

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Final Appraisal Determination

### Methadone and buprenorphine for the management of opioid dependence

#### 1 Guidance

- 1.1 Methadone and buprenorphine (oral formulations), using flexible dosing regimens, are recommended as options for maintenance therapy in the management of opioid dependence.
- 1.2 The decision about which drug to use should be made on a case by case basis, taking into account a number of factors, including the person's history of opioid dependence, their commitment to a particular long-term management strategy, and an estimate of the risks and benefits of each treatment made by the responsible clinician in consultation with the person. If both drugs are equally suitable, methadone should be prescribed as the first choice.
- 1.3 Methadone and buprenorphine should be administered daily, under supervision, for at least the first 3 months. Supervision should be relaxed only when the patient's compliance is assured. Both drugs should be given as part of a programme of supportive care.

#### 2 Clinical need and practice

- 2.1 The term 'opioids' refers to opiates and other semi-synthetic and synthetic compounds with similar properties. Opiates 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 diamorphine (heroin), which is produced from poppy compounds. Opioid

dependence can cause a wide range of health problems and is often associated with misuse of other drugs (including alcohol). Diamorphine is the most widely misused opiate, and its misuse can lead to accidental overdose. Injecting diamorphine may also be associated with the spread of blood-borne viruses such as HIV and hepatitis B or C. The mortality risk of people dependent on illicit diamorphine is estimated to be around 12 times that of the general population. Psychiatric comorbidity – particularly anxiety, but also affective, antisocial and other personality disorders – is common among opioid-dependent people.

- 2.2 Associated social problems include marital and relationship breakdown, unemployment, homelessness, and child neglect, which often results in children being taken into the care system. There is also a clear association between illicit drug use and crime. Some opioid-dependent people become involved in crime to support their drug use. It is estimated that half of all recorded crime is drug related, with associated costs to the criminal justice system in the UK estimated at £1 billion per annum in 1996.
- 2.3 Biological, psychological, social and economic factors influence when and why a person starts taking illicit opioids. Use of opioids can quickly escalate to misuse (repeated use despite adverse consequences) and then dependence (opioid tolerance, withdrawal symptoms, compulsive drug-taking). The ‘Diagnostic and statistical manual of mental disorders’ (fourth edition; DSM-IV) defines dependence as ‘a maladaptive pattern of substance use, leading to clinically significant impairment or distress’. Dependence syndrome has been defined in the ‘International statistical classification of diseases and related health problems’ (10th revision; ICD-10) as a ‘cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.’ 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 and blood pressure. The body also becomes tolerant of the effects of opioids and the dose needs to be increased to maintain the effect. Getting the next dose can become an important part of each day and can take over a person's life. It is difficult to stop using these drugs and remain abstinent because the person experiences a combination of craving, unpleasant withdrawal symptoms, and the continuation or worsening of personal circumstances that led to opioid misuse in the first place.

- 2.4 When a person manages to remain abstinent, it may be after repeated cycles of cessation and relapse, with extensive treatment histories spanning decades. Nevertheless, some dependent people may make dramatic changes in their drug use without formal treatment. The histories of people using illicit diamorphine who attend treatment services suggest that most people develop dependence in their late teens and early twenties, several years after their first use of illicit opioids, 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, allowing health and social circumstances to improve.
- 2.5 National estimates, which combine local prevalence data and routinely available indicator data, suggest that in the UK the prevalence of problem drug use is 9.35 per 1000 of the population aged 15–64 years (360,811 people), and that 3.2 per 1000 (123,498 people) inject drugs. The National Drug Treatment Monitoring System (NDTMS) estimates that in 2004–05 there were 160,450 people in contact with drug treatment services in England. Most of the people in treatment were dependent on opioids. There are about 40,000 people in prisons in England and Wales at any time who misuse illicit drugs. In one UK survey, 21% of prisoners had used illicit opioids

at some point during their sentence, and 10% had used illicit opioids during the previous week.

- 2.6 The UK has a range of treatment services for opioid dependency. Pharmacological and psychosocial interventions are provided in the community and the criminal justice system, and include inpatient, residential, day-patient and outpatient services.
- 2.7 The interventions used for opioid-dependent people range from needle exchange to maintenance therapy and abstinence. Pharmacological treatments are broadly categorised as maintenance (also known as ‘substitution’ or ‘harm reduction’ therapies), detoxification or abstinence. The aims of the maintenance approach are to provide stability by reducing craving and preventing withdrawal, eliminating the hazards of injecting and freeing the person from preoccupation with obtaining illicit opioids, and to enhance overall function. To achieve this, a substitution opioid regimen (a fixed or flexible dose of methadone or buprenorphine to reduce and stop illicit use) is prescribed at a dose higher than that required merely to prevent withdrawal symptoms. The aim is for people who are dependent on illicit opioids to progress from maintenance to detoxification and then abstinence (when a person has stopped taking opioids). All detoxification programmes require relapse prevention strategies and psychological support after detoxification, because relapse rates are high. Some people can rapidly achieve total abstinence from opioids; others require the support of prescribed medication for longer than a few months. The opioid antagonist naltrexone can be used to help maintain abstinence.
- 2.8 Psychosocial and behavioural therapies play an important role in the treatment of drug misuse. They aim to give people the ability to resist drug misuse and cope with associated problems. For opioid-dependent people, these therapies are often an important adjunct to pharmacological treatments. Maintenance programmes vary in the quantity of psychosocial support delivered in addition to the medication, and in the degree of supervision of

