NICE National Institute for Health and Care Excellence

NICE guidance

Methadone and buprenorphine for the management of opioid dependence

Technology appraisal guidance
Published: 24 January 2007

www.nice.org.uk/guidance/ta114

Your responsibility

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

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 to 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 to 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 1,000 of the population aged 15 to 64 years (360,811 people), and that 3.2 per 1,000 (123,498 people) inject drugs. The National Drug Treatment Monitoring System (NDTMS) estimates that in 2004 to 2005, 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 1 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 and 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 BNF states that methadone is to be used in opioid dependence at an initial dose of 10 to 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 to 120 mg daily.

3.1.3 Methadone is available as an oral solution (1 mg/ml), an oral concentrate (10 mg/ml), tablets or injectable ampoules. Only oral formulations of methadone are considered in this appraisal. Administering methadone orally avoids the risks associated with injecting. Methadone has a long elimination half-life (usually 20 to 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. The cost of methadone oral concentrate (10 mg/ml) is £12.01 per 150 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 to 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 to 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, edition 51). Buprenorphine is also available in 2 mg (£0.96 per tablet) and 400 micrograms (£0.23 per tablet) strengths (BNF, edition 51). 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. 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, 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 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 to 150 mg/day and buprenorphine doses were in the range 1 to 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 2 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 or adverse events and mortality, and non-health outcomes (that is, crime and employment).

Methadone maintenance therapy (MMT) versus no drug therapy or 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 to 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 to 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 4 times more likely to die than those on treatment. The base rates (for those out of methadone treatment) in the included studies included 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 2 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 or 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=1,131) 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 to 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 to 80 mg methadone with 6 to 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 7 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 to 120 mg/day for methadone and 2 to 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 4 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 to 109 mg compared with 1 to 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 to 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 to 39 mg). However, high-dose MMT (60 to 109 mg) produced a non-significantly lower number of illicit-opioid-positive urine tests than moderate-dose MMT (40 to 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, 1 assessed the cost effectiveness of BMT and 2 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, perspectives 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 1-way and probabilistic sensitivity analyses were undertaken.

4.2.6 The model was designed to estimate the cost effectiveness of BMT in 3 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 1 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 2 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 3 an NHS and PSS perspective for a 12-month period for the 3 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 3 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 7 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 2 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 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 utility values 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 the 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 2 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 for 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 1 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 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has opioid dependence and the healthcare professional responsible for their care thinks that methadone and buprenorphine are the right treatments, they should be available for use, in line with NICE's recommendations.

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 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committee is a standing advisory committee of NICE. 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 3 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, Liverpool

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 NICE's 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 of the Guideline Development Group on drug misuse (detoxification).
- Professor John Strang, Professor of Psychiatry of Addictions, National Addiction Centre (Institute of Psychiatry), Chair of the Guideline Development Group on drug misuse (psychosocial management).
- Mr Steve Pilling, Director, National Collaborating Centre for Mental Health.

NICE Project Team

Each technology appraisal is assigned to a team consisting of 1 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

8 Sources of evidence considered by the Committee

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

- Connock M, Juarez-Garcia A, Jowett, S et al (2006). Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. West Midlands Health Technology Assessment Collaboration.

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).

Companies or sponsors:

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

Professional or specialist, and patient or carer groups:

- Addaction
- Addiction Recovery Foundation
- ADFAM
- Alliance (formerly the Methadone Alliance)
- Association of Nurses in Substance Abuse (ANSA)

- British Association for Psychopharmacology
- Families Anonymous
- Federation of Drug and Alcohol Professionals
- Lifeline
- National Drug Prevention Alliance
- National Pharmaceutical Association
- Pharmaceutical Services Negotiating Committee
- Rehabilitation for Addicted Prisoners Trust (RAPt)
- Release
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Physicians of Edinburgh
- Royal College of Psychiatrists
- Royal Pharmaceutical Society
- Specialist Clinical Addiction Network (SCAN)
- Substance Misuse Management in General Practice (SMMGP)
- UK Harm Reduction Alliance
- Turning Point

Other consultees

- Department of Health
- East Leeds PCT
- Great Yarmouth PCT

- Welsh Assembly Government

Commentator organisations (without the right of appeal):

- Action on Addiction
- British National Formulary
- Centre for Research on Drugs and Health Behaviour (Imperial College)
- Department of Addictive Behaviour (St George's Hospital Medical School)
- DrugScope
- Drugs Misuse – Psychosocial Guidelines Development Group
- Drugs Misuse – Detoxification Guidelines Development Group
- HM Prison Service
- Independent Drug Monitoring Unit
- National Addiction Centre (Institute of Psychiatry)
- National Coordinating Centre for Health Technology Assessment
- National Programme on Substance Abuse Deaths, St George's Hospital Medical School
- National Treatment Agency for Substance Misuse (NTA)
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland
- Society for the Study of Addiction
- West Midlands Health Technology Assessment Collaboration

The following individuals were selected from clinical specialist and patient advocate nominations from the professional or specialist, and patient or 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

Update information

March 2014: Implementation section updated to clarify that methadone and buprenorphine are recommended as options for treating opioid dependence.

ISBN: 978-1-4731-7035-3