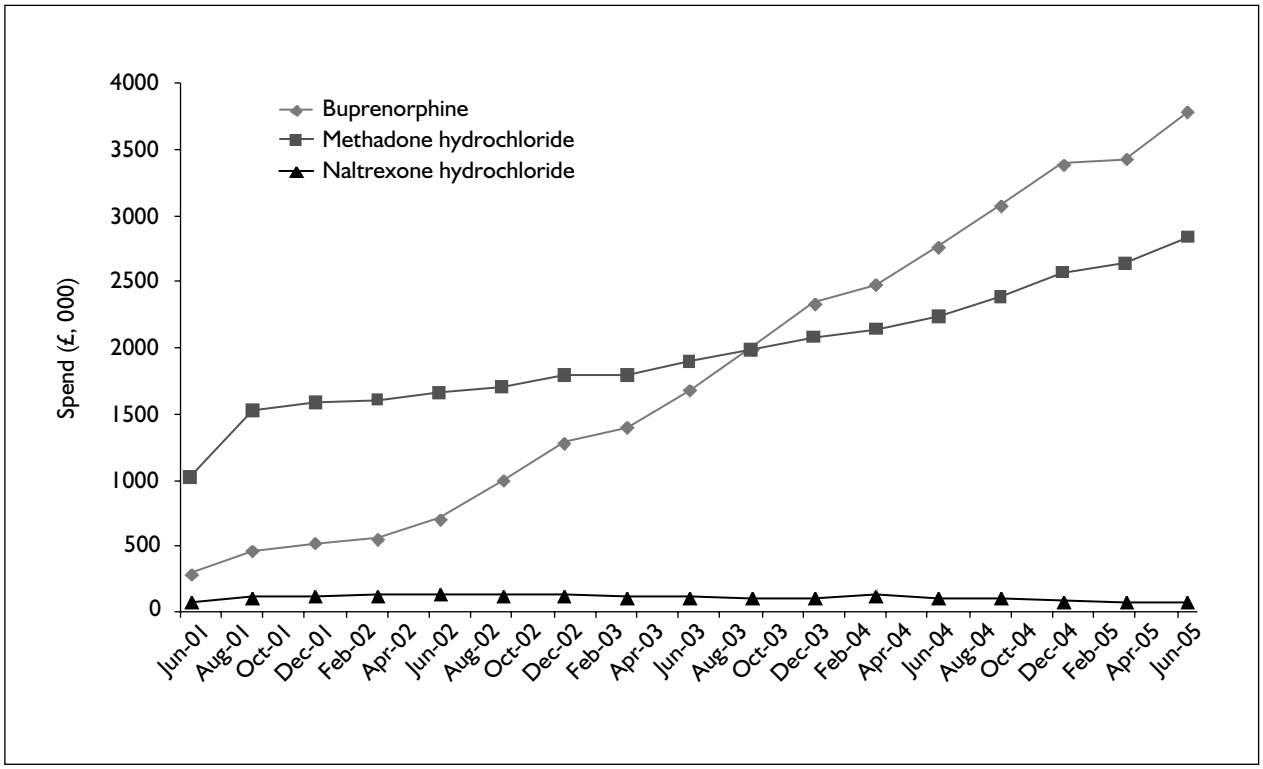

FIGURE 1 *Quarterly expenditure on methadone, buprenorphine and naltrexone in England, 2001–5*

For methadone with a unit drug cost of £0.0135/mg and a quarterly spend of around £2.8 million and an average dose of 50 mg/day, the corresponding calculations result in 45,600 patient days of methadone treatment/day and a total annual spend [at £2594/patient (*Table 2*)] of £105 million, projecting at an annual rise of 1.24-fold in patients treated to nearly £132 million in 2006.

TABLE 2 *Annual cost of methadone treatment per patient*

Item	Cost (£)
Drug	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**

Chapter 2

Definition of the decision problem

Decision problem

Interventions

Methadone and buprenorphine

Methadone is licensed for use in opioid dependence at a dose of 10–20 mg daily, increased by 10–20 mg daily until no signs of withdrawal or intoxification. However, in practice most prescribers would increase at no more than 20 mg per week. In the UK, the usual dose of methadone is 40–60 mg daily, but 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 0.8–4 mg as a single daily dose, adjusted according to response; however, in practice the starting dose is often >4 mg/day. The maximum is 32 mg daily. Licensed dose and doses used in practice are not necessarily concordant, so that consideration will therefore be given to studies employing doses outwith those licensed.

Populations including subgroups

Opioid-dependent adults (18 years and over) are the target population for this report. Where data were available, this report sought to assess the impact of interventions across a range of subgroups including drug use (e.g. injector versus non-injector); co-morbidity (e.g. HIV versus no HIV infection); socio-demographics (e.g. male versus female) and treatment setting (e.g. healthcare versus CJS).

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

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

Key issues

The primary focus of this assessment was clinical and cost outcomes from the perspective of the NHS and Personal Social Services (PSS). The wider societal implications including public health and safety and costs to the CJS were considered.

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 an NHS and PSS 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 with drug therapy?
- Is buprenorphine maintenance therapy (BMT) effective and cost-effective compared with 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, to assess the cost-effectiveness of MMT and BMT in the management of opioid dependence from a broader societal perspective and to assess the effectiveness of MMT compared with methadone detoxification (MDT) and BMT compared with buprenorphine detoxification (BDT).

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Rationale

Scoping searches indicated the existence of a large number of reviews on treatments for opioid-dependent individuals. These include systematic reviews, 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 and 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 randomised controlled trials (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 with those of the systematic reviews to check for comparability.

Identification of studies

Review of systematic reviews

Searches for existing systematic reviews (which included RCTs or non-RCTs) were undertaken using the Aggressive Research Intelligence Facility (ARIF) search protocol, which includes sources such as the Cochrane Library, Internet sites of health technology assessment organisations and MEDLINE (see Appendix 1). In addition, the Cochrane Drugs and Alcohol Group was contacted to seek any recent updates of current Cochrane reviews. The searches were not restricted by date or language.

Review of recent RCTs

The following sources were searched for RCTs:

- Bibliographic databases: Cochrane Library (CENTRAL)(Wiley Internet interface), 2005 Issue 3, MEDLINE (Ovid), 2001–August 2005, MEDLINE In-Process and Other Non-Indexed Citations (Ovid), 12 August 2005, EMBASE (Ovid), 2001–August 2005, PsycINFO (Ovid), 2001–August 2005, International Bibliography of the Social Sciences (BIDS), 2001–August 2005 and 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 the full search strategies.
- Citations of relevant studies.
- Further information was sought from contact with author reports where necessary.
- Research registers of ongoing studies searched were National Research Register, 2005 Issue 3, Current Controlled Trials and ClinicalTrials.gov.
- Invited industry submissions to NICE for this appraisal.

Inclusion and 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 disagreements.

Review of recent RCTs

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 the selection of RCTs and a third reviewer resolved any disagreements.

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 OQAQ (Overview Quality Assessment Questionnaire) instrument developed by Oxman and Guyatt.[46]

Review of recent RCTs

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 (ITT) analysis and description of loss to follow-up. An overall quality score (Jadad) was assigned to each RCT using a modified Jadad[47] instrument (Appendix 5).

Data extraction

One reviewer extracted data from systematic reviews and RCTs into predesigned data forms. Extracted data were 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 was noted.

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

- drug use, that is, changes in illicit drug use; concordance with, and retention in treatment
- health of drug user, that is, drug-related mortality; drug-related morbidity (e.g. blood-borne virus infection rates); HRQoL; use of healthcare system; major adverse effects of treatment (i.e. drug interactions, liver disease, cardiac abnormality, exacerbation of co-morbidity)
- social effects, that is, effects on employment; effects on family
- effects on the CJS, that is, rates of crime; recidivism.

Results

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*.

Review of recent RCTs

A total of 1616 citations were identified in our search for 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.

Scope and quality of included systematic reviews

Given the number of systematic reviews and RCTs identified, 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. *Tables 3* and *4* provide a mapping of the systematic reviews and RCTs to the policy questions of this report.

As can be seen, the majority of evidence was in the form of direct comparisons of MMT (2–100 mg/day) and with placebo/no therapy (19 systematic reviews and one recent RCT), BMT (1–32 mg/day) and compared with placebo/no therapy (11 systematic reviews and three recent RCTs) and comparison of MMT with BMT (12 systematic reviews and three recent RCTs). This evidence base spanned a variety of doses of methadone (5–110 mg/day) and buprenorphine (≤5–32 mg/day). It should be noted that many systematic reviews included the same studies. There was little evidence comparing MMT with MDT (three RCTs) or BMT with BDT (one 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, that is, 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,[64] we found no

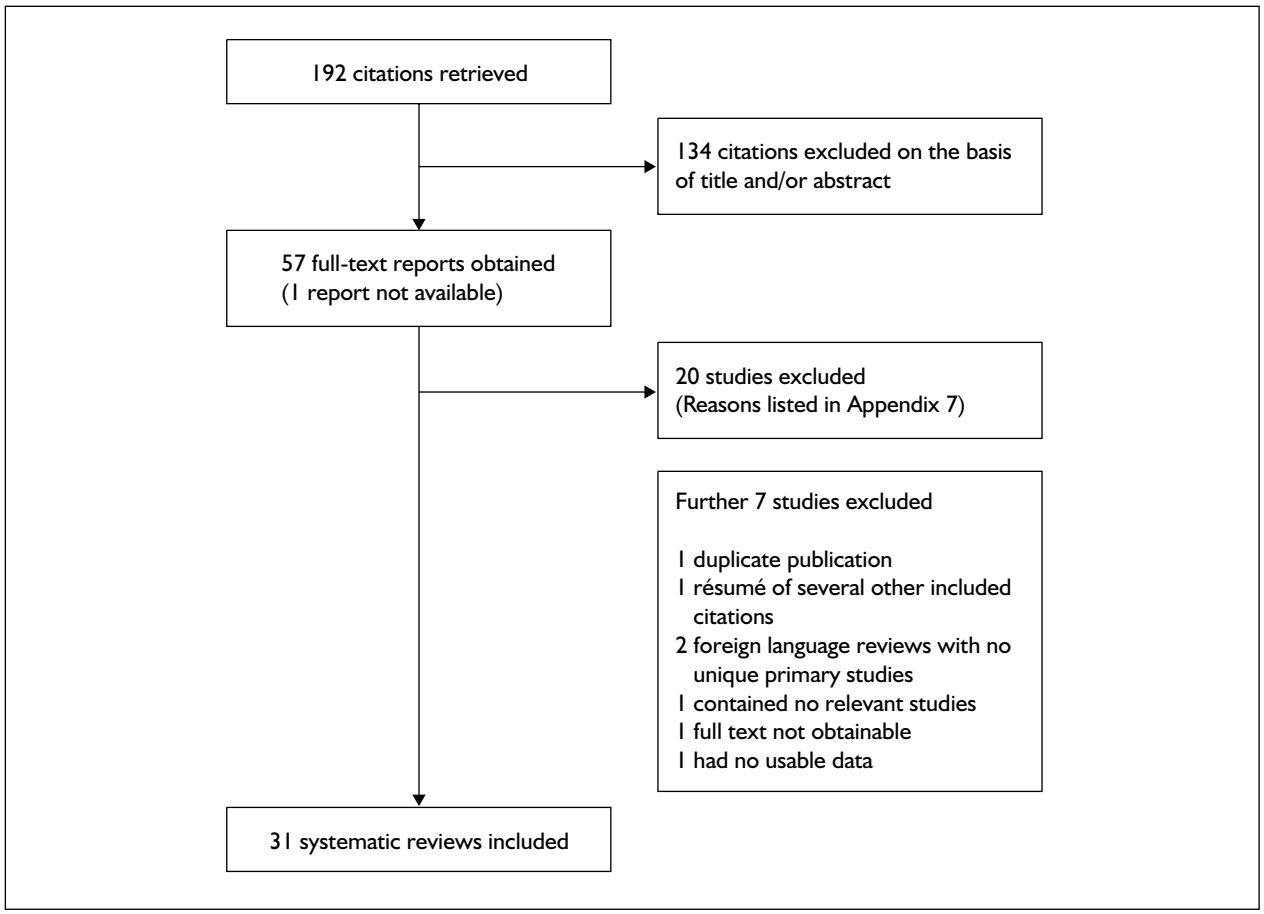

FIGURE 2 *Flow diagram of retrieval of systematic reviews*

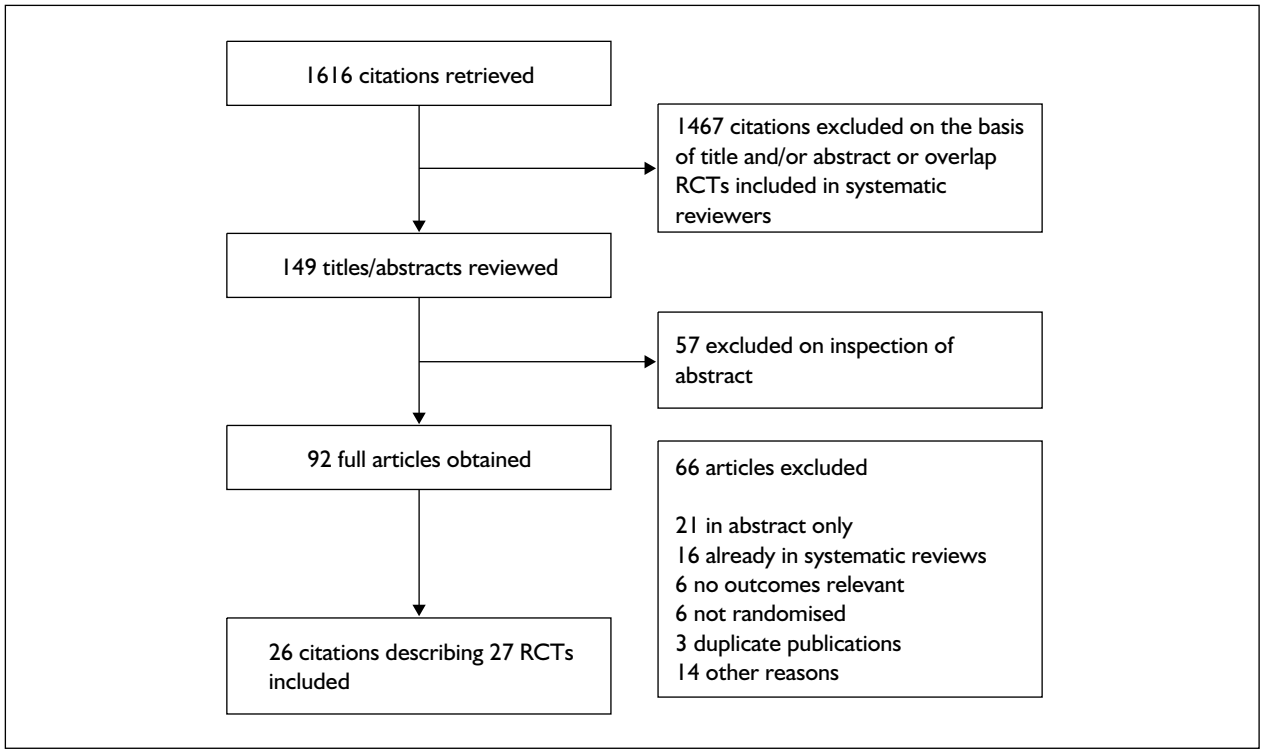

FIGURE 3 *Flow diagram of retrieval of RCTs*

TABLE 3 *Mapping of systematic reviews to policy questions*

Study	MMT[a] vs placebo/no therapy	BMT[a] vs placebo/no therapy	MMT[a] vs BMT[a]	Other comparisons
Caplehorn, 1996[48]	✓	×	×	×
Glanz, 1997[49]	✓	×	×	MMT vs LAAM MT; MMT vs MDT (1 study)
Hulse, 1998[43]	✓	×	×	×
Marsch, 1998[50]	✓	×	×	×
Prendergast, 2000[51]	✓	×	×	×
Sorensen, 2000[52]	✓	×	×	×
West, 2000[53]	✓	✓	✓	×
van Beusekom, 2001[54]	✓	×	×	MMT + co-therapies vs MMT; MMT vs MDT (1 study)
Farre, 2002[55]	✓	✓	✓	MMT vs LAAM MT
Hopfer, 2002[56]	✓	×	×	MMT vs MDT (3 studies)
Layson-Wolf, 2002[57]	✓	✓	✓	MMT and BMT vs LAAM MT
Prendergast, 2002[58]	✓	×	×	×
Simoens, 2002[59]	✓	✓	✓	MMT or BMT + co-therapies vs MMT or BMT; MMT vs MDT (1 study)
Faggiano, 2003[60]	✓	✓	✓	MMT + co-therapies vs MMT; MMT and BMT vs LAAM MT; MMT vs MDT (1 study)
Johansson, 2003[61]	✓	✓	✓	MMT + co-therapies vs MMT; MMT vs LAAM MT; MMT vs MDT (2 studies)
Mattick, 2003a[62]	✓	×	×	MMT vs MDT (3 studies)
Gowing, 2004[63]	✓	×	×	MMT vs MDT (1 study)
Mattick, 2005[64]	✓	✓	✓	BMT vs BDT (1 study)
Simoens, 2005[65]	✓	✓	✓	MMT or BMT + co-therapies vs MMT or BMT
Raisch, 2002[66]	×	✓	✓	BMT vs LAAM MT; BMT oral vs subcutaneous administration
Davids, 2004[67]	×	✓	✓	BMT + co-therapies vs BMT; BMT vs LAAM MT
Lintzeris and Ford, 2004[b]	×	✓	✓	BMT in different settings
Barnett, 2001[68]	×	×	✓	×
Stanton, 1997[69]	×	×	×	MMT + co-therapies vs MMT
Griffith, 2000[70]	×	×	×	MMT + co-therapies vs MMT
Clark, 2002[71]	×	×	×	MMT vs LAAM MT
Fridell, 2003[72]	×	×	×	MMT + co-therapies vs MMT
Kirchmayer, 2003[73]	×	×	×	MMT vs naltrexone MT
Amato, 2004[74]	×	×	×	MMT + co-therapies vs MMT
Roozen, 2004[75]	×	×	×	MMT + co-therapies vs MMT + usual care
Ferri, 2005[76]	×	×	×	MMT + heroin vs MMT

LAAM, *levo*-α-acetylmethadol; MT, maintenance therapy.
[a] At various doses (studies comparing various doses).
[b] Lintzeris and Ford, unpublished study: NTA: BPN evidence, practice to briefing.

TABLE 4 *Mapping of RCTs to policy questions*[a]

Study	MMT[b] vs placebo/no therapy	BMT[b] vs placebo/no therapy	MMT[b] vs BMT[b]	Other comparisons
Dolan, 2003[77]	✓	×	×	×
Ahmadi, 2003b[78]	×	✓	×	×
Ahmadi, 2003c[79]	×	✓	×	×
Marsch, 2005[80]	×	✓	×	×
Kristensen, 2005[81]	×	×	✓	×
Ahmadi, 2003a[82]	×	×	✓	BMT and MMT vs clonidine MT
Lofwall, 2005[83] (update of Strain, 1994[109])	×	×	✓	×
Zanis, 2001[84]	×	×	×	MMT + behavioural therapy vs MMT
Chutuape, 2001[85]	×	×	×	MMT + contingency enhancement vs MMT
Giacomuzzi, 2001[86]	×	×	×	Morphine vs MMT
Jones, 2001[87]	×	×	×	MMT + incentives vs MMT
Pollack, 2002[88]	×	×	×	MMT + enhanced counselling vs MMT + behavioural therapy
Cornish, 2002[89]	×	×	×	MMT + dextromethorphan vs MMT
Dean, 2002[90]	×	×	×	MMT + fluoxetine vs MMT
King, 2002[91]	×	×	×	MMT in different settings
Ritter, 2003[92]	×	×	×	MMT vs LAAM MT
Kosten, 2003[93]	×	×	×	BMT + desipramine vs BMT
Margolin, 2003[94]	×	×	×	MMT + magnesium aspartate vs MMT
Sigmon, 2004[95]	×	×	×	MMT +reinforcement vs MMT
Avants, 2004[96]	×	×	×	MMT + harm reduction programme vs MMT
Brooner, 2004[97]	×	×	×	MMT + standard stepped care vs MMT + enhanced stepped care
Grabowski, 2004[98c]	×	×	×	MMT + amphetamine vs MMT
Lidz, 2004[99]	×	×	×	MMT + behavioural therapy vs MMT
Blanken, 2005[100d]	×	×	×	MMT + heroin vs MMT
Dijkgraaf, 2005[101e]	×	×	×	MMT + heroin vs MMT
Eder, 2005[102]	×	×	×	MMT vs slow release morphine

[a] Several studies performed RCTs that contributed to more than one policy question.
[b] At various doses.
[c] Reports two RCTs.
[d] Outcomes and prognostic analysis based on RCTs of van den Brink and colleagues[103] describing two RCTs (included in the systematic review by Ferri and colleagues[76]).
[e] Economic study based on RCTs of van den Brink and colleagues.[103]

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 *levo*-α-acetylmethadol (LAAM) maintenance therapy (MT).

Quality of evidence

The majority of included systematic reviews and RCTs were of moderate to good quality, but 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 the minimum

quality score was zero and the maximum 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-outs and withdrawals (18/26). Details of quality assessment are presented in Appendices 5–7.

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 30–49 years, in good health, who met DSM 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 the USA, namely Hispanic or 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.[65] Few studies recruited HIV-infected or AIDS individuals or polydrug users, especially alcohol and cocaine.

Settings and delivery

Most studies were conducted in the USA or Australia and virtually all were undertaken in outpatient, inpatient or specialised treatment centres. Methadone doses ranged from 50 to 150 mg/day and buprenorphine doses from 1 to 15 mg/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 were based on a fixed-dose design where all patients in the trial received the same dose. Although these fixed-dose 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 *Table 5*.

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 three consecutive days of treatment, limited adjuvant psychosocial therapy, no rewards for treatment compliance, intensive monitoring, limited length of treatment and relatively short periods of follow-up.[65] The recently updated Cochrane review by Mattick and colleagues,[64] in addition to comparing various fixed doses, also reported trials comparing flexible doses of MMT versus BMT. More recent studies have

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 and/or *observed*	
		Methadone	**Buprenorphine**	**Methadone**	**Buprenorphine**
Johnson, 2000[104]	Induction, week 1–2	Daily: start 20 mg then increase at 10 mg/day to 60 mg/day	Days 1–7: daily start at 4 mg rising to 8 mg/day by day 7 Then 16 mg on 3 days of the week to day 14	20–60	4–8
	Maintenance, week 3–17 (take-away doses permitted)	Increases possible from 60 to 100 mg/day. Mean[a] dose = 90 mg	Active doses on 3 days a week. Four increases possible (one every other week) from 16 to 32 mg on Mondays and Wednesdays (Friday dose 50% higher). Mean[a] dose = 27 mg	60–100	8–16

continued

TABLE 5 *Flexible dose ranges used in RCTs comparing MMT and BMT (cont'd)*

Study	Structure of dose regime	Details of dosage procedure		Daily equivalent dose (mg) possible &/or *observed*	
		Methadone	**Buprenorphine**	**Methadone**	**Buprenorphine**
Mattick, 2003[105]	'Induction' weeks 1–6	Daily dose: 20–40 mg/day	Daily dose: 2–6 mg/day	20–40	2–6
	'Post-induction', weeks 7–13 (no take-away doses)	Daily dose adjustable up to 150 mg/day (only in units of 10 mg) Mean not reported	Alternate day dosing: Start at 2× dose of week 6; adjustable up to 32 mg/dose. Mean not reported	20–150	4–16
Petitjean, 2001[106]	'Flexible', weeks 1–3	Daily: days' 1–3, 30 mg; increase possible (30-mg steps) up to 120 mg by day 15	Daily: days 1–3, 4 mg; increase possible (4-mg steps) up to 16-mg by day 15	30–120	4–16
	'Maintenance', weeks 4–6 (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	30–120 Mean 69.8	8–16 Mean 10.5
Lintzeris, 2004[107]	Weeks 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)	Mean 15.9 (SD 12.7)
	Weeks 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)	Mean 15.7 (SD 14.7)
Fischer, 1999[108]	'Induction', days 1–6	Start at 20 mg/day, rising (20-mg steps) to 80 mg/day	Start at 2 mg/day rising to 8 mg/day	20–80	2–8
	Post-induction, weeks 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	Mean 7.5
Strain, 1994b[109]	'Induction', days 1–4	Days 1–4: 20, 30, 40, 50 mg/day	Days 1–4: 2, 4, 6, 8 mg/day	20–50	2–8
	'Stabilisation' to end of week 2	50 mg/day	8 mg/day	50	8
	'Post-stabilisation' weeks 3–16	Dose increases (and decreases) (10-mg steps) permitted up to 90 mg/day. Mean dose = 83 mg/day	Dose increases (and decreases) (2-mg steps) permitted up to 16 mg/day. Mean dose = 15 mg/day	50–90 Mean 83	8–16 Mean 15
Strain, 1994a[110]	'Induction', days 1–4	Days 1–4: 20, 30, 40, 50 mg/day	Days 1–4: 2, 4, 6, 8 mg/day	20–50	2–8
	'Stabilisation', to end of week 2	50 mg/day	8 mg/day	50	8
	'Post-stabilisation', weeks 3–16	Dose increases (and decreases) (10-mg steps) permitted up to 90 mg/day. Mean dose = 54 mg/day	Dose increases (and decreases) (2-mg steps) permitted up to 16 mg/day. Mean dose = 8.9 mg/day	50–90 Mean 54	8–16 Mean 8.9

SD, standard deviation.
[a] Authors report 'mean maximal Monday and Wednesday doses'.

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 MT. 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.[65]

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 the section 'Treatment outcome modifiers' (p. 25)].

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 are discussed in Appendix 2. Less extensive data were 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 were 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 versus placebo/no therapy

Retention in treatment

All doses of MMT [20–97 mg/day: RR 3.91, 95% confidence interval (CI) 1.17 to 13.2] and BMT (≤5–18 mg/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 (see *Table 37*). Higher doses of MMT (60 mg or more) were almost invariably found to be more effective than lower doses (e.g. 60–109 mg versus 1–39 mg: RR 1.36, 95% CI 1.13 to 1.63) (see *Table 37*).

Opiate use

Doses of MMT (e.g. 60 mg: 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 *Table 38*). Higher doses of MMT were more effective than low doses (e.g. ≥50 versus <50 mg: RR 0.82, 95% CI 0.72 to 0.95). The results of urinalysis were broadly consistent with self-report results but 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. 60–109 versus 40–59 mg: mean difference (self-reported) –1.89, 95% CI –3.43 to –0.35); 60–109 versus 1–39 mg: RR (urine tested) 1.59, 95% CI 1.16 to 2.18] (see *Table 39*).

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 and colleagues[66] 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 with placebo or no therapy, MMT reduced the level of individual reported adverse events but not significantly (RR 0.59, 95% CI 0.33 to 1.04). Lintzeris and Ford in their unpublished systematic review 'NTA: BPN evidence to practice briefing' conducted in 2004 (hereafter referred to as Lintzeris and Ford, 2004) looked at the issue of safety outcomes of MMT and BMT in detail – based on the Australian NEPOD (National Evaluation of Pharmacotherapies for Opioid Dependence) 2004 report.[111] 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 that 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 46*. The authors of the report concluded that the overall rate of serious adverse effects was low.

Mortality
The meta-analysis of observational studies spanning publication years 1974–1995[48] (see *Table 40*) comparing deaths per person years at risk amongst individuals in and out of methadone treatment reported an RR of 0.25 (95% CI 0.19 to 0.33), indicating that patients in methadone treatment were four 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%. Mattick and colleagues[62] reviewed three RCTs of MMT versus no MMT. Follow-up was relatively short. In one study, mortality in the MMT arm exceeded that in the control arm (3/50:1/50) whereas in the other two studies no events were observed in the MMT arm. The pooled RR for mortality did not reach statistical significance (MMT versus no MMT, RR 0.49, 95% CI 0.06 to 4.23). The review by Faggiano and colleagues[60] identified one controlled prospective study,[112] which indicated less overdose mortality at higher dosages of MMT; this result did not reach statistical significance.

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 with 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 (see *Table 49*).

Crime outcomes
The level of criminal activity appeared to be 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) (see *Table 48*).

Other relevant outcomes
Although the level of neonatal deaths was somewhat higher in pregnant mothers on MMT (3.3%) compared with no therapy (1.7%), this difference failed to reach statistical significance (see *Table 54*). No studies reporting quality of life were identified.

BMT versus placebo/no therapy

Retention in treatment
All doses of BMT (≤5–18 mg/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 (see *Table 34*). Higher doses of buprenorphine were almost invariably found to be more effective than lower doses. Marsch and colleagues[80] 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 [8–16 versus 1–4 mg: effect size (d) –0.25, 95% CI –0.15 to –0.35] (see *Table 38*).

Side-effects and adverse events
See the section 'MMT versus placebo/no therapy' (p. 20).

Mortality
The unpublished review of Lintzeris and Ford (2004) indentified one RCT[113] demonstrating the capacity of BMT to reduce mortality compared with placebo and counselling treatment over a 12-month period (0/20 deaths with BMT and 4/20 deaths with placebo).

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

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

Other relevant outcomes
None were identified.

MMT versus BMT

Retention in treatment
Across comparable fixed doses, MMT was more effective than BMT with the exception of low doses, where the two drugs appeared to be equivalent (≤35 mg MMT versus 6–16 mg BMT: RR 1.01, 95% CI 0.66 to 1.54) (see *Table 37*).

A recently updated (as yet unpublished) systematic review by Mattick and colleagues[64] identified seven RCTs that directly compared flexible dosing MMT with BMT. The major characteristics of these are summarised in *Table 6* and the doses used are shown in *Table 5*. Our searches identified no additional RCTs using a flexible dose design

TABLE 6 *Characteristics of studies comparing BMT with MMT with flexible dosing*[a]

Study	Country	*N*	Age (years); % male	Follow-up (weeks)	Comparison(s)	Outcomes
Mattick, 2003[105]	Australia	405	Mean 30; 67%	13	BMT vs MMT	Retention; urine analysis
Lintzeris, 2004[107]	Australia	139	Mean 29; 58%	26	BMT vs MMT	Retention; self-report heroin use
Fischer, 1999[108]	Austria	60	18–39; 68%	24	BMT vs MMT	Retention; urine analysis
Johnson, 2000[104]	USA	220	18–55; 65%	17	BMT vs MMT vs LAAM	Retention; urine analysis; abstinence
Strain, 1994a[110]	USA	164	Mean 32; 71%	24	BMT vs MMT	Retention; urine analysis
Strain, 1994b[109]	USA	51	Mean 33; 71%	16	BMT vs MMT	Retention; urine analysis

[a] Based on systematic review by Mattick and colleagues.[64]

and comparing MMT and BMT. In view of this, we present here the detailed pooled retention in treatment and opioid use results from Mattick and colleagues' systematic review[64] together with our reanalysis of these data, as this will be utilised in the assessment group economic model. Unfortunately, no RCT data were available on flexible dosing for other outcomes such as HIV risk behaviours and mortality. The Forest plot in *Figure 4* summarises the RR for retention in treatment in seven flexible dosing trials of methadone and buprenorphine.

