Gutachten zum Einsatz von Methadon und Buprenorphin bei Opiodabhängigen

Drug misuse - methadone and buprenorphine: Appraisal consultation document

Please note that this consultation is now closed.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE, UK

Appraisal Consultation Document

Methadone and buprenorphine for the management of opioid dependence

The Department of Health and the Welsh Assembly Government have asked the National Institute for Health and Clinical Excellence (NICE or the Institute) to conduct an appraisal of methadone and buprenorphine and provide guidance on their use to the NHS in England and Wales. The Appraisal Committee has had its first meeting to consider both the evidence submitted and the views put forward by the representatives nominated for this appraisal by professional organisations and patient/carer and service user organisations. The Committee has developed preliminary recommendations on the use of methadone and buprenorphine.

This document has been prepared for consultation with the formal consultees. It summarises the evidence and views that have been considered and sets out the preliminary recommendations developed by the Committee. The Institute is now inviting comments from the formal consultees in the appraisal process (the consultees for this appraisal are listed on the NICE website, www.nice.org.uk).

Note that this document does not constitute the Institute's formal guidance on these technologies.The recommendations made in section 1 are preliminary and may change after consultation.

The process the Institute will follow after the consultation period is summarised below. For further details, see the *Guide to the technology appraisal process* (this document is available on the Institute?s website, www.nice.org.uk).

The Appraisal Committee will meet again to consider the original evidence and this Appraisal Consultation Document in the light of the views of the formal consultees.

At that meeting, the Committee will also consider comments made on the document by people who are not formal consultees in the appraisal process.

After considering feedback from the consultation process, the Committee will prepare the Final Appraisal Determination (FAD) and submit it to the Institute.

Subject to any appeal by consultees, the FAD may be used as the basis for the Institute?s guidance on the use of the appraised technology in the NHS in England and Wales.

The key dates for this appraisal are:
Closing date for comments: 21 July 2006
Second Appraisal Committee meeting: 6 September 2006

Details of membership of the Appraisal Committee are given in appendix A and a list of the sources of evidence used in the preparation of this document is given in appendix B.

Note that this document does not constitute the Institute's formal guidance on this technology. The recommendations made in section 1 are preliminary and may change after consultation.

1 Appraisal Committee's preliminary recommendations

1.1 Methadone and buprenorphine, 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 patient?s history of opioid dependence, whether the patient?s aim is to become abstinent, and the patient?s preference. If there is little differential between the two drugs, methadone should be prescribed as first choice.

1.3 Methadone and buprenorphine should be administered under adequate supervision. They should be given as part of a care programme that includes access to psychosocial therapy.

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 includes opium, morphine, codeine and others. 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 dependence on illicit diamorphine can cause physical problems as a result of the spread of blood-borne viruses when it is injected (for example, HIV and hepatitis B or C) and the risk of an accidental overdose. 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 A ssociated social problems include marital and relationship breakdown, unemployment, 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. Many 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 as £1 billion per annum in 1996.

2.3 Biological, psychological, social and economic factors influence when and why a person starts taking illicit opioids. Opioid use quickly escalates to misuse (repeated use despite 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 and blood pressure). The body also becomes tolerant to 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 may take over people?s lives. It is difficult to stop using these drugs and remain abstinent because of a combination of craving, unpleasant withdrawal symptoms, and the continued or worsening personal circumstances that led to drug use in the first place.

2.4 When an opioid-dependent person manages to become abstinent, there are usually 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 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.

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) are injecting. The National Drug Treatment Monitoring System (NDTMS) estimates that in 2004?05 there were 160,450 people in contact with treatment services in England. Because of the lack of substitute medications for other drugs (such as crack cocaine and alcohol), most people in treatment were dependent on opioids. About 70% of people newly presenting for treatment were male. There are about 40,000 people who misuse drugs in prison in England and Wales at any time. In one UK survey, 21% of prisoners had used opiates at some point during their sentence, and 10% of prisoners had used it during the previous week.

2.6 The UK has a range of treatment services for opioid dependency. Medical 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 harm reduction and a substitution regimen), or abstinence (also known as detoxification and withdrawal). In a bstinence strategies, a person who is physically dependent on a drug stops taking it. Some people can achieve abstinence from opioids rapidly; others require the support of prescribed medication for longer than a few months. The opioid antagonist naltrexone can be used to help maintain abstinence. In maintenance strategies, people initially receive a long-acting opioid (methadone or buprenorphine) as a substitute for the illicit drug of unknown purity and quality. They may then progress to abstinence therapy.

