

## **Methadone Maintenance Therapy Versus No Opioid Replacement Therapy for Opioid Dependence<sup>1</sup> — Source link**

Iosief Abraha, Cristina Cusi

**Published on:** 13 Aug 2012

**Topics:** Opioid

Related papers:

- [Methadone Treatment for Opioid Dependence.](#)
- [Methadone Maintenance Therapy for Opioid Dependence](#)
- [Buprenorphine versus methadone maintenance for the treatment of opioid dependence](#)
- [Pain in methadone maintenance therapy](#)
- [Methadone treatment in clinical practice in Italy: need for improvement.](#)

Share this paper:    

View more about this paper here: <https://typeset.io/papers/methadone-maintenance-therapy-versus-no-opioid-replacement-3jz6vhf9p0>

# Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence (Review)

Mattick RP, Breen C, Kimber J, Davoli M, Breen R



**THE COCHRANE  
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2003, Issue 2

<http://www.thecochranelibrary.com>

**WILEY**

## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	3
METHODS . . . . .	3
RESULTS . . . . .	4
DISCUSSION . . . . .	5
AUTHORS' CONCLUSIONS . . . . .	6
ACKNOWLEDGEMENTS . . . . .	6
REFERENCES . . . . .	7
CHARACTERISTICS OF STUDIES . . . . .	7
DATA AND ANALYSES . . . . .	13
Analysis 1.1. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 1 Retention in treatment. . . . .	13
Analysis 1.2. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 2 Morphine positive urines. . . . .	14
Analysis 1.3. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 3 Self reported heroin use. . . . .	15
Analysis 1.4. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 4 Criminal activity. . . . .	16
Analysis 1.5. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 5 Mortality. . . . .	17
WHAT'S NEW . . . . .	17
HISTORY . . . . .	17
CONTRIBUTIONS OF AUTHORS . . . . .	18
DECLARATIONS OF INTEREST . . . . .	18
SOURCES OF SUPPORT . . . . .	18
INDEX TERMS . . . . .	18

[Intervention Review]

# Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Richard P. Mattick<sup>1</sup>, Courtney Breen<sup>1</sup>, Jo Kimber<sup>1</sup>, Marina Davoli<sup>2</sup>, Rosie Breen<sup>3</sup>

<sup>1</sup>National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia. <sup>2</sup>Cochrane Drugs and Alcohol Group, Dept. of Epidemiology ASL RME, Italy, Rome, Italy. <sup>3</sup>School of Health Care, Oxford Brookes University, Oxford, UK

Contact address: Richard P. Mattick, National Drug and Alcohol Research Centre, University of New South Wales, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, 2052, Australia. [R.Mattick@unsw.edu.au](mailto:R.Mattick@unsw.edu.au).

**Editorial group:** Cochrane Drugs and Alcohol Group.

**Publication status and date:** Unchanged, published in Issue 2, 2009.

**Review content assessed as up-to-date:** 23 February 2003.

**Citation:** Mattick RP, Breen C, Kimber J, Davoli M, Breen R. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD002209. DOI: 10.1002/14651858.CD002209.

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## ABSTRACT

### Background

Methadone maintenance was the first widely used form of opioid replacement therapy developed to treat heroin dependence, and it remains the best-researched treatment for this problem. Despite the widespread use of methadone in maintenance treatment for opioid dependence in many countries, it is a controversial treatment whose effectiveness has been disputed.

### Objectives

To evaluate the effects of methadone maintenance treatment (MMT) compared with treatments that did not involve opioid replacement therapy (i.e., detoxification, offer of drug-free rehabilitation, placebo medication, wait-list controls) for opioid dependence.

### Search strategy

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

### Selection criteria

All randomised controlled clinical trials of methadone maintenance therapy compared with either placebo maintenance or other non-pharmacological therapy for the treatment of 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

Six studies met the criteria for inclusion in this review, all were randomised clinical trials, two were double-blind. There were a total number of 954 participants. The method of concealment of allocation was inadequate in one study, not clearly described in four studies, but adequate in a sixth study. Based on the meta-analysis, methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patient in treatment (3 RCTs, RR=3.05; 95%CI: 1.75-5.35) and in the suppression of heroin use (3 RCTs, RR=0.32; 95%CI: 0.23-0.44), but not statistically in criminal activity (3 RCTs, RR=0.39; 95%CI: 0.12-1.25).