These data indicate statistically significant superior retention in treatment with flexible-dose MMT compared with flexible-dose BMT. Given the time-dependent nature of the retention in treatment and the differing follow-up in these studies, 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 the 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 (HRs) and the pooled HR are shown in *Table 7* and also *Figure 6*. Survival curves for individual studies are shown in Appendix 10.

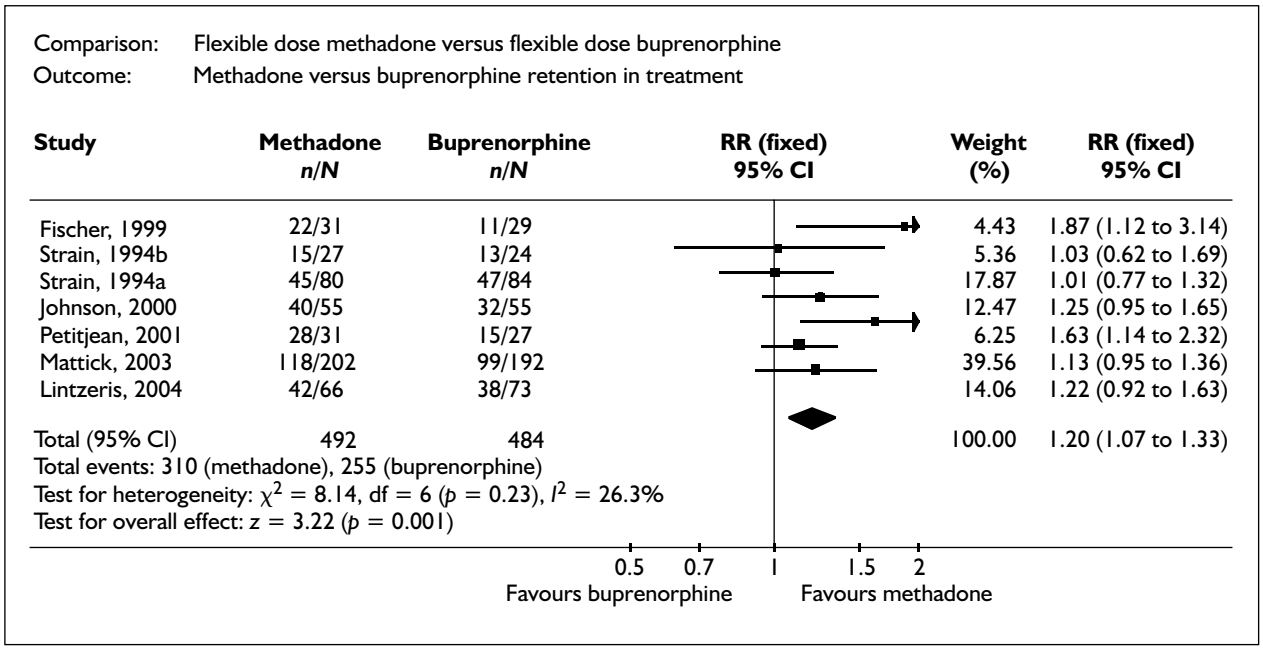

FIGURE 4 *Retention in treatment flexible dosing of MMT versus BMT*

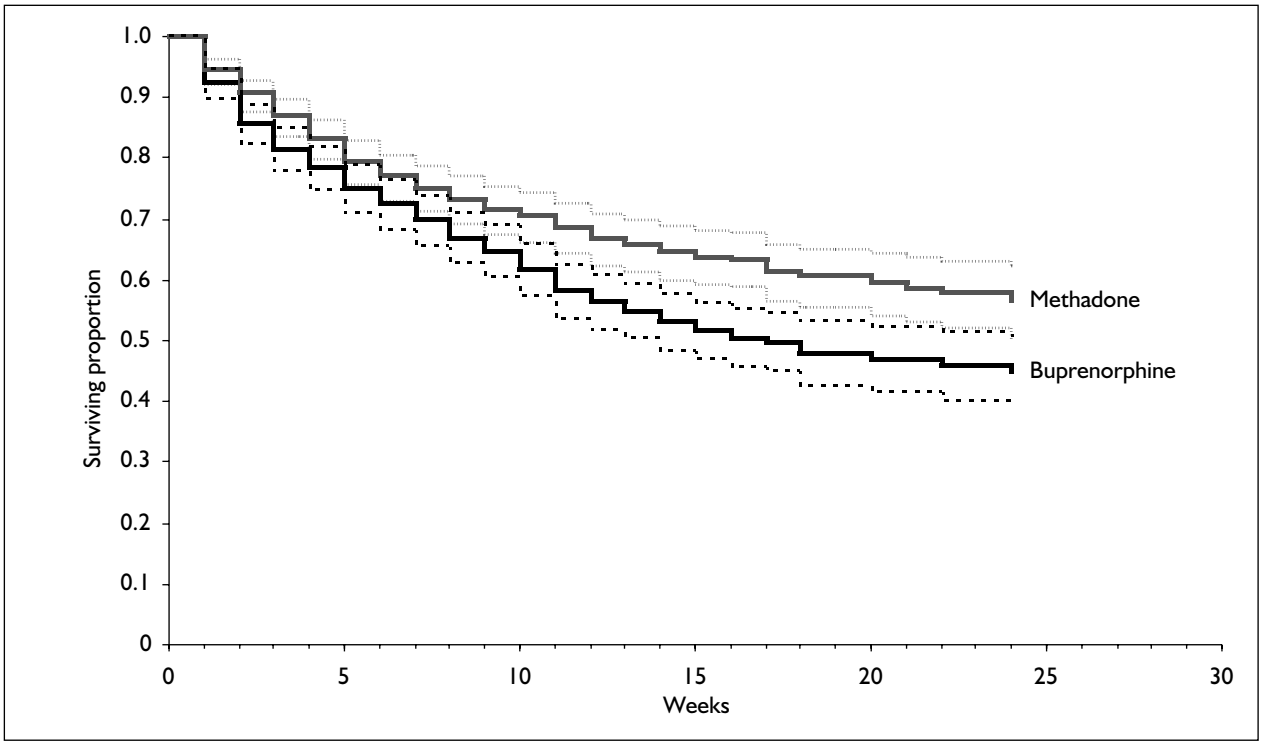

FIGURE 5 *Patient retention with MMT and BMT with flexible dosing (incomplete lines represent approximate 95% confidence intervals)*

TABLE 7 *Hazard ratio of BMT versus MMT with flexible dosing*

Study	Hazard ratio	Lower confidence interval	Upper confidence interval
Mattick, 2003[105]	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[104]	1.71	0.90	3.22
Strain, 1994a[110]	1.06	0.47	2.41
Strain, 1994b[109]	1.03	0.67	1.60
Petitjean, 2001[106]	4.21	1.47	12.03
Pooled (fixed effects)	**1.40**[a]	**1.15**	**1.69**

[a] $p = 0.002$; test for heterogeneity: $Q = 9.44$ on 6 degrees of freedom ($p = 0.150$).

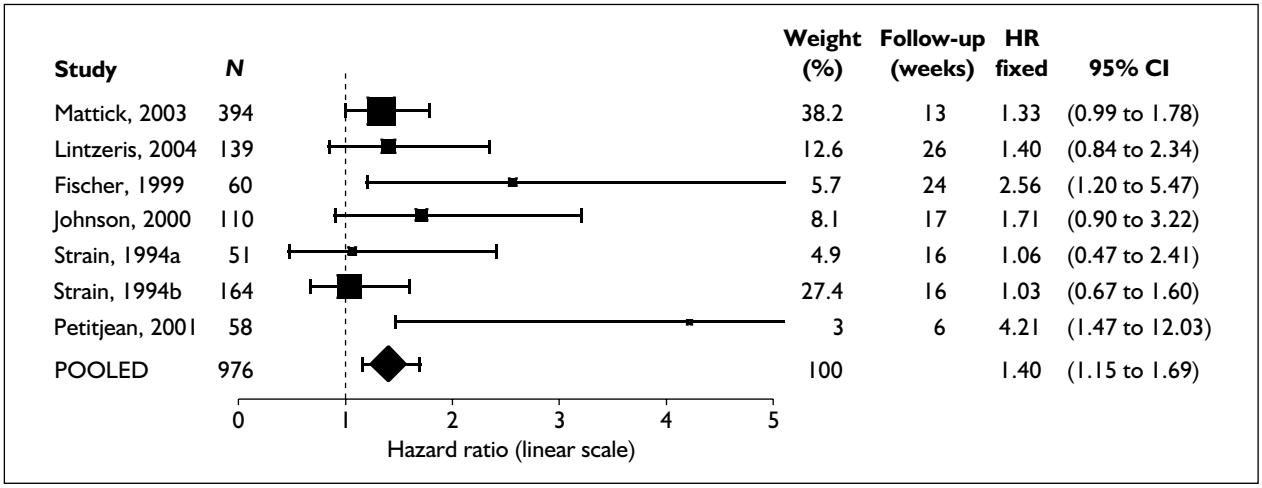

FIGURE 6 *Hazard ratio treatment retention with flexible dosing (buprenorphine versus methadone; fixed effects)*

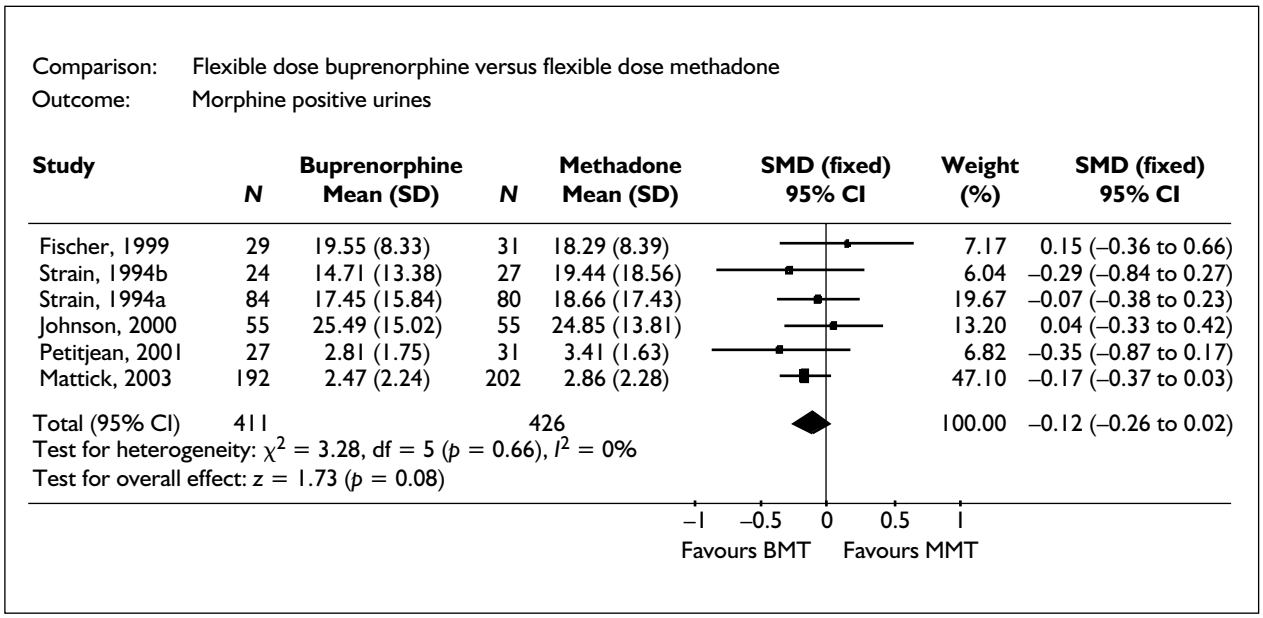

FIGURE 7 *Opioid use with flexible dosing of MMT versus BMT*

Opiate use

There was no significant difference in the level of opiate abuse between flexible-dose MMT and BMT groups, as shown in the Forest plot in *Figure 7*.

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

Side effects and adverse events

See the section 'MMT versus placebo/no therapy' (p. 20).

Mortality

Auriacombe and colleagues[114] made direct comparison of drug overdose deaths in methadone and buprenorphine users in France for the period 1994–8. 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 laboratory-based tests. Total deaths and person-years at risk were methadone 19 and 9360 and buprenorphine 27 and 132,900, respectively. Unfortunately, unknown proportions of these deaths occurred during buprenorphine treatment as distinct from deaths associated with drug diversion and the data are old and probably not safely generalisable to the UK. Lintzeris and Ford (2004) commented that although these data are unlikely to capture all related deaths, they nevertheless suggest that BMT is associated with less mortality than MMT.

After completion of our main literature searches, a recent BMJ editorial suggested that mortality on buprenorphine was five times lower than that on methadone[115] and that therefore methadone was unsafe and should be replaced by buprenorphine. This estimate was based on indirect evidence from numbers of prescriptions issued and recorded numbers of "drug-associated deaths" and should be viewed with considerable caution. We undertook a further (non-systematic) search for observational data on this issue. Two additional studies were identified. Schifano and colleagues[116] reported that 43 deaths associated with buprenorphine had been recorded in the UK during 1980–2002. No correlation was found between buprenorphine associated mortality rate and buprenorphine prescription load; however, the authors argue this may merely reflect the predominant availability until recently of only low-dose formulations. Information on whether the deaths were associated with buprenorphine diversion or treatment was not available or data on person-years at risk. In an Australian study, Gibson and Degenhardt[117] reported death rates in buprenorphine and methadone treatment in terms of deaths/episode of treatment. The buprenorphine rate was based on a single recorded death and must be associated with considerable uncertainty. 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. Generalisability to the UK is problematic.

In summary, the evidence from systematic reviews[48,62] indicates that MMT reduces mortality relative to no MMT. A single RCT[113] provided evidence that BMT was protective relative to no BMT. The few studies[114,117] comparing MMT and BMT are associated with considerable uncertainty and may not be generalisable to the UK.

HIV-related outcomes
No data on BMT and HIV risk behaviour were 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), but this result comes from only one RCT.

Other relevant outcomes
None were identified.

Other MMT and BMT comparisons

MMT or BMT versus other drugs
Compared with LAAM, MMT was more effective (RR 1.64, 95% CI 1.28 to 2.11)[71] whereas BMT was equally effective in the one RCT where this comparison was made (no effect size reported).[66] One RCT found MMT to be more effective in retention than naltrexone[64,73] whereas one RCT reported MMT (10–120 mg) to be less effective than oral heroin (30–120 mg).[76] 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).[76] One RCT showed a similar level of employment of individuals receiving MMT or heroin (see *Table 53*).[76]

MMT or BMT plus co-therapies versus 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.[69] 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[72] identified nine RCTs that directly compared the impact of MMT plus psychosocial interventions with MMT alone (or within standard programme) (see *Tables 37* and *39*). 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 with MMT alone (d = 0.21, 95% CI 0.08 to 0.35) but there was no significant difference in retention on treatment (d = 0.13, 95% CI –0.24 to 0.51). Johansson[61] reported a small but non-significant improvement in opioid misuse when MMT was supplemented with community reinforcement (RR 1.14, 95% CI 0.98 to 1.31) (see *Table 38*).

Johansson[61] identified four studies that directly compared drug MT with contingency management with drug MT alone. Two studies found that opioid use was decreased if individuals had the option to acquire extra methadone if they submitted negative urinalysis,[118,119] while another showed that contingency management increased attendance in therapy sessions.[120] One study found no significant change in use with contingency management.[121]

The addition of psychosocial interventions to MMT appeared to improve individual retention rates further compared with MMT alone, but this additional benefit was small and not statistically significant (effect size d = 0.13, 95% CI –0.24 to 0.51) ($d > 0$ indicates a greater proportion of patients retained in treatment in the intervention group).

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[51,58,61,65] (Lintzeris and Ford, 2004).

Probably the single most comprehensive exploration of treatment modifiers in MMT are the reviews of Prendergast and colleagues,[51,58] who undertook a detailed quantitative synthesis based on meta-analysis and correlational methods. The authors identified 143 controlled studies (RCTs, two 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 drug users comparing therapy either with no therapy or with

minimal therapy. The review included studies examining any drug abuse treatments. Head-to-head dose studies were excluded. Of the 143 studies, 38 (27%) specifically examined MMT. In order to combine studies, the authors converted all outcome results into a single effect size – SMD. 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, but the quality of drug programme implementation and the 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) 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, Lintzeris and Ford (2004) noted that 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 three non-RCTs to examine the impact of two individual characteristics on treatment outcomes. Gerra and colleagues[122] 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 at 12 weeks but less heroin use (urinalysis) in the buprenorphine group. 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 and colleagues[123] found that 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 and colleagues[124] found that 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[122] identified that a history of depression was associated with better treatment response for buprenorphine-treated individuals but not for methadone-treated individuals.

The review of Hopfer and colleagues[56] specifically assessed the impact of opioid use therapies in heroin-dependent individuals aged 19 years or younger. Across four non-RCTs (registry and cross-sectional designs) in 5266 individuals they found an increase in treatment retention and reduction in opioid use with MMT.

Intensity of treatment

The review of Layson-Wolf and colleagues[57] 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 between groups at 52 weeks.

The dispensing and delivery of MMT and BMT in many trials were undertaken under supervision. Lintzeris and Ford (2004) identified only one published study to examine directly the impact on treatment outcome of different supervision levels of buprenorphine dosing. Auriacombe and colleagues[125] quasi-randomly assigned 202 individuals entering office-based buprenorphine treatment into three groups: low supervision (initial 2 weeks on buprenorphine supervised followed by weekly dispensing); medium supervision (3 months of supervised buprenorphine treatment, followed by weekly dispensing); and high supervision (6 months of supervised dispensing). Outcomes were most favourable in the high supervision group [retention 75%, urine drug screen (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 3-day treatment compared with daily treatment has been investigated in a number of RCTs[126–131] and compared with daily methadone treatment.[104,105,107] We found no studies that compared the frequency of MMT dosing.

Treatment setting

Lintzeris and Ford (2004) identified two RCTs that directly compared outcomes of individuals treated in a specialist centre or in a primary care setting. O'Connor and colleagues[132] randomised 46 (presenting to primary care) and demonstrated enhanced outcome for the primary care group (less heroin use, trend towards better retention), whereas Gibson and colleagues[133] found no significant differences amongst 101 individuals randomised to primary care or clinic. Johansson[61] identified another two studies comparing MMT delivery in different settings. Fiellin and colleagues[134] found in 47 individuals no difference in opioid use or retention when treated with methadone by primary care physicians or by an individual narcotic treatment programme. King and colleagues[91] 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-month follow-up.

The review by Lintzeris and Ford (2004) noted a growing body of RCTs indicating that buprenorphine treatment can be effectively delivered in primary care compared with placebo[135] and methadone.[107]

No reviews identified trials directly comparing MMT or BMT in prison settings with non-prison settings.

Study design

As discussed above, although the majority of studies included in reviews have been double-blind MMT and BMT RCTs, observational studies were included, particular for mortality. The bias of observational studies was quantified by Prendergast and colleagues,[51] who found the mean effect size of randomised or non-randomised two-group studies to be some three-fold less (drug use 0.32; crime 0.23) than single-group before-and-after studies (drug use 1.28; crime 0.76).

MMT versus MDT

The overview of Amato and colleagues[136] identified two controlled trials with 340 individuals that 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 and colleagues[63] found one RCT[137] comparing 91 opioid-dependent individuals on MMT with 88 on MDT. There was no difference in HIV or sex risk behaviours at 6- or 12-month follow-up.

BMT versus BDT

The review of Mattick and colleagues[64] identified one RCT that compared BMT with BDT. This RCT, by Kakko and colleagues,[113] compared 20 patients undergoing BMT with 20 undergoing BDT. They reported 20% mortality in the BDT group compared with 0% in the BMT group.

Summary

- Thirty-one systematic reviews (including either RCT or 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 30–49 years, in good health, who met DSM III or IV criteria for opioid dependence, had no serious psychiatric or medical co-morbidities and had not undergone 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 included 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 versus no drug therapy/placebo*: A number of RCT meta-analyses have consistently shown that fixed-dose MMT has superior levels of retention (e.g. 20–97 mg versus placebo: pooled RR 3.91, 95% CI 1.17 to 13.2) in treatment and opiate use (e.g. 35–97 mg versus no treatment: pooled effect size 0.65, 95% CI 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

versus <50 mg: pooled RR 1.25, 95% CI 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 with no therapy.

- *BMT versus no drug therapy/placebo*: two RCT meta-analyses show that fixed-dose BMT has superior levels of retention in treatment (e.g. 6–12 mg versus placebo: pooled RR 1.74, 95% CI 1.06 to 2.87) and opiate use (6–16 mg versus placebo: pooled RR 1.74, 95% CI 1.06 to 2.87) than placebo or no therapy, with higher fixed doses of BMT being more effective than lower fixed doses (retention in treatment, e.g. 8–16 versus 1–4 mg: effect size 0.21, 95% CI 0.12 to 0.31. One small RCT has shown that the level of mortality with fixed-dose BMT is significantly less than with placebo.
- *BMT versus 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 seven RCTs directly compared flexible-dose MMT with flexible-dose 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 30 to 60 or 120 mg for methadone and from 2 or 4 to 8 or 16 mg for buprenorphine. Retention in treatment was superior for flexible-dose MMT than for flexible-dose BMT (pooled HR 1.40, 95% CI 1.15 to 1.69), but there was no significant difference in opiate use (SMD 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 with MMT. A pooled RCT analysis showed no significant difference in the rate of serious adverse events with MMT compared with 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 a primary care or outpatient clinic setting.
- *MMT versus MDT and BMT versus 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 the studies were conducted in the USA 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.

Chapter 4
Economic analysis

Systematic review of economic evaluations – published evaluations

The aim of this section is to assess the cost-effectiveness of MMT or BMT compared with alternative available therapies or no treatment for the management of opioid dependence from an NHS perspective.

This section of the report has three components:

- a review of existing economic evaluations of the use of MMT and BMT 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.

Methods

Search strategy

A comprehensive search for literature on the cost and cost-effectiveness of methadone and buprenorphine as substitute 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 – 2005 week 1, EMBASE (Ovid) 1980–August 2005, Cochrane Library (NHS EED and DARE) (Wiley Internet interface) 2005 Issue 3, HEED database August 2005
- industry submissions
- Internet sites of national economic units.

Full details of search strategies are given in Appendix 1.

Inclusion and exclusion criteria

Inclusion and exclusion criteria applied for economic searches are shown in *Table 8*.

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 predesigned data extraction form and were independently checked 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[138] to assess

TABLE 8 *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	Buprenorphine or methadone employed in MT 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/buprenorphine dose as part of its intervention
Comparator	Any comparator regime used in MT (including no therapy or placebo) or the intervention drug used in withdrawal/detoxification therapy
Outcome	Quality of life estimates, cost estimates, cost-effectiveness

non-model studies and Phillips and colleagues' consensus on health economic criteria quality assessment (QA) criteria[139] 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.

Results

Of the 28 papers that were identified and reviewed in full, only 11 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. 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[140,141] 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 was 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. Eleven published economic evaluations met the inclusion criteria. Key features of these studies are summarised in *Table 9*. A summary of the ICERs reported in the published analyses is provided in *Tables 10–12*.

Eight economic evaluations considered MMT as a primary intervention, with the remaining three evaluations considering BMT. Each study took a different approach, for example, the evaluation undertaken, perspective taken, treatment comparators chosen and the economic models developed. Most studies were considered to be of high quality.

Quality assessment

Phillips and colleagues' QA criteria[139] were used to measure the quality of the six studies reporting an economic model. A summary of the quality results is presented in Appendix 8. All six modelling studies met at least 75% of the QA criteria. The quality of these six non-model studies was judged to be variable, with the exception of one study. Sirotnik and Bailey[142] 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 *Tables 8* and *9*). In addition to cost per QALY, both Doran and colleagues[143] and Harris and colleagues[144] also considered cost per heroin-free day and Zaric and colleagues[145,146] considered cost per life-year gained. Two studies reported outcomes in terms of life-years; Barnett[147] reported a cost per life-year gained and Sheerin and colleagues[148] reported a cost per life-year saved. Three studies reported outcome measures other than cost per QALY or life-year; Goldschmidt[149] reported a cost per effectiveness measure unit (i.e. successful patient) and a cost per heroin-free patient, Sirotnik and Bailey[142] reported a dollar-benefit to society and Zarkin and colleagues[150] reported a cost–benefit ratio (*Table 10*).

Perspective

Five studies took a societal perspective (i.e. including direct and indirect costs associated with healthcare resource use, criminal activity and earnings), namely those of Dijkgraaf and colleagues[101] Goldschmidt,[149] Harris and colleagues,[144] Sirotnik and Bailey[142] and Zarkin and colleagues.[150] The remaining six studies took the perspective of a healthcare system: Barnett and colleagues[147,151] and Zaric and colleagues[145,146] reported results from the perspective of the US healthcare system, Sheerin and colleagues[148] took the perspective of the New Zealand health system and Doran and colleagues[143] took the perspective of the Australian Health Service.

Treatment comparators

The three studies that reported BMT as the primary intervention all used MMT as the comparator.[143,144,147] The remaining studies used a

TABLE 9 *Summary of published economic analyses*

Study	Drug regimen	Form of economic analyses	Perspective taken	Model used	Time horizon (years)	Outcome measure
Barnett, 1999[147]	MMT	Cost-effectiveness	US healthcare system	Markov	Lifetime	Cost per life-year gained
Barnett *et al.*, 2001[151]	BMT	Cost–utility	US healthcare system	Dynamic	10	Cost per QALY gained
Dijkgraaf, *et al.*, 2005[101]	MMT	Cost–utility	Societal	None	1	Cost per QALY gained
Doran *et al.*, 2003[143]	BMT	Cost-effectiveness	Australian Health Service provider	None	1	Cost per heroin-free day
Goldschmidt, 1976[149]	MMT	Cost-effectiveness	Societal	None	1	Cost per 'effectiveness measure unit' (EMU): 'Normabider criterion' (successful patients) and 'heroin-free' patients
Harris *et al.*, 2005[144]	BMT	Cost-effectiveness and cost–utility	Societal	None	NA	Cost per heroin-free day Cost per QALY gained
Masson *et al.*, 2004[152]	MMT	Cost-effectiveness and cost–utility	US healthcare system	Markov	10	Cost per life-year gained and QALY gained
Sheerin *et al.*, 2004[148]	MMT	Cost-effectiveness	New Zealand healthcare system	Markov	10	Cost per life-year saved
Sirotnik and Bailey, 1975[142]	MMT	Cost–benefit	Societal	None	1	Dollar-benefit to society
Zaric *et al.*, 2000a[145]	MMT	Cost–utility	US healthcare system	Dynamic	10	Cost per life-year gained and cost per QALY gained
Zaric *et al.*, 2000b[146]	MMT	Cost–utility	US healthcare system	Dynamic	10	Cost per life-year gained and cost per QALY gained
Zarkin *et al.*, 2005[150]	MMT	Cost–benefit	Societal	Monte-Carlo	Lifetime	Cost–benefit ratio

NA, not applicable.

TABLE 10 *Summary of published economic analyses reporting cost per life-year saved/gained or cost per QALY (MMT)*

Drug regimen	Comparator	Study	Year	Time horizon (years)	ICER	Costs converted to UK£ 2004	Comment
MMT	Drug-free treatment	Barnett[147]	1999	Lifetime	US$5,250 per life-year gained	£3,904 per life-year gained	
	MMT plus heroin	Dijkgraaf *et al.*[101]	2005	1	MMT + heroin MMT alone dominated		Unclear how generalisable the results are to the present report
	MDT	Masson *et al.*[152]	2004	10	US$16,9997 per life-year saved US$46,217–19.997 per QALY gained		
	Five treatment options	Sheerin *et al.*[148]	2004	10	NZ$25,035–25,397 per life-year saved	£8,737–8,864 per life-year saved	Study focused on a Maori and non-Maori comparison. This population is not deemed relevant to the present report
	Four populations determined by prevalence of HIV: 5, 10, 20, 40	Zaric *et al.*[145]	2000a	10	US$9,700–17,200[a] per life-year gained US$6,300–10,900[a] per QALY gained	£6,904–12,243 per life-year gained £4,484–7,759 per QALY gained	Dynamic model incorporating population effects associated with 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.*[146]	2000b	10	US$8,200–10,900[b] per QALY gained	£5,837–7,759 per QALY gained	Dynamic model incorporating population effects associated with infectious diseases and therefore not appropriate for direct comparison with other static models

[a] Dependent on the prevalence rate assumed within the population.
[b] These results were also reported in the previously published paper.[145]

TABLE 11 *Summary of published economic analyses reporting cost per life year saved/gained or cost per QALY (BMT)*

Drug regimen	Comparator	Study	Year	Time horizon (years)	ICER	Costs converted to UK£ 2004	Comment
BMT	Conventional treatment (i.e. MMT)	Barnett *et al.*[151]	2001	10	5% HIV prevalence US$14,000–84,700[a] cost per QALY gained 40% HIV prevalence US$10,800–66,700[a] cost per QALY gained	£9,965–60,289 per QALY gained £7,687–47,477 per QALY gained	Dynamic model incorporating population effects associated with 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 study examines the effect of adding BMT to the US healthcare system in addition to individuals already receiving MMT, 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
	MMT	Doran *et al.*[143]	2003	1	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	Uses the same RCT data[62] as the Schering-Plough economic submission. Sensitivity analysis indicates that costs of BMT and MMT could be equivalent
	MMT	Harris *et al.*[144]	2005	1	Cost per heroin-free day Excluding costs attributed to crime: MMT dominated BPN Including costs attributed to crime: BMT had lower costs and less HFD than 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. This study was funded by the company (Reckett and Coleman)

[a] Dependent on the prevalence rate assumed within the population.

