NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Methadone and buprenorphine for the management of opioid dependence

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Opioid dependence can cause a wide range of health problems and is often associated with simultaneous misuse of a number of drugs (including alcohol). Opioids are a group of psychoactive substances derived from the poppy plant that includes opium, morphine, codeine, and others. The term 'opiate' is also used for the semi-synthetic drug heroin that is produced from poppy compounds. The term 'opioids' refers to opiates, and other semi-synthetic and synthetic compounds with similar properties. Heroin is the most widely misused opiate and dependence on illicit heroin can cause a number of other physical problems as a result of the spread of blood borne viruses (for example, HIV and hepatitis) and the risk of an accidental overdose. Injecting drug users may be exposed to blood-borne infections through the sharing of infected needles, syringes or other injecting paraphernalia. The mortality risk of individuals dependent on heroin is estimated to be around 12 times that of the general population. Psychiatric comorbidity is common in opioid-

dependent populations, particularly anxiety, and affective, antisocial and other personality disorders.

Associated social problems include marital and relationship breakdown, unemployment and homelessness and child neglect, often resulting in children being taken into the care system. There is also 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. However, the majority of those who steal to buy drugs were involved in crime before their drug use became a problem for them.

Biological, psychological, social and economic factors influence when and why a person starts taking opioids. Opioid use quickly escalates to misuse (repeated use with adverse consequences) and then dependence (opioid tolerance, withdrawal symptoms, compulsive drug-taking). Dependence has been defined in the Diagnostic and Statistical Manual (DSM) as a maladaptive pattern of substance use, leading to clinically significant impairment or distress. Physical and psychological dependence can develop within a relatively short period of continuous use (2–10 days), and is characterised by an overwhelming need to continue taking the drug in order to avoid withdrawal symptoms (such as sweating, anxiety, muscle tremor, disturbed sleep, loss of appetite, and raised heart rate, respiratory rate, blood pressure and temperature). The body also becomes tolerant to the effects of opioids and therefore the dose needs to be increased to maintain the effect. Getting the next dose can become an important part of each day and may take over people’s lives. 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 drug use in the first place.

When a dependent opioid user manages to become abstinent, there are usually repeated cycles of cessation and relapse, with extensive treatment

histories extending over decades. Nevertheless, some dependent users may make dramatic changes in their drug use without recourse to formal treatment. The natural histories of heroin users attending treatment services suggest 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 misuse.

National prevalence estimates, which combine local prevalence data and routinely available indicator data, suggest that in the UK problem drug use is 9.35 per 1000 of the population aged 15–64 years (360,811 people), with 3.2 per 1000 (123,498 people) injecting. The National Drug Treatment Monitoring System (NDTMS) 2004–5 estimates that there were 160,450 people in contact with treatment services in England. As a result of the lack of substitute medications for other drugs (such as crack cocaine and alcohol) the majority of these were dependent on opioids. Data suggest that approximately 70% of people newly presenting for treatment were male. There are approximately 40,000 drug misusers in prison in England and Wales at any one time. In one UK survey, 21% of prisoners had used opiates at some point during their sentence, and 10% of prisoners during the previous week.

1.2 Current management

The UK has a range of treatment services for opioid dependency. Medical and psychosocial interventions are provided in the community and criminal justice system and include inpatient, residential, day-patient and outpatient settings.

There are two broad strategies for the treatment of opiate dependence; maintenance (also known as harm reduction and a substitution regimen), and abstinence (also known as detoxification and withdrawal). In abstinence treatment for opioid drug misuse, an individual who is physically dependent on that drug stops taking it. Individuals receiving treatment may decide to become abstinent, or may initially receive maintenance therapy with a long acting opioid substitute (methadone or buprenorphine) and then progress to abstinence therapy. Maintenance of abstinence can be aided by the use of the opioid antagonist naltrexone.

Some individuals can achieve abstinence from opioids rapidly others require the support of prescribed medication for longer than a few months. An alternative to attempting to stop opioid use altogether is the maintenance approach. In maintenance therapy, the expensive illicit drug of unknown purity and quality is substituted for a pharmaceutically produced drug of more certain dose. The aim of this approach is to reduce craving and prevent withdrawal, eliminate the hazards of needles, free the individual from preoccupation with obtaining illicit opioids, enhance overall function and provide stability, therefore enabling the individual to make use of available psychosocial interventions. Substitute opioids are prescribed in doses higher than that required merely to prevent withdrawal symptoms. Following dose titration (‘induction’) a stable dose is established, based on the presence of desired clinical effects such as the elimination of craving and prevention of withdrawal symptoms, (‘maintenance’).

