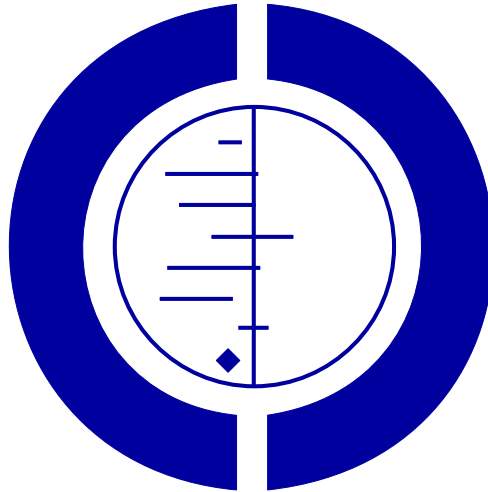


# Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Review)

Mattick RP, Kimber J, Breen C, Davoli M



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## ABSTRACT

### Background

Buprenorphine has been reported as an alternative to methadone and LAAM for maintenance treatment of opioid dependence, differing results are reported concerning its relative effectiveness indicating the need for an integrative review.

### Objectives

To evaluate the effects of buprenorphine maintenance against placebo and methadone maintenance in retaining patients in treatment and in suppressing illicit drug use.

### Search strategy

We searched the following databases up to 2001, inclusive: Cochrane Drugs and Alcohol Review Group Register, the Cochrane Controlled Trials Register, MEDLINE, EMBASE, Current Contents, Psychlit, CORK [www.state.vt.su/adap/cork], Alcohol and Drug Council of Australia (ADCA) [www.adca.org.au], Australian Drug Foundation (ADF -VIC) [www.adf.org.au], Centre for Education and Information on Drugs and Alcohol (CEIDA) [www.ceida.net.au], Australian Bibliographic Network (ABN), Library of Congress databases, available NIDA monographs, the College on Problems of Drug Dependence Inc. proceedings, the reference lists of all identified studies and published reviews. Authors of identified RCT's were asked about any other published or unpublished relevant RCT.

### Selection criteria

Randomised clinical trials of buprenorphine maintenance versus either placebo or methadone maintenance for opioid dependence.

### Data collection and analysis

Reviewers evaluated the papers separately and independently, rating methodological quality of concealment of allocation; data were extracted independently for meta-analysis and double-entered.

### Main results

Thirteen studies met the inclusion criteria, all were randomised clinical trials, all but one were double-blind. The method of concealment of allocation was not clearly described in 11 of the studies, otherwise methodological quality was good. Buprenorphine given in flexible doses appeared statistically significantly less effective than methadone in retaining patient in treatment (RR= 0.82; 95% CI: 0.69-0.96). Low dose buprenorphine is not superior to low dose methadone. High dose buprenorphine does not retain more patients than low dose methadone, but may suppress heroin use better. There was no advantage for high dose buprenorphine over high dose methadone in retention (RR=0.79; 95% CI:0.62-1.01), and high dose buprenorphine was inferior in suppression of heroin use. Buprenorphine was statistically significantly superior to placebo medication in retention of patients in treatment at low doses (RR=1.24; 95% CI: 1.06-1.45), high doses (RR=1.21; 95% CI: 1.02-1.44), and very high doses (RR=1.52; 95% CI: 1.23-1.88). However, only high and very high dose buprenorphine suppressed heroin use significantly above placebo.

## Authors' conclusions

Buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, but it is not more effective than methadone at adequate dosages.

## SYNOPSIS

Buprenorphine can reduce heroin use, although it is not as effective as methadone

Methadone is the most widely used replacement for heroin in medically-supported maintenance or detoxification programs. Two other drugs are sometimes used to try and help lower their use of heroin, buprenorphine and LAAM (levo-alpha-acetylmethadol). Buprenorphine is an opioid drug that is not as powerful as heroin and methadone, although the effects may last longer. It is easier to withdraw from buprenorphine than methadone, and can be taken once every two days. The review of trials found that buprenorphine can reduce heroin use effectively, although it is not as effective as methadone.

## BACKGROUND

Heroin dependence is becoming increasingly prevalent, with associated increases in the spread of infectious disease (e.g., HIV, hepatitis B and C) and overdose deaths. One of the main forms of treatment has been methadone maintenance treatment. As set out by elsewhere (Mattick 1998, Mattick 2003), maintenance treatment with oral methadone appears to be an effective and accepted intervention for opioid (heroin) dependence, and it is widely used in some countries. Yet, methadone maintenance treatment (MMT) has a number of negative characteristics which potentially influence its effectiveness and which have led to an interest in alternative pharmacotherapies and methods of treatment delivery (Mattick 1998). The negative aspects of methadone are set out below.

Methadone is a full opioid agonist at  $\mu$ -receptors. Thus, one negative aspect of methadone is its potential to produce and/or maintain dependence on opioids, such that patients experience withdrawal if a daily dose is missed, and detoxification can be a lengthy and difficult process which can discourage patients from attempting withdrawal. Additionally, because of its full agonist action, there is no ceiling to the level of respiratory depression or sedation which methadone can induce, and methadone overdose can therefore be fatal. Although it is a long-acting opioid, in some countries and settings, the inconvenience of daily dosing and clinic visits may be unattractive to clients, and restrictions imposed by the daily dosing schedule on clients' general lifestyle and on opportunities to sustain employment may also limit its acceptance to heroin users. The provision of takeaway doses of methadone results in problems of diversion of the drug for illicit use by those not in treatment, although the extent of this problem varies across countries. Finally, heroin users have developed their own "lore" regarding methadone's negative effects, although their views may not always be accurate or favourable. Thus, despite its many advantages, methadone maintenance appears to have limited suitability for some patients. These factors may restrict the

ability of methadone to attract certain users into treatment, and the examination of alternative medications to broaden the range of pharmacotherapies been the focus of research in recent years.

There are a number of alternatives to methadone as a maintenance agent in the management of opioid dependence. The most promising of these involve pharmacotherapies which treat patients with a pharmaceutical grade opioid which has a longer duration of action than methadone. These include the opiate partial agonist buprenorphine and the full agonist levo-alpha-acetylmethadol (LAAM) (Mattick 1998). This review focuses on the role of buprenorphine as a maintenance therapy in the management of opioid dependence.

Buprenorphine is a potent synthetic opioid analgesic initially used for the management of acute pain. Pharmacologically, buprenorphine causes morphine-like subjective effects and produces cross-tolerance to other opioids. Unlike methadone and heroin (which are full agonists), buprenorphine is a partial agonist and exerts weaker opioid effects at opioid receptor sites. This partial agonist action appears to make buprenorphine safer in overdose. Other benefits of buprenorphine may include an easier withdrawal phase and, because of the longer duration of action, the option of alternate day dosing.

It was during the initial development of buprenorphine as an analgesic in the 1970's that its potential utility as a substitution agent in the treatment of opioid dependence was recognised. Early work (Jasinski 1978) using buprenorphine administered by the subcutaneous route, characterised it as an opioid with low physical dependence liability with a minimal withdrawal syndrome. Subsequently, others (Fudala 1990) provided evidence that buprenorphine does produce a mild to moderate  $\mu$ -agonist withdrawal syndrome.) It was thought that at doses somewhat greater than those used for analgesia, it could be used in the treatment of opioid dependence (Jasinski 1978).

Evidence on the efficacy of buprenorphine has come from placebo-controlled trials (Johnson 1995a, Ling 1998), fixed dosing studies of buprenorphine versus methadone maintenance treatment (Bickel 1988; Johnson 1992; Kosten 1993; Ling 1996; Fischer 1999; Uehlinger 1998) and variable dosing studies of buprenorphine versus methadone maintenance treatment (Strain 1994a; Strain 1994b; Mattick 2003). Clinical trials conducted in the U.S. showed buprenorphine to be superior to placebo medication, but when buprenorphine and methadone maintenance were compared in a series of impressive studies using fixed doses of the drugs, the results were mixed. Some of the fixed dose studies showed no difference in efficacy, whereas others showed superiority for methadone and yet others showed the reverse pattern. The investigators in these fixed dose studies frequently concluded that the doses of buprenorphine, or methadone, chosen were too low or that poor induction regimes led to poor retention. A series of variable (or flexible) dose studies have been conducted and shown essentially equivalent results for the two drugs. Given the mixed results, it seems particularly important to attempt a systematic integration of the literature, and separately assessing the fixed and variable dose studies and discussing the results in the light of the differing doses and other individual trial features. Additionally, this review separately summarises the available placebo-controlled trial results.

## OBJECTIVES

The present systematic review had the objective of providing an evaluation of the buprenorphine maintenance treatment in the management of opioid dependence.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

Literature was reviewed for all of the trials of buprenorphine maintenance against methadone maintenance or placebo medication in the management of opioid dependence. Controlled clinical trials which were not randomised may be reviewed qualitatively, but not quantitatively using meta-analysis. Only randomised clinical trials were integrated using meta-analytic techniques.

### Types of participants

Individuals who were dependent on heroin or other opioids were the target population for this review. No distinction was made between those using heroin and those in methadone treatment prior to entering the research trial treatment.

### Types of intervention

Buprenorphine maintenance therapy, using sublingual tablet or ethanol-based solution containing buprenorphine, were compared

with methadone maintenance therapy or placebo. Studies using methadone or buprenorphine for detoxification without a maintenance phase, were not included.

### Types of outcome measures

Outcome measures examined in this review included:

Primary outcomes

- 1) retention in treatment;
- 2) urinalysis results positive for heroin metabolite (i.e., morphine);
- 3) urinalysis results positive for cocaine;
- 4) urinalysis results positive for benzodiazepines;
- 5) self report use of heroin
- 5) criminal activity

Secondary outcomes

- 1) physical health
- 2) psychological health
- 8) use of other drugs

## SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Drugs and Alcohol Group search strategy

This search strategy was developed in consultation with a drug and alcohol research information specialist, and included a number of search strategies:

1. Search Cochrane Drugs and Alcohol Review Group Register for trials of buprenorphine and methadone maintenance therapy to 2001.
2. Search Cochrane Controlled Trials Register for trials of buprenorphine and methadone maintenance therapy to 2001.
3. Search Electronic databases for published articles without language restrictions. MEDLINE (1966-2001) was searched using the Cochrane Collaboration optimised search strategy used to identify randomised trials in conjunction with the following to identify studies comparing buprenorphine and methadone maintenance therapy.

MEDLINE (OVID)

- #1 exp buprenorphine/ or buprenorphine. ti, ab, rw, sh.
- #2 exp methadone/ or methadone. ti, ab, rw, sh.
- #3 exp opioid related disorders
- #4 1 and 2 and 3

EMBASE (OVID) (1980-2001) was searched using the following terms:

- #1 exp buprenorphine/ ct (limit to clinical trials)
- #2 exp methadone/ ct
- #3 exp drug dependence or exp substance abuse or exp drug abuse or #4 1 and 2 and 3

As several drug and alcohol journals are not indexed on the main electronic databases, the following databases were searched up

until 2001: Current Contents, Psychlit, CORK [www.state.vt.su/adap/cork], Alcohol and Drug Council of Australia (ADCA) [www.adca.org.au], Australian Drug Foundation (ADF -VIC) [www.adf.org.au], Centre for Education and Information on Drugs and Alcohol (CEIDA) [www.ceida.net.au], Australian Bibliographic Network (ABN), and Library of Congress databases were also searched for studies and book chapters with the key terms:

buprenorphine, methadone, clinical trial, and randomised control trial. Available NIDA monographs and the College on Problems of Drug Dependence Inc. proceedings were searched for studies with the key terms: buprenorphine, methadone, clinical trial, and randomised control trial.

4. The references of all identified studies and published reviews were inspected for more trials.

5. International drug and alcohol treatment conference proceedings were hand searched.

6. Authors of identified RCT's were consulted to find out if there were any other published or unpublished RCT's comparing the efficacy of buprenorphine and methadone maintenance as therapies for opioid dependence.

## METHODS OF THE REVIEW

Each potentially relevant study located in the search was obtained and independently assessed for inclusion by two of three reviewers. Data extraction for that study was undertaken by the same two reviewers, again independently. Each reviewer reviewed the same number of studies. A standardised checklist was used for data extraction. Disagreement was dealt with by the third reviewer, acting as a mediator. Unresolved disagreements on inclusion, study quality or extraction were referred to the editor.

It is generally the case that these trials were blinded. As such, methodological quality was assessed by evaluation of the randomisation procedure and the likelihood that randomisation was concealed and not biased:

A. Low risk of bias (allocation clearly independent of clinical staff, and double-blind assignment);

B. Moderate risk of bias (some doubt about whether there was independence of the allocation procedure and whether the trial was double blind);

C. High risk of bias (inadequate concealment of allocation and/or no blinding).

A standardised effect size was calculated for each study, based on the urinalysis outcome measure reported. For retention data, relative risk (RR) and 95% confidence intervals were calculated through a random effect model for these dichotomous outcomes. A standardised mean difference was calculated for continuous outcomes (urine results and self-reported heroin use and criminal

activity). The pooled effect size estimate was derived for each domain of measurement (retention in treatment, urine analysis results for heroin/morphine, urine analysis results for cocaine, and urine analysis results for benzodiazepines).