2.8 The aim of the maintenance approach is to reduce craving and prevent withdrawal, eliminate the hazards of needles, free the person from preoccupation with obtaining illicit opioids, enhance overall function and provide stability, enabling the person to make use of psychosocial interventions. Substitute opioids are prescribed in doses higher than that required merely to prevent withdrawal symptoms. After 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?).

2.9 Psychosocial and behavioural therapies play an important role in the treatment of drug misuse; the therapies aim to give people the ability to resist substance use and cope with problems related to drug use. For opioid users they 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. Prescribing guidelines in the UK recommend that when a person starts maintenance opioids, they should take each dose under the supervision of a nurse, doctor or community pharmacist for the first 3 months of treatment. As the person begins to work on major life changes, the need for daily collection of the medication and supervision may change. For maintenance to work, a number of ancillary services must meet best recommended practice criteria. Initial assessment should include oral fluid or urine testing, and the patient may need to be seen by a doctor or specialist drug worker several times within the first few weeks of induction and dose titration.

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

2.11 The number of people on 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 period it was estimated that 8700 people were on buprenorphine treatment, at an average dose of 10 mg/day.

3 The technologies

3.1 Methadone (Martindale Pharmaceuticals, Rosemont Pharmaceuticals, AAH 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)?.

3.2 Methadone is used in opioid dependence at an initial dose of 10?40 mg daily, increased by up to 10 mg daily (with a maximum weekly increase of 30mg) until no signs of withdrawal or intoxication are seen. The usual maintenance dose range is 60?120 mg daily, although larger doses may also be used. Methadone is available as oral solution or injectable ampoules. Only the oral form of methadone is considered in this appraisal.

3.3 Administering methadone orally avoids the risks associated with injecting. Methadone has a long elimination half-life, and this allows for a single 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, 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. For full details of side effects and contraindications, see the SPC.

3.4 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, sedatives or tricyclic antidepressants may also induce serious respiratory depression. The risk of death during methadone initiation 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 insidious and toxic effects may become life threatening several hours after taking a dose. During the initiation 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 they are stable the frequency of medical assessment can be reduced.

3.5 The cost of methadone oral solution (1 mg/ml) is £1.35 per 100 ml excluding VAT (?British national formulary?, edition 51). Costs may vary in different settings because of negotiated procurement discounts.

3.6 Buprenorphine (Schering Plough) has both partial opioid agonist and antagonist activity and provides a milder, less euphoric and less sedating effect than full opioid agonists such as diamorphine or methadone (these effects are less pronounced with methadone than with diamorphine).

3.7 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.

3.8 Buprenorphine differs from methadone in its mode of action, in various ways. Buprenorphine has a high affinity for opioid receptors and this reduces the impact of additional illicit diamorphine or other opioid use by preventing illicit diamorphine from occupying these receptors. For this reason buprenorphine may be better suited to people who wish to cease using illicit diamorphine completely. The high affinity of buprenorphine for opioid receptors

means that it has a prolonged duration of action at higher doses, which does not correlate with its plasma concentration. This potentially allows alternate-day and 3-days-a-week dispensing regimens. Buprenorphine also has a relatively good safety profile, and doses many times greater than normal therapeutic doses appear rarely 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. In people dependent on high doses of opioids, buprenorphine may precipitate symptoms of withdrawal because of its partial antagonist activity. For full details of side effects and contraindications, see the SPC.

3.9 The cost of buprenorphine is £2.88 per 8 mg tablet excluding VAT (?British national formulary? edition 51; also available in 400 microgram, and 2 mg strengths). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee considered evidence from a number of sources (see appendix B). 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.

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 included in these reviews overlap. 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, 3 in Australia, 3 in Iran, 2 in the Netherlands, 2 in Austria and 1 in Norway.

4.1.2 Most of the 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 all those younger than 18 years of age were excluded from most trials.

4.1.3 Most studies were undertaken in outpatient, inpatient 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 three consecutive days of treatment, limited adjuvant psychosocial therapy, no rewards for treatment compliance, intensive monitoring, limited length of treatment and relatively short periods of follow up (in most cases up to 1 year).

4.1.4 Most trials to date have used a fixed-dose design, in which all those included are given a fixed dose of methadone or buprenorphine. Methadone doses range from 50?150 mg/day and buprenorphine from 1?15 mg/day. More recently, some 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 people receive a flexible individualised dose of methadone or buprenorphine.