TABLE 12 *Summary of published economic analyses reporting 'alternative' outcome measures*

Drug	Comparator	Study	Year	Time horizon (years)	ICER	Comment
MMT	Therapeutic community programme (TCP)	Goldschmidt[149]	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 inpatient detoxification programme; and an outpatient MMT programme	Sirotnik and Bailey[142]	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.*[150]	2005	Lifetime	Benefit–cost ratio (i.e. MMT treatment compared with no MMT treatment) over a lifetime was 37.72	Dynamic model incorporating population effects associated with infectious diseases and therefore not appropriate for direct comparison with other static models

NA, not applicable.

variety of comparators: Sheerin and colleagues[148] and Sirotnik and Bailey[142] compared five treatment modalities, including MMT as an option; Barnett[147] compared MMT with a drug-free treatment regime; Dijkgraaf and colleagues[101] compared MMT with MMT plus heroin; Goldschmidt[149] compared MMT with a therapeutic community programme; Zarkin and colleagues[150] compared the cost of MMT among a simulated population of 1 million; Zaric and colleagues[145] compared the cost-effectiveness and cost–utility of MMT within four different populations with a high or low prevalence of HIV; and subsequently Zaric and colleagues[146] compared the cost-effectiveness and cost–utility of the expansion of a MMT programme within the same HIV prevalent populations.

Barnett and colleagues[151] reported 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 BMT to the US healthcare system in addition to individuals already receiving MMT, 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 with MMT, Doran and colleagues[143] produced results that were favourable to MMT in the base case 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 becomes more widely used. Harris and colleagues[144] showed that 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 expressed serious concern about the quality of the crime data.

Economic models

Six of the studies developed an economic model.[145–148,150,151] Barnett[147] and Sheerin and colleagues[148] developed Markov models with a time horizon of a lifetime and 10 years, respectively. Zarkin and colleagues[150] developed a Monte Carlo simulation with a lifetime time horizon. Papers by Barnett and colleagues[151] and Zaric and colleagues[145,146] 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,[153] with one exception; Barnett and colleagues[151] 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 US$5 and $30. Under the 'worst case' scenario, i.e. high prevalence community at $30 per BMT dose, the cost per QALY of BMT compared with MMT was reported to be US$66,700 [£47,477 (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 and colleagues.[145,146] All three studies took the perspective of the US healthcare system, and all used a time horizon of 10 years. Barnett and colleagues[151] used BMT as the primary intervention and Zaric and colleagues[145,146] used MMT. All three papers report results in terms of cost per QALY, and in the case of Zaric and colleagues[145] cost per life-year gained, within HIV-prevalent populations. Barnett and colleagues[151] and Zaric and colleagues[146] use two populations, with either a high (40%) or low (10%) HIV prevalence. Zaric and colleagues[145] 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 paper[145] include the same results as reported in their other paper.[146]

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 the form of a meta-analysis is impossible because of the heterogeneity between studies and therefore an attempt is made to reduce the discussion further to the few high-quality studies that are likely to provide the most relevant comparison with the policy questions of the current report.

To this end, the studies summarised in *Table 10*, 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[149] and Sirotnik and Bailey[142] are both now about 30 years old and therefore some of the treatment regimens considered are dated. The latter study, although satisfying the quality criteria, appears to be a rather crude cost–benefit analysis with the data reported as 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, by Zarkin and colleagues,[150] used a transmission dynamic model, with a lifetime time horizon with respect to heroin use, treatment for heroin criminal behaviour, employment and healthcare 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.[154,155] 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 a 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. Hence, in summary, none of these studies are considered to provide appropriate comparisons for the current report. *Tables 10* and *11* 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, by Barnett and colleagues[151] and Zaric and colleagues[145,146] (both of the Zaric 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 used new data collected alongside trials. Harris and colleagues[144] 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 and colleagues[101] 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 last two, more recent studies were considered more relevant and appropriate to the current study.

Three studies, by Zaric and colleagues[145,146] and Barnett and colleagues,[151] 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. Sheerin and colleagues[148] report a study based in New Zealand which compared Maori with non-Maori drug users (distinguishing between males and females) and compared MMT alone with five different 'treatment options' for HCV infection. Given that 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 by Dijkgraaf and colleagues[101] reports a cost–utility analysis of MMT combined with heroin compared with 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 and 6, 10 and 12 months and primary cost data were also collected alongside the trial. The results showed that MMT plus heroin dominated MMT alone. The focus of the authors' conclusion was that, although the treatment cost of MMT plus heroin was more expensive than that of 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 and colleagues,[143] Harris and colleagues[144] and Barnett and colleagues,[147] appear to provide the most relevant comparison with the current report. The study by Doran and colleagues[143] 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 and colleagues,[144] reports a randomised trial of the relative cost-effectiveness of BMT compared with MMT, and was deemed to be of high quality. Thus, focusing 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 and colleagues.[143] For the second outcome (cost per QALY), the cost of treating with BMT was AUS$39,404 [£17,326 (2005)]. 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[147] reports the results of an evaluation which compared MMT with drug-free treatment in terms of cost per life-year gained and is a study that is deemed the most relevant to the current report. The effectiveness parameters are populated by literature review and cost parameters sourced by previously published papers by the same author. The authors used a Markov model to simulate a cohort of 1000 25-year-old opioid-dependent 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 US$75,372. Thus, the cost per additional life-year was reported to be US$5250 (£3904).

Summary

- Twenty-eight potentially relevant includable economic evaluations were identified. Of these, 11 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 ICER reported as a cost per QALY gained. There were three cost-effectiveness analyses and two cost–benefit analyses. Six papers reported use of an economic model: two used Markov models, one used a Monte Carlo simulation and three used 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 perspectives, countries of origin, sources 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, perspectives and comparators required to make their results generalisable to the NHS and PSS context.
- Only one study, by Barnett,[147] compared the cost-effectiveness of 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 BMT directly with MMT that were appropriate for policy questions of the current report, namely by Doran and colleagues[143] and Harris and colleagues.[144] The latter study 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 Doran and colleagues[143] found MMT to dominate BMT, with MMT being more effective and less costly.
- No studies assessing the cost-effectiveness of BMT compared with no drug therapy were found.
- One study, by Masson and colleagues,[152] showed MMT to be more costly than MDT but to be more effective in preventing opiate abuse.

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 that included a cost-effectiveness analysis.

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 1-year time horizon. The model was structured to consider overall maintenance therapy versus no drug treatment, BMT versus no drug treatment and BMT versus 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 the 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 three 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

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". [**Confidential information removed**]. However, this research is marked as confidential. Furthermore, we were unable to find published evidence available to suggest that 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 specialists 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 email 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 0–5%). The mean response to question 2 was 20.4% (range 5–50%). Therefore, it appears that the Schering Plough model overestimates the number of patients who cannot take methadone for medical reasons, although this figure may be more reflective of patient preference.

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, a utility value and cost are attached to each arm of the tree. Data on retention in treatment and dosing are from one trial alone, namely that by Mattick and colleagues.[105] They detail the initial 13 weeks of a double-blind RCT comparing flexible-dose BMT and MMT. The open-label stages of the same trial were reported separately by Doran and colleagues,[143] providing data for retention in treatment at 6 months. Retention rate data were presented with mean and standard deviations (SDs) and α and β distributions (*Table 13*). We note that the economic model is based on data on one specific RCT whereas an updated systematic review identifies a total of seven 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 the induction dosing schedule used by Mattick and colleagues[105] may be suboptimal, leading to lower treatment retention rates for BMT.

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

TABLE 13 *Probability of retention in treatment (adapted from Appendix 1 of the Schering-Plough submission)*

Treatment	Treatment time	Probability		Distribution	
		Mean	SD	α	β
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

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 Schering-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 and colleagues,[80] 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 BMT 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 CIs will be explained in detail later.

Utility values

Due to the lack of utility data, values in the Schering-Plough submission were based on those from Harris and colleagues' paper,[144] and an adjustment factor assumed by Barnett and colleagues[151] was then applied to these values "for not being in treatment". The latter study used adjustments of 0.9 for quality of life in maintenance therapy and 0.8 for an IDU, therefore a reduction of 0.1 in IDUs 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 Barnett and colleagues' study.

Resource utilisation and costs

Resource use and costs in the Schering-Plough submission were derived from several studies. Mattick and colleagues[105] provided the data for the number of counselling sessions per week (one session per week) and number of urine tests conducted (every fortnight). A time and motion study reported in the paper by Doran and colleagues[143] provided data for the time taken to dispense and supervise patients taking methadone or buprenorphine. Rates of healthcare usage were taken from the NTORS reported by Gossop and colleagues.[26] Rates differed for patients in treatment and not in treatment. The use of healthcare 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 the Seven Boroughs Buprenorphine Study by Ridge and colleagues,[156] the BNF and Curtis and Netten.[157] Due to the model representing 1 year, discounting was not applied. The cost data used in this model appear to be entirely reasonable and the correct methodology was applied.

Model results

BMT versus no drug treatment

The results of the Schering-Plough model for buprenorphine versus no treatment for the 20% of 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 MMT 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.

MMT versus 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 with BMT.

Maintenance therapy versus no drug treatment

Running the Schering-Plough model for MT versus no treatment gave an ICER of £12,584 per QALY. This result was obtained by using the results of the two comparisons 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 MT actually represents a mixture of methadone (80%) and 'no treatment' (20%). Therefore, this is not a true comparison of MT versus no treatment, because by setting the threshold, the relevant comparator has been ignored.

Deterministic sensitivity analysis was performed on the different decisions. For MT 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.

Assessment group economic model

Introduction

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

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 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£ and costs and benefits are not discounted due to the model assessing only 12 months.

Description of the model

The model follows patients for 1 year and the main parameter of interest is retention in treatment. The model considers the proportion of patients retained in treatment at 2, 6, 13 and 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, a utility value and cost are attached to each arm of the tree in *Figure 8*.

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 the section 'Schering-Plough (buprenorphine) submission' (p. 38)].

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 the section 'Treatment outcomes' (p. 20)]. The recent updated Cochrane systematic review by Mattick and colleagues[64] identified seven trials (including their own[105]) that compared methadone and buprenorphine with flexible dosing. The pooled HR obtained of 1.40 (95% CI 1.15 to 1.69) was used to estimate the RR of dropping out from the treatment. A Weibull distribution (shape parameter = 0.7215, scale parameter = 0.0893) (*Figure 9*) was fitted to the buprenorphine data (*Table 14*) 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 HR derived from the seven studies of flexible dosing (HR methadone versus buprenorphine = 1/1.396 = 0.716).

Level and nature of drug misuse

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

Opioid-positive or -negative urine data were reported in six of seven RCT studies of MMT versus BMT with flexible dosage.[104–106,108–110] Weekly data for those retained in treatment through time were available from only two studies.[104,105] Weekly, bi-weekly or tri-weekly data were reported for completers only (those still in treatment at end of follow-up) in several studies[106,108,109,110] and Strain and colleagues[109,110] reported overall data for periods of different dosage regimen. The urinalysis results from Mattick and colleagues[105] and Johnson and colleagues[104] were combined (weighted according

TABLE 14 *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; SE, standard error; UCI, upper confidence interval.

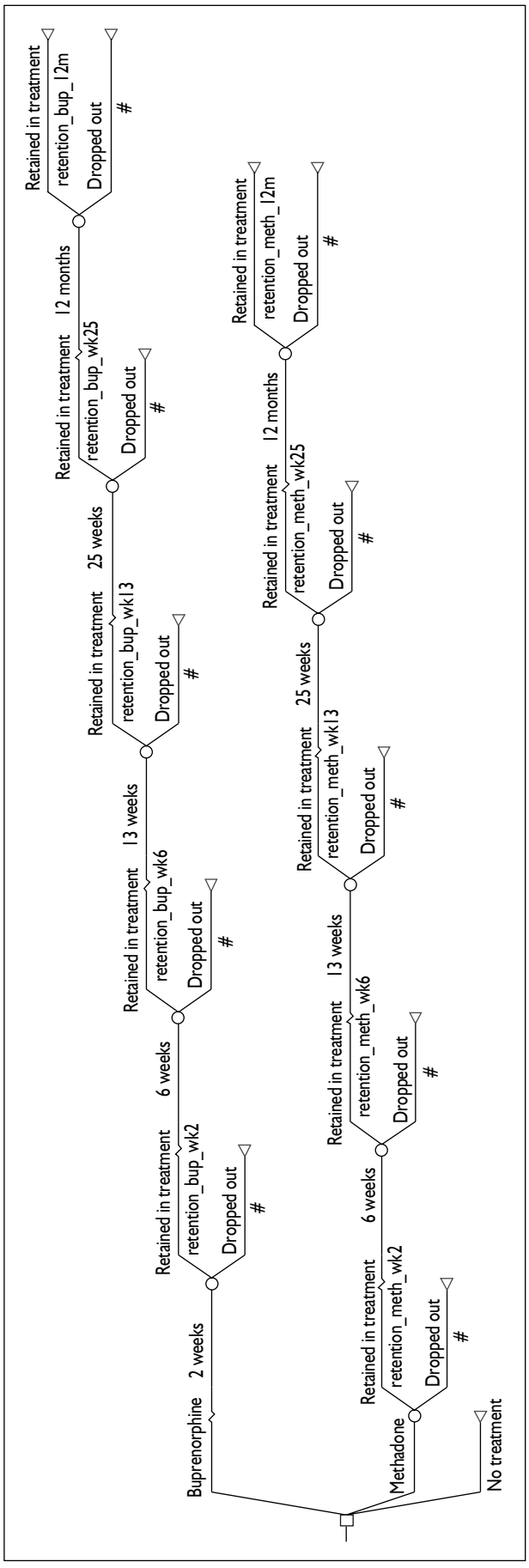

FIGURE 8 *Decision tree for maintenance treatment with buprenorphine or methadone*

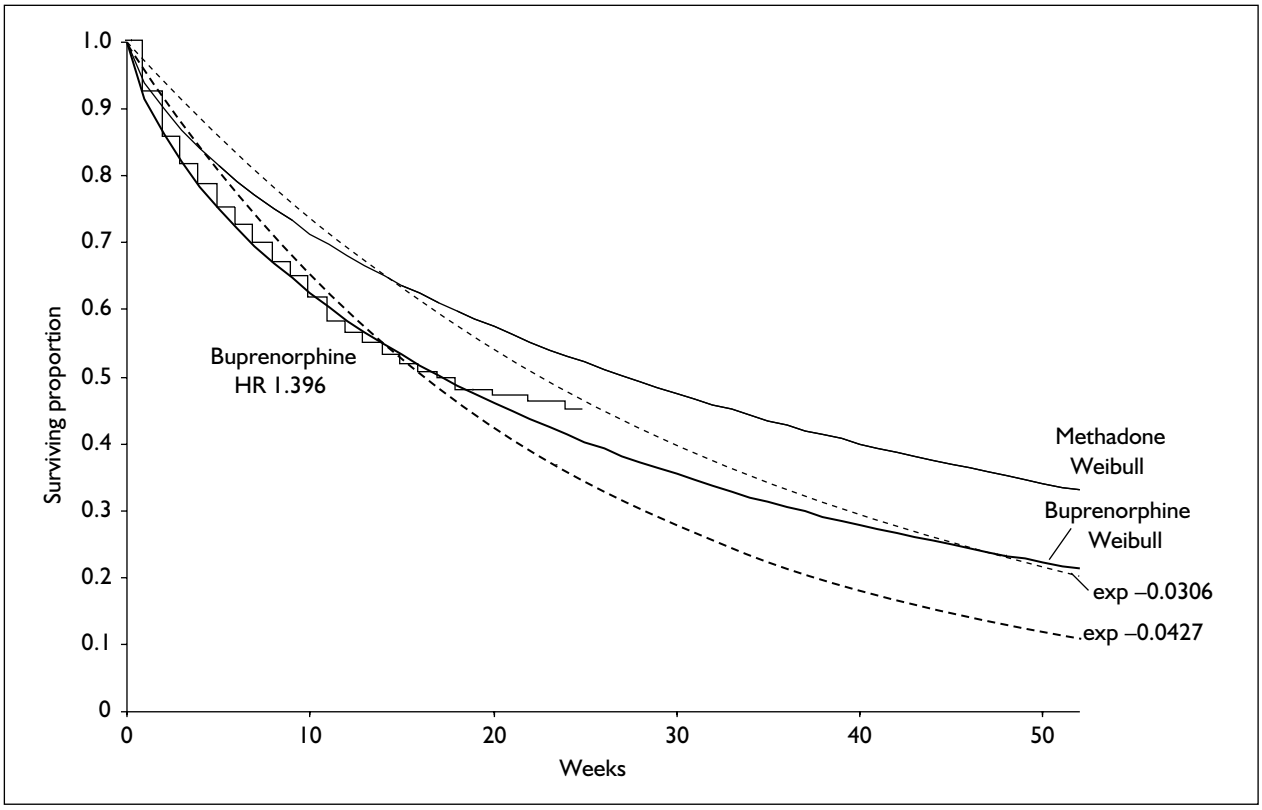

FIGURE 9 *Weibull fit to buprenorphine retention in treatment and derived methadone curve*

to study size in each arm) and are shown in *Table 15*. The analysis assumes that the percentage of negative urines is equivalent to the percentage of the retained patients at each time point who are drug free at that time.

For those not retained in treatment, it was assumed that patients return to their pretreatment habits irrespective of their period of MMT or BMT. At entry into treatment in Mattick and colleagues study[105] 15.7% of urines were opioid-

TABLE 15 *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

free and 84.3% positive. This is close to the 89% reported to be heroin abusers at entry into MMT by Gossop and colleagues[158] 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.[26] 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 QALY. In the non-reference case analysis we also include cost implications as far as possible for a societal perspective which includes the CJS and victim costs of crime. Therefore, the identification of costs for the model has been conducted from both the NHS/PSS and the societal perspective. Every effort has been made to use the information available to estimate accurately the magnitude of these costs. The estimation of costs for the model is divided into costing the treatment programmes and costing the consequences of drug misuse. The model uses a half-cycle correction for costs; therefore, if a patient who is in treatment at 2 weeks then drops out of treatment at 6 weeks, it is assumed they have been in treatment from weeks 2–4 and off treatment for weeks 4–6.

NHS/PSS perspective (reference case)

MT included both pharmacological treatment and counselling. In this model, MT for both BMT and MMT assumes a flexible dosing regimen and uses data on mean dose from the Mattick trial[105] shown in *Table 16*. Where no published SDs were available, the SDs for the probabilities were based on SD = rate/$\sqrt{N}$. In the maintenance period, N = 202 and 192 for patients treated with methadone and buprenorphine, respectively.[105] The 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 that patients in treatment attended one counselling session per week and had one urine test per fortnight to monitor treatment success (*Table 17*). When patients dropped out of treatment, counselling and urine testing did not occur. Data were obtained from the Mattick trial, and the same approach as described above was used for the calculation of SDs. Unit cost information used in the industry submission was also used here.

Data on resource use for the reference cases, required for the model, were extracted using data

TABLE 16 *Maintenance therapy doses (mg) per day*[a]

Period	Buprenorphine				Methadone			
	Mean	SD	Range		Mean	SD	Range	
			Lower limit	Upper limit			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 and 8	10.80	0.72	2	32	53.60	3.28	10	150
Weeks 8 and 9	10.90	0.67	4	32	54.10	3.28	10	150
Weeks 9 and 10	11.20	0.67	4	32	54.40	3.28	10	150
Weeks 10 and 11	11.00	0.72	2	32	55.20	3.28	10	150
Weeks 11 and 12	11.10	0.72	2	32	56.40	3.28	10	150
Weeks 12 and 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

[a] Data from Mattick and colleagues.[105]

TABLE 17 *Maintenance therapy resource use*[a]

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

[a] Data from Mattick and colleagues.[105]
[b] As used in the industry submission.

supplied by 'problem drug users' within NTORS that covered healthcare services, the CJS and employment. This study, described in detail by Gossop and colleagues,[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 those reported by the NTORS participants in the 12 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 inpatient stays amongst those in short-term treatment. These items are presented in *Table 18*. Where published SDs 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 2004 UK£. 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's report.[157] The unit costs for an Accident and Emergency (A&E) visit and for inpatient hospital stays have been calculated using estimates provided by Godfrey and colleagues[159] and updated to 2004 figures using the Hospital and Community Health Services (HCHS) pay and prices index. Based on Godfrey and colleagues, the A&E costs assume that many of these visits would be serious and therefore would involve an overnight stay. Godfrey and colleagues note that the unit cost for community health visits may be an underestimate as it does not take into account expensive outpatient visits to a psychiatrist.

TABLE 18 *NHS/PSS perspective resource use and costs*[a]

Healthcare costs breakdown	Resource use	Source	Unit cost (£)	Source	Total (£)
Successful health states					
Successful/drugs free/reduction/<1 year					
GP visits per year	5.6	Gossop *et al.*, 2001[158]	21	Curtis and Netten, 2004[157]	118
Rate of A&E visits per year	0.8	Gossop *et al.*, 2001[158]	318	Godfrey *et al.*, 2002[159]	254.40
Rate of inpatient hospital stays per year	2.8	Gossop *et al.*, 2001[158]	251	Godfrey *et al.*, 2002[159]	702.80
Rate of outpatient mental health visits per year	0.8	Gossop *et al.*, 2001[158]	56	Godfrey *et al.*, 2002[159]	45
Rate of inpatient mental health visits per year	0.4	Gossop *et al.*, 2001[158]	162	Godfrey *et al.*, 2002[159]	64.80
Total annual healthcare costs					**1184**
Unsuccessful health states					
Unsuccessful/drugs misused					
GP visits per year	3.6	Gossop *et al.*, 2001[158]	21	Curtis and Netten, 2004[157]	76
Rate of A&E visits per year	0.7	Gossop *et al.*, 2001[158]	318	Godfrey *et al.*, 2002[159]	222.60
Rate of inpatient hospital stays per year	1.75	Gossop *et al.*, 2001[158]	251	Godfrey *et al.*, 2002[159]	439
Rate of outpatient mental health visits per year	1.3	Gossop *et al.*, 2001[158]	56	Godfrey *et al.*, 2002[159]	72.80
Rate of inpatient mental health visits per year	1.5	Gossop *et al.*, 2001[158]	162	Godfrey *et al.*, 2002[159]	243
Total annual healthcare costs					**1053**

[a] SD = rate/$\sqrt{}$($N^{\text{opioid dependent}} \times P^{tx}$) or SD = rate/$\sqrt{}$[$N^{\text{opioid dependent}} \times (1 - P^{tx})$]. P^{tx}, proportion of patients in treatment.

TABLE 19 *Dispensing fees*[a]

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	0.43	Paid for each occasion treatment is dispensed
Supervised self-administration	1.80	2.42	

[a] Source: Seven Boroughs Study.[156] Figures based on prescribing and dispensing on FP10.

Drug costs are taken from the BNF (No. 50, September 2005) with methadone costing £0.0135/mg and buprenorphine £0.48/mg. The latter uses the cost of 2-mg tablets rather than 8-mg tablets as the model assumes a flexible dosing regimen which requires smaller tablets. The average costs for dispensing methadone and buprenorphine were taken from the Seven Borough Buprenorphine Study.[156] The model uses the average fees charged by pharmacies presented in *Table 19* based on the prescription forms used by GPs when prescribing (FP10). The frequency and type of dispensing for a patient entering maintenance treatment for 12 months were based on the following assumptions:

- first 3 months: supervised dispensing, 6 days per week (as per DoH guidelines)
- second 3 months: unsupervised dispensing, 6 days per week
- months 6–12: three times per week unsupervised dispensing.

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 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 are 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 that for 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 and colleagues[159,161] provide 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 was higher for users in treatment in the first year than those not in treatment. The report containing these data highlights this unexpected result but does not give any further explanation, and states that additional analysis of these data was not possible within the project. However, a subsequent re-analysis[141] on the same NTORS data 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, these data should be viewed with some caution as they are self-report data which have 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. Godfrey and colleagues[159] used estimates provided by Brand and Price[162] and the pattern of offences self-reported by NTORS clients to estimate the victim costs associated with criminal behaviour. Victim costs refer to an estimated average cost per drug addict or patient in treatment imposed on and incurred by victims of crime. This includes measures in anticipation of crime such as security measures and direct costs such as material or physical damage or loss. Resource use and costs are presented in *Table 20*.

Estimation of QALYs

Early in the literature review process for the current report, there appeared to be very limited published data available on the quality of life associated with drug abuse. Many of these available data appeared not to be appropriate for the purpose of the current evaluation because they related specifically to quality of life for patients suffering some of the potential consequences of drug abuse such as HIV or AIDS.[145,146,151] At that point, it was considered appropriate to seek some entirely new data from the experimental health

TABLE 20 *Societal perspective resource use and costs*

CJS costs breakdown	Resource use	Source	Unit cost (£)	Source	Total (£)
Successful health states					
(Successful/drug free/reduction/<1 year)					
Rate of drug arrests per year	0.8	NTORS study	3,551	Godfrey *et al*., 2002a[159]	2,840.80
Rate of acquisitive crime arrests per year	1.6	NTORS study	1,346	Godfrey *et al*., 2002a[159]	2,153.60
Average time held in policy custody per year (nights)	1.2	NTORS study	69	Godfrey *et al*., 2002b[161]	82.80
Rate of court appearances in 1 year	1.4	NTORS study	699	Harries, 1999[163]	978.60
Time spent in prison per year (days)	34	NTORS study	68.86	Godfrey *et al*., 2002b[161]	2,341
Total annual CJS costs					**8,397**
Annual victim costs			8,893	Godfrey *et al*., 2002a[159]	**8,893**
Total annual social costs					**17,290**
Unsuccessful health states					
Rate of drug arrests per year	0.3	NTORS study	3,551	Godfrey *et al*., 2002a[159]	1,065.30
Rate of acquisitive crime arrests per year	1.35	NTORS study	1,346	Godfrey *et al*., 2002a[159]	1,817.10
Average time held in policy custody per year (nights)	2	NTORS study	69	Godfrey *et al*., 2002b[161]	138
Rate of court appearances in 1 year	2.2	NTORS study	699	Harries, 1999[163]	1,537.80
Time spent in prison per year (days)	36	NTORS study	68.86	Godfrey *et al*., 2002b[161]	2,479
Total annual CJS costs					**7,037**
Annual victim costs			30,827	Godfrey *et al*., 2002a[159]	**30,827**
Total annual social cost					**37,864**

utilities panel coordinated 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 report. We use the results of our own utility exercise coordinated by PenTAG in the reference case analysis of the current report. We use the utility values estimated by the two most recently published studies[101,144] in our sensitivity analysis to the reference case and the results compared with our base case. The utility values estimated by Harris and colleagues[144] were also used in the modelling exercise of industry submission from Schering-Plough.

The PenTAG panel is funded jointly by the UK DoH, 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.

Ten 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 drug free while on treatment. Data were used to estimate the average proportion of drug-free patients for the first 2 weeks (referred to as the 'induction phase'[105]) and the average proportion of patients who were drug 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 2 weeks and on treatment for weeks 3–52. The weights for injector and non-injectors were taken

TABLE 21 *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 3–52	0.7458 (0.1836)	0.7455 (0.1837)

from NTORS[26] assuming that 44% of those abusing drugs are injectors. The mean weighted QALYs are presented in *Table 21*.

For those not retained in treatment, we assumed that patients returned to their pretreatment 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 β distribution for QALYs we used the method of moments methodology.

Assessment of cost-effectiveness

Data on the incremental cost per QALY are presented in two ways. First, mean costs and QALYs for the alternative interventions are presented and the incremental cost per QALY is calculated where appropriate. The second mode of presentation uses the results of the probabilistic sensitivity analysis and shows cost-effectiveness acceptability curves (CEACs) and scatterplots of incremental costs and outcomes. CEACs were used to illustrate uncertainty in results due to statistical variability around the parameter estimates. The curves demonstrate the likelihood 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 22*. A normal distribution was used for the doses of methadone and buprenorphine, and means and SDs are given in *Table 16*. The model was run for 10,000 simulations.

Three separate incremental analyses were conducted: MMT versus no therapy, BMT versus BMT and BMT versus MMT.

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

Normal distributions			
Parameter		**Mean**	**SD**
Survival analysis			
Log of HR 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 and 2)	0.702	3.161	1.343
QALY value on methadone (3 weeks and over)	0.746	3.448	1.175
QALY value on buprenorphine (weeks 1 and 2)	0.704	3.177	1.336
QALY value on buprenorphine (3 weeks and over)	0.746	3.445	1.175

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

Deterministic sensitivity analysis for reference case

The sensitivity analysis focused 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 the 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 week 13 alternate-day (three days per week) supervised dispensing and from week 14 to week 52 alternate-day unsupervised dispensing.

Utility score using utility values from Harris and colleagues[144]

A sensitivity analysis was performed using the utility values from Harris and colleagues[144] 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) was used (methadone = 0.59 and buprenorphine = 0.62 (*Table 23*)). This approach was taken because the model should reflect expected values of health states during a specific period *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 that 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 and colleagues.[151]

TABLE 23 *Utility values used in the sensitivity analysis*

Source	Buprenorphine	Methadone
Harris *et al.*, 2005[144]	0.62	0.59
Dijkgraaf *et al.*, 2005[101]	0.73	0.73

Utility score using utility values from Dijkgraaf and colleagues[101]

A further analysis was performed using the utility values from Dijkgraaf and colleagues[101] (*Table 23*). This study compared MMT with methadone plus heroin. Utility values were obtained from patients using the EQ-5D questionnaire at baseline and 6, 10 and 12 months and an overall QALY value 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 that 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 was 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 CJS only.

Results

Reference case: NHS/PSS perspective

Tables 24 and *25* 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 and 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 24 *Cost-effectiveness results of all strategies*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
No treatment	1053		0.6230		
Methadone	1971	918	0.6900	0.0670	13,697
Buprenorphine	2491	520	0.6774	–0.0126	(Dominated)

TABLE 25 *Cost-effectiveness results of BMT versus no treatment*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
No treatment	1053		0.6230		
Buprenorphine	2491	1438	0.6774	0.0544	26,429

TABLE 26 *Non-reference case: cost-effectiveness results of all strategies from a societal perspective*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Methadone	28,345		0.6900		
Buprenorphine	30,992	2,647	0.6774	–0.0126	(Dominated)
No treatment	38,917	10,572	0.6230	–0.0670	(Dominated)

TABLE 27 *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	30,992		0.6774		
No treatment	38,917	7,925	0.6230	–0.0544	(Dominated)

Non-reference case: societal perspective

Costs to the CJS 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 26* and for buprenorphine versus no treatment in *Table 27*. All strategies are dominated by MMT, and BMT is dominant over no treatment. Again, the QALY difference between MMT and BMT is very small.

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, on comparing *Figures 11* and *13*, BMT is more likely to be cost-effective when compared with no treatment than when compared with MMT.

Deterministic sensitivity analysis

Dispensing of buprenorphine. By assuming less frequent dispensing (alternate days) and unsupervised dispensing of buprenorphine in weeks 14–52, 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 28* and for BMT versus no treatment in *Table 29*.