Maintenance programmes vary in regard to the quantity of psychosocial support delivered in addition to the medication, and in terms of the degree of supervision of methadone consumption. Substitute opioids are mainly prescribed in tier 3 settings (community and primary care prescribing programmes). Prescribing guidelines in the UK recommend that when initiating prescribing of the maintenance opioids, dose consumption should usually be supervised by a nurse, doctor or community pharmacist on a daily basis for the first 3 months of treatment. As the client who is on maintenance begins to work on major life changes, the need for daily collection and supervision may change. For prescribing to work, a number of ancillary services must meet best recommended practice. Initial assessment should include oral fluid or urine testing, and the patient may need to be seen by a doctor or specialist drug worker a number of times within the first few weeks of induction and dose titration.

Psychosocial and behavioural therapies play an important role in the treatment of drug misusers; the therapies aim to give patients the ability to resist substance use and cope with problems related to drug use. For opiate users they are often an important adjunct to pharmacological treatments. A

NICE clinical guideline due for publication in July 2007 will evaluate the place of psychosocial interventions in the treatment of drug misuse.

The government's 'Drug strategy' (2004) aims to; reduce the harm caused by illegal drugs (including treatment through the criminal justice system), increase enrolment in drug treatment programmes, and reduce the use of Class A and illicit drugs.

2 The technologies

Table 1 Summary description of methadone and buprenorphine

Generic name	Methadone	Buprenorphine
Proprietary name	Methadone (non-proprietary)	Subutex
Manufacturer	• Generics UK • Martindale Pharmaceuticals • Rosemont Pharmaceuticals • AAH Pharmaceuticals • Thornton & Ross	• Schering-Plough
Dose	10mg or greater (usually 60-120 mg per day)	0.8–32 mg
Acquisition cost excluding VAT ('British national formulary' edition 50)	£0.0135/mg	£0.48/mg

Methadone is a synthetic opioid mμ-receptor agonist with pharmacological activity similar to morphine. The summary of product characteristics (SPC) for methadone states that it is indicated for 'use in the treatment of opioid drug addictions (as a narcotic abstinence syndrome suppressant)'.

Methadone is used in opioid dependence at a dose of 10–40 mg daily, increased by 10–20 mg per week until no signs of withdrawal or intoxication are seen. The usual dose range is 60–120 mg daily, although larger doses

may also be employed. Methadone is available as a tablet, oral solution or injectable ampoules. Only oral methadone is considered in this appraisal.

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 it 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 10–80 hours). For comparison, the half-life for morphine is 3 hours. The liver is the main site for the breakdown of methadone, and it is eliminated in the form of the metabolites and by excretion of the drug itself in urine and faeces.

Methadone administered orally 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. In stabilised methadone maintenance patients, methadone does not have the pronounced narcotic effects seen with shorter-acting opioids such as heroin. Some drugs, such as rifampicin, phenytoin, barbiturates and some antiviral drugs used in the treatment of HIV infection, speed up the elimination of methadone from the body. Other drugs, such as fluvoxamine, may have the opposite effect on methadone metabolism. Knowledge of these interactions usually allows the appropriate adjustment of methadone dose for effective treatment.

Induction with methadone presents a potential risk of respiratory depression and should be undertaken with care. Interactions between methadone and either alcohol, sedatives or tricyclic antidepressants may also induce serious respiratory depression. The risk of death during methadone induction has been calculated as nearly seven times greater than the risk of death before entering maintenance treatment. 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. This process needs to be monitored by a doctor or trained nurse, and may require regular visits to a community prescribing centre. Initially patients may need to be seen at least fortnightly, but when stable the frequency of medical assessment can be reduced.

Buprenorphine is a partial opioid mμ-receptor agonist agonist, 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.

The SPC for buprenorphine states that it is indicated for ‘substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment’. Buprenorphine is used in opioid dependence, in the form of a sublingual tablet at an initial recommended single daily dose of 0.8–4 mg, adjusted according to response. In practice, a starting dose of more than 4 mg/day is often used. The maximum daily dose is 32 mg.

Buprenorphine has a number of differences from methadone in its mode of action. Because 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, means that it has a prolonged duration of action at higher doses, which potentially allows alternate-day and 3-days-a-week dispensing regimes. Buprenorphine also has a relatively good safety profile, and doses many times greater than normal therapeutic doses rarely appear to 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.

Currently, the decision about which drug treatment to offer is based on local availability, on the client’s previous history, current situation, social support network and expressed wishes. Decisions are taken together with the patient

and based on the clinician's judgment of the required degree of structure, monitoring and support.

The number of people in methadone maintenance therapy based on the quarterly drug spend for summer 2005 and assuming an average dose of 50 mg/day, was estimated at 45,600. For the same time period it was estimated that 8700 people were in buprenorphine treatment, with an average dose of 10 mg/day.