## Authors' conclusions

Methadone is an effective maintenance therapy intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use better than treatments that do not utilise opioid replacement therapy. It does not show a statistically significant superior effect on criminal activity.

## PLAIN LANGUAGE SUMMARY

### Methadone maintenance treatment can keep people who are dependent on heroin in treatment programs and reduce their use of heroin

Methadone is the most widely used replacement for heroin in medically-supported maintenance or detoxification programs. Several non-drug detoxification and rehabilitation methods are also used to try and help people withdraw from heroin. However the review found that people have withdrawn from trials when they are assigned to a drug-free program. Consequently, there are no trials comparing methadone maintenance treatment with drug-free methods other than methadone placebo trials, or comparing methadone maintenance with methadone for detoxification only. These trials show that methadone can reduce the use of heroin in dependent people, and keep them in treatment programs.

## BACKGROUND

Currently, the major form of medical therapy for heroin dependence internationally involves orally administered methadone. Methadone is an analgesic medication developed to treat pain in the 1940s. It has been, and is still, prescribed widely for the management of pain in America, Australia and Europe.

It was in New York in the 1960s, during an increase in heroin use and heroin dependence, that researchers (Dole 1965; Dole Nyswander 1967) examined different prescribed opioids to manage heroin dependence, and reported that they found that methadone was most suitable to the task. They believed that long-term heroin use caused a permanent metabolic deficiency in the central nervous system and an associated physiological disease, which required regular administration of opiates to correct the metabolic deficiency (Dole 1969 & Nyswander, 1965). The disorder of opioid dependence has been represented in the International Classification of Disease of the World Health Organisation. It is a chronic or long-term and relapsing disorder, and some believe that it requires ongoing maintenance medication.

The aspects of methadone that have led to its use as a substitute drug for heroin include the number of pharmacological features of opioids. At the basis of methadone maintenance treatment (MMT) is the observation that opioid analgesics can be substituted for one another (Jaffe 1990). Methadone at adequate doses (of 20mg to more than 100 mg) prevents or reverses withdrawal symptoms (Ward 1992), and thus reduces the need to use illegal heroin (Jaffe 1990). Methadone remains effective for approximately 24 hours, requiring a single daily dose rather than the more frequent administration of three to four times daily which occurs with the shorter-acting heroin (Jaffe 1990). Methadone can “block” the euphoric effects of heroin, discouraging illicit use and thereby relieving the user of the need or desire to seek heroin (Dole 1969). This allows the opportunity to engage in normative activities, and “rehabilitation” if necessary. Methadone can cause death in overdose, like other similar medications such as morphine, and for this reason it is a treatment which is dispensed under medical supervision and relatively strict rules. In summary, methadone is a long-acting opioid analgesic with well-understood pharmacological characteristics which make it suitable for stabilising opioid dependent patients in a maintenance treatment approach.

There is evidence that the quality of the therapeutic relationship with staff in methadone clinics plus the intensity of these ancillary services, combined with the dose of methadone prescribed will all act to enhance the outcome for methadone treatment (Ward 1992), although this is not the focus of this review.

Methadone maintenance treatment remains one of the best researched treatments for opioid dependence (Cooper 1983; Gerstein 1990; Hargreaves 1983; Mattick 1993; Ward 1992). It is the only treatment for opioid dependence which has been clearly demonstrated to reduce illicit opiate use more than either no-treatment (Dole 1969; Yancovitz 1991), drug-free treatment (Gunne 1981), placebo medication (Newman 1979; Strain 1993a; Strain 1993a), or detoxification (Vanichseni 1991) in clinical controlled trials. These trials have been conducted by different research groups, in markedly differing cultural settings, yet have converged to provide similar results.

## OBJECTIVES

The present systematic review aimed to provide an evaluation of the effectiveness of methadone maintenance treatment on opioid dependence compared with treatments that did not include an opioid replacement therapy. The focus of the review is on retention in treatment, opioid use as measured by objective urine results and from self-report, as well as criminal activity and patient mortality.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

The literature was reviewed for all clinical controlled trials of MMT against another treatment which does not use opioid replacement therapy.

#### Types of participants

Individuals who were opioid dependent were the target population for this review. No distinction was made between those using heroin and those who have been in methadone treatment prior to entering the research trial treatment. No restrictions were imposed in terms of studies of outpatients, inpatients, those with comorbid states, etc.