methadone consumption. Substitute opioids are mainly prescribed in community and primary care prescribing programmes. The Department of Health guidelines for the UK recommend that when a person starts maintenance opioid therapy, they should take each dose under the supervision of a nurse, doctor or community pharmacist for a minimum of 3 months, and this supervision should be relaxed only when their compliance is assured. However, the need for supervised consumption should take into account social factors, such as whether the person has a job or childcare responsibilities. Initial assessment should include oral fluid or urine testing, and the person may need to be seen by a doctor or specialist drug worker several times within the first few weeks of induction and dose titration. As the person progresses with their maintenance therapy, the need for supervision may change.

2.9 The government's 'Drug strategy' (2004) aims to reduce the harm caused by illicit drugs by:

- increasing the number of people entering drug treatment programmes through the criminal justice system
- reducing the use of Class A and illicit drugs by people under the age of 25
- increasing enrolment in drug treatment programmes.

2.10 In England in 2004, 532,700 individual items of buprenorphine were prescribed for opioid dependence, with a total annual drug cost of about £14.5 million. Methadone treatment in England in 2004 accounted for 1,954,700 individual items prescribed for opioid dependence and a total annual drug cost of about £17 million.

### 3 The technologies

#### 3.1 *Methadone*

- 3.1.1 Methadone (Rosemont Pharmaceuticals, AAH Pharmaceuticals, Martindale Pharmaceuticals, and Thornton & Ross) is a synthetic opioid receptor agonist with pharmacological activity similar to that of 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)’.
- 3.1.2 The ‘British national formulary’ (BNF) states that methadone is to be used in opioid dependence at an initial dose of 10–40 mg daily, which is increased by up to 10 mg daily (with a maximum weekly increase of 30 mg) until no signs of withdrawal or intoxication are seen. The usual maintenance dose range is 60–120 mg daily.
- 3.1.3 Methadone is available as a solution (1 mg/ml and 10 mg/ml), tablets or injectable ampoules. Only the oral form of methadone is considered in this appraisal. Administering methadone orally avoids the risks associated with injecting. Methadone has a long elimination half-life (usually 20–37 hours), which allows for a once-daily dosing schedule. Methadone appears to have no serious long-term side effects associated with chronic administration. In people stabilised on a methadone maintenance regimen, the drug does not have the pronounced narcotic effects seen with shorter-acting opioids such as illicit diamorphine. Some drugs, including rifampicin, phenytoin, phenobarbital 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 and fluoxetine, may have the opposite effect on methadone metabolism. Knowledge of these interactions usually enables the appropriate adjustment of methadone dose for effective treatment. For full details of side effects, contraindications and drug interactions, see the SPC.

- 3.1.4 Initiation of treatment with methadone presents a potential risk of respiratory depression and should be undertaken with care. Interactions between methadone and other respiratory depressants such as alcohol, benzodiazepines and the newer non-benzodiazepine hypnotics (Z-drugs), other sedatives or tricyclic antidepressants may also induce serious respiratory depression. There is a risk of death early in methadone treatment as a result of excessive initial doses, failing to recognise cumulative effects, giving methadone to people with impaired liver function (due to chronic hepatitis) or failing to inform patients of the dangers of overdose if they are using other drugs at the same time. The relatively slow onset of action and long half-life mean that methadone overdose and toxic effects may become life threatening several hours after a dose is taken. During the initiation phase, the methadone dose should be adjusted carefully 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 by the patient to a community prescribing centre. Initially patients may need to be seen at least fortnightly, but when they are stable, the frequency of medical assessment can be reduced.
- 3.1.5 The cost of methadone oral solution (1 mg/ml) is £1.35 per 100 ml excluding VAT (BNF, edition 51). Costs may vary in different settings because of negotiated procurement discounts.

## **3.2 Buprenorphine**

- 3.2.1 Buprenorphine (Schering Plough) has both partial opioid agonist and opioid antagonist activity, and provides a milder, less euphoric and less sedating effect than full opioid agonists such as diamorphine or methadone (although these effects are less pronounced with methadone than with diamorphine).
- 3.2.2 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 available in the form of sublingual tablets, transdermal patches and injectable ampoules. In the

management of opioid dependence, sublingual tablets are used at an initial recommended once-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, with an adequate maintenance dose being in the range 12–24 mg/day. The maximum daily dose is 32 mg.