The results were integrated from the meta-analytic review into a discussion taking into consideration other publications such as studies of the pharmacology of methadone and buprenorphine. Convergence of the evidence from the meta-analysis and the narrative review was taken to indicate a robust conclusion.

## DESCRIPTION OF STUDIES

The information provided in the tables present the characteristics of the excluded and the included studies.

Eleven studies were not included. One study by (Bickel 1988) was essentially a trial of detoxification or withdrawal. The study by Bouchez (Bouchez 1998) was a non-randomised comparison of methadone, buprenorphine and morphine sulphate.

The study by Bridge (Bridge 1996) was a placebo-control trial which has not been published to date, but will be included when available. One was a trial of dosing schedule (Johnson 1995b).

The remaining were a number of interim reports of trials included in this review, and data from only one article for each trial were included in the review.

In total, thirteen studies were included in this review. Eleven of these thirteen studies involved comparisons of methadone and buprenorphine. Two of these studies had a placebo-controlled comparison against buprenorphine.

The studies selected for this review had two distinct dosing approaches. Six studies used flexible dosing (Fischer 1999, Johnson 2000, Mattick 2003, Petitjean 2001, Strain 1994a, Strain 1994b) where dose is titrated according to patient preference within an upper and lower dose limit. Seven studies used fixed dosing schedules (Johnson 1992, Johnson 1995a, Kosten 1993, Ling 1996, Ling 1998, Pani 2000, Schottenfeld 1997) where patients are randomised to receive a given dose, without dose adjustment after stabilisation.

As most of the studies with fixed dosing schedules had more than one dose comparison, we have broadly classified the treatment groups as 'low dose' and 'high dose' for the respective pharmacotherapy. In the case of methadone, dose ranges between 20mg and 35mg were classified as low dose and between 60 and 80 as high dose. In the case of buprenorphine studies where methadone was the comparator, dose ranges between 2mg and 4mg were classified as low dose and between 6mg and 12mg as high dose. In the case of the buprenorphine studies where placebo (i.e 0mg or 1mg) is the comparator (Johnson 1995a & Ling 1998) we only included one buprenorphine dose level in the comparison, 8mg. This was

considered to be the most clinically relevant dose based on the average doses reached in the flexible dosing studies (~10mg). Specific study doses are provided in the Characteristics of Included table. Johnson 2000 is classified as a flexible dose study, so the 20mg methadone fixed dose group from that study were not included in the analyses. Because of the design of these studies, we were also able to conduct analyses of low dose buprenorphine versus low dose methadone, low dose buprenorphine versus high dose methadone, high dose buprenorphine versus low dose methadone, high dose buprenorphine versus high dose methadone, and buprenorphine versus placebo medication.

The treatment groups and doses included in the "Methadone low dose" analysis included: 20mg (Johnson 1992), 35mg (Kosten 1993), 30mg (Ling 1996), and the 20mg (Schottenfeld 1997) groups. The treatment groups and doses included in the "Methadone high dose" analysis included: 60mg (Johnson 1992), 65mg (Kosten 1993), 80mg (Ling 1996), 60mg (Pani 2000), and the 65mg (Schottenfeld 1997) groups. The treatment groups and doses included in the "Buprenorphine low dose" analysis included: the 2mg (Kosten 1993) and 4mg (Schottenfeld 1997) groups. The treatment groups and doses included in the "Buprenorphine high dose" analysis included: the 8mg (Johnson 1992), 6mg (Kosten 1993), 8mg (Ling 1996), 8mg (Pani 2000) and 12mg (Schottenfeld 1997) groups.

All studies were assessed to determine whether they provided data for the six outcome measures of interest including retention in treatment, urine results for morphine, cocaine, and benzodiazepines, self-reported heroin use, and criminal activity. After reviewing the studies, we decided to exclude the outcomes self-reported heroin use from the analyses as only five studies reported on this outcome (Johnson 2000, Kosten 1993, Mattick 2003, Pani 2000, Schottenfeld 1997) and criminal activity as only one study reported this outcome (Mattick 2003). These groups plus the flexible dose studies provided data on retention in treatment, morphine (heroin metabolite) in urine, cocaine metabolites in urine, or benzodiazepines in urine.

The retention in treatment data are dichotomous outcome measures. The urine data are presented as a continuous outcome measure but are based on data requested directly from authors. This was necessary as urine results in the literature are routinely reported as the percentage of urine samples collected per treatment group that were positive or negative for a given drug (e.g. heroin) across the study period. This 'count data' is not compatible with the analysable data fields in RevMan (i.e. continuous, dichotomous, individual patient data). Based on advice provided by Cochrane statisticians, we asked authors to calculate the number of positive urines in each treatment group and derive a mean number of positive urines with a standard deviation, allowing for analysis of urine results as continuous data. These additional data were not available for studies by Kosten 1993 and Pani 2000, and urine results are therefore not presented for these studies.

## METHODOLOGICAL QUALITY

Of the thirteen studies included in this review, twelve were conducted under double blind conditions. One study (Fischer 1999) was an open comparative trial. In order to maintain the double-blind where methadone was compared with buprenorphine, patients were given both an oral solution of either active or placebo methadone syrup and a sublingual preparation of active or placebo buprenorphine. Blinding was not tested in the trials.

Only two of the studies described a method of concealment of allocation, which was clearly adequate. Ling (Ling 1998) used a random number table to have pharmacy staff pre-label medications in a blinded fashion. Mattick (Mattick 2003) used a randomizations list generated in the USA prior to the study, controlled by the dispensing pharmacist who worked separately from the clinical and research staff. The remainder of the trials did not describe concealment of allocation process in sufficient detail to be clear that the allocation concealment method was adequate. There were no trials where the concealment method could be defined as clearly inadequate.

The number of participants in these studies varied between 51 subjects in one study up to 736 subjects in the study by Ling (1998). The largest comparative trial of methadone against buprenorphine included was reported by Mattick (Mattick 2003) with 405 participants. Many of the studies had quite small numbers of patients in each individual treatment group. The characteristics of the patients and the inclusion and exclusion criteria were well described in all of the studies.

The dosage of both methadone and buprenorphine varied across the studies. Doses of methadone as low as 20 milligrams in some studies and ranged up to 150 milligrams in other studies. Buprenorphine ranged from 2 milligrams up to 32 milligrams. More importantly, many of the studies used a fixed dosage of either methadone or buprenorphine. That is, patients were often entered into a specific condition where a dose of, for example 30 milligrams of methadone, may have been prescribed and not tailored to patient need. This strategy had the consequence for some of the investigators of causing them to comment in the discussion of their results that the results may have altered if they had of used a different dosage. A number of studies have used flexible doses buprenorphine and methadone although in some of those studies there have been ceiling doses placed on the maximum allowed dose with the ceiling dose being lower than might be prescribed in day to day practice. For these reasons in the tables presented in this meta-analysis data are presented separately for flexible dosage studies from mixed dosage studies. In addition, in order to more fully explicate the results, analyses were undertaken of high doses of buprenorphine and high doses of methadone, high dose buprenorphine versus relatively low doses methadone, low doses buprenorphine versus high doses of methadone, and

low doses of buprenorphine versus low doses of methadone. Also, there is an analysis of buprenorphine versus placebo medication.

The outcome measures seemed to be consistent across studies. Retention was routinely reported. In addition, urine results were reported. Only five studies provided self report data concerning heroin use (Kosten 1993, Schottenfeld 1997, Johnson 2000, Pani 2000, Mattick 2003), but one of these studies did not provide a measure of variance to allow an estimate of the standard deviation (Schottenfeld 1997) and could not be included in the meta-analysis, and only one study provided data concerning criminal activity (Mattick 2003).

## RESULTS

### 1. Selection of Studies/Participants/Interventions:

There were thirteen studies included in this review (2544 participants).

Characteristics of the participants were generally well described. Majority of participants in these studies were male, consistent with the profile of the heroin dependant users generally. They tended to be approximately 30 years of age, again consistent with what is known about heroin users presenting for treatment.

The interventions ranged in duration from 6 weeks through to 52 weeks. By and large the interventions used clinically relevant doses of medication, although as noted earlier a number of the studies used fixed doses of medication and this created some limitations in terms of generalisability to day-to-day clinical practice. Specifically, in day-to-day clinical practice flexible dosing is used.

### 2. Quantitative Analysis

#### 2a. Flexible Dose Buprenorphine versus Flexible Dose Methadone

As noted earlier, the flexible dose studies reported probably provide the best estimate of the likely impact of methadone and buprenorphine in day-to-day clinical practice, as they mirror clinical practice in terms of dose adjustments and in terms of the doses employed in the studies. The six studies included in the flexible dose buprenorphine versus flexible dose methadone analysis (837 participants) showed that methadone was more likely to retain patients than buprenorphine (six studies, 837 participants; RR= 0.82; 95% CI: 0.69-0.96). The Chi-square test for heterogeneity was not significant. Inspection of the relative risks for retention in treatment for these six flexible dose studies showed two studies had significant poor retention for buprenorphine, but the other four studies showed no statistical significant difference. While there was a difference in retention favouring methadone, turning to the effect of buprenorphine and methadone on drug use, the flexible dose studies showed no significant difference between the two interventions in terms of heroin use, based on results of morphine urinalysis (six studies, 837 participants; SMD= -0.12; 95% CI:

-0.26- 0.02), or in terms of self-reported heroin use (two studies, 326 participants; SMD= -0.10; 95% CI: -0.32- 0.12). Similarly, there was no statistically significant difference between the flexible dose methadone and buprenorphine trials in terms of cocaine positive urines (five studies, 779 participants; SMD= 0.11; 95% CI: -0.03 - 0.25) or benzodiazepine positive urines (four studies, 669 participants; SMD= 0.11; 95% CI: -0.04-0.26).

In the one study that reported on criminal activity, there was no statistically difference between the buprenorphine and methadone groups (SMD= -0.14; 95% CI: -0.41- 0.14).

#### 2b. Low Dose Buprenorphine versus Low Dose Methadone

The comparison of low dose buprenorphine and low dose methadone (two studies, 121 participants) indicated no statistically significant difference in retention in treatment (RR = 0.74; 95% CI: 0.52-1.06), nor was there evidence of differences in morphine positive urines and cocaine positive urines based on one trial. There was no difference in self-reported heroin use (one study with 44 participants; SMD= -0.28; 95% CI: -0.35- 0.90).

#### 2c. Low Dose Buprenorphine versus High Dose Methadone

When low dose buprenorphine is compared to high dose methadone (2 RCTs, 120 participants) there was no statistical difference in retention in treatment (RR= 0.69; 95%CI: 0.45-1.06). The trials involved did not show heterogeneity. The results show that low dose buprenorphine is not more effective than high dose methadone in retaining patients in treatment, and it is not superior to high dose methadone in suppressing heroin use as indexed by the extent of morphine positive urines (one study, 57 participants; SMD= 0.88; 95% CI: 0.33 - 1.42). However, the overall effect is only based on one study, as data from the second study (Kosten 1993) concerning the urine results were not available for this review. There was, also, no statistically significant difference of the effect of low dose buprenorphine and high dose methadone beyond the effect of on cocaine, as shown from data on cocaine positive urines (one study, 57 participants; SMD= -0.08; 95% CI: -0.60- 0.44).

There was no statistically significant difference in self-reported heroin use (one study, 38 participants; SMD= -0.06; 95% CI: -0.70- 0.58). However, the results from Schottenfeld 1997 on self-reported heroin use, which could not be included in this meta-analysis, did show a significant advantage for high dose methadone (65mg) over low dose buprenorphine (4mg).

#### 2d. High Dose Buprenorphine versus Low Dose Methadone

When comparing high dose buprenorphine there was one study which favoured high dose buprenorphine in terms of retention, one study that favoured low dose methadone, and two studies showed no statistically significant difference. The test for heterogeneity was significant for the retention data (chi-square=11.47, df=3, p=0.0095) therefore no summary measure is provided. However, high dose buprenorphine was superior to low dose methadone

in terms of heroin use as shown from morphine positive urines (three studies, 317 participants; SMD= -0.23; 95%CI: -0.45- -0.01), but again the chi-square test for heterogeneity was significant ( $p=0.041$ ), even though direction of the estimates were homogeneous. In terms of cocaine positive urines, no benefit was shown for high dose buprenorphine compared with low dose methadone, based on only one study (59 participants).

There was no difference in self-reported heroin use (one study, 37 participants; SMD= -0.64; 95% CI: -0.06- 1.33).

## 2e. High Dose Buprenorphine versus High Dose Methadone

Comparing high dose buprenorphine and high dose methadone, the data on retention in treatment (5 RCTs, 449 participants) showed no statistical difference between the two interventions (RR=0.79; 95% CI:0.62-1.01), but suggest that high doses of buprenorphine are less likely to retain patients than high dose methadone. The trials involved in this comparison (Johnson 1992, Kosten 1993, Ling 1996, Pani 2000, Schottenfeld 1997) did not show any evidence of heterogeneity. High dose buprenorphine was also significantly less able to suppress heroin use as shown by morphine positive urines (3 studies, 314 participants: SMD=0.27; 95%CI: 0.05-0.50) while no statistically significant difference was found in terms of cocaine use based on the cocaine urine analysis results of only one study (57 participants).