3 The evidence

The remit of this appraisal is 'to appraise the clinical and cost effectiveness of oral methadone and sublingual buprenorphine as substitute opiates for the management of opiate misusers and to identify those groups of misusers (in the community and prison settings) who are most likely to benefit from being prescribed oral methadone and those most likely to benefit from sublingual buprenorphine. Also, to advise on the optimum doses and context of care required to secure effective outcomes, and to provide guidance to the NHS in England and Wales'.

Methadone and buprenorphine are licensed for use in both detoxification and maintenance therapy. The main focus of the Assessment Group and the manufacturer's submission was to appraise the technologies within maintenance therapy. However, where evidence from the trials allows, maintenance therapy has been compared with detoxification therapy.

3.1 Clinical effectiveness

Thirty one systematic reviews (SRs) met the inclusion criteria of the Assessment Group. The reviews included evidence from randomised controlled trials (RCTs) and other types of study. Many of the studies included in these reviews overlap. The Assessment Group identified an additional 27 RCTs published since 2001. The majority of systematic reviews and RCTs were of moderate to good quality. Of the 28 RCTs, 16 were conducted in USA, 3 in Australia, 3 in Iran, 3 in Holland, 2 in Austria and 1 in Norway.

The majority of evidence reported is for men aged 30 to 49 years, in good health, who met Diagnostic and Statistical Manual III or IV criteria for opioid dependence, had no serious psychiatric or medical comorbidities and had not undergone therapy for drug misuse in the months before maintenance therapy was started. Pregnant women and those younger than 18 years of age were excluded from most trials.

Most studies were undertaken in outpatient, inpatient or specialised treatment centres, and very few were conducted in community or in laboratory settings. Various delivery options were reported, but generally delivery of methadone maintenance therapy (MMT) and buprenorphine maintenance therapy (BMT) was characterised by fixed doses of medication, no take-home medication, discharge of individuals who missed 3 consecutive days of treatment, limited adjuvant psychosocial therapy, no rewards for treatment compliance, intensive monitoring, limited length of treatment and relatively short periods of follow up (in most cases up to 1 year).

The majority of trials to date have used a fixed dose design, in which all included individuals are given a fixed dose of methadone and buprenorphine. Methadone doses range from 50–150 mg/day and buprenorphine from 1–15 mg/day. More recently, some studies have employed a flexible dosing design, which the Assessment Group believes is more reflective of real-world practice, in which participants receive an individualised dose of methadone or buprenorphine.

3.1.1 Results

The studies reported various outcome measures and outcome metrics (for example, relative risks (RR), mean differences (MD), standard mean difference (SMD)). For this reason and due to the heterogeneity of the trials, no pooled analysis has been carried out for outcome measures across SRs and RCTs. Results from pooled analyses of individual SRs are presented where available.

The two main outcomes reported were treatment retention and illicit use of opioids, the latter being reported in a variety of ways (for example, proportion

of individuals taking opioids, mean level of heroin coupled with self-report methods and/or urinalysis) making meta-analysis more difficult for this outcome. Limited data were available for HIV-related outcomes, side effects/adverse events and mortality and non-health outcomes (that is, crime and employment).

For full details for all outcomes of the RCTs see Assessment Report pages 111–117, for full details for all outcomes of SRs see pages 163–181. Unless otherwise stated, where a relative risk is stated, 95% confidence intervals (95% CIs) are also presented.

Methadone maintenance therapy (MMT) versus no drug therapy/placebo

Treatment retention was reported in 3 systematic reviews and 1 RCT.

Table 2 Treatment retention (methadone versus placebo/no therapy)

Comparison (daily dose) Methadone versus placebo/no therapy	No. of studies	Type of studies	No. of patients	Duration of follow-up (weeks)	Relative risk (95% CI) (unless otherwise indicated)	Heterogeneity test (p-value)
20–50 mg versus no therapy	3	RCT	505	26	3.05 (1.75 to 5.35)	0.02
20–97 mg versus placebo	2	RCT	348	15-32	3.91 (1.17 to 13.2)	0.001
35–97 mg versus no therapy	6	RCT/CCT	1013	6-152	d 0.92 (0.54 to 1.29)	< 0.05
30–60 mg versus no therapy	1	RCT	382	16	68% retained in treatment group. 65% retained in wait list group NS	NA
CCT – comparative controlled trial; d – effect size[1]; NA – not applicable; NS – not significant						

Five SRs and one RCT provided details of self-reported opioid use.

[1] The 'd' statistic of effect size is calculated by subtracting the mean of control group from the mean of treatment group and dividing by the standard deviation. Conventionally, effect sizes of *d* = 0.2 are considered "small", *d* = 0.5 "medium", and *d* = 0.8 "large".