Utility scores. Using the utilities from the industry submission[144] in the model resulted in BMT no

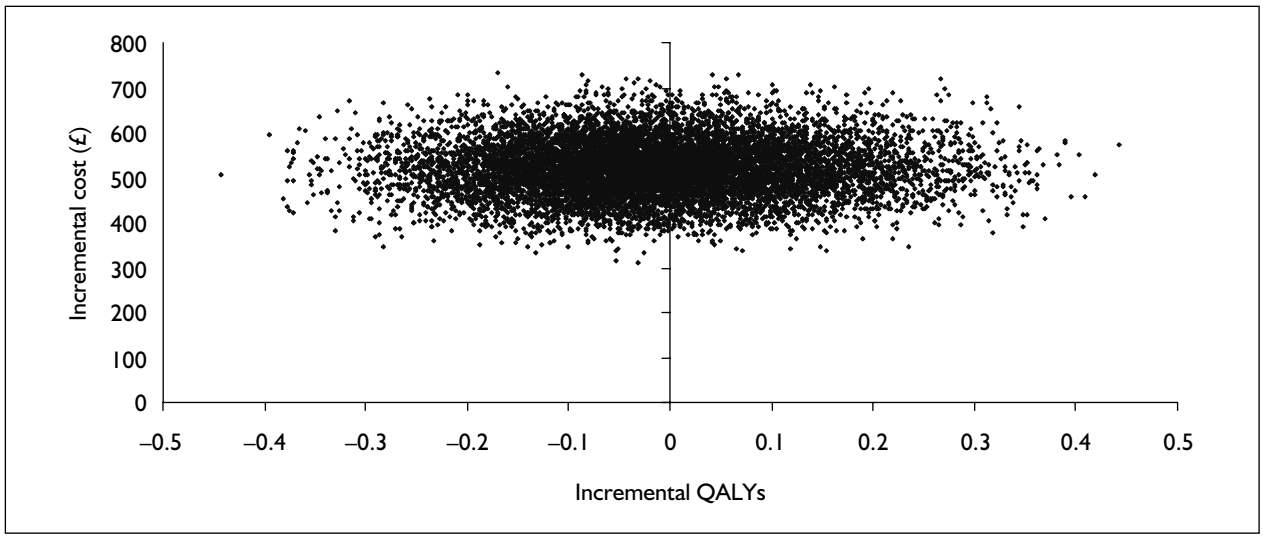

FIGURE 10 *Incremental cost-effectiveness plane for BMT compared with MMT*

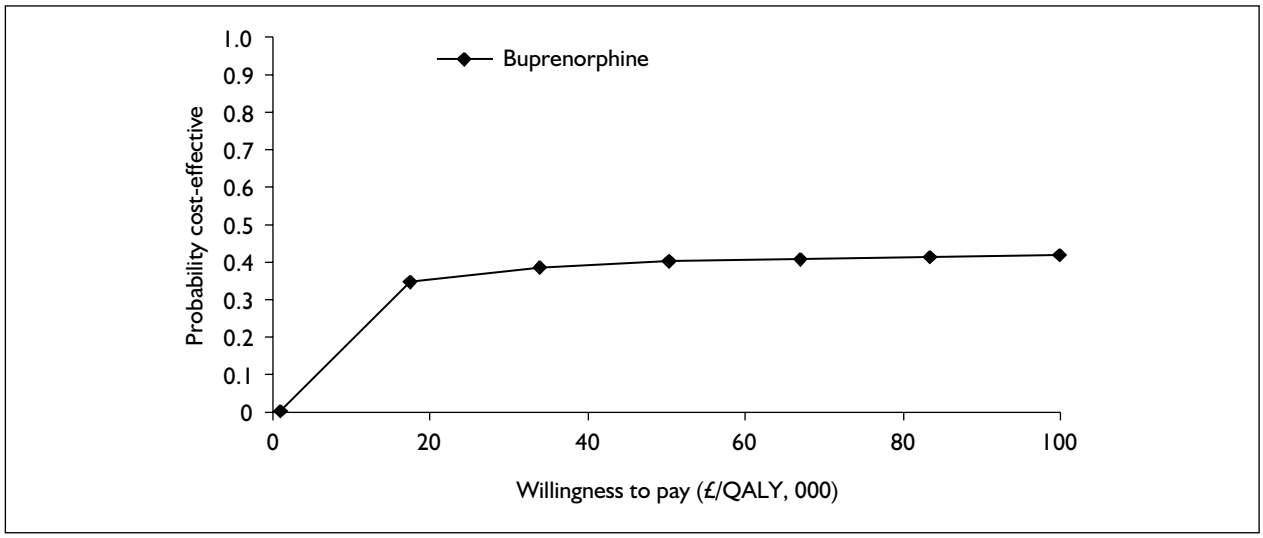

FIGURE 11 *CEAC for BMT compared with MMT*

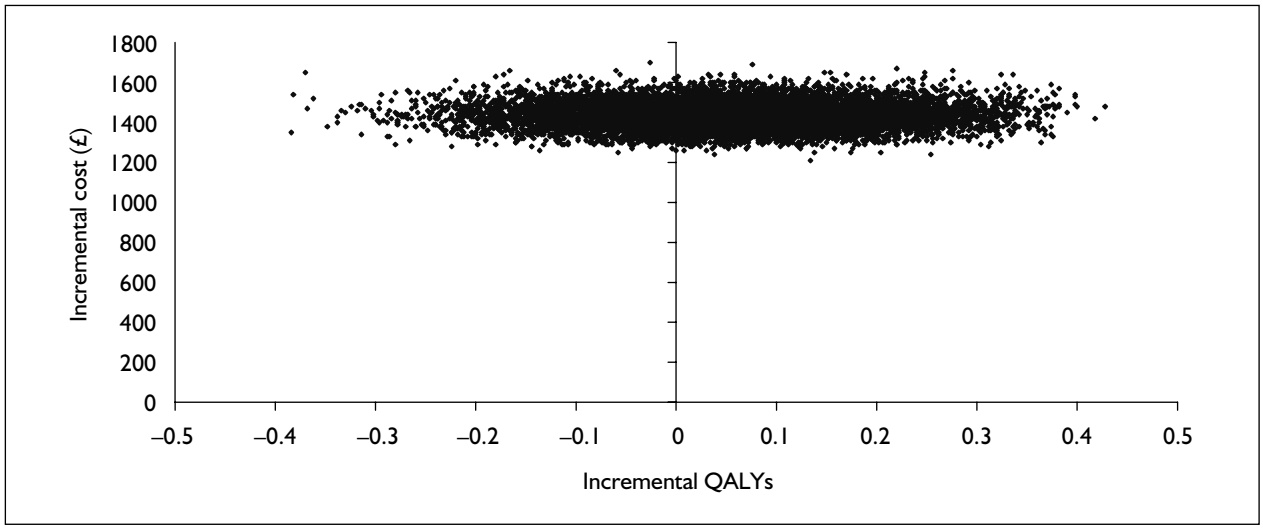

FIGURE 12 *Incremental cost-effectiveness plane for BMT compared with no treatment*

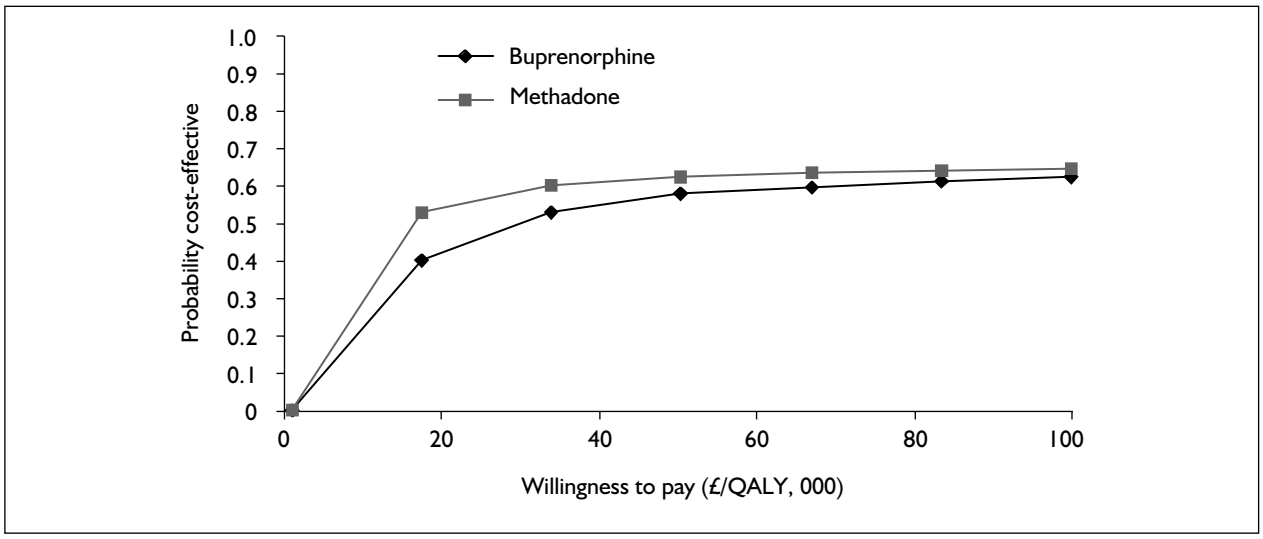

FIGURE 13 *CEACs for BMT and MMT compared with no treatment*

TABLE 28 *Sensitivity analysis: cost-effectiveness results for all strategies*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Alternative buprenorphine dispensing					
No treatment	1,053		0.6230		
Methadone	1,971	918	0.6900	0.0670	13,697
Buprenorphine	2,363	413	0.6774	–0.0126	(Dominated)
Using alternative utilities					
Harris et al., 2005[144]					
No treatment	1,053		0.5050		
Methadone	1,971	918	0.5525	0.0475	19,320
Buprenorphine	2,491	520	0.5573	0.0048	108,333
Dijkgraaf et al., 2005[101]					
No treatment	1,053		0.6300		
Methadone	1,971	918	0.6858	0.0558	16,447
Buprenorphine	2,491	520	0.6755	–0.0103	(Dominated)
Exclusion of victim costs from a societal perspective					
No treatment	8,090		0.6230		
Methadone	9,767	1,677	0.6900	0.0670	25,033
Buprenorphine	10,147	379	0.6774	–0.0126	(Dominated)

TABLE 29 *Sensitivity analysis: cost-effectiveness results of BMT versus no treatment*

Strategy	Cost (£)	Cost difference (£)	QALYs	QALY difference	ICER (£/QALY)
Alternative buprenorphine dispensing					
No treatment	1,053		0.6230		
Buprenorphine	2,363	1,310	0.6774	0.0544	24,074
Using alternative utilities					
Harris et al., 2005[144]					
No treatment	1,053		0.5050		
Buprenorphine	2,491	1,438	0.5573	0.0523	27,490
Dijkgraaf et al., 2005[101]					
No treatment	1,053		0.6300		
Buprenorphine	2,491	1,438	0.6755	0.0455	31,598
Exclusion of victim costs from a societal perspective					
No treatment	8,090		0.6230		
Buprenorphine	10,147	2,057	0.6774	0.0544	37,806

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,[101] the ICER for MMT versus no treatment is slightly higher than the reference case, and BMT is still dominated by MMT.

Comparing BMT with no treatment, the values used by the industry submission give a very similar result to the reference case. However, the Dijkgraaf values[101] 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 dominant and had an ICER of £37,806 per QALY gained. Both demonstrate the considerable impact that the inclusion of victim costs has on the results.

Summary

- The assessment group developed a decision tree with a Monte Carlo simulation model to assess the cost-effectiveness of BMT and MMT compared with no drug therapy and BMT compared with MMT. 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.
- According to this model, both MMT and BMT are cost-effective strategies compared with no drug therapy. These findings were robust to sensitivity analysis.
- Although MMT was dominant in comparison with BMT from the perspectives of both the NHS/PSS and society (inclusion of the CJS 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 while on treatment, whereas the Schering-Plough model 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 were found in the published literature, our model used entirely new and unique data on utilities derived specifically for this project. The industry submission used utility data elicited from patients. In contrast, we used utilities derived from a panel representing a wider societal perspective. Finally, unlike the Schering-Plough submission, which used data from only one trial, the clinical data in this model were 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 1-year time horizon, both the economic models of the assessment group and Schering-Plough did not take into account any differences in mortality between MMT and BMT.

Chapter 5

Assessment of factors relevant to the NHS and other parties

Compared with no drug therapy, both BMT and MMT are associated with small gains in HRQoL of opioid abusers. By keeping opioid abusers in drug therapy, neither buprenorphine not methadone is 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 therefore most clinicians (and many patients) have a reasonably good understanding of how to use it safely and effectively. Buprenorphine has only been available in the UK for 5 years, 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.

Chapter 6
Discussion

Clinical effectiveness

Thirty-one systematic reviews (including either RCT or 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-dependent users 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 versus no drug therapy/placebo

A number of RCT meta-analyses have consistently shown that fixed-dose MMT has superior levels of retention (e.g. 20–97 mg versus placebo: pooled RR 3.91, 95% CI 1.17 to 13.2) in treatment and opiate use (e.g. 35–97 mg versus no treatment: pooled effect size 0.65, 95% CI 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 versus <50 mg: pooled RR 1.25, 95% CI 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 with no therapy.

BMT versus no drug therapy/placebo

Two RCT meta-analyses show that fixed-dose BMT has superior levels of retention in treatment (e.g. 6–12 mg versus placebo: pooled RR 1.74, 95% CI 1.06 to 2.87) and opiate use (6–16 mg versus placebo: pooled RR 1.74, 95% CI 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 8–16 mg versus 1–4 mg: effect size 0.21, 95% CI 0.12 to 0.31). One small RCT has shown the level of mortality with fixed-dose BMT to be significantly less than with placebo.

BMT versus MMT

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

MMT versus MDT and BMT versus 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

Eleven 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, countries of origin, sources 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 with flexible-dose BMT and utility values obtained from the literature.

MMT versus no drug therapy

The ICER was £12,584/QALY.

BMT versus no drug therapy

The ICER was £30,048/QALY.

MMT versus BMT

In a direct comparison, MMT was found to be slightly more effective (QALY difference of 0.00055) and less costly than BMT.

Assessment group model

MMT versus no drug therapy

The ICER was £13,697/QALY.

BMT versus no drug therapy

The ICER was £26,429/QALY.

MMT versus 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.

Strengths, limitations and uncertainties of assessment

The main strengths of this report are that its economic analysis is 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 versus BMT.
- This pooling was based on a meta-analysis using the time-dependent nature (i.e. HRs) of the outcomes. Additional searching brought to our attention a recent critical appraisal, authored by Caplehorn and Deeks,[164] of Mattick and colleagues' flexible-dose RCT[105] comparing methadone and buprenorphine. They question the trialists' conclusion that the two drugs are equivalent for retaining patients in treatment and point to a lack of ITT analysis of data on withdrawal from treatment in the RCT report. We therefore reanalysed the HR for this trial (according to ITT) and also the pooled HR for the seven comparative trials of flexible dosing. Although the Mattick trial HR is increased slightly (1.38, 95% CI 1.04 to 1.83), the effect on the pooled HR would have negligible impact on our modelling of cost-effectiveness (1.42, 95% CI 1.17 to 1.71, compared with 1.40, 95% CI 1.15 to 1.69).
- 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 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 the 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- or heroin-dependent users, without significant co-morbidities. The majority of data come from studies conducted in Australia and the USA and therefore direct applicability to the UK may be questioned. There was a limited evidence base for MMT and BMT in the primary care and criminal justice settings or in particular opiate-dependent users such as drug injectors and HIV-infected individuals. 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 versus non-injectors) and treatment settings (e.g. criminal justice versus healthcare setting) suggested equivalent MMT and effectiveness of MMT and BMT.
- 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 with no therapy, BMT and MMT may improve mortality. However, that there was a difference in mortality between MMT and BMT remains uncertain.
- 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 CJS costs alone were higher for patients in treatment than those out of treatment. Excluding victim costs of crime changed the societal perspective results: MMT no longer was dominant over BMT or no treatment and had an ICER of at least £25,000; BMT also was no longer dominant over no treatment and had an ICER of more than £37,000.
- There was insufficient clinical evidence to estimate the cost-effectiveness of a strategy of BMT or MMT compared with a detoxification strategy.

Chapter 7
Conclusions

Implications for service provision

Both flexible-dose MMT and BMT are more clinically effective and more cost-effective than no drug therapy in opiate-dependent users. In direct comparison, flexible-dose MMT (daily equivalent dose from 20 or 30 to 60 or 120 mg) was found to be somewhat more effective in maintaining individuals in treatment than BMT (daily equivalent dose from 2 or 4 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-dependent users' preferences.

Suggested research priorities

In general, the quality of the clinical evidence base included in this report was good. However, most studies have been conducted in the USA 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 the 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. Ongoing UK trials that were 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:

1. Safety and effectiveness of methadone and buprenorphine as delivered in the UK. Specifically, the key differences between the UK and the conditions of previous RCTs is the issue of unsupervised dispensing. Current UK guidelines (Orange Guidelines, DoH 1999) suggest that treatment with methadone and buprenorphine should be initiated under conditions of supervised self-administration, 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.
2. Potential safety concerns regarding methadone and buprenorphine. Specifically:
   (a) 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 the section 'Treatment outcomes' (p. 20)]. 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.
   (b) Drug interactions. The key drug interactions for methadone and buprenorphine concern the concomitant use of other sedatives, especially benzodiazepines, alcohol and (tricyclic) antidepressants. These sedative drugs are routinely identified in most 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.
3. Patient subgroups. Although the findings regarding substitution treatment are fairly robust, there continue to be uncertainties regarding the safety and efficacy of substitution medications and their best modes of delivery in particular patient subgroups, such as within the

CJS, or within young people (below the age of 21 years). These aspects would benefit from future research.

4. Cost-effectiveness. The body of evidence on 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 major uncertainties in cost-effectiveness identified by current economic models, particularly the utility data in opioid-dependent users and how these relate to treatment success. Economic models need to be updated on the availability of such future data.

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Contribution of authors

Ariadna Juarez-Garcia (Research Fellow) 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. Amanda Burls (Senior Clinical Lecturer) contributed to the design of the the research protocol, obtained clinical and patient expertise for the report, contributed to the structuring of the economic model and commented on the final report. Martin Connock (Systematic Reviewer) 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 (Senior Lecturer) drafted the background section, provided clinical advice throughout the project and assisted in the construction of the utility scenarios. Emma Frew (Research Fellow) 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 (Information Specialist) designed and executed the searches of bibliographic databases and other electronic sources and wrote the literature searching sections. Sue Jowett (Research Fellow) 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 (Systematic Reviewer) contributed to the review of the clinical effectiveness evidence. Tracy Roberts (Senior Lecturer) 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 (Senior Research Associate) undertook the review of previous economic evaluations, applied the inclusion and exclusion criteria, extracted data and appraised studies. Nick Lintzeris (Senior Lecturer) provided access to an unpublished systematic review regarding the safety of buprenorphine and provided clinical advice during the project. Rod Taylor (Reader in Health Services Research) 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.

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Appendix 1

Literature search strategies

Systematic reviews

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

Ovid MEDLINE, 1966 to August week 1 2005

1 (methadone or buprenorphine or methadose or subutex).mp. (10,103)
2 exp opioid related disorders/ (12,317)
3 substance withdrawal syndrome/ (14,177)
4 substance related disorders/ (52,782)
5 heroin dependence/ (5893)
6 (substance abuse or substance misuse or substance dependen$).mp. (22,005)
7 (opioid abuse or opioid misuse or opioid dependen$).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 (84,788)
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. (276,647)
19 letter.pt. (533,452)
20 editorial.pt. (175,896)
21 editorial.pt. (175,896)
22 animals/ (3,775,268)
23 human/ (8,914,050)
24 22 not (22 and 23) (2,893,184)
25 11 not (18 or 19 or 20 or 24) (5875)
26 or/12-17 (24,830)
27 25 and 26 (49)
28 from 27 keep 1-49 (49)

Ovid MEDLINE In-process and Other Non-indexed Citations, 12 August, 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)

EMBASE (Ovid), 1980 to 2005 week 33

1 (methadone or buprenorphine or methadose or subutex).mp. (14,929)
2 (substance abuse or substance misuse or substance dependen$).mp. (17,119)
3 (opioid abuse or opioid misuse or opioid dependen$).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/ (13,158)
9 or/2-8 (29,623)
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/ (22,406)
17 meta-analysis.ti. (5388)
18 or/11-17 (37,978)
19 10 and 18 (61)
20 from 19 keep 1-61 (61)

Clinical effectiveness – randomised controlled trials

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

Ovid MEDLINE, 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/ (11,455)
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 (22,157)
11 1 and 10 (1772)
12 randomized controlled trial.pt. (77,138)
13 controlled clinical trial.pt. (14,355)
14 randomized controlled trials.sh. (25,065)
15 random allocation.sh. (14,027)
16 double blind method.sh. (26,619)
17 single blind method.sh. (4790)
18 or/12-17 (132,130)
19 (animals not human).sh. (858,647)
20 18 not 19 (118,597)
21 clinical trial.pt. (146,258)
22 exp clinical trials/ (59,324)
23 (clin$ adj25 trial$).ti,ab. (53,914)
24 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (26,524)
25 placebo$.ti,ab. (33,401)
26 random$.ti,ab. (141,076)
27 placebos.sh. (4730)
28 research design.sh. (14,772)
29 or/21-28 (304,643)
30 29 not 19 (266,803)
31 30 not 20 (151,695)
32 20 or 31 (270,292)
33 11 and 32 (453)
34 limit 33 to yr="2001 - 2005" (339)
35 from 34 keep 1-339 (339)

Ovid MEDLINE In-process and Other Non-indexed Citations, 12 August, 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)

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$).mp. (12,801)
3 (opioid abuse or opioid misuse or opioid dependen$).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/ (10,844)
9 or/2-8 (19,913)
10 1 and 9 (2544)
11 randomized controlled trial/ (83,862)

12 exp clinical trial/ (278,742)
13 exp controlled study/ (1,442,477)
14 double blind procedure/ (37,680)
15 randomization/ (13,701)
16 placebo/ (40,769)
17 single blind procedure/ (4489)
18 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (1,461,304)
19 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (50,581)
20 (placebo$ or matched communities or matched schools or matched populations).mp. (64,814)
21 (comparison group$ or control group$).mp. (73,516)
22 (clinical trial$ or random$).mp. (396,288)
23 (quasiexperimental or quasi experimental or pseudo experimental).mp. (870)
24 matched pairs.mp. (1071)
25 or/11-24 (1,663,543)
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)

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 (14,662)
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)

Sociological Abstracts (CSA Illumina), 2001–August 2005

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

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

methadone or methadose or subutex or buprenorphine

Ongoing trials

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

Current Controlled Trials and Clinical Trials.gov

buprenorphine or methadone or methadose or subutex

Quality of life

Ovid MEDLINE, 1966 to July week 4 2005

1 substance abuse$.mp. or exp Substance-Related Disorders/ (150,166)
2 exp Opioid-Related Disorders/ or opioid$ abuse$.mp. (12,376)
3 opioid$ 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/ (47,551)
8 life style/ (21,846)
9 health status/ (26,839)
10 health status indicators/ (9303)
11 or/7-10 (96,714)
12 or/1-6 (150,406)
13 11 and 12 (2097)
14 limit 13 to yr="2004 - 2005" (253)
15 from 14 keep 1-253 (253)

Economic evaluation

Ovid MEDLINE, 1966 to August week 1 2005

1 (methadone or buprenorphine or methadose or subutex).mp. (10,103)
2 exp opioid related disorders/ (12,317)
3 substance withdrawal syndrome/ (14,177)
4 substance related disorders/ (52,782)
5 heroin dependence/ (5893)
6 (substance abuse or substance misuse or substance dependen$).mp. (22,005)
7 (opioid abuse or opioid misuse or opioid dependen$).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 (84,788)
11 1 and 10 (6434)
12 economics/ (23,981)
13 exp "costs and cost analysis"/ (117,204)
14 cost of illness/ (7215)
15 exp health care costs/ (24,676)
16 economic value of life/ (4499)
17 exp economics medical/ (9672)
18 exp economics hospital/ (13,430)
19 economics pharmaceutical/ (1505)
20 exp "fees and charges"/ (21,731)
21 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (209,242)
22 or/12-21 (306,036)
23 11 and 22 (274)
24 from 23 keep 1-274 (274)

EMBASE (Ovid), 1980 to 2005 week 33

1 (methadone or buprenorphine or methadose or subutex).mp. (14,929)
2 (substance abuse or substance misuse or substance dependen$).mp. (17,119)
3 (opioid abuse or opioid misuse or opioid dependen$).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/ (13,158)
9 or/2-8 (29,623)
10 1 and 9 (3802)
11 cost benefit analysis/ (21,209)
12 cost effectiveness analysis/ (39,107)
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. (124,174)
17 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (59,100)
18 (technology adj assessment$).tw. (1187)
19 or/11-18 (187,759)
20 10 and 19 (193)
21 from 20 keep 1-193 (193)

Cochrane Library (NHSEED) (Wiley Internet interface), 2005 Issue 3

See systematic reviews strategy

HEED, August 2005

Methadone OR methadose OR subutex OR buprenorphine

Searches for existing models

Ovid MEDLINE, 1966 to August week 1 2005

1 (methadone or buprenorphine or methadose or subutex).mp. (10,103)
2 exp opioid related disorders/ (12,317)
3 substance withdrawal syndrome/ (14,177)
4 substance related disorders/ (52,782)
5 heroin dependence/ (5893)
6 (substance abuse or substance misuse or substance dependen$).mp. (22,005)
7 (opioid abuse or opioid misuse or opioid dependen$).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 (84,788)
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/ (35,727)
17 or/12-16 (46,850)
18 11 and 17 (60)
19 from 18 keep 1-60 (60)

EMBASE (Ovid), 1980 to 2005 week 33

1 (methadone or buprenorphine or methadose or subutex).mp. (14,929)
2 (substance abuse or substance misuse or substance dependen$).mp. (17,119)
3 (opioid abuse or opioid misuse or opioid dependen$).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/ (13,158)
9 or/2-8 (29,623)
10 1 and 9 (3802)
11 decision support techniques/ (479)
12 markov.mp. (2733)
13 exp models economic/ (11,849)
14 decision analysis.mp. (1889)
15 cost benefit analysis/ (21,209)
16 or/11-15 (37,099)
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 the use of either 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 38*) and urine confirmed opioid use (see *Table 39*) 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 58*.

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 ITT. More recent trials have attempted to deal with this problem using the Treatment Effectiveness Score (TES) as proposed by Ling and colleagues.[165] According to the TES, each patient is given a score from 0 to 100% calculated as number of negative (or positive) urine samples divided by the total number of possible urine samples that could have been taken. Missing urine samples (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 and colleagues[105]). Abstinence rates for those who remain in treatment might therefore be regarded as a best-case scenario whereas the all-case analysis is a worst-case scenario.

Appendix 3

Characteristics of systematic reviews

Details are given in *Tables 30–35*.

TABLE 30 *Systematic reviews with studies addressing effectiveness of methadone at different doses or versus placebo/no treatment in maintenance therapy*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Caplehorn, 1996[48]	Journal	1966 to 1995	5 (24,219 patient-years) *5 relevant*	Cohort	MA	Heroin dependent	1. MMT	1. Discharged from MMT	Mortality
Faggiano, 2003[60]	Cochrane	1947 to 2001	21 (5984) *19 relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid dependent	1. MMT	1. Methadone different doses	Illicit drug use Trt retention Abstinence Mortality
Farre, 2002[55]	Journal	1966 to 1999 (December)	13 (1944) *10 relevant*	RCTs (double blind)	MA	Opioid dependent	1. MMT	1, Methadone different doses 2. Placebo	Illicit drug use Trt retention
Glanz, 1997[49]	Journal	1966 to 1996	12 (1362) *2 relevant*	RCTs	MA	Opioid dependent	1. MMT	1. Methadone different doses	Illicit drug use Trt retention Side-effects
Gowing, 2004[63]	Cochrane	Database origins to 2003 (July)	28 (7900) *21 relevant*	RCTs, cohort, case–control, descriptive	Narrative	Opioid dependent	1. MMT	1. No MMT (*1 RCT, 2 cohort, 2 case–control, 4 descriptive studies*) Time points (*12 single-group descriptive studies*)	HIV risk behaviours
Hopfer, 2002[56]	Journal	Not reported	14 (6263) *3 relevant (methadone)*	Non-randomised studies. Surveys and descriptive studies	Narrative	Heroin-using youth	1. MMT	Time points (*3 single-group studies*)	Illicit drug use Trt retention
Hulse, 1998[43]	Journal	1966 to 1996	7 (not reported) *5 relevant*	Case–control	MA	Opiate-using pregnant women	1. MMT no heroin 2. MMT + heroin 3. MMT ± any opiate 4. Heroin no methadone 5. Any opiate	1. No opiates	Neonatal mortality Birth weight

continued

TABLE 30 *Systematic reviews with studies addressing effectiveness of methadone at different doses or versus placebo/no treatment in maintenance therapy (cont'd)*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Johansson, 2003[61]	Book chapter	1966 to 2000	69 (7881) *17 relevant*	RCTs (double blind)	MA	Opioid dependent	1. MMT	1. Placebo 2. No treatment 3. MMT different doses	Illicit drug use Trt retention
Layson-Wolf, 2002[57]	Journal	1996 to 2001 (May)	Unclear (unclear) *5 relevant*	RCTs + unclear	Narrative	Opioid dependent	1. MTT	1. Placebo 2. No treatment 3. MMT different doses	Illicit drug use Trt retention
Marsch, 1998[50]	Journal	Not reported *end not later than 1997*	30 (7980) *30 relevant*	Controlled studies (≥2 groups) and 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[62]	Cochrane	1966 to 2001	6 (954) *4 relevant*	Controlled clinical trials (RCTs)	MA	Opioid dependent	1. MMT	1. No trt 2. Drug-free trt 3. Placebo 4. MMT different doses	Illicit drug use Trt retention Criminality Mortality
Mattick, 2005[64]	Cochrane	1996 to 2005	13 (2560) *4 relevant*	RCTs	MA	Opioid dependent	1. MMT	1. MMT different doses	Illicit drug use Trt retention
Prendergast, 2002[58]	Journal	Not reported *(studies from 1965 to 1996)*	78 (12,168) *? relevant (8 methadone)*	Controlled studies (≥2 groups) and single-group pre-, post-studies	MA	Drug abusers	1. Methadone programmes	1. No or minimal trt	Illicit opiate use Crime
Prendergast, 2000[51]	Journal	Not reported *(studies from 1965 to 1996)*	143 (35,879) *38 relevant*	Controlled studies (≥2 groups) and single-group pre-, post-studies	MA	Drug abusers	1. Methadone programmes	1. No or minimal trt	Illicit opiate use Crime
Simoens, 2005[65]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *No. relevant: unclear*	RCTs	Narrative	Opioid dependent[b]	1. MMT	1. Unspecified/unclear	Abstinence Illicit drug use Trt retention

continued

TABLE 30 *Systematic reviews with studies addressing effectiveness of methadone at different doses or versus placebo/no treatment in maintenance therapy (cont'd)*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Simoens, 2002[59]	HTA	1990 to 2002	92 (not reported) *8 RCT and 6 other relevant*	RCTs, single-group pre-, post-, and quasi-experimental studies	Narrative	Opioid dependent[c]	1. MMT	1. Placebo 2. MMT different doses 3. Single group time points	Abstinence Illicit drug use Trt retention Criminality Others
Sorensen, 2000[52]	Journal	1988 to 1998	33 (17,771) *16 longitudinal and 7 cross-sectional relevant*	Longitudinal and cross-sectional	Narrative	Drug abusers	1. MMT	1. Single-group time points 2. No MMT (*cross-sectional studies*)	HIV risk behaviours
Van Beusekom, 2001[54]	HTA	Not reported (*studies up to 2000*)	222 (not reported) *unclear*	RCTs, cohort, cross-sectional, guidelines and others	Narrative	Opioid dependent	1. MMT	1. MMT different doses 2. No trt 3. Not clearly determinable	Illicit drug use Trt retention Mortality
West, 2000[53]	Journal	Not reported to 2000	9 (995) *4 relevant*	Controlled comparative studies	MA	Opioid dependent	1. MMT	1. MMT different doses	Illicit drug use

HTA, Health technology assessment; MA, meta-analysis; trt, treatment.
[a] All reviews contain narrative elements therefore 'narrative' refers to reviews restricted to narrative methods and lacking meta-analysis.
[b] In MTT community programmes.
[c] Involved in community maintenance or detoxification or residential rehabilitation treatment.