- 3.2.3 Buprenorphine is chemically distinct from methadone. Buprenorphine has a high affinity for opioid receptors and this reduces the impact of additional illicit diamorphine or other opioid use by preventing these drugs from occupying the opioid receptors. The high affinity of buprenorphine for opioid receptors means that it has a prolonged duration of action at higher doses, which can allow alternate-day dosing regimens. Buprenorphine also has a relatively good safety profile. Even higher than normal therapeutic doses rarely result in clinically significant respiratory depression because of its partial agonist activity at the opioid receptor involved ( $\mu$ ). The safety of buprenorphine mixed with high doses of other sedative drugs such as alcohol or benzodiazepines remains unclear. Starting buprenorphine treatment in opioid-dependent people may precipitate symptoms of withdrawal because buprenorphine displaces any residual illicit opioid agonists from receptors and because its partial agonist activity reduces the stimulation of receptors. In addition, whereas methadone is an agonist, buprenorphine is an antagonist at the receptor subtype involved in mood ( $\kappa$ ), which may mean that it produces less dysphoria. For full details of side effects and contraindications, see the SPC. Buprenorphine has abuse potential, as tablets can be crushed and then injected.
- 3.2.4 The cost of buprenorphine is £2.88 per 8 mg tablet excluding VAT (BNF 51). Buprenorphine is also available in 2 mg (£0.96 per tablet) and 400 mg (£0.23 per tablet) strengths (BNF 51). Costs may vary in different settings because of negotiated procurement discounts.

## 4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B). Methadone and buprenorphine are licensed for use in both detoxification and maintenance therapy. The main focus of the Assessment Group's report and the manufacturer's submission was use of the technologies in maintenance therapy.

### 4.1 *Clinical effectiveness*

- 4.1.1 Thirty-one systematic reviews 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 were included in several of the reviews. The Assessment Group identified an additional 27 RCTs published since 2001. Most of the systematic reviews and RCTs were of moderate to good quality. Of the 27 RCTs, 16 were conducted in the USA, three in Australia, three in Iran, two in the Netherlands, two in Austria and one in Norway.
- 4.1.2 Most of the evidence reported is for men aged 30–49 years, in good health, who met DSM-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 all people younger than 18 years were excluded from most trials.
- 4.1.3 Most studies were undertaken in outpatient or inpatient settings or specialised treatment centres, and very few were conducted in community 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, supervised consumption (no take-home medication), discharge of people 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).

- 4.1.4 Most trials used a fixed-dose design, in which all those included were given a fixed dose of methadone or buprenorphine. Methadone doses were in the range 50–150 mg/day and buprenorphine doses were in the range 1–15 mg/day. Some recent studies have used a flexible-dosing design (in which a person's dose is adjusted during treatment as necessary). The Assessment Group judged this to be a better reflection of current practice in the UK, where each person receives a flexible individualised dose of methadone or buprenorphine.
- 4.1.5 The two main outcomes reported in the included systematic reviews and RCTs were retention on treatment and illicit use of opioids, the latter being reported in a variety of ways (for example, proportion of people taking illicit opioids, or the mean rate of diamorphine intake assessed by self-report methods and/or urinalysis), making meta-analysis more difficult. Limited data were available for HIV-related outcomes, side effects/adverse events and mortality, and non-health outcomes (that is, crime and employment).

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

- 4.1.6 The results from the meta-analyses showed that fixed-dose MMT has superior levels of retention on treatment compared with placebo or no treatment. One meta-analysis (n = 505), which used doses of 20–50 mg/day of methadone compared with no therapy, gave a relative risk (RR) of remaining on treatment of 3.05 (95% confidence interval [CI] 1.75 to 5.35). In another systematic review (n = 348), which pooled the results from trials that used daily doses in the range 20–97 mg methadone, the RR of remaining on treatment was 3.91 (95% CI 1.17 to 13.2).
- 4.1.7 The results from the meta-analyses showed that fixed-dose MMT resulted in lower rates of illicit opioid use compared with placebo or no treatment. One systematic review (n = 246), which compared 60 mg methadone daily with no therapy, gave an RR of illicit opioid use (self-reported) of 0.31 (95% CI 0.23 to 0.42). Another systematic review (n = 347), comparing doses of 50 mg or

more methadone with placebo, resulted in an RR of illicit opioid use of 0.82 (95% CI 0.69 to 0.98).

- 4.1.8 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 or risk scores and seroconversion rates (development of antibodies) were in general better in the MMT groups compared with no therapy. The results showed no statistically significant differences between MMT and BMT for the self-reported outcomes of number of sex partners and frequency of unprotected sex.
- 4.1.9 A meta-analysis of observational studies that compared the number of deaths (per person years of exposure) in people in and out of methadone treatment reported an RR of 0.25 (95% CI 0.19 to 0.33), indicating that people who were not taking methadone or were discharged from treatment were four times more likely to die than those on treatment. The base rates (for those out of methadone treatment) in the included studies showed a wide variation.
- 4.1.10 The level of criminal activity decreased in people on MMT compared with those on 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. (Effect sizes are calculated by subtracting the mean of the control group from the mean of the treatment group and dividing by the standard deviation; conventionally, effect sizes of 0.2 are considered 'small', 0.5 'medium', and 0.8 'large'.)

