Methadone and buprenorphine for the management of opioid dependence

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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Executive summary

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
In a direct comparison, MMT was found to be slightly more effective (QALY difference of 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

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NIHR Health Technology Assessment Programme

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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.

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