TABLE 31 *Systematic reviews with studies addressing the effectiveness of methadone versus buprenorphine in maintenance therapy*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Barnett, 2001[68]	Journal	Not clear to 1998	5 (540) *5 relevant*	RCTs (double blind)	MA	Opioid dependent	1. MMT	1. BMT	Illicit drug use Trt retention
Davids, 2004[67]	Journal	Not reported	Unclear (not reported) *13 relevant*	Experimental and observational follow-up	Narrative	Opioid dependent	1. MMT	1. BMT	Selective
Faggiano, 2003[60]	Cochrane	1947 to 2001	21 (5984) *4 relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid dependent	1. MMT	1. BMT	Illicit drug use Trt retention Abstinence Side-effects
Farre, 2002[55]	Journal	1996 to 1999 (December)	13 (1944) *6 relevant*	RCTs (double blind)	MA	Opioid dependent	1. MMT	1. BMT	Illicit drug use Trt retention
Johansson, 2003[61]	Book chapter	1966 to 2000	69 (7881) *8 relevant*	RCTs (double blind)	MA	Opioid dependent	1. MTT	1. BMT	Illicit drug use Trt retention
Layson-Wolf, 2002[57]	Journal	1996 to 2001 (May)	Unclear (unclear) *3 relevant*	RCTs + unclear	Narrative	Opioid dependent	1. MTT	1. BMT	Illicit drug use Trt retention
Lintzeris and Ford, 2004	Unpublished	Not clear to 2003	24 (>4400) *17 relevant*	RCTs (14) + population studies (3)	Narrative	Opioid dependent	1. MMT	1. BMT	Illicit drug use Trt retention Mortality
Mattick, 2005[64]	Cochrane	1966 to 2001	13 (2560) *10 relevant*	RCTs	MA	Opioid dependent	1. MTT	1. BMT	Illicit drug use Trt retention
Raisch, 2002[66]	Journal	1966 to 2000 (November)	Unclear (not reported) *3 relevant*	Unclear, review articles also used	Narrative	Opioid dependent	1. MTT	1. BMT	Selective
Simoens, 2005[65]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *14 relevant*	RCTs	Narrative	Opioid dependent[b]	1. MMT	1. BMT	Abstinence Illicit drug use Trt retention
Simoens, 2002[59]	HTA	1990 to 2002	92 (not reported) *13 RCTs*	RCTs, single-group pre-, post-, and quasi-experimental studies	Narrative	Opioid dependent[c]	1. MMT	1. BMT	Abstinence Illicit drug use Trt retention Criminality, etc.
West, 2000[53]	Journal	Not reported to 2000	9 (995) *9 relevant*	Controlled comparative studies	MA	Opioid dependent	1. MMT	1. BMT	Illicit drug use

HTA, health technology assessment; MA, meta-analysis; trt, treatment.
[a] All reviews contain narrative elements, therefore 'narrative' refers to reviews restricted to narrative methods and lacking meta-analysis.
[b] In MTT community programmes.
[c] Involved in community maintenance or detoxification or residential rehabilitation treatment.

TABLE 32 *Systematic reviews with studies of methadone effectiveness versus other treatments (except buprenorphine), or with methadone + a potential modifier of effectiveness*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Amato, 2004[74]	Cochrane	1985 (January) to 2003 (April)	12 (981) *12 relevant*	RCTs	MA	Opioid dependent	1. Psychosocial (8 types)	1. Psychosocial + pharmacotherapy (MMT)	Illicit drug use Trt retention
Clark, 2002[71]	Cochrane	1966 (January) to 2000 (August)	18 (3766) *18 relevant*	RCTs (15) Controlled prospective (3)	MA	Heroin dependent	1. MMT	1. LAAM MT	Illicit drug use (heroin) Trt retention Side-effects Mortality
Faggiano, 2003[60]	Cochrane	1947 to 2001	21 (5984) *3 relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid dependent	1. MMT	1. LAAM MT 2. MMT + CRA	Illicit drug use Trt retention Side-effects Criminality
Farre, 2002[55]	Journal	1966 to 1999 (December)	13 (1944) *2 relevant*	RCTs (double blind)	MA	Opioid dependent	1. MMT	1. LAAM MT	Illicit drug use Trt retention
Ferri, 2005[76]	Cochrane	1966 to 2005	4 (577) *4 relevant*	RCTs	Narrative	Opioid dependent	1. MMT	1. MMT + Heroin	Illicit drug use Trt retention Crime Social functioning
Fridell, 2003[72]	Book chapter	Unclear to 1999 (March)	Unclear (not reported) *unclear, 27? relevant*	RCTs	MA	Drug dependent	1. Methadone	1. Methadone + psychosocial	Illicit drug use (*heroin*) Trt retention
Glanz, 1997[49]	Journal	1966 to 1996	12 (1362) *12 relevant*	RCTs	MA	Opioid dependent	1. MMT	1. LAAM MT	Illicit drug use Trt retention Side-effects
Gowing, 2004[63]	Cochrane	Database origins to 2003 (July)	28 (7900) *5 relevant*	RCTs 2 Cohort 3 Case–control 2 Other 21	Narrative	Opioid dependent *injecting*	1. MMT	1. MMT + other 2. Injected MMT (*time points in 1 cohort and 4 descriptive studies*)	HIV risk behaviours
Griffith, 2000[70]	Journal	Not reported	30 (1613) *30 relevant*	Randomised and non-randomised pre-, post-studies	MA	Single- or poly-drug dependent	1. MMT	1. MMT + CRA 2. MTT + other	Illicit drug use

continued

TABLE 32 *Systematic reviews with studies of methadone effectiveness versus other treatments (except buprenorphine), or with methadone + a potential modifier of effectiveness (cont'd)*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Johansson, 2003[61]	Other (book chapter)	1966 to 2000	69 (7881) *20 relevant*	RCTs (double blind)	MA	Opioid dependent	1. MMT	1. LMT 2. Heroin MT 3. MMT + CRA 4. MMT + antidepressants	Illicit drug use Trt retention
Kirchmayer, 2003[73] and 2002[166]	Cochrane	1973 to 2003 (February)	11 (707) *1 relevant*	Controlled clinical trials	MA	Opioid dependent	1. MMT	1. Naltrexone MT	Illicit drug use Trt retention
Layson-Wolf, 2002[57]	Journal	1996 to 2001 (May)	Unclear (unclear) *2 relevant*	RCTs + unclear	Narrative	Opioid dependent	1. MMT	1. LMT 2. Slow provision of MMT	Illicit drug use Trt retention
Prendergast, 2002[58]	Journal	Not reported (*studies 1965 to 1996*)	78 (12,168) *No. relevant unclear (8 methadone)*	Controlled studies (≥2 groups) and single-group pre-, post-studies	MA	Drug abusers	1. Methadone programmes	1. No or minimal trt	Illicit drug use Crime
Roozen, 2004[75]	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
Simoens, 2005[65]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *No: relevant unclear*	RCTs	Narrative	Opioid dependent[b]	1. MMT	1. Unspecified/unclear	Abstinence Illicit drug use Trt retention
Simoens, 2002[59]	HTA	1990 to 2002	92 (not reported) *12 RCTs and 1 other relevant*	RCTs, single-group pre-, post- and quasi-experimental studies	Narrative	Opioid dependent[c]	1. MMT	1. LAAM 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[69]	Journal	Not reported	15 (not reported) *2 relevant*	RCTs	MA	Illicit drug users	1. MMT	1. MMT + family–couples	Illicit drug use

continued

TABLE 32 *Systematic reviews with studies of methadone effectiveness versus other treatments (except buprenorphine), or with methadone + a potential modifier of effectiveness (cont'd)*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Van Beusekom, 2001[54]	HTA	Not reported (*studies up to 2000*)	222 (not reported) *unclear*	RCTs, cohort, cross-sectional, guidelines and others	Narrative	Opioid dependent	1. MMT	1. MMT + various other (e.g psychosocial) 2. MMT different dose 3. Not clear	Illicit drug use Trt retention Mortality

CoRa, community reinforcement approach; CRA, contingency reinforcement approach; HTA, health technology assessment; MA, meta-analysis; trt, treatment.
[a] All reviews contain narrative elements, therefore, 'narrative' refers to reviews restricted to narrative methods and lacking meta-analysis.
[b] In MTT community programmes.
[c] Involved in community maintenance or detoxification or residential rehabilitation treatment.

TABLE 33 *Systematic reviews with studies addressing effectiveness of buprenorphine at different doses or versus placebo/no treatment*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Davids, 2004[67]	Journal	Not reported	Unclear (not reported) *2 relevant*	Experimental and observational follow-up	Narrative	Opioid dependent	1. BMT	1. Placebo	Selective[b]
Faggiano, 2003[60]	Cochrane	1947 to 2001	21 (5984) *2 relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid dependent	1. BMT	1. BMT different doses	Illicit drug use Trt retention Abstinence
Farre, 2002[55]	Journal	1966 to 1999 (December)	13 (1944) *2 relevant*	RCTs (double blind)	MA	Opioid dependent	1. BMT	1. BMT different doses	Illicit drug use Trt retention
Johansson, 2003[61]	Book chapter	1966 to 2000	69 (7881) *6 relevant*	RCTs (double blind)	MA	Opioid dependent	1. BMT	1. Placebo 2. BMT different doses	Illicit drug use Trt retention

continued

TABLE 33 *Systematic reviews with studies addressing effectiveness of buprenorphine at different doses or versus placebo/no treatment (cont'd)*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Layson-Wolf, 2002[57]	Journal	1996 to 2001 (May)	Unclear (unclear) *1 relevant*	RCTs + unclear	Narrative	Opioid dependent	1. BMT	1. BMT different doses	Illicit drug use Trt retention
Lintzeris and Ford, 2004	Un-published	Not clear to 2003	24 (>4400) *6 relevant*	RCTs	Narrative	Opioid dependent	1. BMT	1. Placebo 2. BMT different doses	Illicit drug use Trt retention
Mattick, 2005[64]	Cochrane	1966 to 2005	13 (2560) *4 relevant*	RCTs	MA	Opioid dependent	1. BMT	1. BMT different doses	Illicit drug use Trt retention
Raisch, 2002[66]	Journal	1966 to 2000 (November)	Unclear (not reported) *2 relevant*	Unclear, review articles also used	Narrative	Opioid dependent	1. BMT	1. Placebo 2. BMT different doses	Selective[b]
Simoens, 2005[65]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *No. relevant unclear*	RCTs	Narrative	Opioid dependent[c]	1. BMT	1. Unspecified/unclear	Abstinence Illicit drug use Trt retention
Simoens, 2002[59]	HTA	1990 to 2002	92 (not reported) *13 relevant*	RCTs, single-group pre-, post- and quasi-experimental studies	Narrative	Opioid dependent[d]	1. BMT	1. BMT different doses	Abstinence Illicit drug use Trt retention Criminality, etc.
West, 2000[53]	Journal	Not reported to 2000	9 (995) *3 relevant*	Controlled comparative studies	MA	Opioid dependent	1. BMT	1. BMT different doses	Illicit drug use

HTA, health technology assessment; MA, meta-analysis; trt, treatment.
[a] All reviews contain narrative elements, therefore 'narrative' refers to reviews restricted to narrative methods and lacking meta-analysis.
[b] Selective = outcomes selected inconsistently across primary studies.
[c] In MTT community programmes.
[d] Involved in community maintenance or detoxification or residential rehabilitation treatment.

TABLE 34 *Systematic reviews with studies addressing effectiveness of buprenorphine maintenance therapy versus other treatments (except methadone) or buprnorphine + a potential moderator of effectiveness*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Davids, 2004[67]	Journal	Not reported	Unclear (not reported) *2 relevant*	Experimental and observational follow-up	Narrative	Opioid dependent	1. BMT	1. BMT + psychosocial 2. LAAM MT	Selective[b]
Faggiano, 2003[60]	Cochrane	1947 to 2001	21 (5984) *1 relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid dependent	1. BMT	1. LAAM MT	Illicit drug use Trt retention Abstinence Side-effects
Johansson, 2003[61]	Book chapter	1966 to 2000	69 (7881) *1 relevant*	RCTs (double blind)	MA	Opioid dependent	1. BMT (outpatient)	1. BMT (special clinic)	Illicit drug use Trt retention
Layson-Wolf, 2002[57]	Journal	1996 to 2001 (May)	Unclear (unclear) *1 relevant*	RCTs + unclear	Narrative	Opioid dependent	1. BMT	1. LAAM MT	Illicit drug use Trt retention
Lintzeris and Ford, 2004	Un-published	Not clear to 2003	24 (>4400) *15 relevant*	RCTs + quasi-RCT (1)	Narrative	Opioid dependent	1. BMT	1. BMT in different setting 2. BMT dose regimens	
Mattick, 2005[64]	Cochrane	1996 to 2005	13 (2560) *1 relevant*	RCTs	MA	Opioid dependent	1. BMT	1. LAAM MT	Illicit drug use Trt retention
Raisch, 2002[66]	Journal	1966 to 2000 (November)	Unclear (not reported) *5 relevant*	Unclear, review articles also used	Narrative	Opioid dependent	1. BMT	1. LAAM MT 2. Dose regimens 3. Subcutaneous administration	Selective[b]
Simoens, 2005[65]	Journal	Studies from 1990 to 2002	45 [48 trials] (not reported) *No. relevant unclear*	RCTs	Narrative	Opioid dependent[c]	1. BMT	1. Unspecified/unclear	Abstinence Illicit drug use Trt retention
Simoens, 2002[59]	HTA	1990 to 2002	92 (not reported) *12 RCTs relevant*	RCTs, case–control, quasi-experimental	Narrative	Opioid dependent[d]	1. BMT	1. BMT at different dose times 2. BMT + hydromorphine MT 3. LAAM MT 4. Reducing buprenorphine doses	Abstinence Illicit drug use Trt retention Criminality, etc.

HTA, health technology assessment; MA, meta-analysis; trt, treatment.
[a] All reviews contain narrative elements, therefore 'narrative' refers to reviews restricted to narrative methods and lacking meta-analysis.
[b] Selective = outcomes selected inconsistently across primary studies.
[c] In MTT community programmes.
[d] Involved in community maintenance or detoxification or residential rehabilitation treatment.

TABLE 35 *Systematic reviews with studies that compare methadone maintenance therapy with methadone withdrawal therapy*

Study	Data sources	Search start and end dates	No. of primary studies (total no. of patients) *No. of relevant studies*	Primary study designs included	Meta-analysis/ narrative[a]	Target population	Interventions included	Comparators	Outcomes
Faggiano, 2003[60]	Cochrane	1947 to 2001	21 (5984) *1 relevant*	RCTs (11) Controlled prospective (10)	MA	Opioid dependent	1. MMT (*RCT at different doses*)	1. MDT (RCT; zero dose following stable doses)	Illicit drug use Trt retention
Gowing, 2004[63]	Cochrane	Database origins to 2003 (July)	28 (7900) *1 relevant*	RCTs, cohort, case–control, descriptive	MA	Opioid dependent *injecting*	1. MMT (*RCT prison setting*)	1. Methadone withdrawal (*RCT prison setting*)	HIV risk behaviours
Hopfer, 2002[56]	Journal	Not reported	14 (6263) *3 relevant (methadone)*	Non-randomised: surveys, case–control, descriptive	Narrative	Heroin-using youth	1. MMT	1. MDT	Illicit drug use Trt retention Detoxification duration
Johansson, 2003[61]	Book chapter	2000	69 (7881) *2 relevant*	RCTs (double blind)	MA	Opioid dependent	1. MMT	1. MDT	Illicit drug use Trt retention
Mattick, 2003[62]	Cochrane	1966 to 2001	6 (954) *3 relevant*	Controlled clinical trials (RCTs)	MA	Opioid dependent	1. MMT	1. MDT	Illicit drug use Trt retention Criminality Mortality
Raisch, 2002[66]	Journal	1966 to 2000 (November)	Unclear (not reported) *1 relevant*	Unclear, review articles also used	Narrative	Opioid dependent	1. MMT	1. MDT	Selective
Simoens, 2002[59]	HTA	1990 to 2002	92 (not reported) *1 RCT relevant*	RCTs, single-group pre-, post- and quasi-experimental studies	Narrative	Opioid dependent[b]	1. MMT	1. Methadone withdrawal	Abstinence Illicit drug use Trt retention Withdrawal severity Criminality HIV risk behaviour
Van Beusekom, 2001[54]	HTA	Not reported (*studies up to 2000*)	222 (not reported) *2 relevant*	RCTs, cohort, cross-sectional, guidelines and others	Narrative	Opioid dependent	1. MMT	1. Methadone withdrawal	Illicit drug use Trt: retention Mortality

HTA, health technology assessment; MA, meta-analysis; trt, treatment.
[a] All reviews contain narrative elements, therefore 'narrative' refers to reviews restricted to narrative methods and lacking meta-analysis.
[b] Involved in community maintenance or detoxification or residential rehabilitation treatment.

Appendix 4

Characteristics of included RCTs and key results reported

Details are given in *Table 36*.

TABLE 36 *Details of included randomised controlled trials*

Study	Country/trial year/setting	*N* (*N*/Group)	Population	Intervention/comparator	Jadad score	Follow-up	Main findings
Ahmadi, 2003a[82]	Iran 2002 Outpatient clinic	108 (3 × 36)	I.v. Buprenorphine abusers DSM IV Mean 29.4 years 100% male Mean buprenorphine abuse 1.8 years	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 vs 2, $p < 0.0001$ Group 3 vs 1 or 2
Ahmadi, 2003b[78]	Iran 2000–1 Outpatient clinic	420 (3 groups not reported)	Opioid-dependent DSM IV consecutive admissions Mean 36.3 years 97% male Daily drug abuse for at least 6 months	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 vs 2, $p < 0.001$ Group 3 vs 1
Ahmadi, 2003c[79]	Iran 2000–1 Outpatient clinic	123 (3 × 41)	Heroin-dependent DSM IV Mean 31.4 years 100% male Heroin abuse for at least 6 months	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 vs 3, $p = 0.027$ Group 2 vs 1, $p = 0.027$ Group 3 vs 2 No significant adverse events recorded
Avants, 2004[96]	USA 2000–1 Community-based programme	220 (112/108)	Opioid-dependent DSM IV Mean 37 years 68% male All entering new methadone treatment	Group 1: methadone 85 mg/day + harm reduction programme Group 2: methadone 85 mg/day alone Both groups received counselling	2	12 weeks	Retention in treatment: Group 1 97/112 (87%), Group 2 93/108 (86%). NS Illicit opioid abuse (opiate-free urine for 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 (SD 3.4). $p = 0.01$

continued

TABLE 36 *Details of included randomised controlled trials (cont'd)*

Study	Country/trial year/setting	*N* (*N*/Group)	Population	Intervention/comparator	Jadad score	Follow-up	Main findings
Blanken, 2005[100] Outcomes and prognostic analysis based on RCTs of van den Brink, 2003[103]	The Netherlands 1998–2001 Treatment centres	430 (193/237)	Heroin-dependent Mean 39 years 80% male	Group 1: methadone up to 150 mg/day alone Group 2: methadone 150 mg/day + heroin up to 1 g/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%. $p = 0.0001$ Patients who had attempted detoxification previously were more likely to respond to heroin + methadone than others
Brooner, 2004[97]	USA Not reported Outpatient clinic	127 (65, 62)	Opioid-dependent. DSM III new admissions Mean 38.2 years 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[85]	USA 1994–6 Home and clinic	55 (16/18/19)	Opioid-dependent Mean 38 years 60% male Compliant in methadone treatment for 5 weeks	Group 1: methadone 60 mg 3 days/week + contingency weekly urine testing Group 2: methadone 60 mg 3 days/week + contingency monthly urine testing Group 3: methadone 60 mg 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 and cocaine abstinence: Group 1 56.6%, Group 2 38.9%, Group 3 10.5%. $p < 0.002$
Cornish, 2002[89]	USA Not reported Inpatients	15 (10/5)	Opioid-dependent DSM IV Mean 44 years 100% male Standardised in methadone for 10 days before study	Group 1: methadone 5–70 mg/day + dextromethorphan (120–240 mg/day) Group 2: methadone 5–70 mg/day + placebo	3	14 days	Adverse events: Group 1 174 events, Group 2 21 events

continued

TABLE 36 *Details of included randomised controlled trials (cont'd)*

Study	Country/trial year/setting	*N* (*N*/Group)	Population	Intervention/comparator	Jadad score	Follow-up	Main findings
Dean, 2002[90]	Australia Not reported Not reported	29 (25/24)	Opioid-dependent Mean 35 years 67% male Beck Depression Inventory score >21 In methadone treatment ≥3 months	Group 1: methadone (dose not reported) + fluoxetine 20 mg/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[101] Economic study based on van den Brink, 2003[103]	The Netherlands 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 months 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 over methadone alone QALY gain: 0.0588 (0.016–0.099). $p = 0.01$ Cost savings (€): 12,793 (1083–25,229). $p = 0.032$ 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[77]	Australia 1997–8 Prison	382 (191/191)	Heroin-dependent Mean 27 years 100% male	Group 1: wait list Group 2: methadone 30–60 mg/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%). $p < 0.001$ HCV: Group 1: 31.7 per 100 person-years, Group 2 24.3 person-years. NS HIV: Both group 0%

continued

TABLE 36 *Details of included randomised controlled trials (cont'd)*

Study	Country/trial year/setting	*N* (*N*/Group)	Population	Intervention/comparator	Jadad score	Follow-up	Main findings
Eder, 2005[102]	Austria 1999–2001 Addiction clinic	64 (32, 32)	Opiate-dependent DSM IV Mean 28–29 years 87% male	Group 1: slow-release morphine (mean 620 mg/day) 7 weeks then methadone (mean 89 mg/day) 7 weeks Group 2: methadone (mean 80 mg/day) 7 weeks then slow-release morphine (mean 709 mg/day) 7 weeks 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[86]	Austria Not reported Outpatients University Clinic	60 (30, 30)	Heroin dependent ICD-10 Mean 31 years 9–12 years morphine/methadone dependence	Group 1: methadone Group 2: morphine sulfate Both groups received counselling, doses not reported	1	6 months	Quality of life (German version of Lancashire instrument: subjective and objective 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 group 2 in 6/20 objective domains. $p < 0.05$ Group 1 experienced fewer adverse side-effects and used illicit drugs less than Group 2
Grabowski, 2004(ii)[98]	USA Not reported Research clinic	96 (33/32/31)	Cocaine- and heroin-dependent DSM IV Mean 37 years 59% male	Group 1: methadone 1.1 mg/kg/day alone Group 2: methadone 1.1 mg//kg/day + risperidone 2 mg/day Group 3: methadone 1.1 mg/kg/day + risperidone 4 mg/day All 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 difference between groups ($p = 0.120$) Illicit opiate use (urinalysis): NS ($p > 0.90$) HIV: no conversions during the study Depression (Beck depression inventory): no significant difference between groups ($p > 0.24$)

continued

TABLE 36 *Details of included randomised controlled trials (cont'd)*

Study	Country/trial year/setting	*N* (*N*/Group)	Population	Intervention/comparator	Jadad score	Follow-up	Main findings
Grabowski, 2004(i)[98]	USA Not reported Research clinic	96 (40/30/28)	Cocaine- and heroin-dependent DSM IV Mean 37 years 67% male No previous methadone treatment	Group 1: methadone 1.1 mg/kg/day alone Group 2: methadone 1.1 mg//kg/day + *d*-amphetamine 30 mg/day Group 3: methadone 1.1 mg/kg/day + *d*-amphetamine 60 mg/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 ($p > 0.68$)
Jones, 2001[87]	USA 1996–7 Residential followed by outpatient	70 (44, 36)	Opiate-dependent pregnant women DSM III with cocaine abuse Mean 28 years	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[91]	USA Not reported Community treatment clinic	78 (25/27/26)	Opioid-dependent Mean 45 years 67% male 12 months of successful prior methadone treatment	Group 1: methadone (dose not reported) routine care in the clinic setting Group 2: methadone (dose not reported) delivered in treatment clinic + monthly reported schedule Group 3: 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%), Group 3 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 2 71%, Group 3 33%. $p < 0.001$

continued

TABLE 36 *Details of included randomised controlled trials (cont'd)*

Study	Country/trial year/setting	*N* (*N*/Group)	Population	Intervention/comparator	Jadad score	Follow-up	Main findings
Kosten, 2003[93]	USA Not reported Outpatient facility	160 (40/40/40/40)	Opioid- and cocaine-dependent DSM IV Mean 36–38 years 66% male	Group 1: buprenorphine 16 mg/day + desipramine 150 mg/day + contingency management (financial vouchers) Group 2: buprenorphine 16 mg/day + placebo + contingency management (financial vouchers) Group 3: buprenorphine 16 mg/day + desipramine Group 4: buprenorphine 16 mg/day + placebo	4	13 weeks	Retention in treatment: NS (data not reported) Illicit drug use (opiate- and cocaine-free urines): Group 1 50%, Group 2 25%, Group 3 29%, Group 4 29%. $p = 0.05$ Illicit drug use (opiate-free urines): Group 1 65%, Group 2 49%, Group 3 43%, Group 4 54%. $p = 0.10$ Depression (number of depression inventories): NS (data not reported)
Kristensen, 2005[81]	Norway Not reported Not reported	50 (25/25)	Opioid-dependent ICD-10 Mean 36 years 75% male >10 years drug treatment experience	Group 1: buprenorphine 16 mg/day (fixed) Group 2: methadone mean 106 mg/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%. $p < 0.01$
Lidz, 2004[99]	USA 1995–8		In MMT	Group 1: methadone + vocational problem solving (VPS) Group 2: methadone + job seekers workshop (JSW) Group 3: methadone + both VPS and JSW	2	12 months	No interventions produced greater employment or better overall rehabilitation
Lofwall, 2005[83] (update of Strain, 1994[109])	USA Not reported University research unit	164 (80/84)	Opioid-dependent DSM IIIR Mean 32.5 years 71% male Patients not in treatment	Group 1: methadone 50 mg/day Group 2: buprenorphine 8 mg/day	3	16 weeks	Safety (liver function tests): NS Side-effects (self-report): NS

continued

TABLE 36 *Details of included randomised controlled trials (cont'd)*

Study	Country/trial year/setting	*N* (*N*/Group)	Population	Intervention/comparator	Jadad score	Follow-up	Main findings
Margolin, 2003[94]	USA	18 (2 × 9)	Opiate abusers DSM IV Mean 38.8 years 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[80]	USA Not reported Outpatient clinic	134 (44, 44, 45)	Opioid-dependent DSM IV Mean 33 years 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[88]	USA Not reported Outpatient clinic	23 (11, 12)	Opioid-dependent DSM III Mean 39.5 years 43% male In methadone treatment. Mean of 20 years 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 and 2 <11%. $p > 0.37$
Ritter, 2003[92]	Australia 1999–2001 Primary care	101 (52, 49)	Opioid-dependent Mean 33 years 69% male In methadone treatment >8 weeks	Group 1: flexible methadone (mean 65 mg/day) Group 2: flexible LAAM (mean 232–249 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, $p = 0.34$

continued

TABLE 36 *Details of included randomised controlled trials (cont'd)*

Study	Country/trial year/setting	*N* (*N*/Group)	Population	Intervention/comparator	Jadad score	Follow-up	Main findings
Sigmon, 2004[95]	USA 2000–1 University research unit	46 (14, 16, 16)	Cocaine abusers using opiates and cocaine Mean 42.4 years 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 weeks	Cocaine abstinence (% cocaine-negative urines). No significant difference between groups
van den Brink, 2003(i)[103a]	The Netherlands 1998–2000 Not reported	375 (139, 117, 119)	Heroin inhalers DSM IV Mean 40 years 79% male Compliant in methadone treatment for at least 4 weeks	Group 1: methadone 12 months Group 2: methadone + heroin 12 months Group 3: methadone 6 months then methadone + heroin 6 months 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 and 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 not applicable, Group 2 5/117, Group 3 1/119
van den Brink, 2003(ii)[103a]	The Netherlands 1998–2000 Not reported	174 (98, 76)	Heroin injectors DSM IV Mean 40 years 82% male Compliant in methadone treatment for at least 4 weeks	Group 1: methadone 12 months 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 and social): Group 1 31/98 (31%), Group 2 42/76 (56%). Difference $p < 0.05$ Serious adverse events related to heroin: group 1 not applicable, Group 2 4/76

continued

TABLE 36 *Details of included randomised controlled trials (cont'd)*

Study	Country/trial year/setting	*N* (*N*/Group)	Population	Intervention/comparator	Jadad score	Follow-up	Main findings
Zanis, 2001[84]	USA Not reported Community-based programme	109 (62, 47)	Mean 43.5 years 61% male Compliant in methadone treatment for at least 3 months Unemployed	Group 1: methadone (dose not reported) + cognitive vocational problem-solving skills Group 2: methadone (dose not reported) + counselling interpersonal problem solving	2	12 weeks	Achieved employment within 6 months follow-up: Group 1 43/58 (58.6%), Group 2 16/43 (37%). $p < 0.05$

NS, not significant.
[a] Included in the systematic review by Ferri and colleagues[76] and discussed in the review of reviews and source for Blanken and colleagues[100] and Dijkgraaf and colleagues.[101]

Appendix 5

Quality assessment instruments

Systematic reviews

A modified version of the Oxman and Guyatt[46] assessment tool and scale was used to assess the quality of reviews. This consists of the following nine quality interrogations each answerable as 'yes', 'no' or 'partially/can't tell', carrying scores of 2, 0 and 1, respectively.