4.1.5 The two main outcomes reported were retention on treatment and illicit use of opioids, the latter being reported in a variety of ways (for example, proportion of people taking opioids, mean rate of heroin intake 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).

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 relative risk 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 opiate use compared with placebo or no treatment. One systematic review, (n = 246) that compared 60 mg methadone daily with no therapy gave an RR of opioid use (self-reported) of 0.31 (95% CI 0.23 to 0.42). In another systematic review (n = 347), comparing doses of 50 mg or more methadone with placebo resulted in an RR of 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 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 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 patients on BMT (16 mg) compared with 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 opioid use (self-reported or urinary confirmed), adverse events, HIV risk behaviour or crime.

Methadone maintenance therapy versus buprenorphine maintenance therapy

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 opioid use between users of fixed doses of MMT and users of fixed doses of BMT. A high fixed dose of MMT was more effective than a low fixed dose of BMT (at least 50 mg compared with less than 8 mg), RR 0.29 (95% CI 0.16 to 0.53). Results were mixed for comparisons of lower fixed-dose MMT (less than 50 mg) and higher fixed-dose 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 opiate-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 superior 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 opiate 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. Ten 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 it was commented that these data were unlikely to capture all related deaths.

Dosages

4.1.18 Higher doses of MMT (for example, 50 mg or more) were found to be more effective than lower doses (less than 50 mg) in 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]). Higher doses of MMT were more effective than lower doses in reducing self-reported 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 opioid-positive urine tests compared with much lower doses of MMT (1?39 mg). However, a comparison of high-dose MMT (60?109 mg) with moderate-dose MMT (40?59 mg) produced a non-significant lower number of opioid-positive urine tests.

Treatment settings

4.1.19 Although the 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 in outpatient clinics.

Summary

4.1.20 The results from the meta-analyses showed that fixed-dose MMT has superior levels of retention on treatment and lower rates of self-reported opiate use compared with placebo or no treatment, 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.

4.1.21 Meta-analyses show that fixed-dose BMT has superior levels of retention on treatment compared with placebo or no treatment, 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 have rates of retention on treatment superior to those of comparable fixed doses of BMT. High fixed doses of MMT are more effective than lower fixed-dose BMT, while for lower fixed dose MMT and higher fixed dose BMT results were mixed in their effectiveness at preventing opioid use.

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 opiate use.

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

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 assessed the cost effectiveness of BMT compared directly with MMT. The studies reported results using a range of outcome measures. The Assessment Group reported that direct comparisons 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 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 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 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 with MMT for the remaining 80% of patients; and maintenance therapy (methadone and buprenorphine) versus drug-free treatment for the overall patient group.

4.2.7 The model includes data on patients retained on treatment at specified time points up to 6 months, and then follows those retained in treatment at 6 months for a further 6 months. For those not retained in treatment it was assumed that they return to their pre-treatment habits irrespective of their period of 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 methadone and buprenorphine users.

4.2.8 In the scenario in which BMT was compared with no treatment for the 20% of patients 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 patients who could be treated with either therapy, BMT was dominated by MMT as it 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 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 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, accident and emergency visits, inpatient hospital stays, outpatient mental health visits and inpatient mental health stays.

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 was 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 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 were taken from the combined analysis of opioid-negative urine samples from two studies. For those not retained in treatment it was assumed that patients return to their pre-treatment habits irrespective of their period of 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 the estimate of the proportion of drug-taking patients who were injecting and not injecting.

4.2.14 Health outcomes were expressed as quality adjusted life-years (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 in 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 and 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 BMT is dominant over no treatment.

4.2.17 A number of sensitivity analyses were conducted on the reference and non-reference case. 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 versus 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) 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 done using the utility values from a large published study that compared MMT with methadone and diamorphine. Using the utilities from the industry 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 by the industry submission resulted in an ICER of £27,500 per QALY gained. Using the utility values from the large published study, the ICER for BMT versus no treatment was £31,600 per QALY gained.

4.2.19 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. 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 showed greater retention 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 compared with those on placebo, a reduction in use of illicit opiates while in treatment was also shown. 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 opiate 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 of the potential increased risk of death for people using methadone compared with buprenorphine, particularly 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 delivery of the drugs, 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 practice in the trials and current NHS practice (such as the dose used, levels of supervised delivery and levels of psychosocial intervention). The Committee also heard from the patient experts that the cost of illegal street drugs in the countries where the trials were conducted differed from the costs in the UK, and that this could also affect the degree of retention in maintenance programmes. The Committee was persuaded 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 was most commonly used.