There was no difference in self-reported heroin use (two studies, 74 participants; SMD= -0.02; 95% CI: -0.48- 0.45). This lack of significance is consistent with the results from Schottenfeld 1997 on self-reported heroin use, which could not be included in this meta-analysis, and which did not show a significant advantage for high dose methadone (65mg) over high dose buprenorphine (12mg).

## 2f. Low dose buprenorphine maintenance versus placebo

Turning to the results on the two trials (487 participants) comparing low dose buprenorphine (2mg or 4 mg) versus placebo medication (0mg or 1mg, respectively) (Johnson 1995a, Ling 1998), the results showed a benefit for low dose buprenorphine above placebo in terms of retaining patients in treatment (RR=1.24; 95% CI: 1.06-1.45). However, low dose buprenorphine patients had no less heroin use as indexed by morphine positive urines, cocaine positive urine results, and benzodiazepine positive urines, although these latter two results came from only one of the two trials (Johnson 1995a).

## 2g. High dose buprenorphine maintenance versus placebo

The results on the two trials (463 participants) comparing high dose (8mg) buprenorphine versus placebo medication (Johnson 1995a, Ling 1998), the results showed a benefit for buprenorphine above placebo in terms of retaining patients in treatment (RR=1.21; 95% CI: 1.02-1.44). Not only were patients better retained by buprenorphine but they had less heroin use as indexed by morphine positive urines. There was an advantage for placebo

in terms of cocaine positive urine results, but this is based on only one study (Johnson 1995a). By way of contrast, buprenorphine was superior to placebo in terms of its ability to suppress benzodiazepine use, again this result coming from one trial (Johnson 1995a).

## 2h. Very high dose buprenorphine maintenance versus placebo

Finally, turning to the one trial (366 participants) comparing very high dose (16mg) buprenorphine versus placebo medication (Ling 1998), the results showed a benefit for buprenorphine above placebo in terms of retaining patients in treatment (RR=1.52; 95% CI: 1.23-1.88). Not only were the patients in this single trial better retained by buprenorphine, but they had less heroin use when receiving 16mg of buprenorphine than placebo patients as indexed by morphine positive urines.

Other measures (e.g. use of other drugs, physical health, and psychological health) were too infrequently and irregularly reported in the literature to be usefully integrated in the quantitative part of this review.

## DISCUSSION

Buprenorphine is superior to placebo in terms of retention based on the large study by Ling 1998 and the study by Johnson 1995a, and it is superior in terms of its ability to suppress heroin use.

When compared with methadone, the results of the meta-analysis indicate that methadone is statistically significantly better able to retain patients than buprenorphine in flexible dosing approaches, the difference being slight in favour of methadone. Methadone is better able to suppress heroin use than buprenorphine, especially if high-dose methadone is used (and vice-versa). Similar conclusions have been reached by other recent meta-analytic reviews of these treatments (West 2000; Barnett 2001).

One explanation which has been advanced by authors in some of the studies included here for the poorer retention in buprenorphine treatment (Fischer 1999, Petitjean 2001) is that they inducted patients too slowly onto buprenorphine and this was the cause of the poorer retention in that medication group. It is possible that retention is affected by too slow induction, and given the apparent relative safety of buprenorphine it may be possible to induct people to higher doses at a more rapid rate and to overcome the problem of slightly poorer retention for buprenorphine compared with methadone. However, there are a number of other possible explanations for the poorer retention on buprenorphine than methadone. In particular, it may well be that buprenorphine, being a partial agonist, does not retain people because it does not have a full opioid effect and is less satisfying to patients. Another possibility is that patients in the initial stages of dosing who have recently ingested heroin suffer a mild withdrawal syndrome by virtue of buprenorphine (a partial agonist) displacing heroin (a full agonist) from opioid receptors in the central nervous system,

and this mild withdrawal may lead patients to leave treatment. A further possibility is that buprenorphine is simply easier to withdraw from and, on that basis, patients are more at liberty to leave treatment without the severe withdrawal syndrome that can accompany methadone withdrawal. Of course, these factors may all act together to cause buprenorphine to have a slightly poorer outcome in terms retention than methadone. Future research should be undertaken to address this particular issue.

These results show that, despite the effectiveness of buprenorphine when compared with placebo, when methadone is given in high doses buprenorphine is not a better treatment. These findings could be taken to suggest that buprenorphine will be inferior to methadone in day-to-day practice, but we point out that some of doses used in the high dose methadone conditions are rarely used in day-to-day clinical practice. If it were possible to get clinicians and patients to agree to prescribe and take high dose methadone then the clinical implication of this may be important, but the reality is that most often methadone is prescribed in the range of an average of 50 to 60 milligrams. At this level, as shown in the flexible dose studies earlier, there does not appear to be any reliable difference in heroin use between methadone and buprenorphine, overall.

The clinical trials represented in this review are of reasonable quality, and whilst many of them did not fully explain how randomisation was concealed, they appear to have used doses which are clinically relevant and to have treated patients for significant periods of time. Based on the nature of the trials, it would appear the external validity or generalisability of the results is quite good, particularly from those trials which have used large sample sizes and adequate doses.

## AUTHORS' CONCLUSIONS

### Implications for practice

The implication of the results of the meta-analytic review conducted and reported herein are clear for clinical practice. Buprenorphine is an effective treatment for heroin use in a maintenance therapy approach compared with placebo. However, methadone maintenance treatment at high dose is associated with higher rates of retention in treatment and better suppression of heroin than buprenorphine maintenance treatment. Buprenorphine maintenance should be supported as a maintenance treatment, only where higher doses of methadone cannot be administered. The reasons for not applying the best available treatment should be investigated rather than promoting less effective treatment approaches.

Given buprenorphine's different pharmacological properties, it may have advantages in some settings and under some policies where its relative safety and alternate-day administration are useful clinically compared to methadone.

### Implications for research

Overall, the quality of the studies included in this meta-analytic review was quite good. The trials did use sample sizes which varied from relatively small to quite large, but they were mostly double-blind trials. There does not appear to be any need for further randomised control trials of the relative efficacy of methadone compared with buprenorphine. There does appear to be a need to undertake studies which will clarify retention in the first few weeks or months of treatment in buprenorphine versus methadone. One way of addressing this issue would be to compare a standard induction as used in some of the trials reported herein with a rapid induction onto buprenorphine, with the potential to have a further comparison of induction onto methadone. Problems in the methods of induction onto buprenorphine within the trials analysed might partly explain the inferiority of buprenorphine shown in this review. It would be ideal if such a trial were to be conducted under double blind conditions, particularly in terms of the rapid versus standard induction onto buprenorphine. Other outcome measures such as self-reported drug use, criminal activity, physical health, and psychological health which were too infrequently and irregularly reported in the literature to be analysed in the current review could be included in future studies.

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## POTENTIAL CONFLICT OF INTEREST

The first reviewer, Richard P. Mattick is the first author on one trial of buprenorphine versus methadone for maintenance therapy in opioid dependence (see reference in the Included Studies).

## SOURCES OF SUPPORT

### External sources of support

- Commonwealth Department of Health and Aged Care, Canberra AUSTRALIA

### Internal sources of support

- National Drug and Alcohol Research Centre, University of New South Wales, Sydney AUSTRALIA

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\* Indicates the major publication for the study

**T A B L E S****Characteristics of included studies**

<b>Study</b>	<b>Fischer 1999</b>
Methods	Two group, open, randomised clinical trial, with participants randomised “externally . . . independent of the investigators”, but the method of concealment of allocation is unstated.
Participants	Geographic region: Austria N=60 age range = 18-39 years 68% male
Interventions	24 weeks of maintenance, flexible dosing. Buprenorphine (tablets) mean dose 7.5mg/day (range 2mg to 8 mg). Methadone mean dose 63mg/d (range 20mg to 80mg).
Outcomes	Retention in treatment, urinalysis for opioids, cocaine, and benzodiazapines.

### Characteristics of included studies (Continued)

Notes Prior to entering trial, all subjects were screened for one week and maintained with slow release oral morphine (Kapanol CSR).  
Exclusions: dependence on other drugs (except cannabis), pregnancy, HIV positivity or seriously illness.  
Weekly group psychotherapy was provided.

Allocation concealment B

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#### Study Johnson 1992

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Methods Three group, double-blind, double dummy, randomised clinical trial stratified by age, gender, and Clinical Institute Narcotic Assessment (CINA) scores, but the method of concealment of the allocation method is unstated.

Participants Geographic region: USA  
N=162  
age range = 21-50 years  
70% male

Interventions 17 weeks of maintenance, fixed dosing.  
Buprenorphine (solution) 8mg/day,  
Methadone 20mg/day or 60mg/day.

Outcomes Retention in treatment,  
urinalysis for opioids, abstinence.

Notes Exclusions: acute or chronic medical or psychiatric conditions, pregnancy.  
Participants were offered but not required to attend 30 to 60 minutes of individual counselling per week

Allocation concealment B

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#### Study Johnson 1995a

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Methods Three group, double-blind, randomised clinical trial, but the method of concealment of the allocation is unstated.

Participants Geographic region: USA  
N=150  
age range = 18-50 years  
69% male

Interventions 2 weeks of maintenance, fixed dosing. Buprenorphine(solution) 0mg/day or 2mg/day, or 8mg/day.

Outcomes % on original dose, % requesting a dose change,  
urinalysis for opioids and cocaine, dose adequacy.

Notes Exclusions: major medical conditions, chronic medications, history of serious psychiatric illness, prior drug abuse with buprenorphine, treatment at clinic in past three months

Allocation concealment B

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#### Study Johnson 2000

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Methods Four group, double-dummy, double-blind, randomised clinical trial using a random number generator, but the method of the concealment of the allocation is unstated.

Participants Geographic region: USA  
N=220  
age range = 18-55 years  
65% male

Interventions 17 weeks of maintenance, flexible dosing, mean doses not specified.

### Characteristics of included studies (Continued)

	Buprenorphine (formulation not specified) 16mg to 32mg on two weekdays, with 50% higher dose over weekends, Methadone 60-100mg/day, LAAM 75-115mg on two weekdays, with 40% higher dose over weekends, and a fixed dose 20mg/day Methadone control group.
Outcomes	Retention in treatment, urinalysis for opioids, continuous abstinence from opioids, self-reported drug use, patient rating of severity of drug problem, urinalysis for cocaine, continuous abstinence from cocaine, breath alcohol readings, side effects, and sex differences.
Notes	Exclusions: serious psychiatric or medical conditions. 45% of patients met DSM-IV criteria for cocaine abuse or dependence.
Allocation concealment	B

#### Study **Kosten 1993**

Methods	Four group, double-dummy, double-blind, randomised clinical trial, but the method of concealment of the allocation is unstated
Participants	Geographic region: USA N=125 (140 intention-to-treat) mean age = 32 years 73% male
Interventions	24 weeks of maintenance, fixed dosing. Buprenorphine (solution) 2mg/day or 6mg/day, Methadone 35mg/day or 65mg/day.
Outcomes	Retention in treatment, urinalysis, self-reported drug use, opioid withdrawal ratings.
Notes	65% of patients met DSM III-R criteria for cocaine dependence. For the first 6 weeks patients attended twice weekly relapse prevention group therapy, and for the remaining time, weekly group therapy. Three types of analyses were used (intention to treat, completer, and efficacy).
Allocation concealment	B

#### Study **Ling 1996**

Methods	Three group, double-dummy, double-blind, randomised clinical trial with a computer generated random numbers list, but the method of concealment of the allocation is unstated.
Participants	Geographic region: USA N=225 age range = 18 - 65 years 60% male
Interventions	52 weeks of maintenance (efficacy evaluation based on first 26 weeks), fixed dosing. Buprenorphine (solution) 8 mg/day, Methadone 30mg/day or 80mg/day.
Outcomes	Retention in treatment, urinalysis for opioids, cocaine, amphetamines, benzodiazapenes, craving, and opioid withdrawal symptoms.
Notes	Exclusions: current involvement in a methadone maintenance program, acute hepatitis, dependence on alcohol, sedative-hypnotics, cocaine, amphetamines (DSM III-R), pregnancy/breastfeeding, current use of anticonvulsants, disulfiram or neuroleptics.

**Characteristics of included studies (Continued)**

All participants were encouraged to attend weekly individual counseling sessions.  
Medication and counseling were free

Allocation concealment B

**Study Ling 1998**

Methods Four group, double-blind, randomised multisite clinical trial using a random number table to pre-label medications by pharmacy staff

Participants Geographic region: USA  
(12 sites)  
N=736  
68% male

Interventions 16 weeks of maintenance, fixed dosing.  
Buprenorphine (solution) 1mg or 4mg or 8mg or 16mg/day.

