Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation

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Executive summary

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Background
Opiate dependence is becoming increasingly prevalent, with associated increases in the spread of infectious disease (e.g. HIV, hepatitis B and C) and overdose deaths. Methadone has traditionally been the mainstay drug used in the management of opioid-dependent individuals. Buprenorphine has been reported as an alternative to methadone.

Objectives
The primary objective of this assessment report was to assess the clinical and cost-effectiveness of buprenorphine maintenance therapy (BMT) and methadone maintenance therapy (MMT) for the management of opioid-dependent individuals from the perspective of the NHS and Personal Social Services (PSS).

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

- Is MMT effective and cost-effective compared with no drug therapy?
- Is BMT effective and cost-effective compared with no drug therapy?
- Is MMT or BMT more effective and cost-effective?

We also sought to explore the variation in effectiveness of BMT and MMT across drug doses, patient subgroups and treatment settings; assess the cost-effectiveness of BMT and MMT from a wider societal perspective; and compare the effectiveness of BMT with buprenorphine detoxification therapy (BDT) and MMT with methadone detoxification therapy (MDT).

Methods
Comprehensive bibliographic searches were undertaken, from 1996 or the year of database inception to August 2005, so as to identify clinical effectiveness and cost-effectiveness studies. Given the number of systematic reviews already published in this area, the assessment of clinical effectiveness was based on a review of these reviews plus an updated search for randomised controlled trials (RCTs). Industry submissions to the National Institute for Health and Clinical Excellence were searched for additional clinical effectiveness and cost-effectiveness evidence. A decision tree was developed with a Monte Carlo simulation model to assess the cost-effectiveness of BMT and MMT. This model was designed to estimate costs, from the perspective of the NHS and PSS and outcomes in terms of quality-adjusted life-years (QALYs) for 1 year for the three strategies. Retention in treatment and opiate abuse parameters were sourced from the meta-analysis of RCTs directly comparing flexible-dose MMT with flexible-dose BMT. Utilities were derived from a panel representing a wider societal perspective.

Results
Clinical effectiveness
Thirty-one systematic reviews (including either RCT or non-RCT evidence) met the inclusion criteria of this report. Many of the studies included in these reviews overlap. In addition, 28 RCTs published more recently (since 2001) were identified. The majority of systematic reviews and RCTs were of moderate to good quality, focused on short-term (up to 1-year follow-up) outcomes of retention in treatment and the level of opiate use (self-report or urinalysis) in those individuals retained in treatment. Most studies employed a trial design that compared a fixed-dose strategy (i.e. all individuals received a standard dose) of MMT or BMT and were conducted in predominantly young men who fulfilled the Diagnostic and Statistical Manual of Mental Disorder IV criteria as opiate-dependent or heroin-dependent users, without significant co-morbidities. However, flexible dosing (i.e. individualised doses) of MMT and BMT is more reflective of real-world practice and was therefore focused on in this report.

MMT versus no drug therapy/placebo
A number of RCT meta-analyses have consistently shown that fixed-dose MMT has superior levels of retention [e.g. 20–97 mg versus placebo: pooled relative risk (RR) 3.91, 95% confidence interval (CI) 1.17 to 13.2] in treatment and opiate use
(e.g. 35–97 mg versus no treatment: pooled effect size 0.65, 95% CI 0.41 to 0.89) than placebo or no treatment, with higher fixed doses of MMT being more effective than lower fixed doses (retention in treatment, e.g. ≥50 mg versus <50 mg: pooled RR 1.25, 95% CI 0.94 to 1.67). There was evidence, primarily from non-randomised observational studies, that fixed-dose MMT reduces mortality, HIV risk behaviour and levels of crime compared with no therapy.

**BMT versus no drug therapy/placebo**

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

**BMT versus MMT**

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

**Treatment modifiers**

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

**Cost-effectiveness**

**Previous economic evaluations**

Eleven economic evaluations met the inclusion criteria of this report. Eight studies assessed the cost-effectiveness of MMT and two BMT for opiate abuse. Direct comparison of the results between the studies is not readily possible because of their different approaches to modelling, different time horizons, comparators and perspective, country of origin, source of preference weights and effectiveness data used. Although most of the included papers were considered to be of high quality, none used all of the appropriate parameters, effectiveness data, perspective and comparators required to make their results generalisable to the NHS context.

**Industry economic evidence**

One company (Schering-Plough) submitted cost-effectiveness evidence. This submission was based on an economic model that had a 1-year time horizon and sourced data from a single RCT of flexible-dose MMT compared with flexible-dose BMT and utility values obtained from the literature.

**MMT versus no drug therapy**

The incremental cost-effectiveness ratio (ICER) was £12,584/QALY.

**BMT versus no drug therapy**

The ICER was £30,048/QALY.

**MMT versus BMT**

As with the industry model, in a direct comparison, MMT was found to be slightly more effective (QALY difference 0.00055) and less costly than BMT.

**Assessment group model**

**MMT versus no drug therapy**

The ICER was £13,697/QALY.

**BMT versus no drug therapy**

The ICER was £26,429/QALY.

**MMT versus BMT**

As with the industry model, in a direct comparison, MMT was slightly more effective (QALY difference 0.0126) and less costly than BMT (–£520).

When considering social costs, both MMT and BMT gave more health gain and were less costly than no drug treatment. These findings were robust to deterministic and probabilistic sensitivity analyses.
Discussion
Strengths, limitations and uncertainties
The principal strengths of this report are that its cost-effectiveness analyses were based on retention in treatment and opiate abuse outcomes sourced from a systematic review and meta-analysis of RCT evidence directly comparing flexible-dose MMT with BMT (more reflective of real-world clinical practice than fixed-dose design trials); pooling was based on a meta-analysis using the time-dependent nature (i.e. hazard ratios) of the outcomes; utilities were derived from a panel representing a wider societal perspective; and the inclusion of wider societal costs. Potential limitations and uncertainties included the small sample size and potential representativeness of the utility panel sample, the short time horizon of the cost-effectiveness analysis and the lack of data to allow the exploration of the cost effectiveness across opiate-dependent user subgroups and treatment settings.

Conclusions
Implications for service provision
Both flexible-dose MMT and BMT are more clinically effective and more cost-effective than no drug therapy in dependent opiate users. In direct comparison, a flexible dosing strategy with MMT (daily dose equivalent 20–120 mg) was found to be somewhat more effective in maintaining individuals in treatment than flexible-dose BMT (daily dose equivalent 4–16 mg) and therefore associated with a slightly higher health gain and lower costs. However, this needs to be balanced by the more recent experience of clinicians in the use of buprenorphine, the possible risk of higher mortality of MMT and individual opiate-dependent users’ preferences.

Suggested research priorities
Future research should be directed towards the safety and effectiveness of MMT and BMT as it is delivered in the UK, potential safety concerns regarding methadone and buprenorphine, specifically mortality and key drug interactions, efficacy of substitution medications (in particular patient subgroups, such as within the criminal justice system, or within young people) and uncertainties in cost-effectiveness identified by current economic models.

Publication
The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care. The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

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Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 04/22/01. The protocol was agreed in August 2005. The assessment report began editorial review in June 2006 and was accepted for publication in July 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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