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

- 4.1.11 One systematic review of randomised studies reported retention on treatment for various doses of buprenorphine compared with placebo or no therapy. Five RCTs (n = 1131) used doses of less than 5 mg buprenorphine, resulting

in an RR of 1.50 (95% CI 1.19 to 1.88). Four RCTs (n = 887) used a dose of 6–12 mg, resulting in an RR of 1.74 (95% CI 1.06 to 2.87). Four RCTs (n = 728) used a dose of 18 mg, resulting in an RR of 1.74 (95% CI 1.02 to 2.96).

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

### **Methadone maintenance therapy (MMT) versus buprenorphine maintenance therapy (BMT)**

4.1.13 Four meta-analyses of RCTs showed that fixed doses of MMT had retention on treatment superior to that of comparable fixed doses of BMT. One study (n = 540) compared 50–80 mg methadone with 6–12 mg buprenorphine, giving a hazard ratio (HR) of 1.26 (95% CI 1.01 to 1.57). Another systematic review (n = 211) compared doses of up to 35 mg methadone with up to 5 mg buprenorphine, resulting in an RR of 1.47 (95% CI 1.10 to 2.00).

4.1.14 Four systematic reviews of RCTs compared self-reported illicit opioid use between people on fixed doses of MMT and people on fixed doses of BMT. A high fixed dose of MMT (50 mg or more) was more effective than a low fixed dose of BMT (less than 8 mg) with an RR of 0.29 (95% CI 0.16 to 0.53). Results were mixed for comparisons of lower fixed doses of MMT (less than 50 mg) and higher fixed doses of BMT (8 mg or more).

4.1.15 A recently updated and unpublished Cochrane systematic review of seven RCTs directly compared flexible-dosing MMT with flexible-dosing BMT in 976 illicit-opioid-dependent people. No further RCTs comparing flexible-dose MMT and BMT were identified by the Assessment Group's searches. The daily equivalent doses in these flexible-dosing trials were 20–120 mg/day for

methadone and 2–16 mg/day for buprenorphine. Treatment retention was higher for flexible MMT compared with flexible BMT dosing (pooled HR 1.40, 95% CI 1.15 to 1.69) although there was no statistically significant difference in illicit opioid use for BMT compared with MMT (standardised mean difference –0.12, 95% CI –0.26 to 0.02 ).

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

4.1.17 Comparison of data from population cross-sectional studies suggests that the level of mortality with BMT may be lower than that with MMT, although other authors have commented that these data were unlikely to capture all related deaths.

## **Dosages**

4.1.18 Higher doses of MMT (for example, 60 mg or more) were found to be more effective than doses of less than 50 mg for improving retention on treatment (for example, 60–109 mg compared with 1–39 mg resulted in an RR of remaining on treatment of 1.36 [95% CI 1.13 to 1.63]). Doses of MMT higher than 50 mg were more effective than doses of less than 50 mg in reducing self-reported illicit opioid use (for example, 50 mg or more compared with less than 50 mg resulted in an RR of 0.82 [95% CI 0.78 to 0.95]). Higher doses of MMT (60–109 mg) were also associated with a statistically significantly lower number of illicit-opioid-positive urine tests compared with much lower doses of MMT (1–39 mg). However, high-dose MMT (60–109 mg) produced a non-significantly lower number of illicit-opioid-positive urine tests than moderate-dose MMT (40–59 mg).

## Treatment settings

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

## Summary

4.1.20 The results from the meta-analyses showed that fixed-dose MMT has higher levels of retention on treatment and lower rates of self-reported illicit opioid use compared with placebo or no treatment. Higher fixed doses of MMT are 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.

4.1.21 Meta-analyses show that fixed-dose BMT has higher levels of retention on treatment compared with placebo or no treatment, 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 is statistically significantly less than that with placebo.

4.1.22 A number of RCT meta-analyses show that fixed doses of MMT are associated with higher rates of retention on treatment than similar fixed doses of BMT. High fixed doses of MMT are more effective than lower-fixed-dose BMT at preventing illicit opioid use, but results are mixed for lower-fixed-dose MMT and higher-fixed-dose BMT.

4.1.23 In the studies analysed, rates of retention on treatment with flexible-dose MMT are superior to those with flexible-dose BMT, although there is no statistically significant difference in illicit opioid use.