Outcomes Retention in treatment,  
urinalysis for illicit opioids,  
craving, and global ratings by patients and staff

Notes Exclusions: MMT in last 30 days, alcohol dependence, serious medical condition incl. AIDS. Patients using neuroleptics, anticonvulsants or disulfiram.

Allocation concealment A

**Study Mattick 2003**

Methods Two group, double-dummy, double-blind, randomised multisite clinical trial stratified for sex, randomised in blocks of 10, randomisation list generated in USA and controlled by the dispensing pharmacist separate from the clinical staff and research staff

Participants Geographic region: Australia  
(3 sites)  
N=405  
mean age =  
30 years  
67% male

Interventions 13 week of maintenance, flexible dosing.  
Buprenorphine (tablets) mean dose 10.1mg (range 2mg to 32mg/day),  
Methadone mean dose 52.1mg (range 20mg to 150mg/day).

Outcomes Retention in treatment,  
urinalysis for opioids, self-reported heroin use and criminal behaviour.

Notes In preparation for submission for publication.  
Exclusions: acute liver disease, pregnancy/ breast-feeding, dependence on alcohol or sedative/hypnotics, use of anti-convulsants or neuroleptics on a daily basis, methadone treatment in the last month.

Allocation concealment A

**Study Pani 2000**

Methods Two group, double-dummy, double-blind, randomised multisite clinical trial, but the method of concealment of randomisation is unstated.

Participants Geographic region: Italy  
N=72  
mean age =  
28 years

### Characteristics of included studies (Continued)

	86% male
Interventions	24 weeks of maintenance, fixed dosing. Buprenorphine (tablets)8mg/day, Methadone 60mg/day.
Outcomes	Retention in treatment, urinalysis for opioids, craving, self- reported heroin use, psychosocial adjustment and psychopathology.
Notes	Exclusions: serious medical conditions, hypnotic-sedative or alcohol dependence
Allocation concealment	B

#### Study **Petitjean 2001**

Methods	Two group, double-blind, double-dummy randomised trial, but the method of concealment of allocation is unstated.
Participants	Geographic region: Switzerland N=58 mean age = 27 years 83% male
Interventions	6 weeks of maintenance, flexible dosing. Buprenorphine (tablets) mean dose 10.5mg (range 8 to 16mg/day), Methadone mean dose 69.8mg (range 30 to 120mg/day).
Outcomes	Retention in treatment, urinalysis for opioids and cocaine, heroin craving, and adverse events.
Notes	Exclusions included previous treatment with buprenorphine, treatment with methadone in last 30 days, sedative-hypnotic or alcohol dependence, serious medical or psychiatric illness.
Allocation concealment	B

#### Study **Schottenfeld 1997**

Methods	Four group, double-dummy, double-blind, randomised clinical trial, using a computer generated random number list, but the method of concealment of the allocation is unstated.
Participants	Geographic region: USA N=116 mean age = 32 years 68% male
Interventions	24 weeks of maintenance, fixed dosing. Buprenorphine (solution) 4mg/day or 12mg/day, Methadone 20mg/day or 65mg/day.
Outcomes	Retention in treatment, urinalysis for opioids and cocaine, self reported opioid and cocaine use, self reported withdrawal symptoms.
Notes	Inclusion: dependence on opioids and cocaine (DSM III-R) Exclusion: current alcohol or sedative dependence, current psychosis or suicide risk, pregnancy, inability to read/understand the ratings forms and checklists. All participants were required to participate in weekly relapse prevention group counselling sessions.
Allocation concealment	B

#### Study **Strain 1994a**

Methods	Two group, double-dummy, double-blind, randomised clinical trial, but the method of concealment of allocation is unstated.
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### Characteristics of included studies (Continued)

Participants	Geographic region: USA N=164 mean age = 32 years 71% male
Interventions	6 months maintenance, flexible dosing. Buprenorphine (solution) mean dose 8.9mg/day (range 2mg to 16 mg/day), Methadone mean dose 54mg/day (range 20mg to 90mg/day).
Outcomes	Retention in treatment, compliance with treatment (attendance and counselling contact) urinalysis for opioids, cocaine, benzodiazapenes (3 x week)
Notes	Exclusions: chronic medical or major mental illness, pregnancy, prior methadone episodes longer than 21 days, previous buprenorphine treatment for opioid dependence, methadone positive urine. Patients were assigned an individual counsellor and individualised treatment plan for weekly meetings as well as weekly group therapy based on a relapse prevention model.
Allocation concealment	B

### Study **Strain 1994b**

Methods	Two group, double-dummy, double-blind, randomised clinical trial, stratified for race and gender, but the method of concealment of allocation is unstated
Participants	Geographic region: USA N=51 mean age = 33 years 71% male
Interventions	16 weeks maintenance, flexible dosing. Buprenorphine (solution) mean dose 11.2mg, (range 2mg to 16mg/day), Methadone mean dose 66.6mg (range 20mg to 90mg/day).
Outcomes	Retention in treatment, compliance with treatment (attendance & counselling contacts), urinalysis for opioids, cocaine, benzodiazapenes.
Notes	Inclusion: self reported cocaine use in previous 30 days or cocaine positive urine. Exclusion: chronic medical or major mental illness, pregnancy, prior methadone treatment lasting longer than 21 days, previous treatment episode with buprenorphine for opioid dependence. Patients were assigned an individual counsellor and given weekly group therapy focusing on education and relapse prevention.
Allocation concealment	B

### Characteristics of excluded studies

Bickel 1988	This study was a detoxification trial, rather than a maintenance trial, as participants were stabilised on buprenorphine for three weeks and then are doses decreased to withdrawal.
Bouchez 1998	This study was a non-randomised comparison of methadone, buprenorphine, and morphine sulphate in 39 patients (with n = 9, n = 22, and n = 8, respectively).
Eder 1998	This study was an Interim report of the Fischer et al. (1999) study which is already included in the review.
Johnson 1995b	This study compared daily and alternate day dosing of buprenorphine, where the alternate day dosing group receive placebo on the alternate days.

### Characteristics of excluded studies (Continued)

O'Connor 1998	This study compared buprenorphine maintenance in a primary care setting versus buprenorphine delivered in a specialist opioid replacement (i.e., methadone) clinic setting. It is not a comparison of buprenorphine in a primary care clinic versus methadone in a methadone clinic.
Oliveto 1994	This paper presents data from a secondary analysis of the data published by Kosten (1993).
Schottenfeld 1998	This paper presents data from a secondary analysis of the data previously published by Kosten (1993).
Stine 1994	This paper is a secondary publication drawing on the data previously published by Kosten (1993).
Strain 1996	This paper is a secondary publication drawing on the data previously published by by Strain (1994a).
Uehlinger 1998	This paper presents preliminary data analyses that are reported in full in Petitjean (2000).

## GRAPHS

### Comparison 01. Flexible dose buprenorphine versus flexible dose methadone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 retention in treatment	6	837	Relative Risk (Random) 95% CI	0.82 [0.69, 0.96]
02 morphine positive urines	6	837	Standardised Mean Difference (Fixed) 95% CI	-0.12 [-0.26, 0.02]
03 cocaine positive urines	5	779	Standardised Mean Difference (Fixed) 95% CI	0.11 [-0.03, 0.25]
04 benzodiazepine positive urines	4	669	Standardised Mean Difference (Fixed) 95% CI	0.11 [-0.04, 0.26]
05 self-reported heroin use	2	326	Standardised Mean Difference (Fixed) 95% CI	-0.10 [-0.32, 0.12]
06 Self-reported crime	1	212	Standardised Mean Difference (Fixed) 95% CI	-0.14 [-0.41, 0.14]

### Comparison 02. Low dose buprenorphine versus low dose methadone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 retention in treatment	2	121	Relative Risk (Random) 95% CI	0.74 [0.52, 1.06]
02 morphine positive urines	1	59	Standardised Mean Difference (Fixed) 95% CI	-0.35 [-0.87, 0.16]
03 cocaine positive urines	1	59	Standardised Mean Difference (Fixed) 95% CI	0.08 [-0.43, 0.59]
04 Self-reported heroin use	1	41	Standardised Mean Difference (Fixed) 95% CI	0.28 [-0.35, 0.90]

### Comparison 03. Low dose buprenorphine versus high dose methadone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 retention in treatment	2	120	Relative Risk (Random) 95% CI	0.69 [0.45, 1.06]
02 morphine positive urines	1	57	Standardised Mean Difference (Fixed) 95% CI	0.88 [0.33, 1.42]
03 cocaine positive urines	1	57	Standardised Mean Difference (Fixed) 95% CI	-0.08 [-0.60, 0.44]
04 Self-reported heroin use	1	38	Standardised Mean Difference (Fixed) 95% CI	-0.06 [-0.70, 0.58]

#### Comparison 04. High dose buprenorphine versus low dose methadone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 retention in treatment			Relative Risk (Random) 95% CI	Subtotals only
02 morphine positive urines	3	317	Standardised Mean Difference (Fixed) 95% CI	-0.23 [-0.45, -0.01]
03 cocaine positive urines	1	59	Standardised Mean Difference (Fixed) 95% CI	0.38 [-0.14, 0.89]
04 Self-reported heroin use	1	37	Standardised Mean Difference (Fixed) 95% CI	0.64 [-0.06, 1.33]

#### Comparison 05. High dose buprenorphine versus high dose methadone

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 retention in treatment	5	449	Relative Risk (Random) 95% CI	0.79 [0.62, 1.01]
02 morphine positive urines	3	314	Standardised Mean Difference (Fixed) 95% CI	0.27 [0.05, 0.50]
03 cocaine positive urines	1	57	Standardised Mean Difference (Fixed) 95% CI	0.22 [-0.30, 0.74]
04 Self-reported heroin use	2	74	Standardised Mean Difference (Fixed) 95% CI	-0.02 [-0.48, 0.45]

#### Comparison 06. Low dose buprenorphine versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Retention in treatment	2	487	Relative Risk (Random) 95% CI	1.24 [1.06, 1.45]
02 Morphine positive urines	2	487	Standardised Mean Difference (Random) 95% CI	0.10 [-0.80, 1.01]
03 Cocaine positive urines	1	120	Standardised Mean Difference (Random) 95% CI	0.26 [-0.10, 0.62]
04 Benzodiazepine positive urines	1	120	Standardised Mean Difference (Random) 95% CI	0.03 [-0.33, 0.38]

#### Comparison 07. High dose buprenorphine versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 retention in treatment	2	463	Relative Risk (Random) 95% CI	1.21 [1.02, 1.44]
02 morphine positive urines	2	463	Standardised Mean Difference (Fixed) 95% CI	-0.28 [-0.47, -0.10]
03 cocaine positive urines	1	90	Standardised Mean Difference (Fixed) 95% CI	0.50 [0.05, 0.94]
04 benzodiazepine positive urines	1	90	Standardised Mean Difference (Fixed) 95% CI	-0.81 [-1.27, -0.36]

#### Comparison 08. Very high dose buprenorphine versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Retention in treatment	1	366	Relative Risk (Random) 95% CI	1.52 [1.23, 1.88]
02 Morphine positive urines	1	366	Standardised Mean Difference (Random) 95% CI	-0.65 [-0.86, -0.44]

## INDEX TERMS

### Medical Subject Headings (MeSH)

Buprenorphine [therapeutic use]; Methadone [therapeutic use]; Narcotic Antagonists [therapeutic use]; Narcotics [therapeutic use]; Opioid-Related Disorders [rehabilitation]; Randomized Controlled Trials

### Medical MeSH check words

Humans

## COVER SHEET

<b>Title</b>	Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence
<b>Authors</b>	Mattick RP, Kimber J, Breen C, Davoli M
<b>Contribution of author(s)</b>	Contributions: We are very grateful to the first authors of the original papers analysed herein who provided data on urine results in a form that was compatible with the Cochrane software, so that meta-analysis could occur. Richard Mattick, Jo Kimber and Courtney Breen reviewed the papers, with Jo Kimber and Richard P. Mattick coding data from the papers for meta-analysis. Richard P. Mattick conceptualised the reviews and Jo Kimber conducted the initial literature searches. Richard P. Mattick wrote the analysis sections and discussion. Marina Davoli was the contact editor of the review and contributed to the writing of the final version of the review. Marica Ferri from the Rome Editorial Base provided comments and copyediting on the drafts of this review; Roberto D'Amico from the Cochrane Statistical Methods Group provided advice on statistical analysis issues.
<b>Issue protocol first published</b>	2000/3
<b>Review first published</b>	2002/4
<b>Date of most recent amendment</b>	05 January 2005
<b>Date of most recent SUBSTANTIVE amendment</b>	05 February 2003
<b>What's New</b>	the study of Mattick 2002 is now published and the reference is changed in Mattick 2003
<b>Date new studies sought but none found</b>	Information not supplied by author
<b>Date new studies found but not yet included/excluded</b>	Information not supplied by author
<b>Date new studies found and included/excluded</b>	Information not supplied by author
<b>Date authors' conclusions section amended</b>	Information not supplied by author
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**Cochrane Library number** CD002207  
**Editorial group** Cochrane Drugs and Alcohol Group  
**Editorial group code** HM-ADDICTN