Table 3 Self-reported opioid use (methadone versus placebo/no therapy)

Comparison (daily dose) Methadone versus placebo/ no therapy	No. of studies	Type of studies	No. of patients	Duration of follow-up (weeks)	Relative risk (95% CI) (unless otherwise indicated)	Heterogeneity test (p-value)
60 mg versus no therapy	1	RCT	256	16	0.31 (0.23 to 0.42)	NA
40–-80 mg versus no therapy	7	BA	1746	8-24	RRs range from 0.31 to 0.60[a]	NA
NR	3	BA	3236	3-12	3/3 results favour methadone	NA
NR	11	RCT/CCT/ BA	NR	NR	Mean effect size 0.78	NR
≥ 50 mg	2	RCT	347	15	0.82 (0.69 to 0.98)	NR
35–97 mg	7	RCT/CCT	1046	6–152	d 0.65 (0.41 to 0.89)	< 0.05
30–60 mg	1	RCT	382	16	25% reported opioid use in methadone group. 67% reported opioid use in wait list group P<0.001	NA

[a] pooling not performed because of observational nature of evidence
NA – not applicable; BA – before and after study; **; CCT – comparative controlled trial; NR – not reported; d – effect size

There were fewer self-reported adverse events with MMT compared with placebo or no therapy, although this difference was not statistically significant (RR 0.59, 95% CI 0.33 to 1.04). Three systematic reviews of non-randomised studies reported the effects of methadone on HIV-related outcomes. HIV risk behaviour scores and seroconversion rates (development of antibodies) were in general better in the MMT groups compared with no therapy. The results were mixed for self-reported outcomes of number of sex partners and frequency of unprotected sex.

A meta-analysis of observational studies that compared the number of deaths per person years at risk between individuals in and out of methadone treatment reported a RR of 0.25 (95% CI 0.19 to 0.33) indicating that methadone patients were four times less likely to die than those not in or discharged from treatment. However, there was considerable heterogeneity between the studies included in the analysis.

The level of criminal activity decreased in individuals on MMT compared with placebo or no therapy. One study reported a reduction in criminal activity in the MMT group that was not statistically significant (RR 0.39, 95% CI 0.12 to 1.25) and two studies reported effect sizes of 0.54 and 0.70.

Buprenorphine maintenance therapy (BMT) versus no drug therapy/placebo

One SR of randomised studies reported treatment retention for various doses of buprenorphine compared to placebo/no therapy.

Table 4 Treatment retention (buprenorphine versus placebo/no therapy)

Comparison (daily dose) Buprenorphine versus placebo/no therapy	No. of studies	Type of studies	No. of patients	Duration of follow-up (weeks)	Relative risk (95% CI) (unless otherwise indicated)	Heterogeneity test (p-value)
≤ 5 mg	5	RCT	1131	16–24	1.50 (1.19 to 1.88)	0.007
6–12 mg	4	RCT	887	17–52	1.74 (1.06 to 2.87)	< 0.001
18 mg	4	RCT	728	4–52	1.74 (1.02 to 2.96)	< 0.001

One small RCT (n=40), included in an unpublished SR, reported a reduction in mortality in patients on BMT (16 mg) compared with placebo and counselling treatment over a 12-month period with a RR 0.05 (95% CI 0 to 0.79). No studies comparing BMT with placebo/no treatment reported data on opioid use (self-reported or urinary confirmed), adverse events, HIV risk behaviour or crime.

Methadone maintenance therapy versus buprenorphine maintenance therapy

Four meta-analyses of RCTs showed that fixed doses of MMT had superior treatment retention to comparable fixed doses of BMT. See assessment report, Table 36, p164 for details of all dose comparisons for SRs and Table 35 p111 and p115 for details of two RCTs that compare fixed doses of MMT to fixed doses of BMT.

Four SRs of RCTs compared self-reported opioid use between fixed doses of MMT and fixed doses of BMT. A high fixed dose of MMT was more effective than fixed dose BMT (≥ 50 mg compared with 8 mg), RR 0.29 (95% CI 0.15 to 0.79). Results were mixed for comparisons of lower fixed dose MMT (< 50 mg compared with ≥ 8 mg) and higher fixed dose BMT. See assessment report, Table 37, p168 for further details.

A recently updated and unpublished Cochrane systematic review of seven RCTs directly compared flexible dosing MMT with flexible dosing BMT in 976 opiate-dependent individuals. No further RCTs comparing flexible MMT and BMT were identified by the Assessment Group's searches. The daily equivalent doses in these flexible dosing trials ranged from 20-120 mg/day for methadone and 2-16 mg/day for buprenorphine. The exact flexible dose ranges and dosing procedures used in RCTs comparing MMT and BMT can be found in table 5, on page 35 of the assessment report.

Treatment retention was superior for flexible MMT than flexible BMT dosing (pooled hazard ratio 1.40, 95% CI 1.15 to 1.69) although there was no significant difference in opiate use (standardised mean difference 0.12, 95% CI –0.02 to 0.26).