## **4.2 Cost effectiveness**

- 4.2.1 Eleven published economic evaluations met the Assessment Group's inclusion criteria for review.
- 4.2.2 Eight studies assessed the cost effectiveness of MMT, one assessed the cost effectiveness of BMT and two compared the cost effectiveness of BMT directly with that of MMT. The studies reported results using a range of outcome measures. The Assessment Group reported that direct comparison of the incremental cost-effectiveness ratios (ICERs) between the studies was not possible because of differences in the approaches to modelling, time horizons, comparators and perspectives, country of origin, sources of preference weights and effectiveness data used.
- 4.2.3 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).

### **Manufacturers' models**

- 4.2.4 No economic evaluations were submitted by the manufacturers of methadone oral solution.
- 4.2.5 The manufacturer of buprenorphine (Schering-Plough) submitted a cost-effectiveness analysis of BMT compared with MMT for opioid-dependent people over a 1-year time horizon. Cost effectiveness was assessed as the incremental cost per quality-adjusted life year (QALY) using a decision-tree-based model. Costs were calculated from an NHS and PSS perspective. Both simple one-way and probabilistic sensitivity analyses were undertaken.
- 4.2.6 The model was designed to estimate the cost effectiveness of BMT in three scenarios: BMT compared with no treatment for the 20% of opioid-dependent people seeking maintenance treatment who are unable to take methadone for 'clinical reasons' (as stated by the manufacturer); BMT compared with MMT

for the remaining 80% of opioid-dependent people; and maintenance therapy (methadone and buprenorphine) compared with drug-free treatment for all opioid-dependent people.

- 4.2.7 The model included data on people retained on treatment at specified time points up to 6 months, and then followed those retained on treatment at 6 months for a further 6 months. It was assumed that people not retained on treatment returned to their pre-treatment habits however long they had been taking maintenance therapy. The data for retention on treatment and dosing for the initial 13 weeks were based on one RCT, which compared flexible dose regimes of BMT and MMT. Data on retention between 13 and 26 weeks and between 6 months and 1 year were based on two open-label stages from the same RCT. Health-related utility values were based on results from a published study and included an adjustment factor from another published study. Data on resource use and costs were derived from several studies. The use of healthcare resources was assumed to be the same for people treated with methadone or buprenorphine.
- 4.2.8 When BMT was compared with no treatment for the 20% of people who could not have MMT, BMT was shown to be more expensive and slightly more effective than no treatment (ICER £30,000 per additional QALY gained).
- 4.2.9 For people who could be treated with either therapy, BMT was dominated by MMT, as BMT was slightly more expensive than MMT and yielded marginally fewer QALYs. However, the difference in QALYs was very small (0.00055) and given the parameter uncertainty in the model, the difference in benefit is highly uncertain.
- 4.2.10 The analysis of maintenance treatment (with either drug) compared with no treatment resulted in an ICER of £12,600 per additional QALY gained. However, the Assessment Group expressed concerns about this result because of the method of analysis, which excluded buprenorphine.

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

### **Assessment Group's model**

4.2.12 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 of BMT compared with MMT. The model estimated costs and outcomes from an NHS and PSS perspective for a 12-month period for the three strategies. Maintenance therapy was assumed to be a flexible-dosing regimen, and the mean daily dose was assumed to be constant from week 13 onwards. The average cost of dispensing drugs was based on assumptions of supervised self-administration 6 days a week for the first 3 months, then unsupervised self-administration 6 days a week from 3 to 6 months, and unsupervised self-administration three times a week from 6 to 12 months. In addition to drug costs, estimates of resource use included counselling sessions, monitoring of treatment, GP visits, emergency department visits, inpatient hospital stays, outpatient mental health appointments and inpatient mental health admissions.

4.2.13 Data on retention on treatment at 2, 6, 13 and 25 weeks and 12 months were included in the model. The data for retention on treatment in the model were taken from a systematic review that identified seven trials that compared methadone and buprenorphine in flexible dosing (pooled HR of 1.40, 95% CI 1.69 to 1.15). The Assessment Group model also took into account urinalysis data, as some people still misuse drugs when in a maintenance programme. Data on the percentage of retained patients who were drug free were taken from the combined analysis of opioid-negative urine samples from

two studies. It was assumed that patients not retained on treatment returned to their pre-treatment habits however long they were taking maintenance therapy, and that 89% of those not retained on 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 estimates of the proportion of drug-dependent people who were injecting.

4.2.14 Health outcomes were expressed as QALYs. In the absence of published data on quality of life associated with drug misuse, the Assessment Group obtained health-related utility data from a panel of members of the public. The Assessment Group assumed that people not retained on treatment returned to their pre-treatment habits irrespective of their period of MMT or BMT, and used the same estimated QALY for those not retained on treatment for MMT and BMT.

4.2.15 For the reference case, the analysis of MMT compared with no treatment resulted in an ICER of £13,700 per additional QALY gained. BMT was dominated by MMT. The analysis of BMT compared with no treatment resulted in an ICER of £26,400 per additional QALY gained.

4.2.16 An additional non-reference case analysis was also conducted which included costs to the criminal justice system and to victims of crime. Costs to victims of crime included the costs of increased security measures and the direct costs of material or physical damage. Results for the non-reference case were that all strategies were dominated by MMT, and that BMT was dominant over no treatment.