**GRAPHS AND OTHER TABLES**

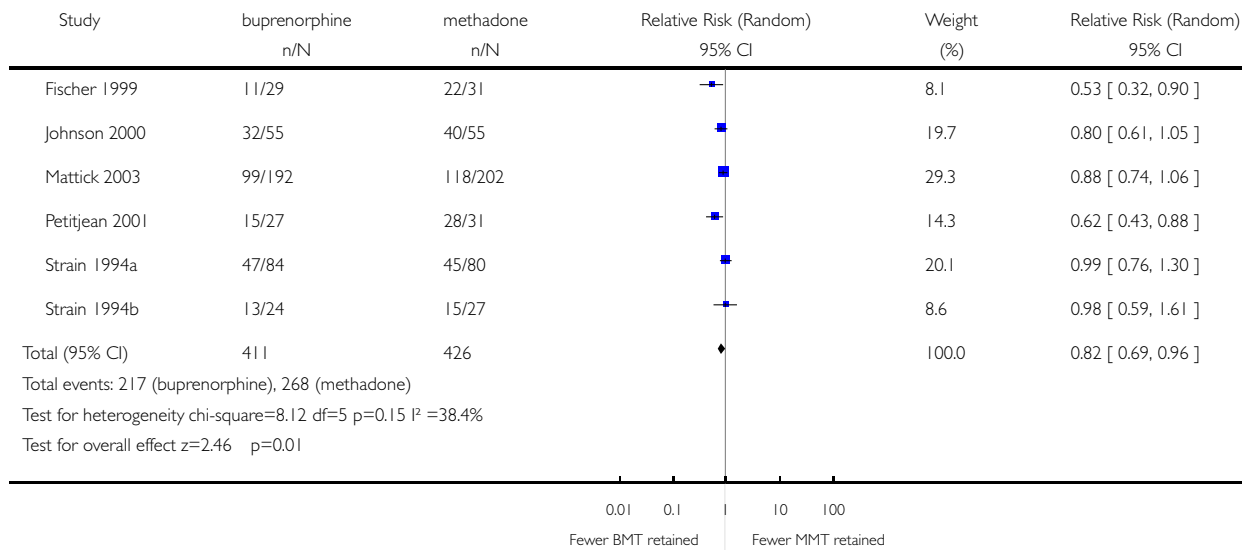
**Fig. 1. Comparison 01. Flexible dose buprenorphine versus flexible dose methadone**

**01.01 retention in treatment**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 01 Flexible dose buprenorphine versus flexible dose methadone

Outcome: 01 retention in treatment



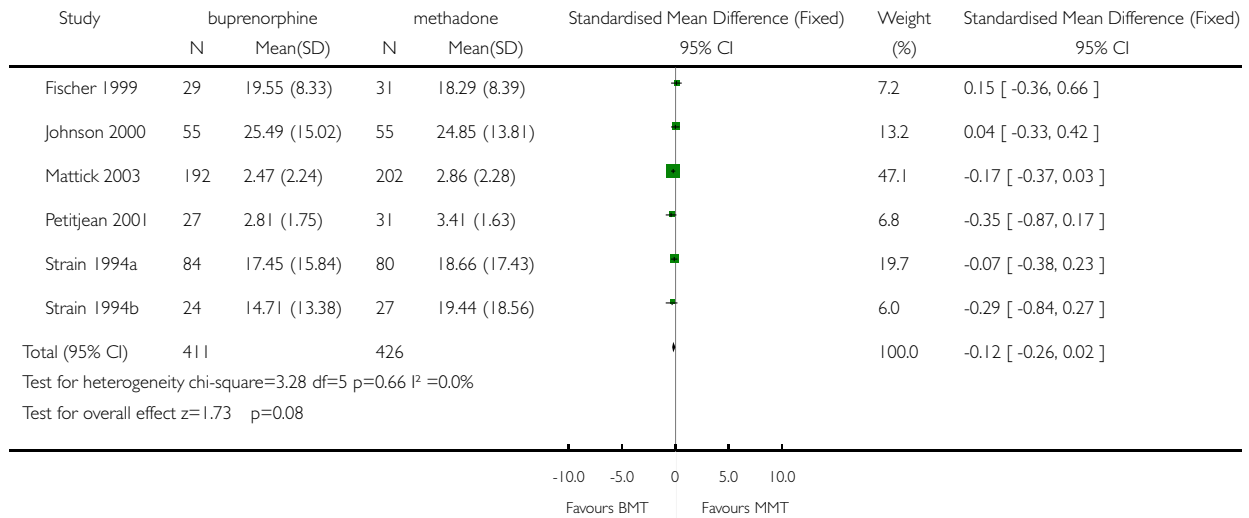
**Fig. 2. Comparison 01. Flexible dose buprenorphine versus flexible dose methadone**

**01.02 morphine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 01 Flexible dose buprenorphine versus flexible dose methadone

Outcome: 02 morphine positive urines



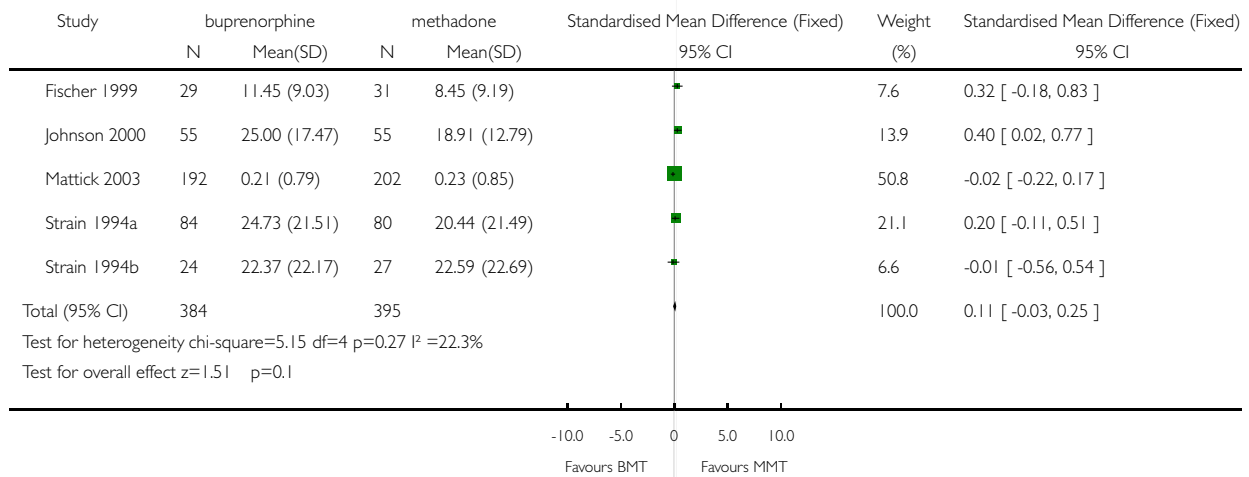
**Fig. 3. Comparison 01. Flexible dose buprenorphine versus flexible dose methadone**

**01.03 cocaine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 01 Flexible dose buprenorphine versus flexible dose methadone

Outcome: 03 cocaine positive urines



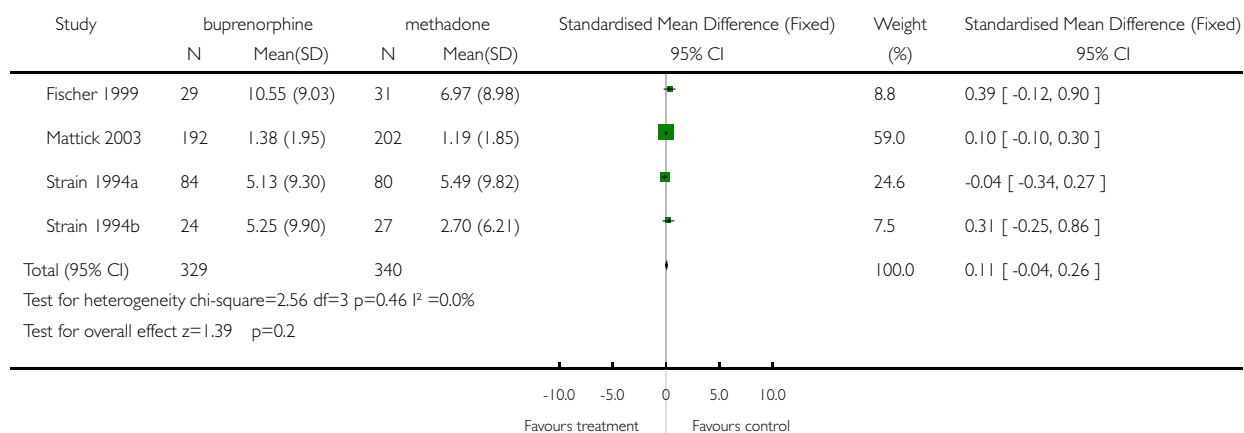
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**01.04 benzodiazepine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 01 Flexible dose buprenorphine versus flexible dose methadone

Outcome: 04 benzodiazepine positive urines



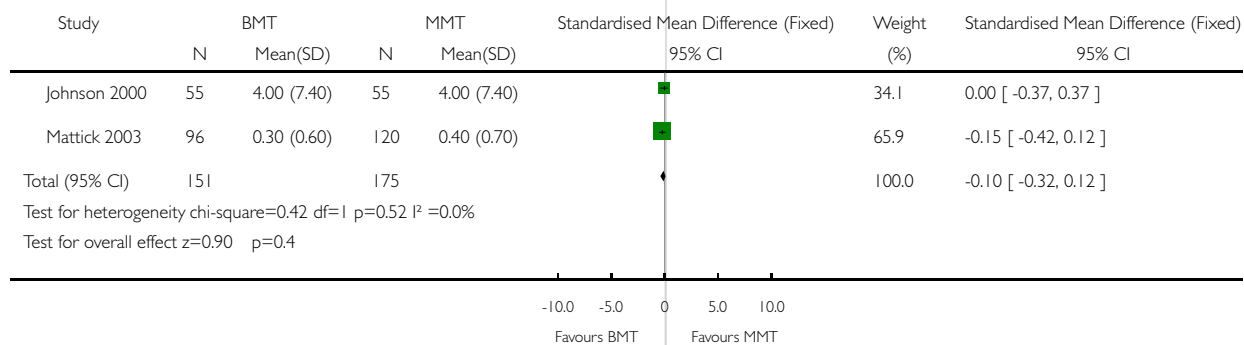
**Fig. 5. Comparison 01. Flexible dose buprenorphine versus flexible dose methadone**

**01.05 self-reported heroin use**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 01 Flexible dose buprenorphine versus flexible dose methadone

Outcome: 05 self-reported heroin use



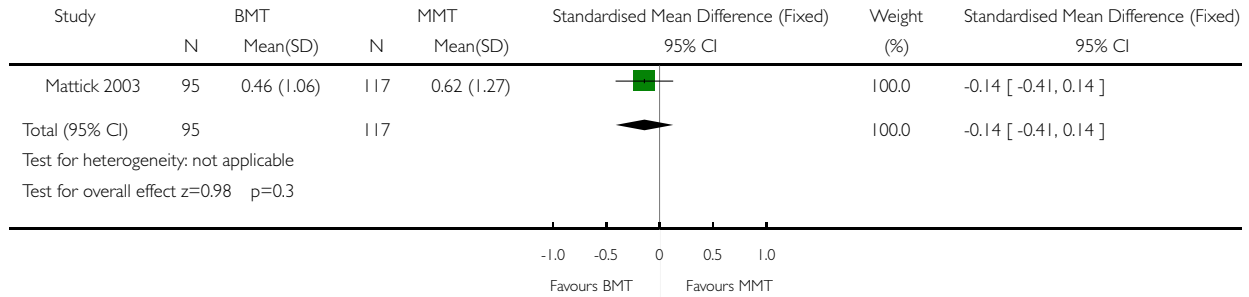
**Fig. 6. Comparison 01. Flexible dose buprenorphine versus flexible dose methadone**

**01.06 Self-reported crime**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 01 Flexible dose buprenorphine versus flexible dose methadone

Outcome: 06 Self-reported crime



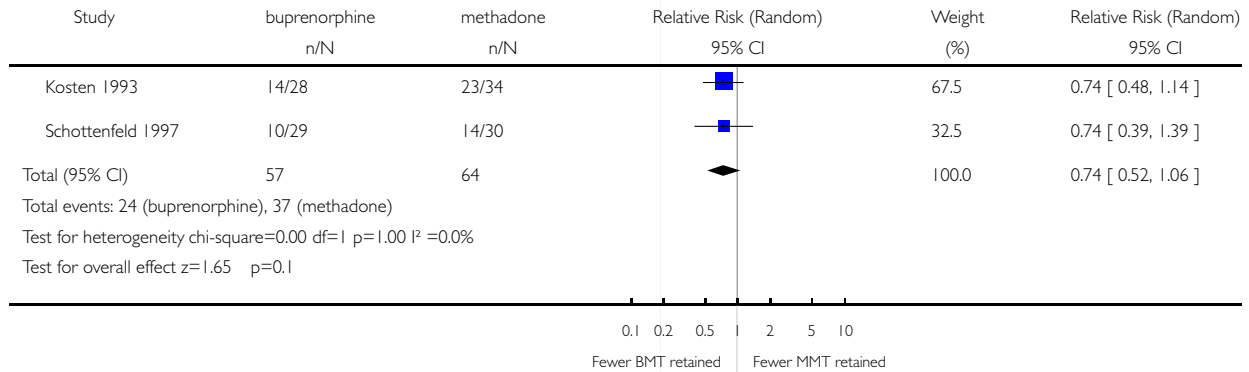
**Fig. 7. Comparison 02. Low dose buprenorphine versus low dose methadone**