In the assessment report, the rates of occurrence in four categories of serious adverse events per 100-individual-years in treatment are provided from the 'National evaluation of pharmacotherapies for opioid dependence' 2004 report, which had access to individual patient level data. Of the 420 individuals treated with methadone, 10 serious adverse events were reported and of the 492 individuals treated with buprenorphine 20 serious adverse events were reported. A pooled RCT analysis showed no significant difference in the rate of serious adverse events with MMT compared with BMT.

An indirect comparison of data from population cross sectional studies suggests that the level of mortality with BMT may be lower than that with MMT, although it was commented that these data were unlikely to capture all related deaths.

Dosages

Higher doses of MMT (e.g ≥50mg) were found to be more effective than lower doses of MMT (<50mg) in treatment retention (for example, 60 - 109 mg compared with 1-39 mg resulted in a RR of 1.36 [95% CI 1.13 to 1.63]). Higher doses of MMT were more effective than low doses of MMT in reducing self-reported opioid use (for example ≥ 50 mg compared with < 50 mg resulted in RR of 0.82 [95% CI 0.72 to 0.95]). Higher doses of MMT (60-109 mg) were also associated with a significantly lower number of opioid-positive urine tests compared with lower doses of MMT (1-39 mg). However, a comparison of high dose MMT (60-109 mg) with moderate dose MMT (40-59 mg) did not produce a significantly lower number of opioid-positive urine tests. See assessment report, Table 38, page 170 for further details.

Treatment settings

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

Maintenance versus detoxification therapy

Two RCTs showed MMT to have superior treatment retention and opiate use than methadone detoxification therapy. One RCT showed BMT to be superior to buprenorphine detoxification therapy.

3.1.2 Summary

The results from the meta-analyses showed that fixed dose MMT has superior levels of treatment retention and opiate use to placebo or no treatment, with higher fixed doses of MMT being more effective than lower fixed doses. There is evidence, primarily from non-randomised observational studies, that fixed dose MMT reduces mortality, HIV risk behaviour and levels of crime compared with no therapy.

Two RCT meta-analyses show that fixed dose BMT has superior levels of treatment retention and opiate use than placebo or no therapy, with higher fixed doses of BMT being more effective than lower fixed doses. One small RCT has shown that the level of mortality with fixed dose BMT to be significantly less than placebo.

A number of RCT meta-analyses show that fixed doses of MMT has superior treatment retention to comparable fixed doses of BMT. High fixed doses of MMT are more effective than fixed dose BMT, while at lower fixed dose MMT and higher fixed dose BMT the two appear to be more equal in their effectiveness at preventing opioid use.

In the studies analysed, treatment retention with flexible MMT is superior to that with flexible BMT dosing, although there is no significant difference in opiate use.

Indirect comparison of data from population cross sectional studies suggests that the level of mortality with BMT may be lower than that with MMT.

3.2 Cost effectiveness

3.2.1 Published evaluations

Eleven published economic evaluations met the Assessment Group's inclusion criteria for review.

Eight studies assessed the cost effectiveness of MMT and three assessed the cost effectiveness of BMT. The studies reported results using a range of outcome measures, five reported incremental cost-effectiveness ratios (ICERs) expressed as cost per additional quality adjusted life year (QALY) gained. Six studies reported use of an economic model. The Assessment Group reported that direct comparisons of the ICERs between the studies was not possible because of their differences in the approaches to modelling, time horizons, comparators and perspectives, country 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 and personal social services (PSS) context.

One study that compared the cost effectiveness of MMT with drug-free treatment found MMT to be a cost effective treatment resulting in an incremental cost effectiveness ratio of US$5,250 (£3,094) per life year gained compared to drug free treatment.

Two studies compared the cost effectiveness of BMT directly with MMT. One reported that MMT dominated (was less costly and more effective) BMT when cost-effectiveness was measured as cost per heroin-free day, but that when cost-effectiveness was measured as cost per additional QALY gained, the ICER for BMT versus MMT was Aus$39,404 (£17,326). The Assessment Group reported that the results of a sensitivity analysis further undermined confidence in the result. The other study reported cost-effectiveness measured as cost per heroin-free day and found MMT dominated BMT.

No studies assessing the cost effectiveness of BMT compared with drug free treatment were identified by the Assessment Group.

One study showed MMT to be more effective and more costly than methadone detoxification and reported an ICER of US$19,997 (£10,626) per additional QALY gained.

3.2.2 Manufacturers' models

No economic evaluations were submitted by the manufacturer of methadone.

The manufacturer of buprenorphine (Schering-Plough) submitted a cost effectiveness analysis of BMT compared with MMT for opioid dependent patients over a 1-year time horizon. Cost effectiveness was assessed as the incremental cost per QALY using a decision tree based model. Costs were calculated from an NHS/PSS perspective. Both simple one-way and probabilistic sensitivity analyses were undertaken.