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 of each of the drugs, and the ongoing costs of psychosocial therapy delivered alongside these drugs.

4.3.5 The Committee concluded that, on the basis of the evidence, both methadone and buprenorphine, in flexible dosing regimens, were individually clinically effective and cost effective, compared with no treatment, for maintenance therapy in the management of opioid dependence.

4.3.6 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 at the lower end of the range of dependence who are planning on becoming abstinent, buprenorphine might 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 was persuaded of the importance of having both drug treatment options available, and that it was likely that decisions on which was appropriate would normally be made on a case by case basis.

4.3.7 The Committee considered the cost-effectiveness evidence for the comparison of methadone and buprenorphine and although methadone dominates buprenorphine for all the scenarios presented, because it is cheaper and yields marginally more QALYs (0.067), the Committee acknowledged that in certain circumstances methadone would not be taken and therefore the appropriate comparator for the alternative treatment (buprenorphine) 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 patient?s history of opioid dependence, whether the patient?s aim is to become abstinent, and patient preference.

4.3.9 The Committee was mindful that methadone is cheaper than buprenorphine and therefore concluded that, in individual cases where there is little differential between the two drugs, methadone should be prescribed as first choice.

4.3.10 The Committee was concerned with the potential risk of diversion of these drugs, particularly methadone with its high risk of death in opioid-naïve people. The Committee also noted the importance of psychosocial therapy alongside the use of these two drugs in maintenance therapy and concluded that these drugs should be administered under adequate supervision and should be delivered as part of a care programme that includes access to psychosocial therapy.

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

6 Proposed recommendations for further research

6.1 None

7 Related guidance

NICE is in the process of producing the following guidance.

7.1 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 Proposed date for 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 It is proposed that the guidance on this technology is considered for review in March 2013. The Institute would particularly welcome comment on this proposed date.

David Barnett

Chair, Appraisal Committee

June, 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 two branches, with the chair, vice-chair and a number of other members attending meetings of both 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
Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Mr Brian Buckley
Lay Representative

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 Representative

Dr Peter I Clark
Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside

Dr Mike Davies
Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips
Industry Representative

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 Representative

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

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Joanna Richardson
Technical Lead, NICE project team

Louise Longworth
Technical Advisor, NICE project team

Emily Marschke
Project Manager, NICE project team

Appendix B. Sources of evidence considered by the Committee

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

A 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.

The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope and assessment report. They are also invited to comment on the appraisal consultation document and consultee organisations are provided with the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

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

B II Professional/specialist and patient/carer groups:

- Addiction Recovery Foundation
- Association of Nurses in Substance Abuse (ANSA)
- 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 (SMMGP)

- UK Harm Reduction Alliance
- Royal College of Psychiatrists
- Specialist Clinical Addiction Network (SCAN)
- 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 (NTA)
- 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 (IDMU)
- 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
- Drugs Misuse ? Psychosocial Guidelines Development Group
- Drugs Misuse ? Detoxification Guidelines Development Group

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 are invited to comment on the ACD.

C

- Dr Ed Day ? Senior Lecturer in Addiction Psychiatry, Queen Elizabeth Psychiatric Hospital ? clinical specialist
- Dr Chris Ford ? GP Clinical Lead, Substance Misuse Management in General Practice (SMMGP)? clinical specialist
- Dr Judith Myles ? Consultant Psychiatrist, Royal College of Psychiatrists ? clinical specialist
- Dr Duncan S Raistrick ? Consultant in Addiction Psychiatry, Specialist Clinical

Addiction Network (SCAN) ? clinical specialist
- Mr Peter McDermott ? Patient Advocate, The Alliance ? patient expert
- Ms Moya Pinson ? Volunteer at Release, Release ? patient expert
- Mr Gary Sutton ? Head, Drug Advice Team, Release ? patient expert

The following individual(s) 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 meeting as observers and to contribute as advisers to the Committee.

D
- Dr Clare Gerada ? Royal Collage of General Practitioners, Chair, Drug Misuse Detoxification Guideline Development Group
- Professor John Strang ? Professor of Psychiatry of Addictions, National Addiction Centre (Institute of Psychiatry), Chair, Drug Misuse Psychosocial Interventions Guideline Development Group
- Mr Steve Pilling ? Director, National Collaborating Centre for Mental Health