**02.01 retention in treatment**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 02 Low dose buprenorphine versus low dose methadone

Outcome: 01 retention in treatment



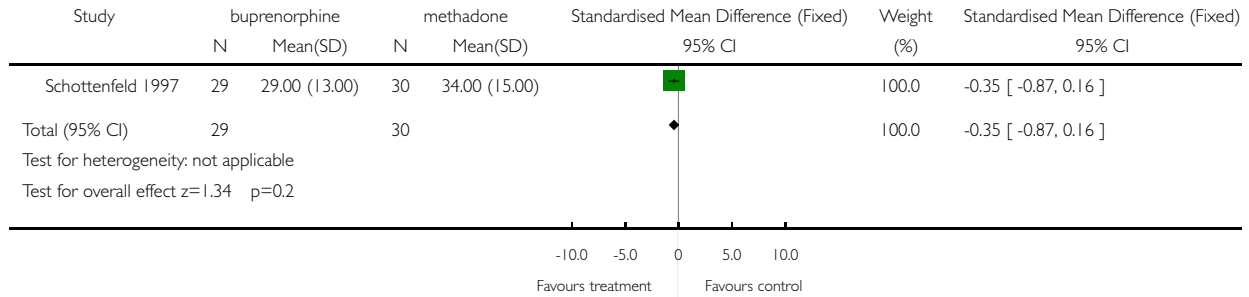
**Fig. 8. Comparison 02. Low dose buprenorphine versus low dose methadone**

**02.02 morphine positive urines**

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Comparison: 02 Low dose buprenorphine versus low dose methadone

Outcome: 02 morphine positive urines



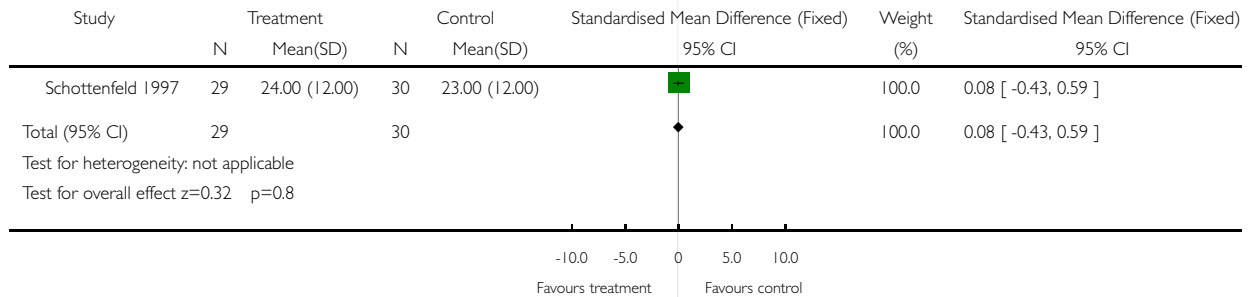
**Fig. 9. Comparison 02. Low dose buprenorphine versus low dose methadone**

**02.03 cocaine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 02 Low dose buprenorphine versus low dose methadone

Outcome: 03 cocaine positive urines



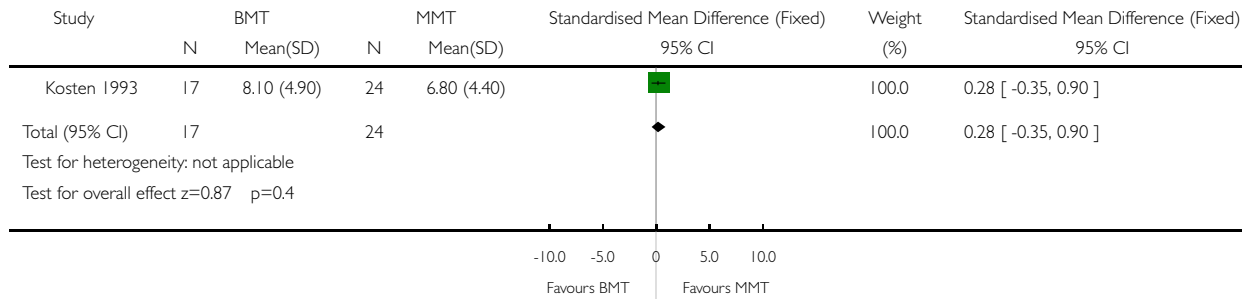
**Fig. 10. Comparison 02. Low dose buprenorphine versus low dose methadone**

**02.04 Self-reported heroin use**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 02 Low dose buprenorphine versus low dose methadone

Outcome: 04 Self-reported heroin use



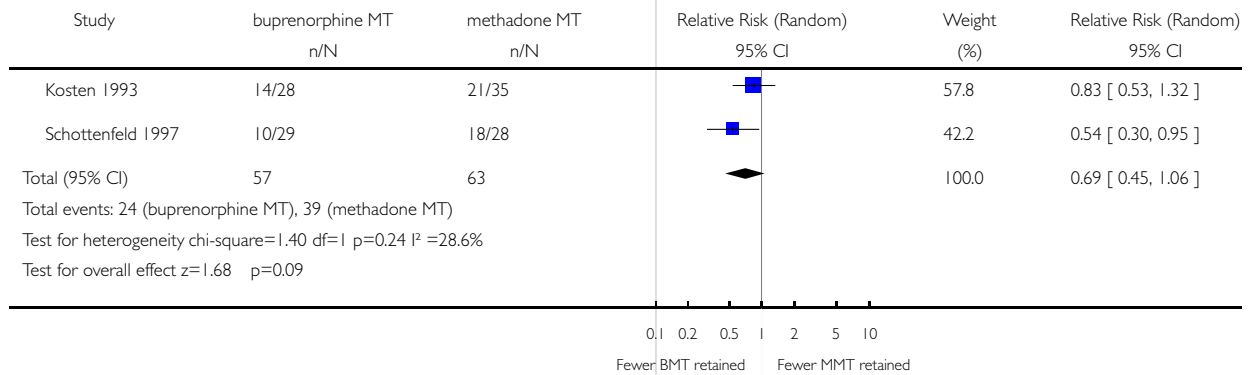
**Fig. 11. Comparison 03. Low dose buprenorphine versus high dose methadone**

**03.01 retention in treatment**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 03 Low dose buprenorphine versus high dose methadone

Outcome: 01 retention in treatment



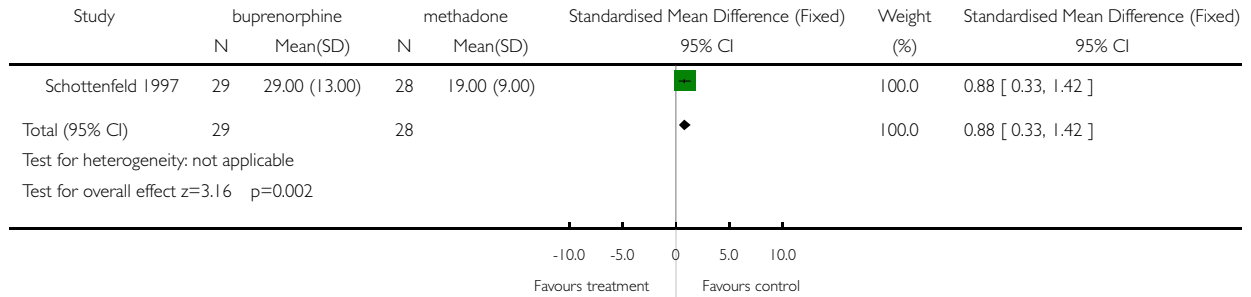
**Fig. 12. Comparison 03. Low dose buprenorphine versus high dose methadone**

**03.02 morphine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 03 Low dose buprenorphine versus high dose methadone

Outcome: 02 morphine positive urines



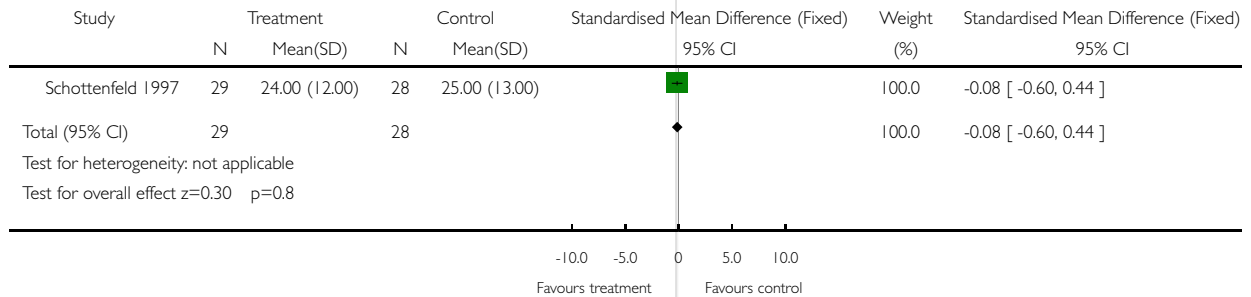
**Fig. 13. Comparison 03. Low dose buprenorphine versus high dose methadone**

**03.03 cocaine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 03 Low dose buprenorphine versus high dose methadone

Outcome: 03 cocaine positive urines



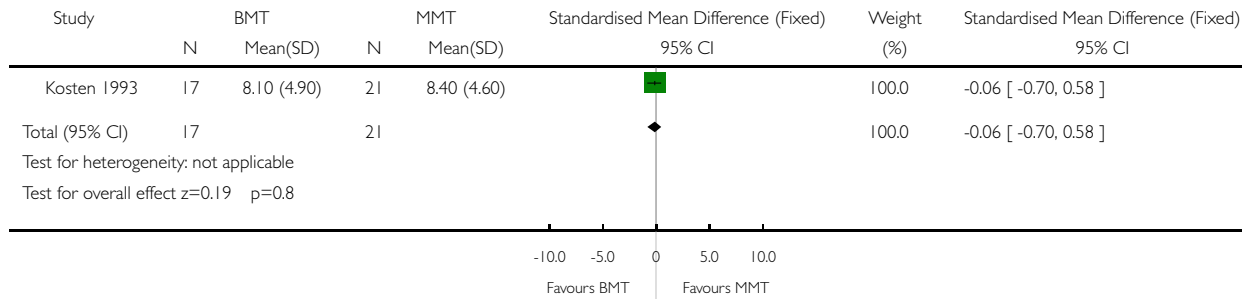
**Fig. 14. Comparison 03. Low dose buprenorphine versus high dose methadone**

**03.04 Self-reported heroin use**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 03 Low dose buprenorphine versus high dose methadone

Outcome: 04 Self-reported heroin use



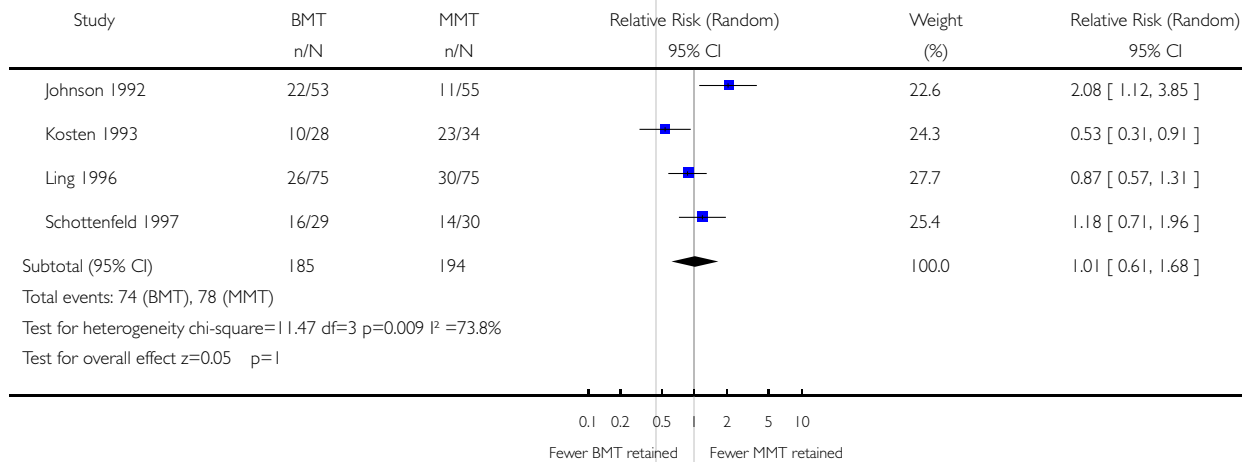
**Fig. 15. Comparison 04. High dose buprenorphine versus low dose methadone**