The model was designed to estimate the cost effectiveness of BMT in three analyses: BMT compared to no treatment for 20% of all patients who are seeking maintenance treatment who are unable to take methadone for clinical reasons (as stated by the manufacturer); BMT compared to MMT for the remaining 80% of patients; and maintenance therapy (methadone and buprenorphine) versus drug free treatment for the overall patient group.

The model includes data on patients retained in treatment at specified time points up to 6 months, and then follows those retained in treatment at 6 months for a further 6 months. Each period of time is associated with a health-related utility value and cost. The data for retention in treatment and dosing for the initial 13 weeks are based on one RCT which compared flexible dose BMT and MMT and data on retention between 13 and 26 weeks are based on an open-label stage from the same RCT reported in another publication.

The trial used a flexible dosing regimen (patients were dosed daily through weeks 1-6, but were able to have alternate day BMT dosing after 6 weeks). Schering-Plough therefore states that although its model assumes daily dosing throughout the whole 12 months, daily dosing buprenorphine may have led to better retention rates that were seen in the trial.

Health-related utility values were based on results from a published study and included an adjustment factor from another published study. This adjustment was a reduction of 0.1 for an injecting drug user although the Assessment Group note that the status of patients regarding injecting drug use included in the model is not clear from the description provided.

Resource use and costs were derived from several studies, all of which the Assessment Group found to be appropriate. The use of healthcare resources were assumed to be the same for both methadone and buprenorphine users. The model was for 1 year, so no discounting was applied.

Results

The manufacturer reported that the analysis of BMT compared to no treatment for the 20% patients who could not have MMT showed BMT to be more

expensive and slightly more effective in terms of QALYs (ICER £30,048 per additional QALY gained).

For patients who could be treated with either therapy, MMT dominated BMT as it was slightly more expensive than methadone and yielded marginally less QALYs. However, the difference in QALYs was very small (0.00055) and given the parameter uncertainty in the model, the difference in efficacy is highly uncertain.

The analysis of maintenance treatment compared to no treatment resulted in an ICER of £12,584 per additional QALY gained. However, the Assessment Group expressed concerns regarding this result due to the method of analysis, which may have ignored the relevant comparator (see Assessment Report p 63).

Sensitivity analysis

The manufacturer notes that the better retention noted for methadone compared with buprenorphine from the pivotal trial did not translate into incremental improvements in the QALYs for methadone. Deterministic sensitivity analyses showed that the model was sensitive to patients retained on buprenorphine and methadone at induction, 13 weeks, 6 weeks, and 6 months. It was also sensitive to changing the health-related utility values at 12 months for buprenorphine or methadone.

Societal costs were not included in manufacturer model, but the manufacturer notes that its model may underestimate the entire benefits of substitution therapy. The manufacturer used absolute probabilities for each time point, whereas the software package it used for analysis requires conditional probabilities. The Assessment Group highlights this problem and is unclear what effect this has on the final results.

3.2.3 Assessment Group's model

The Assessment Group developed a decision tree with Monte Carlo simulation to assess the cost-effectiveness of BMT and MMT compared with drug free therapy and BMT compared with MMT. 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 key effectiveness parameter is treatment retention and the model considers the proportion of patients retained in treatment at 2, 6, 13 and 25 weeks and 12 months. A cost and health-related utility value is assigned to each of these periods. For model structure see page 65 of the assessment report.

The data for treatment retention in the model was taken from the systematic review that identified seven trials that compared methadone and buprenorphine in flexible dosing. The obtained pooled hazard ratio of 1.40 (95% CI 1.69 to 1.15) was used to estimate the relative risk of dropping out of treatment. A Weibull distribution was fitted to the buprenorphine data to allow for extrapolation beyond 24 weeks.

Unlike the Schering-Plough model, the Assessment Group also took into account opioid positive or negative urine data, as some patients within a maintenance programme will still misuse drugs. Data on the percentage of retained patients who are drug free are taken from the combined analysis of opioid negative urine samples from two studies. For those not retained in treatment the Assessment Group assumed that patients return to their pre-treatment habits respective of their period of maintenance therapy and that 89% of those not retained in treatment would be using opioids (based on data from a UK cohort study). Data from the ‘National treatment outcome treatment research study’ (NTORS) were used to inform the proportion of drug-taking patients who were injecting and not injecting. Of the substance-using individuals not on treatment, 61% were injecting (39% were not injecting); of the substance-using individuals on treatment, 44% patients were injecting (56% were not injecting).