#### Types of interventions

Interventions were included if they used methadone maintenance therapy (MMT). The MMT interventions were included even where they also employed other treatments, such as behavioural therapies or outpatient rehabilitation. The control groups were treated with placebo medication, withdrawal or detoxification (with or without ancillary medication), drug-free rehabilitation treatment (such as therapeutic communities), and no treatment or wait-list controls.

#### Types of outcome measures

Outcome measures:

Primary outcomes

- 1) retention in treatment
- 2) mortality
- 3) proportion of urinalysis results positive for heroin (or morphine)
- 4) self-reported heroin use
- 5) criminal activity

Secondary outcomes

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

#### Search methods for identification of studies

The search strategy was developed in consultation with a drug and alcohol research information specialist without language restrictions.

We searched:

1. Cochrane Drugs and Alcohol Review Group Register for trials of methadone maintenance therapy to 2001.
2. Cochrane Controlled Trials Register for trials of methadone maintenance therapy to 2001.
3. MEDLINE (1966-2001) (OVID) was searched using the Cochrane Collaboration sensitive search strategies used to identify randomised trials in conjunction with the following to identify studies comparing methadone maintenance therapy and no methadone maintenance therapy:

#1 exp methadone

#2 (placebo or withdrawal or detoxification or untreated or no treatment or drug free or wait list).ti, ab, rw,sh.

#3 exp pain/ or pain.ti, ab, rw, sh.

#4 (1 and 2) not 3

EMBASE (1980-2001) was searched using the following (OVID):  
#1 exp methadone/ or exp methadone treatment/ ct (limit to clinical trials)

#2 exp drug dependence or exp substance abuse or exp drug abuse

#3 1 and 2

#4 limit to human

#5 placebo or withdrawal or untreated of drug free or detoxification or wait list

#6 4 and 5

As several drug and alcohol journals are not indexed on the main electronic databases, Current Contents, Psychlit (-2001), 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\* searched for studies and book chapters comparing methadone maintenance with other treatment.

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

### Data collection and analysis

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

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

- A. Low risk of bias (allocation clearly independent of clinical staff);
- B. Moderate risk of bias (some doubt about the independence of the allocation procedure); and
- C. High risk of bias (inadequate separation of randomisation from clinical staff).

A standardised effect size was calculated for each study, based on the main outcome measure reported. Where possible (relative risks and 95% confidence intervals for dichotomous outcomes (retention) using a random effects model and standardised mean differences for continuous outcomes were presented. To assess for statistical heterogeneity a test of homogeneity was undertaken. A pooled effect size estimate was derived for each domain of measurement (retention in treatment, urine analysis results for heroin/morphine), self-reported heroin use, and criminal activity. The retention in treatment and urine results were reported as the number of patients retained or the number with a morphine-positive urine result at follow-up, a form of reporting that allowed for dichotomous analysis of those data.

The results were integrated from the meta-analytic review into a discussion taking into consideration other publications including large-scale observational studies, studies of the pharmacology of methadone, and studies of the effect of MMT on HIV serocon-

version. Convergence of the evidence from the meta-analysis and the narrative review was taken to indicate a robust conclusion.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

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

One study was not included. A study by Bale ([Bale 1980](#)) was an attempt to compare methadone against therapeutic community treatment of detoxification. Because the study failed, no useful data could be obtained from it for this review.

In total, six studies were included in this review. The first study by Dole ([Dole 1969](#)) was a two group randomised trial where patients either received methadone or placed on a wait-list. The second study ([Gunne 1981](#)) randomly allocated patients to receive methadone maintenance or to be allocated to a drug-free rehabilitation. None of the patients allocated to drug-free rehabilitation took up the offer, refusing treatment after they had learnt that they would not receive methadone. There were two placebo controlled trials ([Newman 1979](#), [Strain 1993a](#)). Finally, there have been two randomised clinical trials, one assessing methadone maintenance against methadone detoxification and the other assessing methadone maintenance against a wait-list control ([Vanichseni 1991](#), [Yancovitz 1991](#)).

All studies were assessed to determine whether they provided data on retention in treatment, code able results from urine analysis, self-reported drug use (particularly heroin use), criminal activity and mortality. After reviewing the studies, it was realised that it was not possible to include urine results for cocaine and benzodiazepines as these were not reported in an analysable form for most studies. Thus, it was not possible to analyse data on either cocaine or benzodiazepine positive urine from these studies. However, it was possible to code data on retention in treatment, morphine positive urine, self-reported heroin use, criminal activity, and mortality.