4.2.17 A number of sensitivity analyses were conducted on the reference and non-reference cases. With regard to administration of buprenorphine, a sensitivity analysis was conducted assuming that from week 1 to 13 buprenorphine was delivered under supervision on alternate days, and that from week 14 to 52 it was delivered unsupervised on alternate days. BMT was still dominated by MMT. However, the ICER for BMT compared with no treatment was reduced to £24,000 per QALY gained.

4.2.18 Two sensitivity analyses were also carried out on the utility values. The first of these considered the published utility values that had also been used in the manufacturer's analysis; 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) was 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 done using the utility values from a large published study that compared MMT with methadone plus diamorphine. Using the utilities from the manufacturer's submission, the analysis resulted in BMT no longer being dominated by MMT, but the ICER was £108,300 per QALY gained, because of the very small positive difference in QALYs. Using the utility values from the large published study, the ICER for MMT versus no treatment was £16,400 per QALY gained, and BMT was still dominated by MMT. Comparing BMT with no treatment, the values used in the manufacturer's submission resulted in an ICER of £27,500 per QALY gained. Using the utility values from the large published study, the ICER for BMT compared with no treatment was £31,600 per QALY gained.

4.2.19 The final sensitivity analysis examined the impact of excluding the costs to the victims of crime, to produce an evaluation from a societal perspective with costs to the criminal justice system only. In this analysis, MMT was no longer dominant over no treatment, and instead had an ICER of £25,000 per QALY gained. BMT was still dominated by MMT. Comparing BMT with no treatment, BMT was no longer dominant and had an ICER of £37,800 per QALY gained.

### **4.3 Consideration of the evidence**

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of methadone and buprenorphine, having considered evidence on the nature of the condition and the value placed on the benefits of methadone and buprenorphine by people with opioid dependence, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

- 4.3.2 The Committee considered the evidence on the clinical effectiveness of MMT and BMT for maintenance therapy in the management of opioid dependence. The Committee acknowledged that the clinical trials showed that people on methadone or buprenorphine were retained longer in treatment compared with those on placebo. The Committee also acknowledged that the observational and trial data showed that people on methadone or buprenorphine were less likely to die than those on placebo or no therapy. For people on methadone, there was also a reduction in use of illicit opioids compared with those on placebo. For the comparison of methadone with buprenorphine, the Committee noted that the trials showed that people on methadone were retained longer in treatment compared with those on buprenorphine. For illicit opioid use while in treatment, there were no statistically significant differences between the two drugs. The Committee noted that there was uncertainty around the risk of mortality in the published research, and heard from the experts about the potential increased risk of death for people using methadone compared with buprenorphine, and the potential increased risk of death for other people when diversion (where the medication is forwarded on to others for non-prescription uses) of methadone occurs. The Committee considered the importance of supervision of both methadone and buprenorphine and noted that the Assessment Group's model assumed supervised administration of the drugs for 6 days a week for the first 3 months, which is in line with the Department of Health guidelines.
- 4.3.3 The clinical experts raised concerns about the generalisability of the RCTs, none of which were conducted in the UK. The Committee heard from the experts that there were a number of differences between the trials and current NHS practice (such as the dose used, and the levels of supervised delivery and psychosocial intervention). The Committee also noted that access to psychosocial care is limited and variable around the UK. The Committee also heard from the patient experts that the cost of illicit street drugs in the countries where the trials were conducted differed from the cost in the UK, and that this could affect the degree of retention in maintenance programmes.

The Committee heard from the experts that despite the differences between the trials and current NHS practice, the outcomes of the trials could be generalised to opioid-dependent people in England and Wales. The Committee additionally acknowledged that in England and Wales flexible dosing is most commonly used and that programmes of supportive care are generally available.

4.3.4 The Committee considered the cost-effectiveness evidence for the comparisons of flexible doses of methadone and buprenorphine versus no treatment, and acknowledged the inclusion of costs for supervised delivery on a daily basis of each of the drugs for a minimum of 3 months, and the ongoing costs of supportive care, including psychosocial care delivered alongside these drugs. The Committee concluded that, on the basis of the evidence, both methadone and buprenorphine in flexible dosing regimens are clinically effective and cost effective, compared with no treatment, for maintenance therapy in the management of opioid dependence.