Maintenance therapy was assumed to be a flexible dosing regimen. Mean daily dose was assumed to be the same as week 13 from that week onwards. It was assumed that patients in treatment attended one counselling session per week and had one urine test per fortnight. Other health service resource

use was based on data from the NTORS and included GP visits, A&E visits, inpatient hospital stays, outpatient mental health visits and inpatient mental health visits. Buprenorphine drug costs were based on 2mg tablets rather than 8mg as the model assumes flexible dosing. The average cost of dispensing drugs was based on assumptions that: for first three months supervised self-administration, 6 days a week; 3-6 months unsupervised self-administration, 6 days a week; and 6-12 months: three times a week unsupervised self-administration.

An additional non-reference case analysis also included costs associated with drug arrests, police detention, court appearances, prison and victim costs (including measures in anticipation of crime such as security measures, and direct costs such as material or physical damage or loss). In the first year the level of arrests for drug offences and acquisitive crime was higher for users in treatment than those who were not in treatment (self-reported). The report containing these data highlights this unexpected result but does not give any further explanation, and states that additional analysis of the data was not possible within the project. However, a subsequent paper (Healey 2003) conducted a re-analysis on the same NTORS data and found a higher rate of crimes reported at entry (before treatment) than at follow-up (on treatment). Therefore the Assessment Group stated that further analysis to find the reason for this apparent contradiction is needed. In addition, the data should be viewed with some caution because the data used in the Assessment Group's model is self-report data that has not been validated by official crime data. See tables 17, 18 and 19 on pages 71 and 72 of the assessment report for detailed information on costs.

In the absence of published data on quality of life associated with drug misuse, the Assessment Group obtained health-related utility data from the Value of Health Panel. Health states were defined by the Assessment Group in collaboration with a clinician. Members of the general public valued the health states using the standard gamble method. QALYs were calculated by weighting the proportion of patients in relevant health scenarios by the health-

related utility estimates[2]. For further details of the QALY estimates see pages 73 to 74 and pages 190 to 192 of the assessment report.

Results

Table 5 Base case: cost-effectiveness results of all strategies

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

Table 6 Base case: cost-effectiveness results of BMT versus no treatment

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

Table 7 Non-reference case: cost-effectiveness results of all strategies from a societal perspective

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Methadone	28,344.81		0.6900		-
Buprenorphine	30,991.91	2647.105	0.6774	-0.0126	(Dominated)
No treatment	38,917.25	10572.44	0.6230	-0.0670	(Dominated)

[2] Scenarios included: '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'.

Table 8 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	30,991.91		0.6774	-	-
No treatment	38,917.25	7925.34	0.6230	-0.0544	(Dominated)

Sensitivity analysis

A number of sensitivity analyses were conducted on the reference and non-reference case. With regard to dispensing of buprenorphine, a sensitivity analysis was conducted assuming that from week 1 to 13, buprenorphine was dispensed under supervision on alternate days and that from week 14 to 52 it was dispensed alternate days unsupervised. Two sensitivity analyses were also carried out on the utility values. Firstly, considering the published utility values that had also been used in the manufacturer's analysis (referred to as utility analysis 1 below). However instead of using a health-related utility value for a specific point of time, the overall QALY value for both strategies (while on treatment) has been used. For the 'no treatment' and 'drop-out from treatment' health states the Assessment Group assumed a utility value of 0.505. A further analysis was performed using the utility values from a large published study that compared MMT with methadone and heroin (referred to as utility analysis 2 below). The final sensitivity analysis examined the impact of the inclusion of the victim costs of crime, resulting in a societal perspective evaluation with costs to the criminal justice system only.

Table 9 Sensitivity analysis: cost-effectiveness results for all strategies

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Alternative buprenorphine dispensing within base case					
No treatment	1053.25		0.6230		
Methadone	1949.53	896.28	0.6900	0.0670	13,377
Buprenorphine	2362.86	413.33	0.6774	-0.0126	(Dominated)
Using alternative utilities within base case (utility analysis 1)					
No treatment	1053.25		0.5050		
Methadone	1970.97	917.72	0.5525	0.0475	19,320
Buprenorphine	2490.97	520.00	0.5573	0.0048	108,333
Using alternative utilities within base case (utility analysis 2)					
No treatment	1053.25		0.6300		
Methadone	1970.97	917.72	0.6858	0.0558	16,447
Buprenorphine	2490.97	520.00	0.6755	-0.0103	(Dominated)
Exclusion of victim costs from societal perspective					
No treatment	8090.25		0.6230		
Methadone	9767.50	1677.25	0.6900	0.0670	25,033
Buprenorphine	10146.90	379.40	0.6774	-0.0126	(Dominated)

Table 10 Sensitivity analysis: Cost-effectiveness results of BMT versus no treatment

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Alternative buprenorphine dispensing within base case					
No treatment	1053.25		0.6230		
Buprenorphine	2362.86	1309.61	0.6774	0.0544	24,074
Using alternative utilities within base case (utility analysis 1)					
No treatment	1053.25		0.5050		
Buprenorphine	2490.97	1437.72	0.5573	0.0523	27,490
Using alternative utilities within base case (utility analysis 2)					
No treatment	1053.25		0.6300		
Buprenorphine	2490.97	1437.72	0.6755	0.0455	31,598
Exclusion of victim costs from societal perspective					
No treatment	8090.25		0.6230		
Buprenorphine	10146.90	2056.65	0.6774	0.0544	37,806

4 Issues for consideration

No submissions or comments on the assessment report were received from the patient/client groups.