**04.01 retention in treatment**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 04 High dose buprenorphine versus low dose methadone

Outcome: 01 retention in treatment



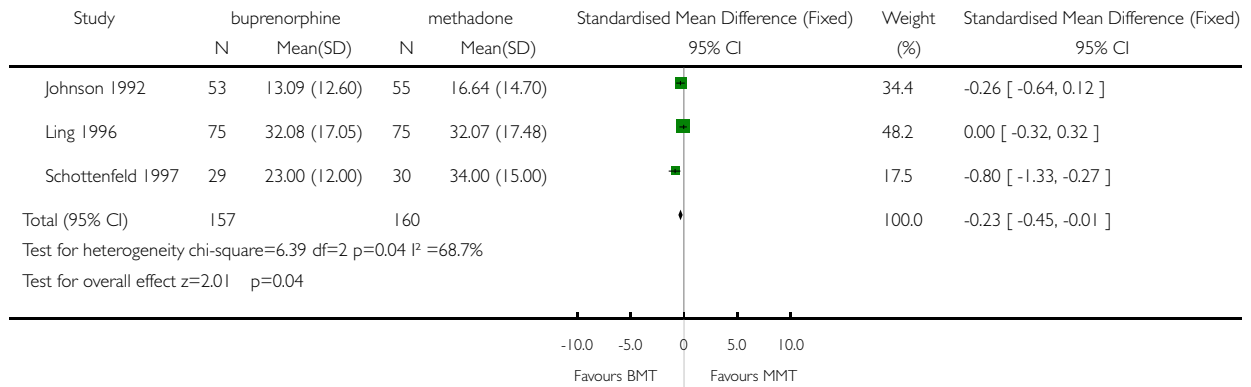
**Fig. 16. Comparison 04. High dose buprenorphine versus low dose methadone**

**04.02 morphine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 04 High dose buprenorphine versus low dose methadone

Outcome: 02 morphine positive urines



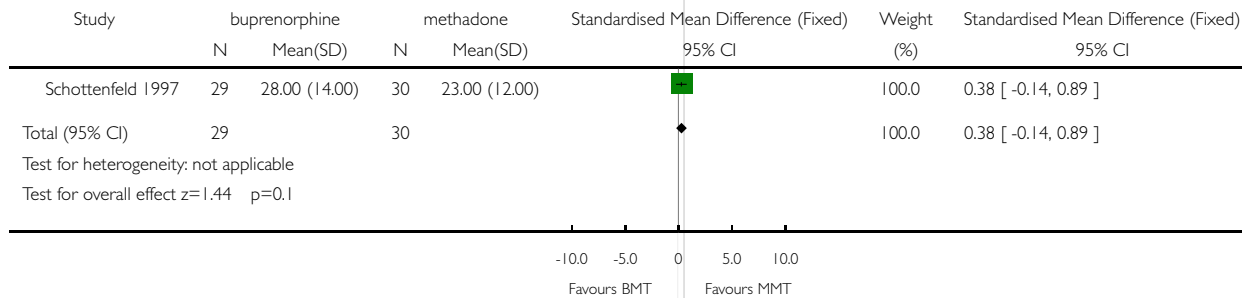
**Fig. 17. Comparison 04. High dose buprenorphine versus low dose methadone**

**04.03 cocaine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 04 High dose buprenorphine versus low dose methadone

Outcome: 03 cocaine positive urines



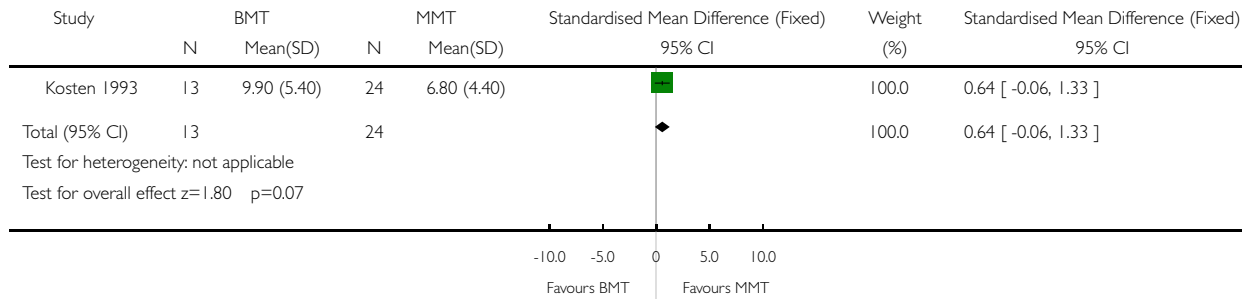
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**04.04 Self-reported heroin use**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 04 High dose buprenorphine versus low dose methadone

Outcome: 04 Self-reported heroin use



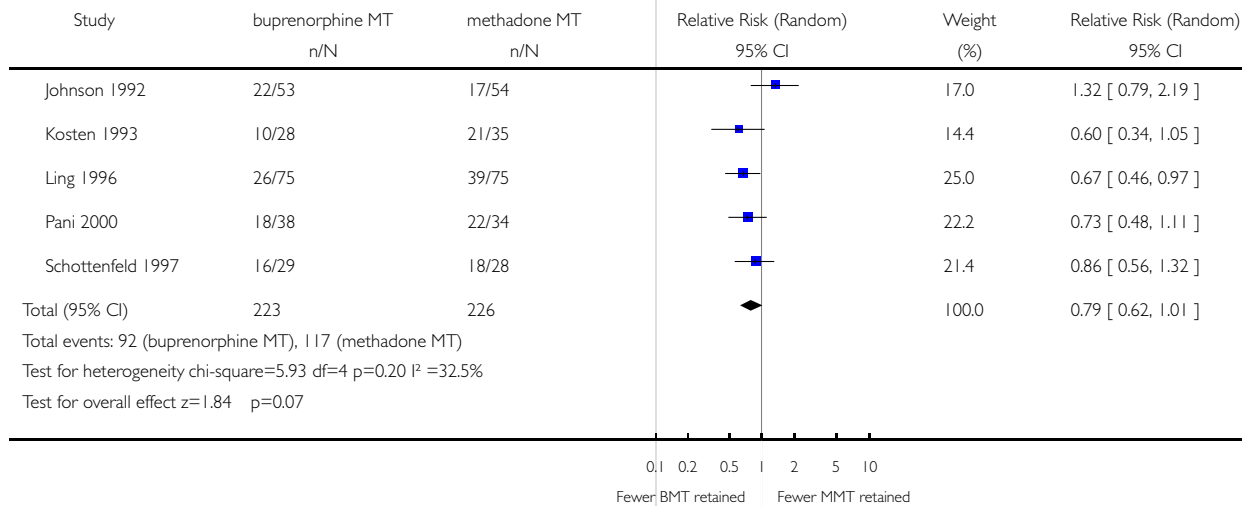
**Fig. 19. Comparison 05. High dose buprenorphine versus high dose methadone**

**05.01 retention in treatment**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 05 High dose buprenorphine versus high dose methadone

Outcome: 01 retention in treatment



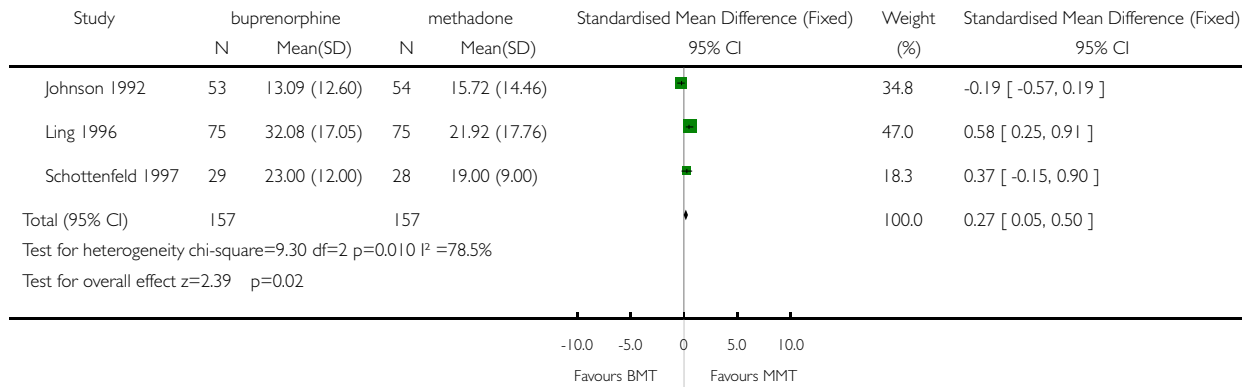
**Fig. 20. Comparison 05. High dose buprenorphine versus high dose methadone**

**05.02 morphine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 05 High dose buprenorphine versus high dose methadone

Outcome: 02 morphine positive urines



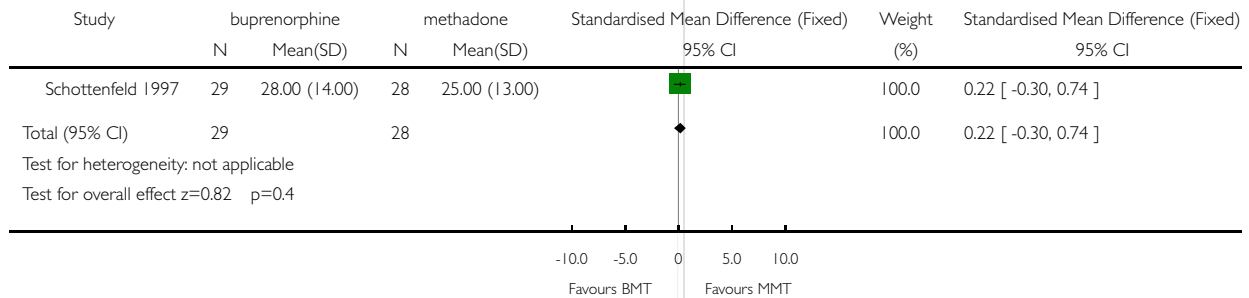
**Fig. 21. Comparison 05. High dose buprenorphine versus high dose methadone**

**05.03 cocaine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 05 High dose buprenorphine versus high dose methadone

Outcome: 03 cocaine positive urines



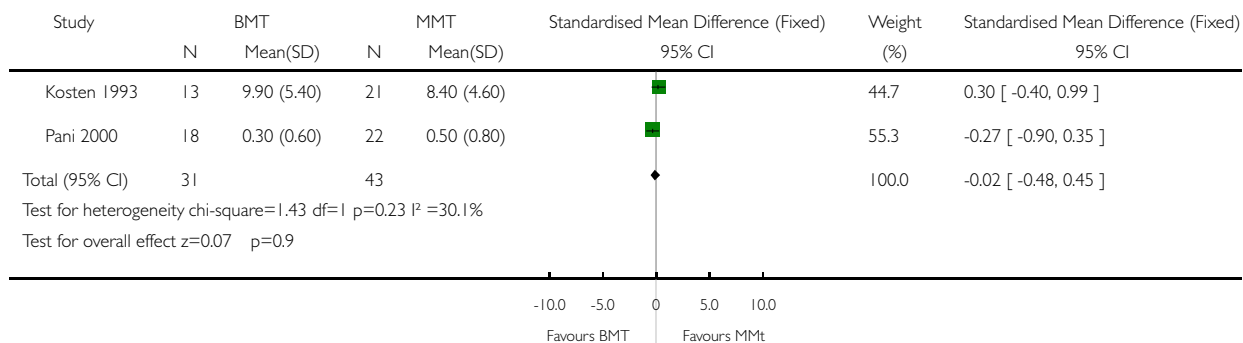
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**05.04 Self-reported heroin use**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 05 High dose buprenorphine versus high dose methadone

Outcome: 04 Self-reported heroin use



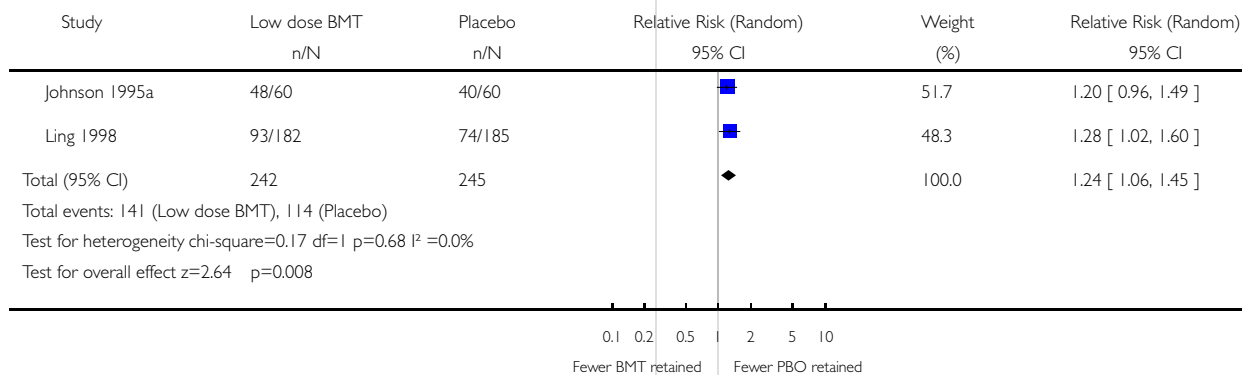
**Fig. 23. Comparison 06. Low dose buprenorphine versus placebo**