1. Were the search methods used to find evidence on the primary question(s) stated?
   (a) ***Yes***, description of databases searched, search strategy, and years reviewed. ***2 points***.
   (b) ***Partially***, description of methods not complete. ***1 point***.
   (c) ***No***, no description of search methods. ***0 points***.
2. Was the search for evidence reasonably comprehensive?
   (a) ***Yes***, at least one computerised database searched and also a search of unpublished or non-indexed literature. ***2 points***.
   (b) ***Can't tell***, search strategy partially comprehensive, at least one of the strategies was performed. ***1 point***.
   (c) ***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?
   (a) ***Yes***, inclusion and exclusion criteria clearly defined. ***2 points***.
   (b) ***Partially***, reference to inclusion and exclusion criteria can be found but are not defined clearly enough. ***1 point***.
   (c) ***No***, no criteria defined. ***0 points***.
4. Was bias in the selection of articles avoided?
   (a) ***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***.
   (b) ***Can't tell***, only one of the strategies used. ***1 point***.
   (c) ***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?
   (a) ***Yes***, criteria defined. ***2 points***.
   (b) ***Partially***, some discussion or reference to criteria. ***1 point***.
   (c) ***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?
   (a) ***Yes***, criteria used addressed the major factors influencing bias. ***2 points***.
   (b) ***Partially***, some discussion, but not clearly described predetermined criteria. ***1 point***.
   (c) ***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?
   (a) ***Yes***, qualitative and quantitative methods are acceptable. ***2 points***.
   (b) ***Partially***, partial description of methods to combine and tabulate; not sufficient to duplicate. ***1 point***.
   (c) ***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?
   (a) ***Yes***, combining of studies appears acceptable. ***2 points***.
   (b) ***Can't tell***, should be marked if in doubt. ***1 point***.
   (c) ***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?
   (a) ***Yes***, data were reported that support the main conclusions regarding the primary question(s) that the overview addresses. ***2 points***.
   (b) ***Partially***. ***1 point***.
   (c) ***No***, conclusions not supported or unclear. ***0 points***.

RCTs

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

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 was given 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 describe that there were no withdrawals.

Appendix 6

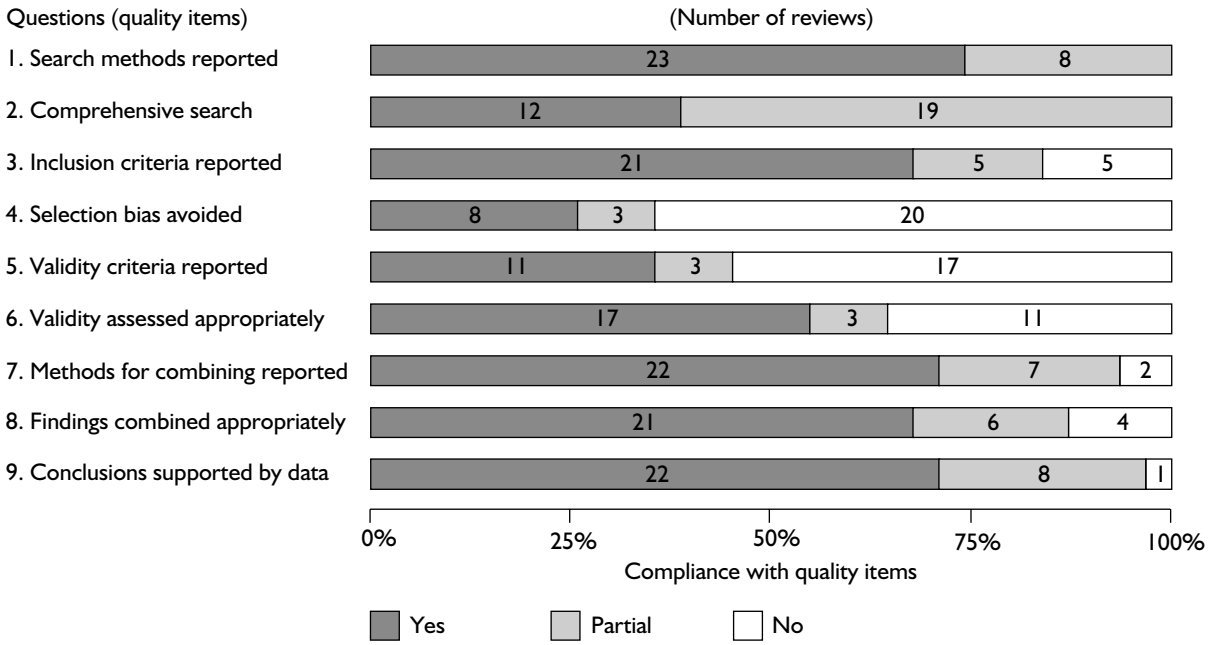
Quality assessment of systematic reviews

Summary of quality scores for included systematic reviews

Review	Score on question[a]									
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total
Amato *et al*., 2004[74]	2	2	2	1	2	2	2	2	2	17
Barnett *et al*., 2001[68]	1	1	0	0	0	0	2	2	2	8
Caplehorn *et al*., 1996[48]	2	2	1	0	0	0	2	2	2	11
Clark *et al*., 2002[71]	2	2	2	1	2	2	2	1	2	16
Davids and Gastpar, 2004[67]	1	1	1	0	0	0	2	2	1	8
Faggiano *et al*., 2003[60]	2	2	2	1	2	2	2	1	2	16
Farre *et al*., 2002[55]	2	1	1	0	2	0	2	2	2	12
Ferri *et al*., 2005[76]	2	2	2	0	2	2	2	2	2	16
Fridell, 2003[72]	2	1	1	0	1	0	1	0	1	7
Glanz *et al*., 1997[49]	1	1	0	0	2	1	2	2	2	11
Gowing *et al*., 2004[63]	2	2	2	1	2	2	2	2	2	17
Griffith *et al*., 2000[70]	1	1	2	0	0	0	1	1	2	8
Hopfer *et al*., 2002[56]	2	1	2	0	0	0	2	2	2	11
Hulse *et al*., 1998[43]	2	1	2	0	1	0	2	2	2	12
Johansson, 2003[61]	2	1	0	0	0	0	2	2	2	9
Kirchmayer *et al*., 2003[73]	2	2	2	1	2	2	2	2	2	17
Layson-Wolf *et al*., 2002[57]	2	1	0	0	0	0	0	1	0	4
Lintzeris and Ford, 2004 (unpublished)	1	1	0	0	0	0	0	0	1	3
Marsch, 1998[50]	1	1	2	0	0	0	2	2	2	10
Mattick *et al*., 2003[62]	2	1	2	1	2	2	2	2	2	16
Mattick *et al*., 2005[64]	2	2	2	1	2	2	2	2	2	17
Mayet *et al*., 2004[167]	2	2	2	1	2	2	2	2	2	17
Prendergast *et al*., 2000[51]	2	2	2	0	1	1	2	2	1	13
Prendergast *et al*., 2002[58]	2	1	2	0	0	0	2	2	2	11
Raisch *et al*., 2002[66]	1	1	2	0	0	0	1	0	1	6
Roozen *et al*., 2004[75]	2	1	2	1	2	2	2	2	2	16
Simoens *et al*., 2005[65]	2	1	2	0	2	0	2	2	2	13
Simoens *et al*., 2002[59]	2	2	2	1	2	1	1	1	2	14
Sorensen and Copeland, 2000[52]	2	1	1	0	0	0	2	2	1	9
Stanton and Shadish, 1997[69]	1	1	2	0	2	2	1	0	1	10
van Beusekom and Iguchi, 2001[54]	2	2	2	0	2	0	1	1	1	11
West *et al*., 2000[53]	2	1	2	0	0	0	1	2	2	10

[a] Score 2, fully matched the criteria; score 1, partially matched the criteria; score 0, no match for the criteria.

Summary of quality assessment results



The quality assessment of the systematic reviews is tabulated below, where reviews are listed in alphabetical order by first author.

Review	Questions	Score	Assessment
Amato *et al.*, 2004[74]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 2	Sources: 1. Electronic: MEDLINE (January 1966–April 2003), PsycINFO (1887–August 2000), EMBASE (January 1980–April 2003) and Cochrane Controlled Trials Register (Issue 3, 2003), etc. 2. Reference lists of articles and handsearched reviews and conference abstracts
	Inclusion criteria reported (Q3)	2	Clearly defined types of studies RCTs, participants (opiate addicts), intervention and control (agonist + psychosocial vs 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) 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 and Q8)	2 and 2	Meta-analysis methods described for dichotomous and continuous outcomes, statistical heterogeneity amongst study effect sizes was estimated; combining of findings appears appropriate

continued

Review	Questions	Score	Assessment
	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. quality of life), 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 a summary RR of only 0.94 (95% 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
Barnett *et al*., 2001[68]	Search methods reported and comprehensive search (Q1 and Q2)	1 and 1	Searched MEDLINE (before 1998) only. Restricted to papers in English language Search strategy was not reported
	Inclusion criteria reported (Q3)	1	Limited to 2 double-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 and Q8)	2 and 2	Meta-analysis undertaken where statistically 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: (a) The variation between trials may be due to differences in dose levels, patient exclusion criteria and provision of psychosocial treatment (b) The difference in the effectiveness of buprenorphine and methadone may be statistically significant, but the differences are small compared with the wide variance in outcomes achieved in different methadone treatment programmes (c) 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? (a) 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

continued

Review	Questions	Score	Assessment
			(b) 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 (c) Effectiveness of buprenorphine compared with methadone was derived from the 5 included trials and was not strongly concluded
Caplehorn *et al.*, 1996[48]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 2	Searched MEDLINE (1966–95) 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 and Q8)	2 and 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 MMT 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 significantly reduces mortality; the combined RR from five studies = 0.25 (95% CI 0.19 to 0.33) The meta-analysis supports the conclusion that MMT patients are about one-quarter as likely to die as those not in MTT
Clark *et al.*, 2002[71]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 2	Sources: 1. Electronic: MEDLINE (January 1996–August 2000), PsycINFO (1887–August 2000), EMBASE (January 1985–August 2000) and Cochrane Controlled Trials Register (Issue 2, 2000), etc. 2. Reference lists of articles and bibliography 3. College on Problems of Drug Dependence (CPDD) abstracts and National Institute on Drug Dependence (NIDA) monographs 4. Pharmaceutical industry: bibliographic index 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) were defined
	Validity for each study assessed appropriately (Q6)	2	Each included study was assessed using the quality items of the quality criteria

continued

Review	Questions	Score	Assessment
	Methods for combining reported and findings combined appropriately (Q7 and Q8)	2 and 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 MT with MMT 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 than methadone patients 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, but 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 to 0.91; weighted mean difference (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, $p = 0.2$
Davids and Gastpar, 2004[67]	Search methods reported and comprehensive search (Q1 and Q2)	1 and 1	Searches: MEDLINE and PSYNDEXplus from their earliest entries (end data were 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 and Q8)	2 and 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 particular emphasis on the issues of MT 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 not 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

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Review	Questions	Score	Assessment
Faggiano *et al*., 2003[60]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 2	Sources: 1. Electronic: MEDLINE (Ovid 1996–2001), EMBASE (1988–2001), ERIC (1988–2001), PsycINFO (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 (opioid-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 and 1	Meta-analysis was conducted for the RCTs, which were classified according to the used range of dose, and for 3 controlled prospective studies 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: (a) Retention rates: high (60–109 mg/day) vs low doses (1–39 mg/day) at short follow-ups: RR 1.36, 95% CI 1.13 to 1.63 (b) Opioid use: high vs middle doses (40–59 mg/day): WMD –1.89, 95% CI –3.43 to –0.35 (c) Opioid abstinence (urine based) at >3–4 weeks: high vs low doses RR 1.59, 95% CI 1.16 to 2.18; high vs middle doses, RR 1.51, 95% CI 0.63 to 3.61 (d) Cocaine abstinence (urine based) at >3–4 weeks: high vs low doses, RR 1.81, 95% CI 1.15 to 2.85
Farre *et al*., 2002[55]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic: PubMed database from 1996 to December 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

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Review	Questions	Score	Assessment
	Inclusion criteria reported (Q3)	1	Study design (double-blinded RCTs), intervention (MMT) and outcome measure were defined. Details of participants (opioid-addicted patients) 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 and Q8)	2 and 2	Meta-analysis was used for pooling both the outcomes of illicit drug use and failure in retention, using random effects model where there was heterogeneity
	Conclusions supported by data (Q9)	2	1. This review examined the question of the effect of MMT strategies on the end-points of retention rate and reduction of illicit opioid use. It included 13 studies 2. Conclusion stated: agonist-maintenance programmes, oral methadone at doses of 50 mg/day or higher is the drug of choice for opioid dependence 3. Is it supported by the data? (a) High vs low doses of methadone in the reduction of illicit opioid use: odds ratio (OR) 1.92, 95% CI 1.32 to 2.78 (b) It concluded that "High doses of methadone were significantly more effective than low doses of buprenorphine (<8 mg/day) for retention rates and illicit opioid use, but similar to high doses of buprenorphine (≥8 mg/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 to 1.67) and OR 1.72 (95% CI 1.26 to 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 to 6.58) and OR 3.39 (95% CI 1.87 to 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 to 1.59) and OR 1.08 (95% CI 0.75 to 1.57) respectively (c) 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 to 2.78)
Ferri *et al.*, 2005[76]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 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 years or older and chronic heroin dependents), intervention (heroin alone or combination with methadone), control treatment (no intervention, MMT, 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

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Review	Questions	Score	Assessment
	Validity criteria reported (Q5)	2	Defined randomisation method, allocation concealment and follow-up
	Validity for each study assessed appropriately (Q6)	2	Assessed all the included studies for each of the aspect of the quality criteria
	Methods for combining reported and findings combined appropriately (Q7 and Q8)	2 and 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 MT 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 effectiveness 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
Fridell, 2003[72]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 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 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 Swedish Council on Technology Assessment in Health Care (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 and Q8)	1 and 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 pyschosocial interventions (with or without drug therapy) for opiate abuse The review concluded that re-educative interventions and psychotherapies have significant effects on relapse compared with treated control groups. The effect sizes are moderate Difficult to assess how much the conclusions are attributable to non-drug vs drug therapy
Glanz *et al*., 1997[49]	Search methods reported and comprehensive search (Q1 and Q2)	1 and 1	Sources: MEDLINE Years of the database searched: 1966–96 No other sources were searched Search used keywords, e.g. heroin addiction, methadone Unknown whether there was a language restriction

continued

Review	Questions	Score	Assessment
	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 and Q8)	2 and 2	Calculated mean risk difference for the dichotomous variables. Meta-analysis was conducted using both fixed-effects model and random-effects 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 the 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: (a) Illicit drug use (heterogeneity detected, considering random-effects model): mean risk difference –0.01, 95% CI –0.07 to 0.04 (b) Patient retention in treatment programme (heterogeneity detected, considering random-effects model): mean risk difference –0.13, 95% CI –0.21 to –0.04 (c) Compliance: (no heterogeneity, fixed-effects model used): mean risk difference 0.04, 95% CI 0.02 to 0.05
Gowing *et al*., 2004[63]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 2	Sources: 1. Electronic: MEDLINE, EMBASE , PsycINFO, CINAHL (searched from commencement to July 2003) 2. Reference lists of articles and handsearched and conference abstracts. No specific action for retrieval of unpublished material
	Inclusion criteria reported (Q3)	2	Clearly defined types of studies [controlled before-and-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 and Q8)	2 and 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

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Review	Questions	Score	Assessment
	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 and 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
Griffith *et al*., 2000[70]	Search methods reported and comprehensive search (Q1 and Q2)	1 and 2	1. Electronic databases: (a) Search in subject indexes: MEDLINE, PsycLIT and PsycINFO (b) Citation searches: Science Citation Index and Social Sciences Citation Index 2. Footnote chasing 3. Handsearching 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 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 and Q8)	1 and 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. 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? Study heterogeneity and susceptability to biases of descriptive studies may compromise validity of conclusions

continued

Review	Questions	Score	Assessment
Hopfer *et al.*, 2002[56]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic databases: MEDLINE and PsycINFO 2. Reference lists Years searched: not reported Search strategy: using keywords 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 and Q8)	2 and 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 were 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 focused 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 MMT 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, MMT 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 MMT. Length of time in treatment, regardless of modality, was the best predictor of outcome. The rise of heroin use among adolescents and young adults calls for descriptive studies and controlled treatment studies 3. Is it supported by data? As no controlled trials were found in the review, the authors made no definitive conclusion on effectiveness
Hulse *et al.*, 1998[43]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic: MEDLINE (1966–June 1996) 2. Reference lists of obtained articles 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 and Q8)	2 and 2	Meta-analysis methods described for dichotomous outcomes in case–control studies (OR 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

continued

Review	Questions	Score	Assessment
	Conclusions supported by data (Q9)	2	This review examined whether heroin use and MMT, 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, 95% CI 2.6 to 14.7) relative to those using methadone alone (RR 1.75, 95% 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, sexually transmitted diseases, other illness, etc.). This appears to be an unsupported conclusion since no data about life style were taken into account in the analyses
Johansson, 2003[61]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic: (a) Searched MEDLINE 1966–2000 using search terms 'alcohol', 'substance use' and 'RCT'. (b) The Cochrane Library 2. Reference lists in published articles and reviews Unknown whether grey literature was searched. In the 'included studies' but not the 'search strategy and method' section, it indicated that a compilation of unpublished articles was 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 and Q8)	2 and 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 of whether MT 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 on buprenorphine vs placebo, 2 were on methadone vs placebo, 9 were on methadone vs LAAM and 6 were on methadone vs buprenorphine 2. Conclusion stated, and is it supported by data? (a) Buprenorphine is superior to placebo in reducing abuse (d = 0.44, 95% CI 0.00 to 0.89) but has little effect on retention (d = 0.13, 95% CI –0.31 to 0.57) (b) Maintenance treatment with agonists (including partial) is effective Compiling the studies of both buprenorphine and methadone vs placebo: in reducing abuse, d =0.55, 95% CI 0.44 to 0.67; d (random model) = 0.62, 95% CI 0.40 to 0.84; retention, d = 0.75, 95% CI 0.63 to 0.87; d (random model) = 0.81, 95% CI 0.45 to 1.17

continued

Review	Questions	Score	Assessment
			(c) Methadone has the same effect as LAAM on abuse (d = –0.06, 95% CI –0.19 to 0.06), but is superior on retention (d = 0.34, 95% CI 0.22 to 0.46) (d) There were no differences between methadone and buprenorphine in terms of primary outcome measures (on abuse d = 0.13, 95% CI –0.33 to 0.28; on retention, d = 0.00, 95% CI –0.15 to 0.16) (e) Methadone at higher dose was superior on abuse and retention: 80–100 vs 50 mg on abuse d = 0.28, 95% CI 0.10 to 0.46, on retention d = 0.25, 95% CI 0.07 to 0.43; 50–80 vs 20–45 mg, on abuse d = 0.36, 95% CI 0.23 to 0.49, on retention d = 0.30, 95% CI 0.17 to 0.43 Buprenorphine 16 vs 8 mg/day had no difference on primary outcome measures but 8–16 mg/day is superior to 1–4 mg/day on abuse (d = 0.25, 95% CI 0.15 to 0.35) and retention (d = 0.21, 95% CI 0.12 to 0.31)
Kirchmayer *et al*., 2003[73]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 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 4, 2001) 2. Handsearching, 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 and Q8)	2 and 2	Meta-analysis (OR and 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 MT 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

continued

Review	Questions	Score	Assessment
Layson-Wolf *et al.*, 2002[57]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic: MEDLINE (January 1966 [1996 presumed misprint] to May 2001) 2. 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 and Q8)	0 and 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 MMT 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
Lintzeris and Ford, 2004 (unpublished)	Search methods reported and comprehensive search (Q1 and Q2)	1 and 1	Sources: "two Cochrane reviews facilitated the process of identifying relevant research regarding the efficacy of buprenorphine 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 and Q8)	0 and 0	For the part of the paper which is relevant to our review, the results were descriptively reported. 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 buprenorphine 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 buprenorphine, recommendations regarding clinical practice and issues regarding treatment dissemination and uptake. Only the use of buprenorphine for maintenance in the first part of this paper is relevant to our review question, and it had 5 RCTs on BMT versus placebo and 11 RCTs on BMT versus methadone

continued

Review	Questions	Score	Assessment
			2. Conclusions stated and relevant to our review: (a) BMT is significantly more effective than placebo therapy, and at high doses it is more effective than at lower doses. (b) High-dose methadone is more effective than 'medium'- or 'low'-dose buprenorphine, while methadone and buprenorphine are comparable at 'medium' and 'low' dose 3. Is it supported by data? (a) Buprenorphine 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 buprenorphine, no quantitative data were given (b) (i) The findings of flexible-dose studies: treatment retention for MT vs BMT: RR 0.82, 95% CI 0.69 to –0.96, $p = 0.01$ (ii) The retention for 50 mg methadone vs 5 mg buprenorphine: 59 vs 84%, $p = 0.001$ (iii) With consideration that methadone and buprenorphine are comparable at both 'medium' dose and 'low' doses, no quantitative data but only *p*-values were given
Marsch, 1998[50]	Search methods reported and comprehensive search (Q1 and Q2)	1 and 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 and Q8)	2 and 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 behaviour 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

continued

Review	Questions	Score	Assessment
			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 3. Evidence: (a) Estimated summary effect size of MMT in reducing IDU: $r = 0.351$ ($d = 0.75$) (mean); 0.185 ($d = 0.38$) (weighted fixed effects) (b) Estimated summary effect size of MMT in reducing HIV risk behaviours: $r = 0.217$ ($d = 0.44$) (mean); $r = 0.18$ ($d = 0.37$) (c) 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, $r = 0.18$ (95% CI 0.12 to 0.24); crime, $r = 0.21$ (95% CI 0.15 to 0.27)
Mattick *et al*., 2003[62]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic databases: Cochrane Drugs and Alcohol Review Group Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE, 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 and Q8)	2 and 2	Standardised effect size (RR) 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 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 MT 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 estimates 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 to 5.35; in suppression of heroin use from 3 RCTs, RR 0.32, 95% CI 0.23 to 0.44; in criminal activity from 3 RCTs, RR 0.39, 95% CI 0.12 to 1.25 Therefore data supports the conclusions

continued

Review	Questions	Score	Assessment
Mattick *et al*., 2005 (updated)[64]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 2	Sources: 1. Electronic databases: Cochrane Library, MEDLINE, EMBASE, Current Contents. PsycLIT, CORK, ADCA, ADF-VIC, CEIDA, ABN, etc., including proceedings 2. Reference lists of all identified studies and published reviews 3. Unpublished relevant RCTs 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 (BMT compared with MMT 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 and Q8)	2 and 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-effects model. SMD was calculated for continuous outcomes and combined using a fixed- or random-effects model as appropriate
	Conclusions supported by data (Q9)	2	1. The review examined the question of the effects of BMT against placebo or MMT in retaining patients and in suppressing illicit drug use 2. Conclusion stated: buprenophine is an effective intervention for use in the MT 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 to 0.96 2. High-dose buprenorphine vs high-dose methadone in retention: RR 0.79, 95% CI 0.62 to 1.01 3. Buprenorphine vs placebo in patients in treatment at low doses, RR 1.24, 95% CI 1.065 to 1.45; high doses, RR 1.21, 95% CI 1.02 to 1.44; at very high doses, RR 1.52, 95% CI 1.23 to 1.88
Prendergast *et al*., 2000[51]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 2	Many databases searched 1965–96 (MEDLINE, Current Contents, PsycINFO and others). Bibliographies were searched, researchers contacted, grey literature and 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

continued

Review	Questions	Score	Assessment
	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 and Q8)	2 and 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 (in addition to a fixed-effects model) 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 for prevention of illicit drug abuse and of criminality. 143 studies of various interventions and study designs were included 2. Effect size (SMD) for methadone studies was provided but no CIs or *p*-values were given and no results for a statistical test for heterogeneity were reported. SMD for methadone studies with comparator group design and single-group design were as follows: drug abuse 0.49 (8 studies) and 1.48 (22 studies); and criminal activity 0.17 (3 studies) and 0.8 (16 studies), respectively 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 effect size correlated with decade of study (older studies larger effect size), methadone dose (bigger dose larger effect size), strength of implementation (stronger implementation smaller effect size) and treatment retention (longer treatment larger effect size) 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 probably limited as all studied programmes operated in a North American setting
Prendergast *et al.*, 2002[58]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Searched online bibliographic databases: Current Contents (Social and Behavioural Sciences), Dissertation Abstracts, ETOH (Alcohol and Alcohol Problems Science database), GPO Monthly Catalog, Magazine and Newspaper Index, MEDLINE, NTIS, PsycINFO, PAIS, Sociological Abstracts and Social Work Abstracts 2. Checked printed sources 3. Requests to colleagues and organisations 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

continued

Review	Questions	Score	Assessment
	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 years or older)), the condition of intervention, comparison condition, setting (USA or Canada), outcome data (quantitative outcome variables) and study type (e.g. design). Data of the document reporting the study were 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 and Q8)	2 and 2	Effect sizes from each individual study were presented in a stem-and-leaf plot. Meta-analysis was conducted for drug use and crime using both fixed- and random-effect models. 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 MMT alone or BMT alone 2. Conclusion stated: drug abuse treatment is effective in reducing drug use and crime in the USA. Effect sizes were associated with the moderating and mediating variables reported in the original studies 3. Is it supported by data? Fixed-effects weighted mean (95% CI): for drug use 0.30 (0.25 to 0.35), for crime 0.13 (0.04 to 0.21). Random effects weighted mean (95% CI): for drug use 0.33 (0.25 to 0.42), for crime 0.13 (–0.004 to 0.27)
Raisch *et al.*, 2002[66]	Search methods reported and comprehensive search (Q1 and Q2)	1 and 1	1. Electronic databases: MEDLINE and HEALTHSTAR (1966 to November 2000) 2. 'Secondary' and 'tertiary' sources were also searched, but it is not clear what the authors are referring to 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), study design (RCT involving head-to head comparisons of active treatments or active/placebo comparisons) and pharmacists' activities in the treatment and prevention of opiate dependence
	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 and 0	Narrative analysis of the results without a combination of quantitative data. There were 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

continued

Review	Questions	Score	Assessment
	Conclusions supported by data (Q9)	1	1. This review aimed to investigate opioid dependence, its treatment and the use of buprenorphine with naloxone as a treatment alternative, but it is not clear how many studies were included by the review 2. Conclusion stated: opioid dependence is a critical unmet health problem in the USA. Buprenophine combined with naloxone represents an innovative treatment for opioid dependence in outpatient settings. This new treatment has advantages over MMT 3. Is the 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 the conclusions are justifiable
Roozen *et al*., 2004[75]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic databases: Biological Abstracts, ERIC, LISA, OSH, Periodical Abstracts, PsycINFO, SERFILE, Sociological Abstracts, EMBASE, 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 keywords Searches were restricted to RCTs published in English language only
	Inclusion criteria reported (Q3)	2	Clearly defined 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) 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 were 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 and Q8)	2 and 2	A meta-analysis of the same variables and separate meta-analyses for the effects of different treatment durations were performed using a 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	1. The review examined the question of the effectiveness of a 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, which compared CRA with usual care in an MMT programme, was relevant to our review question 2. Conclusion stated (relevant to our review topic): there is limited evidence that a CRA is more effective in an MMT programme 3. Is it supported by data? In the study compared of single CRA versus usual care in an MMT programme, in the long term (>16 weeks) CRA was significantly more effective than usual care, based on the consecutive (3 weeks) opiate-negative urine analysis (84 vs 78%) and the 6-month ASI composite scores, but no CIs and *p*-values were given

continued

Review	Questions	Score	Assessment
Simoens *et al*., 2005[65]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic databases: 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 MMT or BMT, 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 and Q8)	2 and 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 MT 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
Simoens *et al*., 2002[59]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 2	Sources: 1. Electronic databases: 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 and 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

continued

Review	Questions	Score	Assessment
	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 the quality of included studies was provided rather than individual analysis study by study
	Methods for combining reported and findings combined appropriately (Q7 and Q8)	1 and 1	Method for narrative combination of study results sketchy; there was a lack of use of quantitative data in drawing conclusions (but quantitative data were 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 141 studies were included The authors concluded that the effectiveness of methadone, buprenorphine (and LAAM) was well established but transferability to a UK setting requires caution. Some evidence supported the proposition that higher doses of methadone and 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
Sorensen and Copeland, 2000[52]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic databases: MEDLINE and PsycINFO 2. Reference lists Years searched: 1988–98 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 and Q8)	2 and 2	Narrative analysis. There are no quantitative data for any of 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 the conclusion supported by data? The authors reported results mostly in a narrative account. It is difficult to determine if the conclusion is justifiable without accessing the primary data

continued

Review	Questions	Score	Assessment
Stanton, 1997[69]	Search methods reported and comprehensive search (Q1 and Q2)	1 and 1	Sources: 1. Three earlier reviews. 2. The database compiled by WR Shadish, who had devoted considerable resources to locating published and unpublished family–couples outcome studies. Included a computer scan of the bibliography from the search plus an update of the computerised searches of *Dissertation Abstracts* and *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 treatments compared 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 and Q8)	1 and 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 synthesised drug abuse outcome studies that included a family–couple therapy treatment condition. It included 15 studies, of which 4 included MMT 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 MMT 3. Is it supported by data? Drugs use: family–couple therapy vs non-family therapy or alternative interventions: self-reported $d = 0.48$, dropout d (DOd) = 0.43, treatment attrition d (Tad) = 0.43 With adults: family–couple therapy vs another form of treatment or intervention: self-reported $d = 0.42$, DO$d = 0.50$, T$ad = 0.48$ With adolescents: family–couple therapy vs another form of treatment or intervention: self-reported $d = 0.39$, DO$d = 0.39$, T$ad = 0.40$
Van Beusekom and Iguchi, 2001[54]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 2	Sources: Cochrane Library, MEDLINE, EMBASE, PsycINFO, 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

continued

Review	Questions	Score	Assessment
	Validity for each study assessed appropriately (Q6)	0	There was little or no reference to study quality in the narrative text of this report and no appendix was provided that might contain such information
	Methods for combining reported and findings combined appropriately (Q7 and Q8)	1 and 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 focused on adequate dosing, efficacy as a substitution drug, 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
West *et al.*, 2000[53]	Search methods reported and comprehensive search (Q1 and Q2)	2 and 1	Sources: 1. Electronic databases: MEDLINE and PsycINFO 2. Reference lists It is not reported whether unpublished and grey literature were searched No time limit was constrained on the search Searches used subject headings, e.g. buprenorphine, opiate 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 and Q8)	1 and 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 a random model or fixed model was used
	Conclusions supported by data (Q9)	2	1. This review's aim was to compare quantitatively the effectiveness of buprenorphine and methadone. It included 9 studies 2. Conclusion stated: the findings suggest a relative equality in the efficacy of buprenorphine and methadone, but patients receiving methadone were less likely to test positive for illicit opiate use. Past experience with MMT 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 the conclusion supported by data? The average unweighted 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 homogeneous 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 ($Z = 3.99$, $p < 0.01$)

Appendix 7

Quality assessment of RCTs

	Ahmadi, 2003b[82]		Ahmadi, 2003c[78]		Ahmadi, 2003[79]		Brooner, 2004[97]		Jones, 2001[87]		Pollack, 2002[88]	
		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 and 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 and 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. Blinding method not described	0	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, nor 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	

	Ritter, 2003[92]		Marsch, 2005[80]		Eder, 2005[102]		Margolin, 2003[94]		Lidz, 2004[99]		Avants, 2004[96]	
		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 and appropriate?	Yes. Independent randomisation telephone service using dynamic balancing method	1	No	0	Yes. Computer-generated randomisation	1	Yes	1	No	0	No	0
Was the method really random?	Yes		Can't tell		Yes		Can't tell		Unlikely		Unlikely	
Was allocation concealed and 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		NA		NA	
Was method of blinding adequately described?	NA	0	Yes. Placebo methods described	1	Yes. Placebo matched to treatments	1	Yes. Placebo matched pills	1	NA	0	NA	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 indicate blinding of patients was reasonably successful		Baseline characteristics of groups balanced		Baseline characteristics of groups balanced	

	van den Brink, 2003[103]		Dijkgraaf, 2005[101]	Blanken, 2005[100]	Sigmon, 2004[95]		Zanis, 2001[84]		Giacomuzzi, 2001[86]	
		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[103] 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[103]	Yes	1	Yes	1	Yes	1
Was method of randomisation well described and appropriate?	Yes	1			Yes	1	No	0	No	0
Was the method really random?	Probably				Probably		Can't tell		Can't tell	
Was allocation concealed and 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?	NA				NA		NA		NA	
Was method of blinding adequately described?	NA	0			NA	0	NA	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	

	Chutuape, 2001[85]		Cornish, 2002[89]		Dean, 2002[90]		Lofwall, 2005[83]	
		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 and appropriate?	No	0	No	0	No	0	No	0
Was the method really random?	Unlikely		Unlikely		Unlikely		Unlikely	
Was allocation concealed and concealment method described?	Not stated		Not stated		Not stated		Not stated	
Was study described as double blind?	No	0	Yes	1	Yes (not described as 'double blind')	1	Yes (not described as 'double blind')	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. Placebo identical	1	Yes. Placebo identical	1	Yes. Identical method of administration	1
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		Baseline characteristics of groups balanced	

Author	Dolan, 2003[77]		Grabowski, 2004[98]		Kosten, 2003[93]		King, 2002[91]		Kristensen, 2005[81]	
	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 and appropriate?	Yes. Random draw from envelopes	1	No	0	No	0	No	0	No	0
Was the method really random?	Yes		Unlikely		Probably		Can't tell		Can't tell	
Was allocation concealed and concealment method described?	No		No		No		No		No	
Was study described as double blind?	No	0	Yes	1	Yes (not possible to blind contingency management)	1	No	0	No	0
Who was blinded?	NA		Patients, clinicians and assessors		Patients, clinicians and assessors		NA		NA	
Was method of blinding adequately described?	NA	0	Yes. Identical placebo	1	Yes. Placebo	1	NA	0	NA	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		Baseline characteristics of groups balanced				Baseline characteristics of groups balanced	

NA, not applicable.