4.3.5 The Committee heard from the experts that it was not always clear which drug (methadone or buprenorphine) should be prescribed in individual cases. In some circumstances there can be clinical reasons for prescribing either methadone or buprenorphine, taking into account the person's history of opioid dependence. For people who are less opioid dependent and are planning on becoming abstinent, buprenorphine may provide greater flexibility and enable earlier detoxification. The Committee also heard that some people may have a preference for one drug over the other, which will affect their compliance with and retention in treatment. The Committee considered carefully the issue of mortality from overdose, particularly when methadone treatment is started. The Committee was also aware of the risks of diversion of these drugs to non-drug-users, especially children, in particular the high mortality risk associated with methadone in opioid-naïve people. However, the Committee considered that the current guidance, while taking account of the adverse effects of therapy in people prescribed the drugs, could not deal individually with all the issues associated with diversion. The Committee was

persuaded of the importance of having both drug treatment options available, and that the decision on which was the most appropriate treatment for an individual should be made on a case by case basis. The Committee concluded that the responsible clinician, in consultation with the person, should estimate the risks and benefits of prescribing methadone or buprenorphine, taking account of the person's lifestyle and family situation (for example, whether they are considered chaotic and might put children and other opioid-naïve individuals living with them at risk).

- 4.3.6 The Committee was aware of the importance of supervised therapy in avoiding the risks associated with adverse effects, in particular those associated with diversion of treatment. The Committee noted that the current Department of Health guideline on supervision explicitly states that, after an initial 3-month supervision period, the level of supervision should only be relaxed when the patient's compliance is assured.
- 4.3.7 The Committee considered the cost-effectiveness evidence for the comparison of methadone and buprenorphine. Although methadone dominates buprenorphine for all the scenarios because it is cheaper and yields marginally more QALYs (0.067), the Committee acknowledged that in certain circumstances a person is not able to take methadone and therefore the appropriate comparator for the alternative treatment in these cases would be no treatment. The ICER in the reference case for buprenorphine versus no treatment is £26,400 per additional QALY gained.
- 4.3.8 Taking all these factors into account, the Committee concluded that the decision about which drug to use should be made on a case by case basis and should consider a number of clinical and patient factors, including the person's history of opioid dependence, their commitment to a particular long-term management strategy and an estimate of the risks and benefits made by the responsible clinician in consultation with the person. However, the Committee was mindful that methadone is cheaper than buprenorphine and

therefore concluded that, if both drugs are equally suitable for a person, methadone should be prescribed as first choice.

- 4.3.9 The Committee also noted the importance of supportive care used alongside these drugs, and concluded that the delivery of both methadone and buprenorphine should be part of a programme of supportive care to ensure maximum benefit. The Committee also considered that this package of care should ideally include psychosocial care, but that methadone and buprenorphine should be provided even when psychosocial care is not available.

## **5 Implementation**

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003, which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website ([www.nice.org.uk/TAXXX](http://www.nice.org.uk/TAXXX)).

*[Note: tools will be available when the final guidance is issued]*

## 6 Recommendations for further research

- 6.1 Randomised controlled trials conducted in the UK comparing methadone and buprenorphine using flexible dosing are required.
- 6.2 Randomised controlled trials conducted in the UK comparing high-dose methadone and high-dose buprenorphine are required.
- 6.3 Research examining the impact of supervised consumption on the prevention of overdose is needed.

## 7 Related guidance

- 7.1 NICE is in the process of producing the following guidance.

Naltrexone for the management of opioid dependence. *NICE technology appraisal guidance* (publication expected March 2007).

Drug misuse: opiate detoxification of drug misusers in the community and prison settings. *NICE clinical guideline* (publication expected July 2007).

Drug misuse: psychosocial management of drug misusers in the community and prison settings. *NICE clinical guideline* (publication expected July 2007).

Community-based interventions to reduce substance misuse among the most vulnerable and disadvantaged young people. *NICE public health intervention guidance* (publication expected February 2007).

## 8 Review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in March 2010.

David Barnett

Chair, Appraisal Committee

October, 2006

## **Appendix A. Appraisal Committee members and NICE project team**

### **A. Appraisal Committee members**

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into three branches, with the chair, vice-chair and a number of other members attending meetings of all branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Dr Darren Ashcroft**

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences,  
University of Manchester

#### **Professor David Barnett (Chair)**

Professor of Clinical Pharmacology, University of Leicester

#### **Dr Peter Barry**

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

#### **Mr Brian Buckley**

Lay Member

**Professor John Cairns**

Public Health and Policy, London School of Hygiene and Tropical Medicine

**Professor Mike Campbell**

Statistician, University of Sheffield

**Professor David Chadwick**

Professor of Neurology, Walton Centre for Neurology and Neurosurgery

**Dr Mark Chakravarty**

Industry Member

**Dr Peter I Clark**

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside

**Dr Mike Davies**

Consultant Physician, University Department of Medicine and Metabolism,  
Manchester Royal Infirmary