**06.01 Retention in treatment**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 06 Low dose buprenorphine versus placebo

Outcome: 01 Retention in treatment



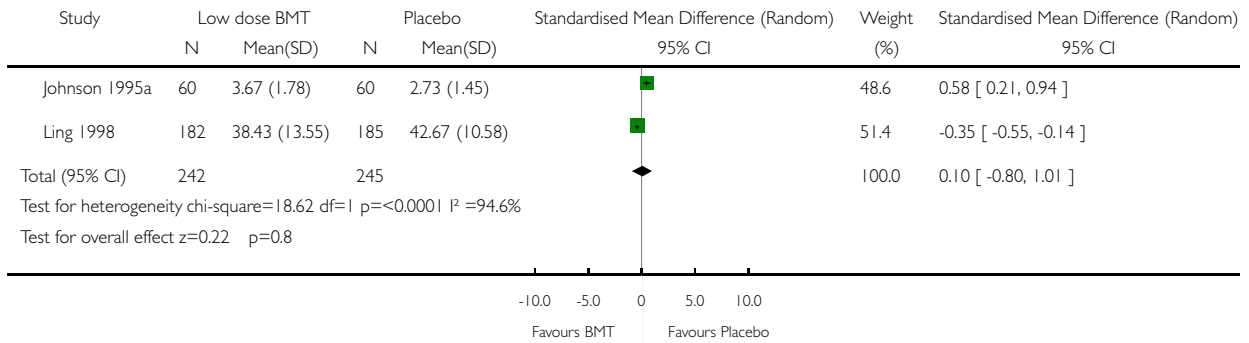
**Fig. 24. Comparison 06. Low dose buprenorphine versus placebo**

**06.02 Morphine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 06 Low dose buprenorphine versus placebo

Outcome: 02 Morphine positive urines



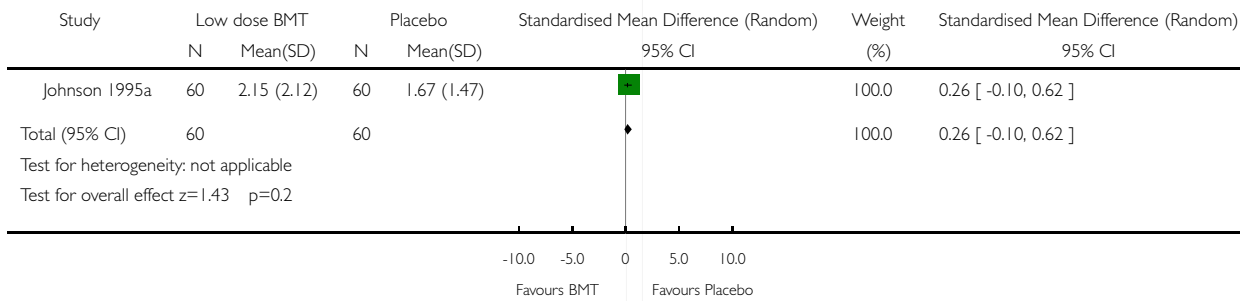
**Fig. 25. Comparison 06. Low dose buprenorphine versus placebo**

**06.03 Cocaine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 06 Low dose buprenorphine versus placebo

Outcome: 03 Cocaine positive urines



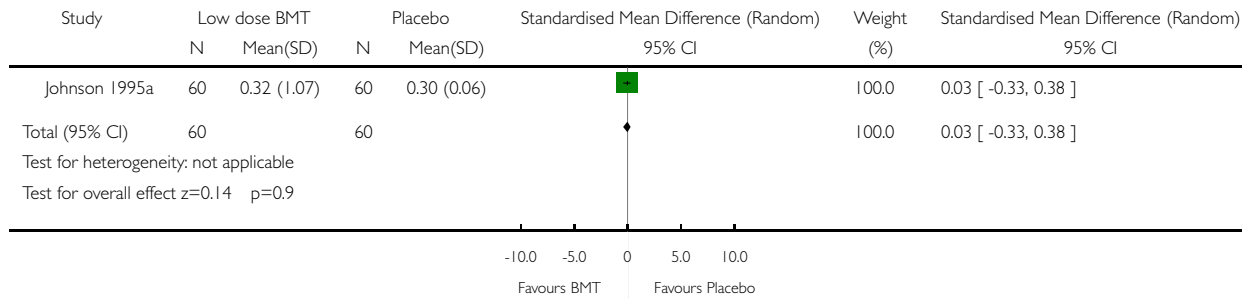
**Fig. 26. Comparison 06. Low dose buprenorphine versus placebo**

**06.04 Benzodiazepine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 06 Low dose buprenorphine versus placebo

Outcome: 04 Benzodiazepine positive urines



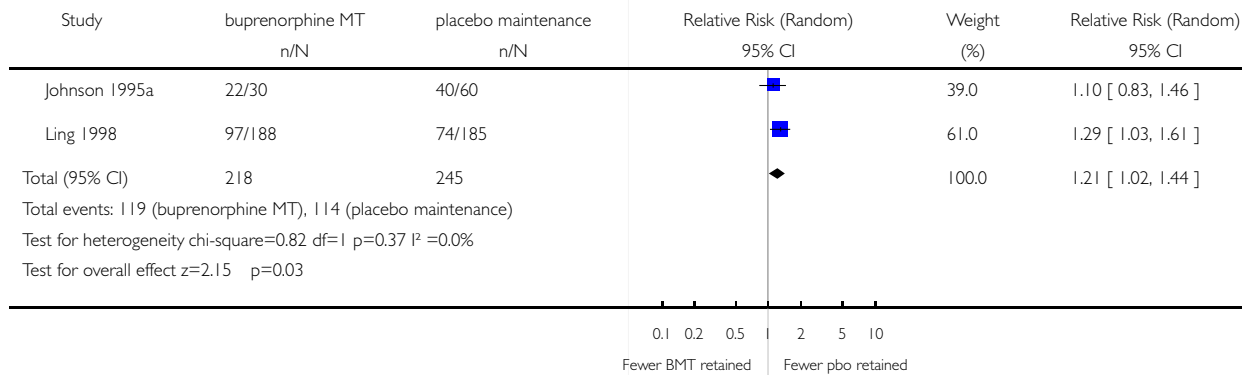
**Fig. 27. Comparison 07. High dose buprenorphine versus placebo**

**07.01 retention in treatment**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 07 High dose buprenorphine versus placebo

Outcome: 01 retention in treatment



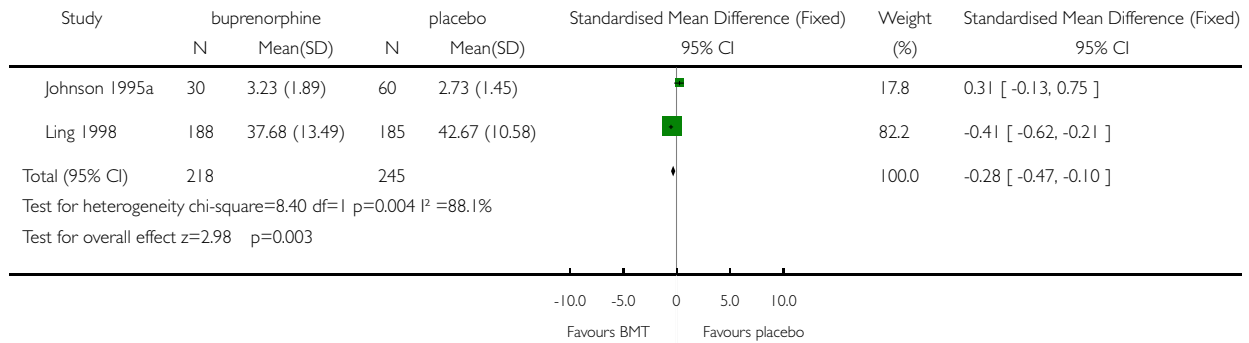
**Fig. 28. Comparison 07. High dose buprenorphine versus placebo**

**07.02 morphine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 07 High dose buprenorphine versus placebo

Outcome: 02 morphine positive urines



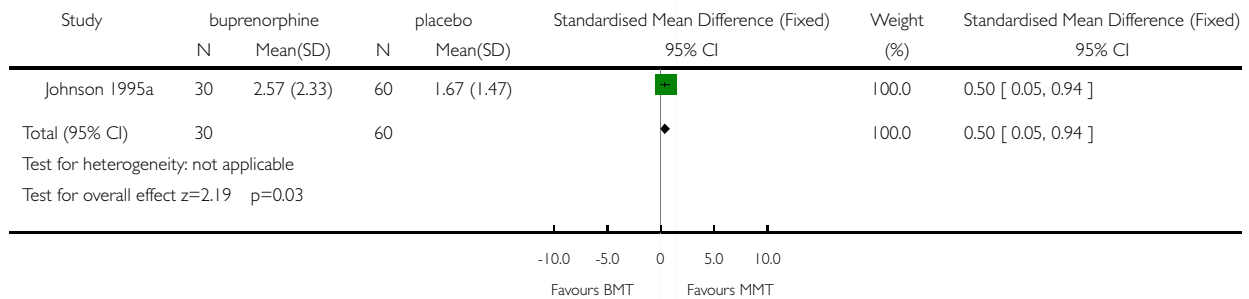
**Fig. 29. Comparison 07. High dose buprenorphine versus placebo**

**07.03 cocaine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 07 High dose buprenorphine versus placebo

Outcome: 03 cocaine positive urines



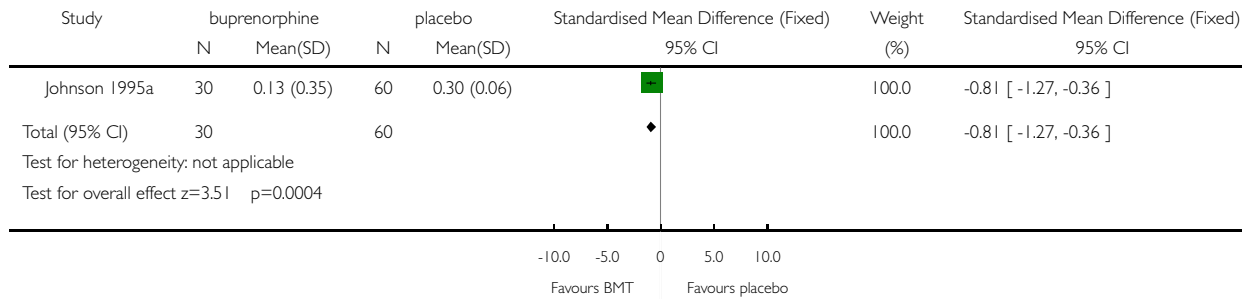
**Fig. 30. Comparison 07. High dose buprenorphine versus placebo**

**07.04 benzodiazepine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 07 High dose buprenorphine versus placebo

Outcome: 04 benzodiazepine positive urines



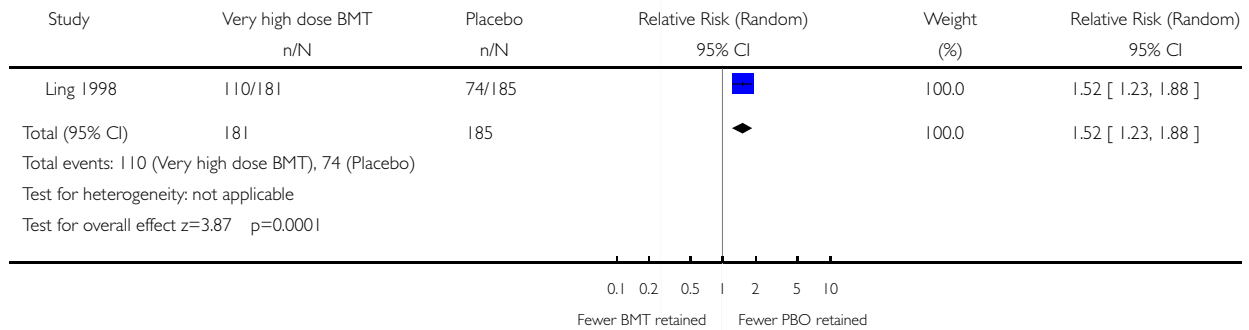
**Fig. 31. Comparison 08. Very high dose buprenorphine versus placebo**

**08.01 Retention in treatment**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 08 Very high dose buprenorphine versus placebo

Outcome: 01 Retention in treatment



**Fig. 32. Comparison 08. Very high dose buprenorphine versus placebo**

**08.02 Morphine positive urines**

Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence

Comparison: 08 Very high dose buprenorphine versus placebo

Outcome: 02 Morphine positive urines