### Risk of bias in included studies

Of the six studies included in this review, two were placebo-controlled trials ([Newman 1979](#), [Strain 1993a](#)). Both of these studies were double-blind but neither of these two studies provided sufficient data to be confident about the concealment of allocation. The first study conducted by Dole ([Dole 1969](#)) seemed to have inadequate concealment of allocation. The other three studies had

reasonable concealment, and particularly the Yancovitz (Yancovitz 1991) had good concealment of allocation.

The sample sizes in these studies were sometimes small, in that two studies having sample sizes of 32 and 34 (Dole 1969; Gunne 1981), respectively. The other four studies had sample sizes ranging from 100 to 240 (Newman 1979; Vanichseni 1991) patients up to 247 to 301 patients (Strain 1993a; Yancovitz 1991).

The dosages of methadone used in these studies appears to have been adequate. In the first study, (Dole 1969) the dose at release from prison was 35 milligrams but patients were entered into a community program where blockade doses of approximately 100 milligrams were standard. In the study by Gunne (Gunne 1981) the doses are not clearly stated. The placebo-controlled study by Newman (Newman 1979) have an average dose on 97 milligrams per day. An average of 74 milligrams per day was reported in the study from Thailand (Vanichseni 1991). Strain (Strain 1993a) used doses of methadone of 50 and 20 milligrams per day. Finally, the study by Yancovitz 1991 used a maintenance dose of approximately 80 milligrams per day. As such, the results from the studies appear to use moderate to high doses on average.

Data on retention in treatment, self-reported heroin use, criminal activity, mortality and morphine positive urine were provided in the studies.

## Effects of interventions

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

Six studies were included in the review. The participants (n=954) were from a range of geographic regions including USA, Sweden, Hong Kong, Thailand and they were largely typical of heroin dependant individuals, in terms of age and gender characteristics. In some studies, only males were included but where females were included the gender distribution was as one would expect with majority of the participants being male.

As shown in the table of included studies, the interventions generally lasted for significant time of several weeks up to two years, although one study only ran for 45 days.

### 2. Quantitative Analysis

Retention in treatment could be coded from three studies, and the results showed that methadone has a superior retention rate compared with control conditions. When compared with placebo medications and with the wait-list control there was an advantage in terms of retention for methadone over the control groups (3 studies, 505 patients; RR= 3.05, 95% CI 1.75-5.35). The relative risk on a random effect model was applied. The chi-square test for heterogeneity was significant (p=0.018). The examination of the graphical representation of the relative risks showed that one study (Newman 1979) did appear to be slightly different from the other two studies, with higher RR, even though all single RRs were in the same direction of a positive effect (Vanichseni 1991; Strain 1993a).

Turning to the data from morphine positive urines, only two studies (Vanichseni 1991; Yancovitz 1991) provided data which were usable because of the way in which the data were typically reported. Specifically, many studies did not provide dichotomous data as to whether patients had morphine positive urines at the follow-up. However, the results from the two studies providing data on the presence/absence of morphine in urine at the follow-up showed an advantage of methadone above the control conditions (2 studies, 409 patients, RR= -0.32, 95% CI -0.40 -0.23), in this case detoxification or wait-list control, in reducing heroin use as shown by a lack of heroin metabolites in urine.

The results from the objective data on morphine positive urine were also supported by self-report data from three studies. In particular, studies from the USA and from Sweden (Dole 1969; Yancovitz 1991; Gunne 1981) all concurred to show an advantage for methadone above control in reduction of heroin use as reported by the patients (3 studies, 230 patients RD=0.32, 95% CI:0.23-0.44). The test for heterogeneity was not significant, indicating the results can be interpreted confidently. The results show clearly an advantage for methadone above the control conditions which included no treatment, referral to drug-free treatment, or frequent contact on a waiting list.

The results for the criminal activity variable, available for three studies, were consistent with the reduction in heroin use, even though the advantage for methadone beyond control in reducing criminal activity was not statistically significant (3 studies, 363 patients RR=0.39, 95% CI:0.12-1.25). The test for heterogeneity was not significant.