Given the context-specific nature of drug use and the effectiveness of opioid treatments, the Assessment Group and consultees suggest that caution must be applied in the direct transferability of the evidence base to the UK; in the US and Australia the criminal justice system is very different and much of maintenance therapy is conducted under long-term supervision.

Caution also needs to be applied in the direct transferability of the outcomes from these trials to all opioid users, given that the majority of the population in the trials were males aged 30 to 49 in good health.

In the Assessment Group's systematic review, RCTs were excluded if the population was a mixture of cocaine and opioid abusers. Many of the comments received on the assessment report state that in clinical practice not that many people present with a purely opioid problem, and that polydrug use needs more consideration. Further discussions are needed as to how these other drugs (crack, cocaine, benzodiazepines, alcohol, cannabis, amphetamines) affect outcomes.

The Assessment Group found no evidence for different subgroups.

The Assessment Group found no evidence comparing prison with non-prison settings.

The Assessment Group found very little data around the issue of maintenance versus detoxification using methadone and buprenorphine. Consultees commented that this type of comparison may lead to misleading conclusions and does not provide the whole picture on detoxification using these technologies.

The Assessment Group identified that higher doses were more effective than lower doses for buprenorphine and methadone but did not identify the most effective dosage for these two technologies. A professional group suggested that further trials are needed that compare high doses (optimal > 15 mg) of buprenorphine to high doses (optimal > 80 mg) of methadone. A flexible approach to dosing was decided upon by the Assessment Group – after consultation with clinical experts – as being the most realistic, and was used

in the economic model. The manufacturer's model also adopted the flexible dosing regime.

By taking a 1-year time horizon, the economic models of both the Assessment Group and the manufacturer did not take into account any differences in mortality between methadone and buprenorphine maintenance therapy. Schering-Plough, in their comments on the assessment report, noted that the assessment report highlights a number of papers in the literature (pages 86-87) that indicate that mortality appears to be higher with methadone than buprenorphine.

MMT was dominant in comparison with BMT from the perspectives of both the NHS/PSS and society (inclusion of the criminal justice system costs). 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. However, Schering-Plough note that the difference in QALYs gained between the treatments was small and subject to uncertainty.

Schering-Plough stated in its submission that 20% of opioid dependent patients are unable to use methadone, and so for these patients buprenorphine is the only option. The Assessment Group questioned this figure and conducted a survey of 200 consultant psychiatrists who work in the field of addiction. The Assessment Group received 58 responses (29%): thirty two respondents felt that there were no medical contraindications to methadone, and the overall response was a mean figure of 0.6% (range 1–5%) of individuals having a medical contraindication to methadone. However, in response to the question 'What percentage of clients do not wish to use methadone?', the mean response was a figure of 20.4% (range 5–50%); this response is in line with the Schering-Plough submission. Schering-Plough notes that patient preference is very likely to influence both retention rates and attraction to therapy rates. A number of the consultees highlighted the need for both drugs to be available, because due to their differences they are both useful in treating different groups of opioid addicts.

Other related NICE guidance currently underway is the appraisal 'Naltrexone as a treatment for relapse prevention in drug misusers', due for publication at the same time as this appraisal (March 2007). There are two clinical guidelines: 'Opiate detoxification of drug misusers in the community and prison settings' and 'Psychosocial management of drug misusers in the community and prison settings', both due for publication in July 2007. Within the Centre for Public Health Evaluation a piece of work examining community projects for drug misusers is also underway.

5 Author

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report:

- Connock M, Juarez-Garcia A, Jowett S et al. (West Midlands Health Technology Assessment Collaboration). 'Methadone and Buprenorphine for the Management of Opioid Dependence: A Systematic Review and Economic Evaluation', January 2005.

B Submissions from the following organisations:

I Manufacturers/sponsors:

- Schering-Plough

II Professional/specialist and patient/carer groups:

- Royal College of Nursing
- Royal College of Physicians
- Royal College of Psychiatrists

III Commentator organisations (without the right of appeal):

- None

C Additional references used:

- Singleton N, Pendry E, Simpson T et al (2005) 'The impact and effectiveness of mandatory drug testing in prisons.' Home Office: Findings 223.