Appendix 8

Quality assessment of economic studies

No.	Phillips criteria	Barnett, 1999[147]	Zaric, 2000a[145], b[146]	Barnett, 2001[151]	Zarkin, 2005[150]	Masson, 2004[152]	Sheerin, 2004[148]
	Structure						
1	Is there a clear statement of the decision problem?	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
3	Is the primary decision-maker specified?	Y	Y	Y	Y	UC	Y
4	Is the perspective of the model stated clearly?	Y	Y	Y	Y	Y	Y
5	Are the model inputs consistent with the stated perspective?	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	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
8	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y	Y	Y	Y	Y
9	Is there a clear definition of the options under evaluation?	Y	Y	Y	Y	Y	Y
10	Have all feasible and practical options been evaluated?	Y	Y	Y	Y	Y	Y
11	Is there justification for the exclusion of feasible options?	Y	NA	Y	NA	N	Y
12	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	Y	Y	Y	Y
13	Is the time horizon of the model sufficient to reflect all important differences between the options?	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	NA	Y	NA (Markov model)	Y
15	Is the cycle length defined and justified in terms of the natural history of disease?	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 (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

continued

No.	Phillips criteria	Barnett, 1999[147]	Zaric, 2000a[145], b[146]	Barnett, 2001[151]	Zarkin, 2005[150]	Masson, 2004[152]	Sheerin, 2004[148]
18	Where expert opinion has been used are the methods described and justified?	NA	NA	Y (briefly)	NA	NA	NA
19	Is the choice of baseline data described and justified?	Y	Y	Y	Y	Y	Y
20	Are transition probabilities calculated appropriately?	Y	Y	Y	Y	UC?	UC
21	Has a half-cycle correction been applied to both costs and outcomes?	Y	N	N	N	Y	N
22	If not, has the omission been justified?	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	Y	N
24	Are the costs incorporated into the model justified?	Y	Y	Y	Y	Y	N (not fully justified)
25	Has the source for all costs been described?	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
27	Are the utilities incorporated into the model appropriate?	NA	Y	Y	Y	Y	NA
28	Is the source of utility weights referenced?	NA	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
30	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	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
32	Have the results been compared with those of previous models and any differences in results explained?	Y	Y	N (reference has been made to previous publications)	Y	Y	N

N, no; NA, not applicable; UC, uncertain; Y, yes.

No.	Drummond adapted criteria (Healey, 2003)[141]	Sirotnik and Bailey, 1975[142]	Goldschmidt, 1976[149]	Strang, 2000[140]	Doran, 2003[143]	Doran, 2004[210]	Harris, 2005[144]
1.	Was a well-defined question posed in an answerable form?	Y	Y	N	Y	Y	Y
2.	Was a comprehensive description of the competing alternatives given?	Y	Y	UC	Y	Y	Y
3.	Was there evidence that the programme's effectiveness was established?	UC	Y	UC	Y	Y	Y
4.	Were all the important and relevant costs and consequences for each alternative identified?	UC	Y	UC	Y	Y	Y
5.	Were costs and consequences measured accurately in appropriate physical units?	UC	UC	Costs Y	Y	Y	Y
6.	Were costs and consequences valued credibly?	UC	UC	Costs Y	Y	Y	Y
7.	Were costs and consequences adjusted for differential timing?	N	N	N	N	N	Y
8.	Was an incremental analysis of costs and consequences of alternatives performed?	N	Y	N	Y	Y	Y
9.	Was allowance made for uncertainty in the estimates of costs and consequences?	N	N	N	Y	N	Y
10.	Did the presentation and discussion of study results include all issues of concern to users?	N	N		Y	Y	Y

N, no; UC, uncertain; Y, yes.

Appendix 9

Treatment outcomes from overview of systematic reviews

Details are given in *Tables 37–64*.

TABLE 37 *Proportion of individuals retained in treatment*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (weeks)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone vs placebo/no therapy									
20–50 mg vs no therapy	Mattick, 2003[62]	3	505	RCT	68	25	26	3.05 (1.75 to 5.35) [R]	0.02
20–97 mg vs placebo	Farre, 2002[55]	2	348	RCT	54	17	15–32	3.91 (1.17 to 13.2) [R][a]	0.001
35–97 mg vs no therapy	Johansson, 2003[61]	6	1013	RCT/CCT	NR	NR	6–152	*d* 0.92 (0.54 to 1.29 [R]	<0.05
Buprenorphine vs placebo/no therapy									
≤5 mg	Mattick, 2005[64]	5	1131	RCT	60	39	16–24	1.50 (1.19 to 1.88) [R]	0.007
6–12 mg	Mattick, 2005[64]	4	887	RCT	65	38	17–52	1.74 (1.06 to 2.87) [R]	<0.0001
18 mg	Mattick, 2005[64]	4	728	RCT	63	41	4–52	1.74 (1.02 to 2.96) [R]	0.0001
Methadone dosages									
60–109 vs 1–39 mg	Faggiano, 2003[60]	5	496	RCT	56	41	17–26	1.36 (1.13 to 1.63) [F]	0.0002
60–109 vs 1–39 mg	Faggiano, 2003[60]	1	140	RCT	35	21	52	1.63 (0.95 to 2.77)	NA
60–109 vs 40–59 mg	Faggiano, 2003[60]	2	347	RCT	80	79	7–13	1.01 (0.91 to 1.12) [F]	0.14
60–109 vs 40–59 mg	Faggiano, 2003[60]	3	560	RCT	57	46	27–40	1.23 (1.05 to 1.45)	0.19
40–57 vs 1–39 mg	Faggiano, 2003[60]	1	166	RCT	52	41	20	1.26 (0.91 to 1.75) [F]	NA
>110 vs 40–59 mg	Faggiano, 2003[60]	1	80	RCT	63	38	27	1.67 (1.05 to 2.66) [F]	NA
>110 vs 60–109 mg	Faggiano, 2003[60]	1	80	RCT	63	65	27	0.96 (0.69 to 1.34)	NA
High (≥50) vs low (<50 mg)	Farre, 2002[55]	8	1041	RCT	55	44	15–40	OR 1.25 (0.94 to 1.67) [R]	0.13
80–100 vs 50 mg	Johansson, 2003[61]	3	478	RCT/CCT	NR	NR	24–40	*d* 0.25 (0.07 to 0.43) [F]	>0.05
50–80 vs 20–45 mg	Johansson, 2003[61]	8	892	RCT/CCT	NR	NR	14–52	*d* 0.30 (0.17 to 0.43) [F]	>0.05
Buprenorphine doses									
16 vs 8 mg	Johansson, 2003[61]	1	370	RCT	NR	NR	16	*d* 0.18 (–0.03 to 0.38)	NA
8–16 vs 1–4 mg	Johansson, 2003[61]	6	1620	RCT	NR	NR	2–24	*d* 0.21 (0.12 to 0.31) [F]	>0.05
Methadone vs buprenorphine									
50–80 vs 6–12 mg	Barnett, 2001[68]	5	540	RCT	NR	NR	16–26	HR 1.26 (1.01 to 1.57) [F]	0.088
20–100 vs 2–16 mg	Davids, 2004[67]	4	NR	RCT/CCT	NR	NR	NR	2/6 favoured B 1/6 favoured low-dose M 2/6 M = B	NA
≥50 vs <8 mg	Farre, 2002[55]	1	57	RCT	NR	NR	24	RR 2.72 (1.12 to 6.58)	NA
≥50 vs ≥8 mg	Farre, 2002[55]	5	529	RCT	NR	NR	17–24	RR 1.14 (0.83 to 1.59)	NA
<50 vs ≥8 mg	Simoens, 2005[65]	4	NR	RCT	NR	NR	NR	3/4 M = B, 1/4 B > M	NA
<50 vs <8 mg	Simoens, 2005[65]	4	NR	RCT	NR	NR	NR	4/4 M > B	NA
≥50 vs ≥8 mg	Simoens, 2005[65]	3	NR	RCT	NR	NR	NR	2/3 M > B, 1/3 B = M	NA

continued

TABLE 37 *Proportion of individuals retained in treatment (cont'd)*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (weeks)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
≥50 vs <8 mg	Simoens, 2005[65]	2	NR	RCT	NR	NR	NR	2/2 M > B	NA
Flexible vs flexible	Simoens, 2005[65]	2	NR	RCT	NR	NR	NR	2/2 M > B	NA
20–100 vs 2–12 mg	Johansson, 2003[61]	6	648	CCT	NR	NR	NR	*d* 0.00 (–0.15 to 0.16) [F]	>0.05
Flexible vs flexible	Mattick, 2005[64]	7	976	RCT	63	53	17–26	1.19 (1.07 to 1.33) [F]	0.23
≤35 vs ≤5 mg	Mattick, 2005[64]	3	211	RCT	58	39	18–24	1.47 (1.10 to 2.00) [F]	0.62
50–80 vs ≤5 mg	Mattick, 2005[64]	3	263	RCT	73	47	18–24	1.54 (1.23 to 1.89) [F]	0.62
≤35 vs 6–16 mg	Mattick, 2005[64]	6	469	RCT	44	43	16–24	1.01 (0.66 to 1.54) [R]	0.003
50–80 vs 6–16 mg	Mattick, 2005[64]	7	708	RCT	56	44	13–24	1.26 (1.01 to 1.56) [R]	0.04
Methadone vs LAAM									
NR vs NR	Clark, 2002[71]	4	464	RCT/CCT	73	56	12	1.64 (1.28 to 2.11) [R]	0.69
NR vs NR	Clark, 2002[71]	6	543	RCT/CCT	54	36	24–48	1.25 (0.91 to 1.73) [R]	<0.0001
≥50 vs 65–80 mg (×3/week)	Farre, 2002[55]	3	524	RCT	49	39	15–40	OR 1.92 (1.31 to 2.81)	0.0008
50–100 vs 30–80 mg	Glanz, 1997[49]	11	1442	RCT	NR	NR	3–52	RD 0.11 (0.03 to 0.19) [R]	<0.05
26–100 vs 36–115 mg (×3/week)	Johansson, 2003[61]	9	1043	RCT/CCT	NR	NR	3–52	*d* 0.34 (0.22 to 0.46) [F]	>0.05
NR vs 2 × 1 mg/mg methadone or 3 × 2.2 mg/mg methadone	Layson-Wolf, 2002[57]	1	NR	CCT	NR	NR	NR	M = L	NA
Buprenorphine vs LAAM									
16–32 vs 75–115 mg	Raisch, 2002[66]	1	110	RCT	NR	NR	17	B = L	NA
Methadone vs naltrexone									
	Kirchmayer, 2003[73]	1	60	RCT	NR	NR	NR	M > N	NA
	Johansson, 2003[61]	1	60	CCT	87	27	12	M > N	NA
	Mattick, 2005[64]	1	204	RCT	84	21	24	RR 4.0, $p < 0.0001$	NA
Methadone vs heroin									
10–120 vs 30–120 mg	Ferri, 2005[76]	1	96	RCT	25	70	52	0.35 (0.21 to 0.59)[a]	NA
Methadone alone vs methadone + heroin (oral + inhaled)									
NR vs NR	Ferri, 2005[76]	2	428	RCT	87	70	24–52	0.24 (1.11 to 1.38) [F][a]	0.35
Methadone alone vs methadone + psychosocial therapy									
	Fridell, 2003[72]	6	739	RCT	NR	NR	12–52	*d* 0.13 (–0.24 to 0.51) [R][a]	0.009
	Amato, 2004[74]	8	510	RCT	79	77	NR	1.06 (0.98 to 1.18)	0.11

continued

TABLE 37 *Proportion of individuals retained in treatment (cont'd)*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (weeks)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone fast induction (1 day) vs methadone slow induction (14 days)									
	Layson-Wolf, 2002[57]	1	NR	CCT	43	39	52	Non-statistically significant difference	NR
Methadone outpatient vs specialist clinic									
	Johansson, 2003[61]	2	119	RCT/CCT	NR	NR	26–52	OP = S	NR
Buprenorphine vs naltrexone									
	Mattick, 2005[64]	1	204	RCT	59	21	24	RR 2.81, $p < 0.0001$	NA

B, buprenorphine; CCT, comparative controlled trial; *d*, effect size; [F], fixed-effects meta-analysis; L, LAAM; M, methadone; N, naltrexone; NA, not applicable; NR, not reported; OP = S, opiate abuse in 2 groups was the same; OR, odds ratio; [R], random-effects meta-analysis; RD, risk difference.

[a] Meta-analysis undertaken by the present authors.

TABLE 38 *Self-reported opioid use*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (weeks)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone vs placebo/no treatment									
60 mg vs no therapy	Gowing, 2004[63]	1	256	RCT	25	81	16	0.31 (0.23 to 0.42)	NA
40–80 mg vs no therapy	Gowing, 2004[63]	7	1746	BA			8–24	0.31 to 0.60[b]	NA
NR	Sorensen, 2000[52]	3	3236	BA			3–12	3/3 positive	NA
23–80 mg	Prendergast,2000[51a]	11	NR	RCT/CCT/ BA	NR	NR	NR	Mean effect size 0.78[c]	NR
≥50 mg	Farre, 2002[55]	2	347	RCT	61	74	15	0.82 (0.69 to 0.98)[d]	NA
35–97 mg vs no treatment	Johansson, 2003[61]	7	1046	RCT/CCT	NR	NR	6–152	*d* 0.65 (0.41 to 0.89) [R][b]	<0.05
Buprenorphine vs placebo/no therapy									
≤ 5 mg	Mattick, 2005[64]	5	1131	RCT	60	39	16–24	1.50 (1.19 to 1.88) [R]	0.007
6–16 mg	Mattick, 2005[64]	4	887	RCT	65	38	17–52	1.74 (1.06 to 2.87) [R]	<0.0001
Methadone dosages									
High (≥50) vs low (<50 mg)	Farre, 2002[55]	5	942	RCT	50	64	15–40	0.82 (078 to 0.95) [R][d]	0.765[d]
80–100 vs 50 mg	Johansson, 2003[61]	3	478	RCT/CCT	NR	NR	24–40	*d* 0.28 (0.10 to 0.46) [F][b]	>0.05
5–80 vs 20–45 mg	Johansson, 2003[61]	8	892	RCT/CCT	NR	NR	15–52	*d* 0.36 (0.23 to 0.49) [F][b]	>0.05
Buprenorphine doses									
16 vs 8 mg	Johansson, 2003[61]	1	370	RCT	NR	NR	16	*d* 0.10 (–0.10 to 0.30)[c]	NA
8–16 vs 1–4 mg	Johansson, 2003[61]	6	1559	RCT	NR	NR	2–24	*d* 0.25 (0.15 to 0.35) [F][c]	>0.05
Methadone vs buprenorphine									
20–100 vs 8–32 mg	Raisch, 2002[66]	3	NR	RCT	NR	NR	NR	2 studies M = B 1 study M > B	NA
≥50 vs <8 mg	Farre, 2002[55]	2	148	RCT	NR	NR	24	0.29 (0.16 to 0.53)	NR
≥50 vs ≥8 mg	Farre, 2002[55]	4	335	RCT	NR	NR	17–24	0.93 (0.63 to 1.33)	NR
<50 vs ≥8 mg	Simoens, 2005[65]	4	NR	RCT	NR	NR	NR	1 M > B, 1 M = B, 2 B > M	NR
<50 vs <8 mg	Simoens, 2005[65]	3	NR	RCT	NR	NR	NR	2/3 M > B, 1/3 M = B	NR
≥50 vs ≥8 mg	Simoens, 2005[65]	3	NR	RCT	NR	NR	NR	1 M > B, 2 M = B	NR
≥50 vs <8 mg	Simoens, 2005[65]	3	NR	RCT	NR	NR	NR	3/3 M > B	NR
Flexible vs flexible	Simoens, 2005[65]	1	NR	RCT	NR	NR	NR	1/1 M = B	NR
20–100 vs 2–12 mg	Johansson, 2003[61]	6	648	RCT/CCT	NR	NR	NR	0.13 (–0.03 to 0.28) [F]	>0.05

continued

TABLE 38 *Self-reported opioid use (cont'd)*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (weeks)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone vs LAAM									
≥50 vs 65–80 mg (×3)	Farre, 2002[55]	2	464	RCT	26	23	15–40	1.38 (0.91 to 2.17)	NR
50–100 vs 30–90 mg	Glanz, 1997[49]	10	1382	RCT			3–52	RD 0.02 (–0.03 to 0.08) [R]	<0.05
26–100 vs 36–115 mg (×3/week)	Johansson, 2003[61]	9	996	RCT/CCT	NR	NR	3–52	*d* –0.06 (–0.19 to 0.06) [F]	>0.05
Buprenorphine vs LAAM									
16–32 vs 75–115 mg	Raisch, 2002[66]	1	110	RCT	NR	NR	17	B = L	NA
Methadone vs heroin									
60 vs 60 mg	Johansson, 2003[61]	1	52	RCT/CCT	59	64	52	M = N	NA
Methadone vs naltrexone									
NR vs NR	Kirchmayer, 2003[73]	1	60	RCT	NR	NR	NR	1/1 M = N	NA
NR vs NR	Johansson, 2003[61]	1	60	CCT	50	50	12	M = N	NA
Contingency management + methadone vs methadone alone									
	Johansson, 2003[61]	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[72]	9	1227	RCT	NR	NR	12–52	*d* 0.21 (0.08 to 0.35)[f]	0.095

Abbreviations as in *Table 37*, plus BA, before-and-after; H, heroin; B = L, opiate abuse in the 2 groups the same; B > M, level of opiate abuse in buprenorphine group lower than methadone group; M > B, level of opiate abuse in methadone group lower than buprenorphine group; 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.

[a] Included self-reported and measured opioid use.

[b] Pooling not performed due to observational nature of evidence.

[c] Effect size: Hedges *g* or *d*.

[d] Calculated by the present authors.

TABLE 39 *Urine-confirmed opioid abstinence*[a]

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Duration of follow-up (months)	Mean difference (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone dosages							
60–109 vs 1–39 mg	Faggiano, 2003[60]	3	237	RCT	At >3–4 weeks	RR 1.59 (1.16 to 2.18–2.00) [F]	0.001
60–109 vs 40–59 mg	Faggiano, 2003[60]	1	59	RCT	At >3–4 weeks	RR 1.51 (0.63 to 3.61) [F]	NA
Methadone vs burprenorphine							
50–80 vs 8–12 mg	Barnett, 2001[68]	4	488	RCT	NR	0.083 (0.027 to 0.140) [F]	0.074
20–80 vs 2–8 mg	West, 2000[53]	9	995	RCT/CCT	1.5–12	$d = -0.0921$[b], NS	<0.001
35–65 vs 2–6 mg	Layson-Wolf, 2002[57]	1	NR	CCT	6	M > B, $p < 0.0003$	NR
20 vs 16–48 mg	Layson-Wolf, 2002[57]	1	220	RCT	4	B > M, $p < 0.005$	NR
60–100 vs 16–48 mg	Layson-Wolf, 2002[57]	1	220	RCT	4	M = B	NR
Methadone vs LAAM							
20 vs 16–48 mg	Layson-Wolf, 2002[57]	1	220	RCT	4	L > M, $p < 0.005$	NA
60–100 vs 16–48 mg	Layson-Wolf, 2002[57]	1	220	RCT	4	M = L	NA
Methadone vs methadone + reinforcement strategies[c]							
	Griffith, 2000[70]	30	NR	RCT/CCT	NR	Weighted Z 0.25 (0.20 to 0.30)[d], $p < 0.001$	<0.001
Methadone + psychosocial therapy vs methadone alone							
	Amato, 2004[74]	5	388	RCT	NR	RR 1.45 (1.10 to 1.88)	0.18

Abbreviations as in *Table 37*, plus L > M, LAAM better than methadone; M > B, methadone better than buprenorphine; NS, not significant.
[a] Proportion of urinalyses that test positive.
[b] Very small effect size.
[c] Includes changes in methadone dose, methadone take homes, vouchers.
[d] Positive vs MMT + reinforcement > MMT alone.

TABLE 40 *All-cause mortality*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (months)	RR (95% CI)	Hetero-geneity test (*p*-value)
Methadone vs placebo									
NR	Mattick, 2003[62]	3	435	RCT	1.4	3.2	12.5	0.49 (0.06 to 4.23) [R][a]	0.14
NR	Caplehorn, 1996[48]	5	3618+	CCT	NA	NA	6–252	Rate ratio[b] 0.25 (0.19 to 0.33) [R][a]	>0.75
Burprenorphine vs placebo									
16 mg	Lintzeris and Ford, 2004 (unpublished)	1	40	RCT	0	20	12	0.05 (0 to 0.79)[a]	NA
Burprenorphine vs methadone									
NR	Lintzeris and Ford, 2004 (unpublished)	2	NR	CS	NR	NR	3–5 years	B < M	NR
Methadone vs LAAM									
Flexible	Clark, 2002[71]	4	1008	RCT/CCT	0.2	0.9	10–12	0.43 (0.11 to 1.69) [F]	0.61
Methadone vs heroin									
20–120 vs 30–120 mg	Ferri, 2005[76]	1	96	RCT	1.9	4.5	12	0.42 (0.04 to 4.51)[a]	NA
Methadone vs methadone + heroin									
NR vs NR	Ferri, 2005[76]	1	174	RCT	1.3	1.0	12	1.2 (0.1 to 20.2)[a]	NA

Abbreviations as in *Table 37*, plus B < M statistically fewer deaths in buprenorphine than methadone-treated individuals; CS, cross-sectional studies.
[a] Meta-analysis undertaken by the present authors.
[b] Based on person-years of exposure.

TABLE 41 *Overdose mortality*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment deaths (%)	Control deaths (%)	Duration of follow-up (months)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone dosages									
>75 vs 5–55 mg	Faggiano, 2003[60]	1	1138	CCT	0	5	72	0.29 (0.02 to 5.34)	NA
>75 vs 55–70 mg	Faggiano, 2003[60]	1	678	CCT	0	3	72	0.38 (0.02 to 9.34)	NA
55–70 vs 5–55 mg	Faggiano, 2003[60]	1	1184	CCT	3	5	72	0.57 (0.06 to 5.06)	NA

Abbreviations as in *Table 37*.

TABLE 42 *Discontinuation due to side-effects*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (months)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone vs LAAM	Glanz, 1997[49]	4	1160	RCT	NR	NR	8–10	RD 0.04 (0.02 to 0.05) [F]	>0.05
Abbreviations as in *Table 37*.									

TABLE 43 *Serious adverse events*[a]

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (months)	RR (95% CI)	Hetero-geneity test (*p*-value)
Methadone vs placebo	Mattick, 2003[62]	2	335	RCT	7.6	13.0	6–12	0.59 (0.33 to 1.04) [F][b]	0.24
Abbreviations as in *Table 37*. [a] Self-reported adverse events during course of study. [b] Meta-analysis undertaken by the present authors.									

TABLE 44 *Suicide attempts*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment deaths (%)	Comparator (%)	Duration of follow-up (months)	RR (95% CI)	Hetero-geneity test (*p*-value)
Methadone vs heroin 60 vs 60–480 mg (oral/i.v.)	Johnansson, 2003[61]	1	51	RCT/CCT	19	4	26	M > H	NA
Abbreviations as in *Tables 37* and *38*, plus M >H, more suicide attempts with methadone than heroin.									

TABLE 45 *Opioid poisonings*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (months)	RR (95% CI)	Hetero-geneity test (*p*-value)
Buprenorphine vs methadone									
NR vs NR	Lintzeris and Ford, 2004 (unpublished)	1	NR	CS	NR	NR	5 years	B > M	NA

Abbreviations as in *Tables 37* and *40*, plus B > M, more poisoning with buprenorphine than morphine.

TABLE 46 *NEPOD adverse events (per 100 patient-years) – pooled RCT*[a]

	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**

SAE, serious adverse event.
[a] Based on the NEPOD[111] report reviewed by Lintzeris and Ford, 2004 (unpublished).

TABLE 47 *Criminal activity – mean number of crimes per week*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Mean difference[a] (95% CI)	Heterogeneity test (*p*-value)
Methadone dosages						
60–109 vs 40–59 mg	Faggiano, 2003[60]	1	59	RCT	0.05 (–0.03 to 0.13)	NA

[a] WMD unless indicated otherwise.

TABLE 48 *Self-reported or objective measures of crime*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%) or mean (SD)	Comparator (%) or mean (SD)	Duration of follow-up (weeks)	Effect size (95% CI) RR (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone vs placebo/no treatment									
	Mattick, 2003[62]	3	363	RCT	3	12	50	0.39 (0.12 to 1.25) [R]	0.28
	Prendergast, 2000[51]	11	NR	RCT/CCT/BA	NR	NR	NR	Mean effect size: 0.54[a]	NR
	Marsch, 1998[50]	24	6994	CCT/BA	NR	NR	1–624	0.70 ("large effect")[b]	0.001
Methadone vs heroin									
10–120 vs 30–120 mg	Ferri, 2005[76]	1	88	RCT	65	43	52	1.01 (0.74 to 1.38)[c]	NA
Methadone vs buprenorphine									
Flexible vs flexible									
	Mattick, 2005[64]	1	212	RCT	0.6 (1.3)	0.5 (1.0)	13	SMD 0.14 (–0.14 to 0.41)	NA

Abbreviations as in *Tables 37* and *38*.
[a] Hedges *g*.
[b] Effect size: *r*-value.
[c] Analysis by the present authors.

TABLE 49 *HIV risk behaviours/risk score*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Duration of follow-up (months)	Effect size [*r*-value] Mean (*p*-value)	Hetero-geneity test (*p*-value)
Methadone vs placebo/no treatment							
	Marsch, 1998[50]	8	1756	CCT or BA or ITS	1–232	0.21 ("small to moderate effect")	0.78
	Gowing, 2004[63]	4		BA	2–9	All studies show reduction in HIV risk score ($p < 0.01$)	NA
	Sorensen, 2000[52]	20	14780	BA/CS	3–103	20/20 M > no Rx	NA

Abbreviations as in *Table 37*, plus BA, before-and-after; CS, cross-sectional studies; ITS, interrupted time series; M > no Rx, methadone better outcome than no treatment.