**Mr Richard Devereaux-Phillips**

Industry Member

**Professor Jack Dowie**

Health Economist, London School of Hygiene

**Dr Fergus Gleeson**

Consultant Radiologist, The Churchill Hospital, Oxford

**Ms Sally Gooch**

Independent Healthcare Consultant

**Mr Sanjay Gupta**

Stroke Services Manager, Basildon and Thurrock University Hospitals NHS Trust

**Professor Philip Home**

Professor of Diabetes Medicine, University of Newcastle upon Tyne

**Dr Peter Jackson**

Clinical Pharmacologist, University of Sheffield

**Professor Peter Jones**

Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

**Dr Mike Laker**

Medical Director, Newcastle Hospitals NHS Trust

**Dr George Levvy**

Chief Executive, Motor Neurone Disease Association, Northampton

**Ms Rachel Lewis**

Nurse Advisor to the Department of Health

**Mr Terence Lewis**

Lay Member

**Professor Jonathan Michaels**

Professor of Vascular Surgery, University of Sheffield

**Dr Neil Milner**

General Practitioner, Sheffield

**Dr Ruairidh Milne**

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology

**Dr Rubin Minhas**

General Practitioner and CHD Clinical Lead, Medway PCT

**Dr Rosalind Ramsay**

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

**Mr Miles Scott**

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

**Dr Lindsay Smith**

General Practitioner, East Somerset Research Consortium

**Mr Roderick Smith**

Director of Finance, Adur, Arun and Worthing PCT

**Dr Ken Stein**

Senior Lecturer, Peninsula Technology Assessment Group (PenTAG), University of Exeter

**Professor Andrew Stevens**

Professor of Public Health, University of Birmingham

The following individuals representing the National Collaborating Centre for Mental Health, which is responsible for developing the Institute's clinical guidelines on detoxification and psychosocial interventions for drugs misuse, were invited to attend the ACD and FAD meetings as observers and to contribute as advisers to the Committee.

- Dr Clare Gerada (Royal College of General Practitioners) – Chair, Guideline Development Group for the clinical guideline on drug misuse (detoxification)
- Professor John Strang (Professor of Psychiatry of Addictions, National Addiction Centre [Institute of Psychiatry]) – Chair, Guideline Development Group for the clinical guideline on drug misuse (psychosocial management)
- Mr Steve Pilling, Director, National Collaborating Centre for Mental Health

## **B. NICE Project Team**

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

### **Joanna Richardson**

Technical Lead

### **Louise Longworth**

Technical Adviser

### **Emily Marschke**

Project Manager

## Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration.

- 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*, February 2006.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and appraisal consultation document (ACD). Consultee organisations have the opportunity to appeal against the final appraisal determination (FAD).

### I Manufacturers/sponsors:

- AAH Pharmaceuticals
- Generics UK
- Martindale Pharmaceuticals
- Rosemont Pharmaceuticals
- Schering-Plough
- Thornton and Ross

### II Professional/specialist and patient/carer groups:

- Addiction Recovery Foundation
- Association of Nurses in Substance Abuse
- British Association for Psychopharmacology
- Federation of Drug and Alcohol Professionals
- National Drug Prevention Alliance
- National Pharmaceutical Association

- Pharmaceutical Services Negotiating Committee
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians of Edinburgh
- Royal College of Physicians
- Royal Pharmaceutical Society
- Substance Misuse Management in General Practice
- UK Harm Reduction Alliance
- Royal College of Psychiatrists
- Specialist Clinical Addiction Network
- Addiction
- ADFAM
- Alliance (formerly the Methadone Alliance)
- Families Anonymous
- Lifeline
- Rehabilitation for Addicted Prisoners Trust (RAPt)
- Release
- Turning Point

III Other consultees

- Department of Health
- East Leeds PCT
- Great Yarmouth PCT
- Welsh Assembly Government

IV Commentator organisations (without the right of appeal):

- British National Formulary
- HM Prison Service
- National Treatment Agency for Substance Misuse
- NHS Confederation
- NHS Purchasing and Supplies Agency

- NHS Quality Improvement Scotland
- Action on Addiction
- Centre for Research on Drugs and Health Behaviour (Imperial College)
- Department of Addictive Behaviour (St George's Hospital Medical School)
- DrugScope
- Independent Drug Monitoring Unit
- National Addiction Centre (Institute of Psychiatry)
- Society for the Study of Addiction
- National Programme on Substance Abuse Deaths, St George's Hospital Medical School
- West Midlands Health Technology Assessment Collaboration
- National Coordinating Centre for Health Technology Assessment
- Guideline Development Group for the NICE clinical guideline on drug misuse (detoxification)
- Guideline Development Group for the NICE clinical guideline on drug misuse (psychosocial management)

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on methadone and buprenorphine for the management of opioid dependence by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Chris Ford, GP Clinical Lead, nominated by Substance Misuse Management in General Practice (SMMGP) – clinical specialist
- Dr Judith Myles, Consultant Psychiatrist, nominated by Royal College of Psychiatrists – clinical specialist
- Dr Duncan S Raistrick, Consultant in Addiction Psychiatry, nominated by Specialist Clinical Addiction Network (SCAN) – clinical specialist
- Mr Peter McDermott, nominated by The Alliance – patient expert
- Ms Moya Pinson, nominated by Release – patient expert
- Mr Gary Sutton, Head of Drug Advice Team, nominated by Release – patient expert