Turning finally to the evidence concerning the ability of methadone to prevent deaths, available for three studies, the results showed a trend in favour on methadone that was not statistically significant (3 studies, 435 patients RR=0.49, 95% CI: 0.06-4.23). Other measures (e.g., use of other drugs, physical health, and psychological health) are too infrequently and irregularly reported in the literature to be usefully integrated in the quantitative review.

## DISCUSSION

The results of the meta-analysis indicate that methadone is able to retain patients in treatment better than the drug-free alternatives (placebo medication, offer of drug-free treatment, detoxification, or wait-list control), to suppress heroin use based on morphine (the heroin metabolite) found in urine samples, and patient self-report. There was a greater reduction in criminal activity and mortality among the MMT patients, but these differences were not statistically significant. There is evidence from other literature showing that mortality is decreased in patients who are in methadone treatment.

Interestingly, the results from these six randomised trials all showed statistically significant positive benefits from methadone treat-



ment, despite their small sample sizes. Additional support for the efficacy of methadone maintenance treatment comes from the results of many observational studies wherein some statistical form of control has addressed alternative explanations of apparent effectiveness. These large scale observational studies have generally supported the results from the randomised clinical trials in showing that methadone maintenance treatment reduces the use of heroin and decreases criminal activity (Ward 1992). As noted earlier there is a broader international literature showing advantages for methadone beyond other treatments in terms of reduction of death (Ward 1992), even though the randomised trial data do not show this result.

Another relevant outcome to be considered would be seroconversion for HIV, which is the object of a separate Cochrane review in progress. Methadone maintenance treatment has been shown to reduce HIV risk taking behaviour (specifically reduction in needle sharing) and thereby has achieved a reduction in the transmission of HIV. Consistent with this it has been shown that methadone maintenance treatment is protective of patients, reducing HIV infection in geographic locations where HIV had spread rapidly among injecting drug users who had not entered treatment. We have commented elsewhere on two large prospective cohort studies in the USA which found methadone maintenance treatment protected against HIV infection. This outcome could not be addressed here as there are no randomised trials of methadone that have included HIV status as a measure, the evidence coming from observational studies (Ward 1992).

It is notable that the doses of methadone used in the randomised clinical trials are probably slightly higher than are being used currently in routine clinical practice in some parts of the world. This relative under dosing in clinical practice may lead to a reduction in the effectiveness of methadone, as the response to methadone treatment is dose-dependent. In addition, it is important to recognise that methadone treatment in these trials was often provided with substantial ancillary services. These ancillary services have included counselling, psycho-social services, medical services and often psychiatric care. The quality of the therapeutic relationship with staff in methadone clinics plus the intensity of these ancillary services, combined with the dose of methadone prescribed will all act to enhance the outcome for methadone treatment. The extent that clinical programs move away from such an approach might be expected to impact on the effectiveness of methadone.

This does not imply that methadone maintenance treatment will become ineffective. Even allowing for some reduction in effectiveness when methadone is not provided in the fashion that it has

been in the clinical trials, it is still likely to be effective. The effects of methadone may be modest, if they are judged by unrealistic expectations of patients can easily achieve enduring abstinence from opioid drugs. Methadone nonetheless attracts and retains more patients than alternative treatments, and it does produce better outcomes amongst those who complete treatment. Methadone maintenance appears to provide better outcomes than simple detoxification programs, where the evidence suggests that short-term detoxification has no enduring effect on drug use (Mattick 1996).

## AUTHORS' CONCLUSIONS

### Implications for practice

The implications of the results of the meta-analytic review conducted and reported herein for clinical practice are that methadone maintenance treatment is an effective intervention for the management of heroin dependence. Methadone retains patients in treatment and reduces heroin use. Methadone should be supported as a maintenance treatment for heroin dependence.

### Implications for research

Overall there are a relatively limited number of randomised clinical trials on the efficacy of methadone treatment compared to placebo. It does not seem feasible at this stage to conduct further randomised trials of methadone treatment. However, evidence on reduction of criminal activity and mortality from clinical trials is lacking calling for an additional systematic review of observational studies. Moreover, monitoring of the outcome of standard methadone treatment in clinical practice may be important as a research activity to demonstrate its ongoing effectiveness, or to determine whether its effectiveness is being compromised through the reduction of ancillary services or reduction in adequate dose levels.

A number of measures (e.g., of other drug use, physical health, and psychological health) were too infrequently and irregularly reported in the literature to be usefully integrated in the quantitative review, but future research might address these important areas.