TABLE 50 *Multiple sex partners (self-report)*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Duration of follow-up (months)	RR (mean range)	Heterogeneity test (*p*-value)
Methadone vs placebo/no treatment							
	Gowing, 2004[63]	4	1029	BA	6–124	0.39–1.40	NA
BA, before-and-after.							

TABLE 51 *Unprotected sex (self-report)*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Duration of follow-up (months)	RR (mean range)	Heterogeneity test (*p*-value)
Methadone vs placebo/no treatment							
	Gowing, 2004[63]	6	1544	BA	6–124	0.46–1.05	NA
BA, before-and-after.							

TABLE 52 *HIV seroconversion*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Duration of follow-up (months)	Seroconversion rate[a]	Heterogeneity test (*p*-value)
Methadone vs placebo/no treatment							
	Sorensen, 2000[52]	5	17984	BA/CS	12–53	12–53	NA
	Gowing, 2004[63]	5	1029	BA or CC or CCT	6–124	3/100 vs 5/1000 per year 1.4 vs 3.1% per patient-year 0.7 vs 4.3 per year	NA
Abbreviations as in *Tables 37* and *38*, plus CC, case–control; CS, cross-sectional. [a] Individual study results (MMT vs control reported).							

TABLE 53 *Employment*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (months)	RR (95% CI)	Hetero-geneity test (*p*-value)
Methadone vs heroin									
NR vs NR	Ferri, 2005[76]	1	88	RCT	50	43	1	1.22 (0.77 to 1.93)[a], M = H	NA
NR vs 480 mg i.v.	Johansson, 2003[61]	1	51	RCT/CCT	14	22	6		NA

Abbreviations as in *Tables 37* and *38*.
[a] Calculation by the present authors.

TABLE 54 *Neonatal mortality*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (months)	RR (95% CI)	Hetero-geneity test (*p*-value)
Methadone[a] vs no therapy									
	Hulse, 1998[43]	3	1983	NR	3.3	1.7	NR	1.75 (0.60 to 4.59)	>0.05

[a] During pregnancy.

TABLE 55 *Retention in treatment: number of weeks*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Mean difference (95% CI) (unless indicated otherwise)	Heterogeneity test (*p*-value)
Methadone dosages						
60–109 vs 1–39 mg	Faggiano, 2003[60]	3	237	RCT	3.54 (2.19 to 4.89) [F]	0.0005
60–109 vs 40–59 mg	Faggiano, 2003[60]	1	59	RCT	–0.30 (–0.77 to 0.17) [F]	NA
Methadone vs buprenorphine						
35–60 vs 2–6 mg	Layson-Wolf, 2002[57]	1	NR	CCT	4 (NR), $p < 0.005$	NA

Abbreviations as in *Table 37*.

TABLE 56 *Opioid use (self-reported: times per week)*

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

TABLE 57 *Opioid use (self-reported: mg per week)*

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

TABLE 58 *Opioid abstinence score*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Duration of follow-up (weeks)	Mean difference (95% CI) (unless indicated otherwise)	Heterogeneity test (*p*-value)
Methadone dosages							
60–109 vs 1–39 mg	Faggiano, 2003[60]	3	337	RCT	>3–4	1.59 (1.16 to 2.18) [F]	0.001
60–109 vs 40–59 mg	Faggiano, 2003[60]	1	59	RCT	>3–4	1.51 (0.63 to 3.61)	NA
Abbreviations as in *Table 37*.							

TABLE 59 *Illicit drug use (self-reported and objective)*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Duration of follow-up (weeks)	Mean difference (unless indicated otherwise)	Heterogeneity test (*p*-value)
Methadone vs placebo/no treatment							
NR mg/day	Marsch, 1998[50]	11	1930	CCT/BA	1–624	$r = 0.35$ (“moderate effect”)	0.53
Abbreviations as in *Tables 37* and *38*.							

TABLE 60 *Injecting use (self-reported)*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (weeks)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone vs placebo/no treatment									
	Gowing, 2004[63]	1	253	RCT	20	54	16	0.37 (0.26 to 0.55)	NA
	Gowing, 2004[63]	7	1700	BA	NR	NR	16–56	0.25 to 0.78[a]	NA
	Sorensen, 2000[52]	9	14780	BA/CS	NR	NR	3–108	8/9 positive studies	NA

Abbreviations as in *Tables 37, 38* and *52*.
[a] Pooling not performed due to observational nature of evidence. BA before & after CC case control CS cross sectional; NR not reported.

TABLE 61 *Sharing injecting equipment*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Duration of follow-up (weeks)	RR (95% CI) (unless indicated otherwise)	Heterogeneity test (*p*-value)
Methadone vs placebo/no treatment							
	Gowing, 2004[63]	1	253	RCT	16	0.45 (0.35 to 0.59)	NA
	Gowing, 2004[63]	7	1491	BA	16–56	Range 0.39 to 0.75[a]	NA

Abbreviations as in *Table 37*.
[a] Pooling not performed due to observational nature of evidence.

TABLE 62 *Morphine-positive urine samples*

Comparison Daily dose (unless indicated otherwise)	Study	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)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Buprenorphine vs placebo/no therapy									
≤5 mg	Mattick, 2005[64]	2	487	RCT	NA	NA	2–16	SMD 0.10 (–0.80 to 1.01) [R]	<0.0001
6–12 mg	Mattick, 2005[64]	2	463	RCT	NA	NA	2–16	SMD –0.28 (–0.47 to –0.10) [R]	0.004
8 mg	Mattick, 2005[64]	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[62]	1	169	RCT	29	60	NR	0.59 (0.39 to 0.87)[a]	NA
Methadone vs buprenorphine									
Flexible vs flexible	Mattick, 2005[64]	6	837	RCT	NA	NA	6–24	SMD 0.12 (–0.02 to 0.26) [F]	0.66
≤35 vs ≤5 mg	Mattick, 2005[64]	1	59	RCT	34 (15)	29 (13)	24	SMD 0.35 (–0.16 to 0.87)	NA
50–80 vs ≤5 mg	Mattick, 2005[64]	1	57	RCT	19 (9)	25 (13)	24	SMD –0.88 (–1.42 to –0.33)	NA
≤35 vs 6–16 mg	Mattick, 2005[64]	3	317	RCT	NA	NA	17–52	SMD 0.31 (–0.11 to 0.72) [R]	0.04
50–80 vs 6–16 mg	Mattick, 2005[64]	3	314	RCT	NA	NA	17–52	SMD –0.25 (–0.75 to 0.25)	0.01

Abbreviations as in *Table 37*.
[a] Meta-analysis undertaken by the present authors.

TABLE 63 *Heroin-positive urine samples*

Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of patients	Type of studies	Treatment-positive patients (%)	Control-positive patients (%)	Duration of follow-up (weeks)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone vs LAAM									
NR vs NR	Clark, 2002[71]	8	262	RCT/CCT	24	21	13–52	1.14 (0.95 to 1.38) [F]	0.34

Abbreviations as in *Table 37*.

TABLE 64 *Self-reported heroin use*

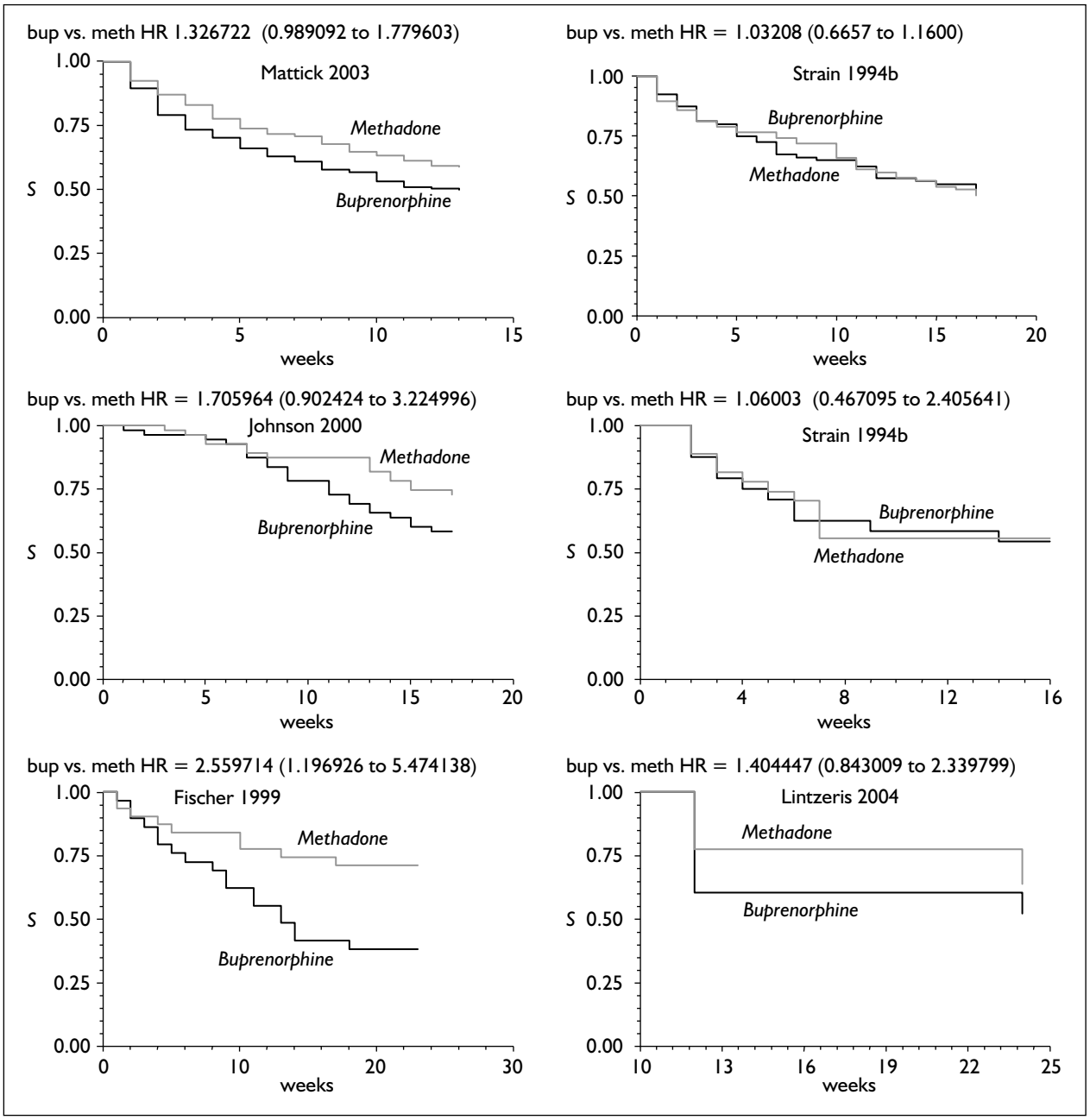
Comparison Daily dose (unless indicated otherwise)	Study	No. of studies	No. of individuals	Type of studies	Treatment (%)	Comparator (%)	Duration of follow-up (weeks)	RR (95% CI) (unless indicated otherwise)	Hetero-geneity test (*p*-value)
Methadone vs buprenorphine									
Flexible vs flexible	Mattick, 2005[64]	3	420	RCT	NA	NA	13–26	SMD 0.12 (–0.07 to 0.31) [F]	0.76
≤35 vs ≤5 mg	Mattick, 2005[64]	1	37	RCT	6.8 (4.3)	8.1 (4.5)	24	SMD –0.29 (–0.96 to 0.38)	NA
50–80 vs ≤5 mg	Mattick, 2005[64]	1	35	RCT	8.4 (4.6)	8.1 (4.5)	24	SMD –0.06 (–0.61 to 0.74)	NA
≤35 vs 6–16 mg	Mattick, 2005[64]	1	34	RCT	6.8 (4.3)	9.9 (5.0)	24	SMD –0.67 (–1.41 to 0.07)	NA
50–80 vs 6–16 mg	Mattick, 2005[64]	2	72	RCT	NA	NA	24	SMD 0.03 (–0.45 to 0.50)	0.24
Methadone vs heroin									
10–120 vs 30–120 mg	Ferri, 2005[76]	1	88	RCT	58	64	52	0.91 (0.66 to 1.27)[a]	NA
NR vs 480 mg (i.v.)	Johnansson, 2003[61]	1	51	RCT/CCT	2	48	26	H > M	NR

Abbreviations as in *Tables 37* and *38*, plus H > M, heroin better than methadone.
[a] Analysis by the present authors.

Appendix 10

Retention in treatment (individual studies, flexible dosing)

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



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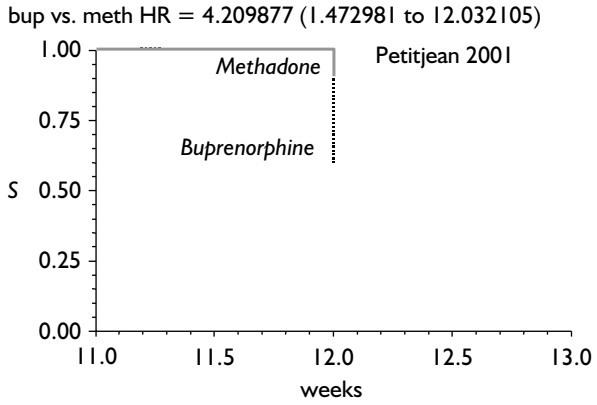
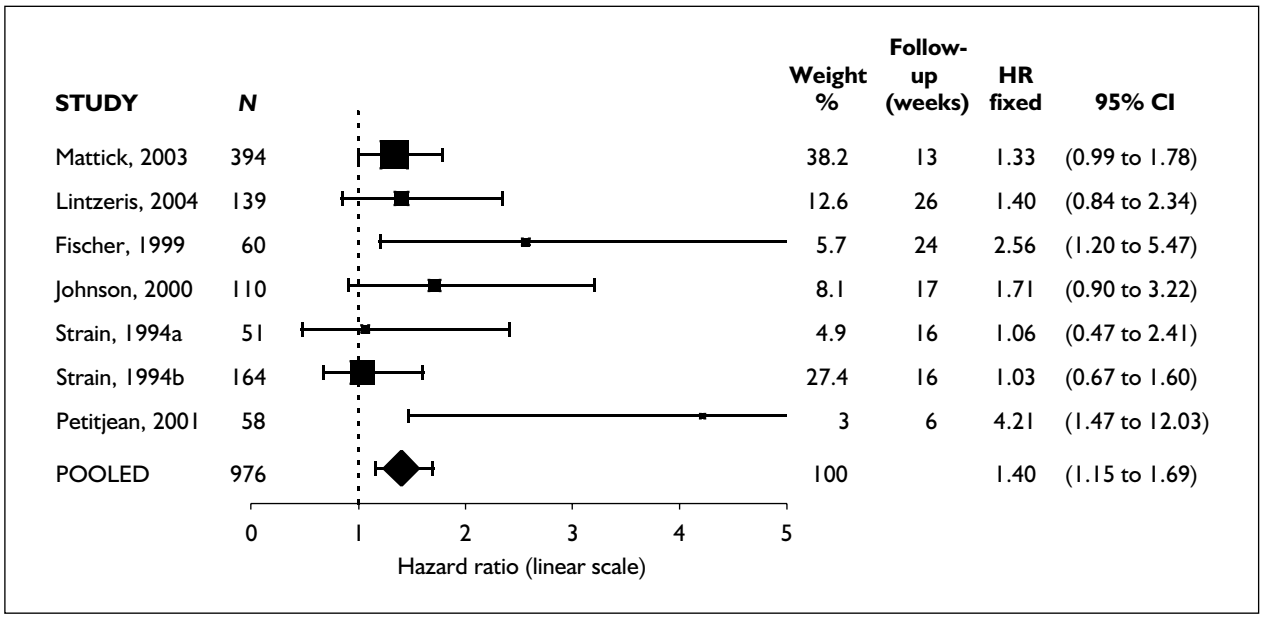


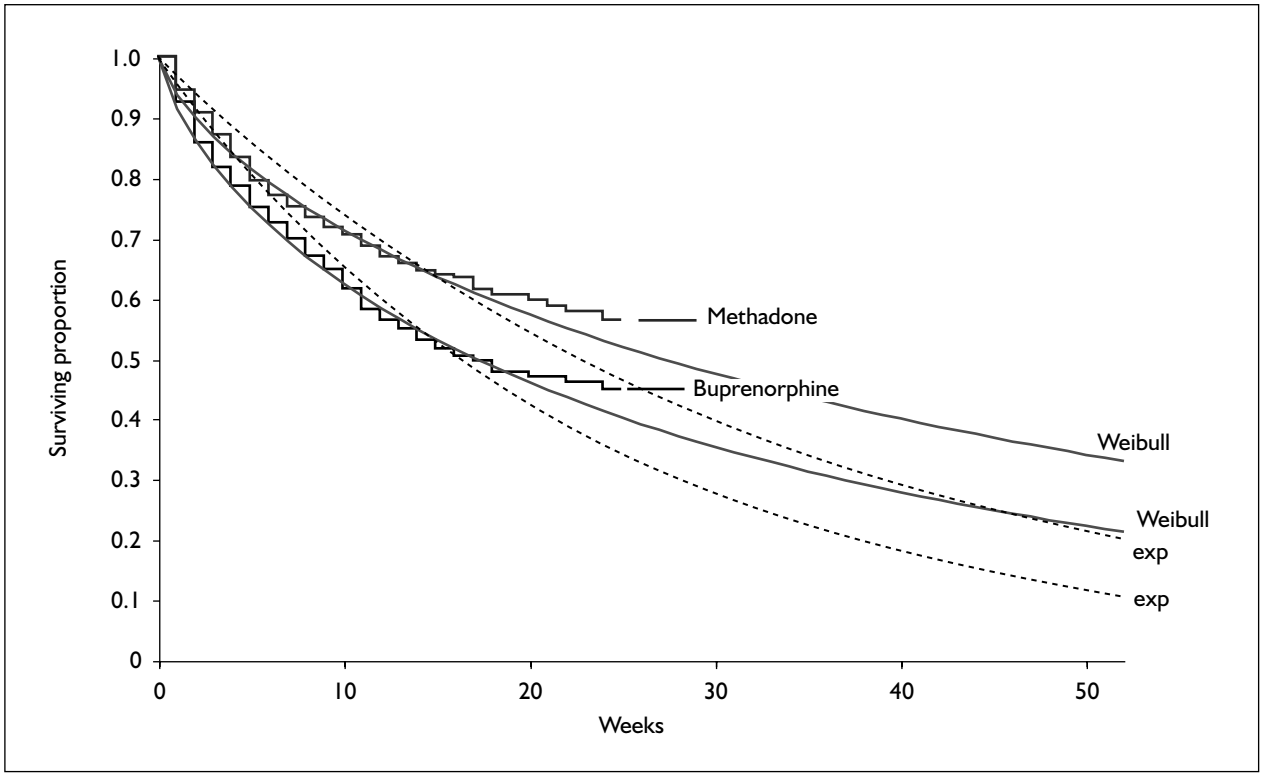
	Buprenorphine group				Methadone group			
Time	**At risk**	**Dead**	**Censored**	***S***	**At risk**	**Dead**	**Censored**	***S***
Mattick, 2003[105]								
1	192	20	0	0.895833	202	15	0	0.925743
2	172	20	0	0.791667	187	11	0	0.871287
3	152	11	0	0.734375	176	8	0	0.831683
4	141	6	0	0.703125	168	11	0	0.777228
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[109]								
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[110]								
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

continued

	Buprenorphine group				Methadone group			
Time	**At risk**	**Dead**	**Censored**	***S***	**At risk**	**Dead**	**Censored**	***S***
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
Fischer, 1999[108]								
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[104]								
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[107]								
12	73	29	0	0.60274	66	15	0	0.772727
24	44	6	38	0.520548	51	9	42	0.636364
Petitjean, 2001[106]								
12	27	11	16	0.592593	31	3	28	0.903226



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



Appendix 11

Table of excluded studies with rationale

TABLE 65 *List of studies excluded from review of systematic reviews*

Reference	Reason for exclusion
Aavitsland, 1998[169]	No search strategy
Office of Technology Assessment, 1990[170]	No search strategy
Anonymous, 1996[171]	No search strategy
Boyarsky and Cance-Katz, 2000[172]	No search strategy
Brewer *et al*., 1998[173]	No description of intervention and comparator
Chapleo, 1997[174]	No search strategy
Doran *et al*., 2005[175]	No search strategy. Review of reviews
Fischer *et al*., 2005[176]	No search strategy. Review of reviews
Gruen *et al*., 2003[177]	No appropriate population
Hermstad *et al*., 1998[178]	Foreign language
Johnson, 1997[179]	No search strategy
Kreek, 1997[180]	No search strategy
Maddux *et al*., 1980[181]	Primary study
Perry *et al*., 2005[182]	Protocol only
Prendergast *et al*., 2001[183]	No intervention
Rayburn and Bogenschutz, 2004[184]	No search strategy
van den Brink and van Ree, 2003[185]	No search strategy
Walter, 1997[186]	No search strategy
Weinmann *et al*., 2004[187]	Foreign language
Wingood and DiClemente, 1996[188]	No intervention
Medical-Technology, 2000[189]	Full text not obtainable

TABLE 66 *Excluded studies from potential RCTs*

Reference	Reason for exclusion
Ahmadi and Ahmadi, 2003[190]	Already in SR (Mattick, 2005[64])
Ahmadi *et al*., 2003[191]	Superseded by Ref. 190
Ahmadi and Ahmadi, 2004[192]	Already in SR (Mattick, 2005[64])
Ahmadi and Bahrami 2002[193]	Already in SR (Mattick, 2005[64])
Ahmadi, 2002[194]	Already in SR (Mattick, 2005[64])
Ahmadi, 2003[195]	Already in SR (Mattick, 2005[64])
Ahmadi, 2003[196]	Not randomised
Amass *et al*., 2001[197]	Not randomised
Annon *et al*., 2001[198]	Abstract
Batki *et al*., 2002[199]	Inappropriate outcomes
Buydens-Branchey *et al*., 2005[200]	Not maintenance
Carpenter *et al*., 2004[201]	Abstract
Carpenter *et al*., 2002[202]	Mixed population, alcohol or illicit drug users
Clark *et al*., 2002[203]	Abstract
Clark *et al*., 2001[204]	Abstract
Coviello *et al*., 2004[205]	Report duplicate of Zanis, 2001[84]
Cunningham *et al*., 2001[206]	Abstract
Curran *et al*., 2001[207]	Not maintenance
Dawe, 2001[208]	Abstract
Dean *et al*., 2004[209]	Not HRQoL, secondary analysis of old study
Doran *et al*., 2004[210]	Economic study
Dürsteler-MacFarland *et al*., 2002[211]	Abstract

continued

TABLE 66 *Excluded studies from potential RCTs (cont'd)*

Reference	Reason for exclusion
Eder *et al*., 2002[212]	Abstract
Epstein *et al*., 2003[213]	Abstract
Fiellin *et al*., 2001[214]	Already in SR (Simoens, 2005[65])
Fudala *et al*., 2003[215]	Already in SR (Mattick, 2005[64])
Galanter *et al*., 2004[216]	Not maintenance
Galanter *et al*., 2004[217]	Duplicate report of ref 126, not maintenance
Gonzalez *et al*., 2003[218]	Study of prognostic factors
Greenwald, 2002[219]	Abstract
Gross *et al*., 2001[220]	Not maintenance; not randomised
Jiang *et al*., 2003[221]	Not randomised, abstract inconsistent with text; not maintenance
Jones *et al*., 2004[222]	Inappropriate outcomes; neonate abstinence syndrome
Jones *et al*., 2005[223]	Switch pharmacotherapy and doubts about randomisation
Jones *et al*., 2005[224]	Inappropriate outcomes
Kakko *et al*., 2003[225]	Already in SR (Mattick, 2005[64])
King *et al*., 2002[226]	Abstract only
Kosten *et al*., 2003[227]	Secondary analysis of old study
Krook *et al*., 2002[228]	Already in SR (Mattick, 2005[64])
Lintzeris *et al*., 2004[229]	Already in SR (Mattick, 2005[64])
Lofwall *et al*., 2004[230]	Superseded by Lofwall, 2005[83]
Mattick *et al*., 2003[231]	Already in SR (Mattick, 2005[64])
Maxwell *et al*., 2002[232]	Not randomised
Mitchell *et al*., 2002[233]	Abstract
Mitchell *et al*., 2004[234]	Switch prior to randomisation
Montoya *et al*., 2004[235]	Already in SR (Lintzeris and Ford 2004)
Neri *et al*., 2005[236]	Inappropriate outcomes; immune system measures
Newcombe *et al*., 2004[237]	Inappropriate outcomes
Petitjean *et al*., 2001[238]	Already in SR (Mattick, 2005[64])
Petry *et al*., 2001[239]	Abstract
Petry and Martin, 2002[240]	Already in SR (Simoens, 2005[65])
Petry *et al*., 2001[241]	Already in SR (Simoens, 2005[65])
Pollack *et al*., 2001[242]	Abstract
Preston *et al*., 2002[243]	Already in SR (Simoens, 2005[65])
Primorac *et al*., 2004[244]	Abstract
Ritter *et al*., 2001[245]	Abstract
Ritter *et al*., 2002[246]	Abstract
Schottenfeld *et al*., 2005[247]	Study of prognostic factors
Schwartz *et al*., 2003[248]	Abstract
Suchman *et al*., 2004[249]	Inappropriate outcomes; study of prognostic factors
Silverman *et al*., 2004[250]	Mixed population; emphasis on cocaine abusers
Sullivan *et al*., 2005[251]	Not randomised
Triffleman, 2001[252]	Abstract
van den Brink *et al*., 2003[103]	Already in SR (Ferri, 2005[76])
White *et al*., 2001[253]	Abstract
Woody *et al*., 2001[254]	Abstract

SR, systematic review.

Appendix 12

Health states and results from PenTAG

Details are given in *Table 67*.

Health state scenarios

Assume on treatment

1. Drugs free
   (a) You may have difficulty getting off to sleep.
   (b) You have no pain or discomfort.
   (c) You hardly ever feel tired.
   (d) Your condition does not affect your work life.
   (e) You will have to develop a new group of friends.
   (f) You hardly ever have problems concentrating.
   (g) You may have reduced libido or an irregular menstrual cycle.
   (h) You will have to collect medication from your community pharmacy at least once a week and possibly every day.
2. Drugs reduction (injectors)
   (a) You may have difficulty getting off to sleep.
   (b) 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.
   (c) You hardly ever feel tired.
   (d) You may find it difficult to obtain and hold down a job. You might incur debts that you find difficult to pay.
   (e) You may find it difficult to be punctual and reliable, leading to disagreements with family and friends.
   (f) You hardly ever have problems concentrating.
   (g) You may have reduced libido or an irregular menstrual cycle.
   (h) 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)
   (a) You may have difficulty getting off to sleep. You may have occasional pain and discomfort, sweats and shakes.
   (b) You may experience chest infections and shortness of breath.
   (c) You hardly ever feel tired.
   (d) You may find it difficult to obtain and hold down a job. You might incur debts that you find difficult to pay.
   (e) You may find it difficult to be punctual and reliable, leading to disagreements with family and friends.
   (f) You may be unable to concentrate due to being constantly preoccupied with your problems.
   (g) You may have reduced libido or an irregular menstrual cycle.
   (h) 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)
   (a) You may experience moderate anxiety or low mood on most days. You may have difficulty in getting off to sleep.
   (b) 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

TABLE 67 *Health states and utilities derived from the Value of Health Panel*

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

disease. You may suffer from loss of appetite, weight loss and dental problems.
(c) You hardly ever feel tired.
(d) You may find it difficult to obtain and hold down a job. You might incur debts that you find difficult to pay.
(e) You may find it difficult to be punctual and reliable, leading to disagreements with family and friends.
(f) You hardly ever have problems concentrating.
(g) You may have reduced libido or an irregular menstrual cycle.
(h) 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)
(a) You may experience moderate anxiety or low mood on most days. You may have difficulty getting to sleep.
(b) You may experience moderate pain or discomfort, sweats and shakes on most days. You may experience chest infections and shortness of breath.
(c) You hardly ever feel tired.
(d) You may find it difficult to obtain and hold down a job. You might incur debts that you find difficult to pay.
(e) You may find it difficult to be punctual and reliable, leading to disagreements with family and friends.
(f) You hardly ever have problems concentrating.
(g) You may have reduced libido or an irregular menstrual cycle.
(h) 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

Database 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	Period	Country	Patients recruited	Designed number	Comparison
A pilot study of a motivational intervention to help opiate-dependent patients on methadone who drink excessively	Complete	January 2001–January 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	NA	NR	Unclear
Do serum methadone concentrations enable optimisation of maintenance doses in opiate dependent substance mis-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 an RCT over 2 years	UK	Opiate 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 stabilisation plus lofexidine-assisted withdrawal in addicts	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

continued

Title	Trial status	Period	Country	Patients recruited	Designed number	Comparison
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 vs methadone
Randomised controlled trial to assess the effectiveness of offering prescriptions of injectable opiates to opiate-dependent 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 vs no choice of treatment received
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 vs 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 mis-users	220 opiate-dependent patients	Unclear
The effectiveness and cost-effectiveness of cognitive behaviour therapy for opiate mis-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 cognitive behaviour therapy vs standard MMT alone
The effectiveness and cost-effectiveness of cognitive behaviour therapy for opiate mis-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 cognitive behaviour therapy vs 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 patients: follow-up continuing	1/2/1998–31/1/2003 (2-stage study; the main stage is an RCT over ~2 years)	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-dependent patients	NR	Dihydrocodeine vs methadone

continued

Title	Trial status	Period	Country	Patients recruited	Designed number	Comparison
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	Unavailable	NR	UK	Opiate addicts	NR	Unclear
Evaluation of liquid vs tablet buprenorphine	Unclear	Start: August 1996. Record first received September 1999. Last updated: June 2005	USA	Opioid-related disorders	NR	Buprenorphine sublingual tablets vs sublingual solution
Buprenorphine/naloxone treatment for opioid dependence – experiment III	Unclear	Start: July 1997. Record first received July 1997. Last updated: July 2005	USA	Heroin dependence, opioid-related disorders	NR	Buprenorphine/ naloxone combination tablet vs methadone
Counselling conditions for buprenorphine in a primary care setting	Unclear	Record first received: December 2002. Last updated: June 2005	USA	Heroin dependence, opioid-related disorders/substance abuse, intravenous	NR	Standard medical management (SMM) vs SMM education about addiction and recovery (enhanced medical management, EMM)
Motivational incentive for enhanced drug abuse recovery: methadone clinics	Unclear	Start: September 2000. Data entry closure: April 2003	USA	Substance-related disorders	NR	Low vs typical incentive values of motivation

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We look forward to hearing from you.

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