## ACKNOWLEDGEMENTS

We acknowledge the assistance of the Cochrane Review Group Coordinating Centre, Rome.

## REFERENCES

### References to studies included in this review

**Dole 1969** *{published data only}*

Dole V, Robinson J, Orraca J, Towns E, Searcy P, Caine E. Methadone treatment of randomly selected criminal addicts. *New England Journal of Medicine* 1969;**280**:1372–1375.

**Gunne 1981** *{published data only}*

Gunne L, Gronbladh L. The Swedish methadone maintenance program: A controlled study. *Drug and Alcohol Dependence* 1981;**7**:249–256.

**Newman 1979** *{published data only}*

Newman R, Whitehill W. Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. *Lancet* 1979;**September 8**:485–488.

**Strain 1993a** *{published data only}*

Strain E, Stitzer M, Leibson I, Bigelow G. Dose-response effects of methadone in the treatment of opioid dependence. *Ann Intern Med* 1993;**119**:23–27.

**Vanichseni 1991** *{published data only}*

Vanichseni S, Wongsuwan B, The Staff of BMA Narcotics Clinic No.6, Choopanya K, Wongpanich K. A controlled trial of methadone in a population of intravenous drug users in Bangkok: implications for prevention of HIV. *International Journal of the Addictions* 1991;**26**(12): 1313–1320.

**Yancovitz 1991** *{published data only}*

Yancovitz S, Des Jarlais D, Peskoe Peyser N, Drew E, Friedman P, Trigg H, Robinson J. A randomised trial of an interim methadone maintenance clinic. *Am J of Pub Health* 1991;**81**:1185–1191.

### References to studies excluded from this review

**Bale 1980** *{published data only}*

Bale R, Van Stone W, Kuldau J, Engelsing T, Elashoff R, Zarcone V. Therapeutic communities vs methadone maintenance. A prospective controlled study of narcotic addiction treatment: design and one year follow-up. *Arch Gen Psych* 1980;**37**:179–193.

### Additional references

**Cooper 1983**

Cooper J, Altman F, Brown, B, Czechowicz D. *Research on the treatment of narcotic addiction: State of the art*. Rockville, MD: National Institute on Drug Abuse, 1983.

**Dole 1965**

Dole V, Nyswander M. A medical treatment of diacetylmorphine (heroin) addiction. *JAMA* 1965;**193**: 80–84.

**Dole Nyswander 1967**

Dole V, Nyswander M. Heroin addiction - a metabolic disease. *Arch Internal Medicine* 1967;**120**:19–24.

**Gerstein 1990**

Gerstein D, Harwood H. *Treating drug problems Volume 1: A study of effectiveness and financing of public and private drug treatment systems*. Washington, DC: National Academy Press, 1990.

**Hargreaves 1983**

Hargreaves W. Methadone dosage and duration for maintenance treatment.. In: J Cooper, F Altman, B Brown, D Czechowicz editor(s). *Research on the treatment of narcotic addiction: State of the art*. Rockville, MD: National Institute on Drug Abuse, 1983.

**Jaffe 1990**

Jaffe, J. Drug addiction and drug abuse. In: A Gilman, T Rall, A Nies, P Taylor editor(s). *The pharmacological basis of therapeutics*. 8th Edition. New York: Pergamon Press, 1990:522–573.

**Mattick 1993**

Mattick R P, Hall W. *A treatment outline for approaches to opioid dependence: Quality assurance project*. Canberra: Australian Government Publishing Service, 1993.

**Mattick 1996**

Mattick RP, Hall W. Are detoxification programmes effective?. *Lancet* 1996;**347**:97–100.

**Ward 1992**

Ward J, Mattick R P, Hall W. *Key issues in methadone maintenance treatment*. Sydney: New South Wales University Press, 1992.

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

#### Dole 1969

Methods	Two group, open, randomised controlled trial. Randomisation: release dates of treatment applicants were selected by lottery. Applicants who were not selected and demonstrated motivation for treatment became untreated controls. Follow-up for 50 weeks.
Participants	Geographic region: USA n = 32 males mean age = 30 years 15% European descent, 10% African-American, 7% Hispanic Participants were inmates eligible for release over a four month period from New York City Correctional Institute for Men. Eligibility criteria: heroin dependence for 5 or more years, record of 5 or more previous convictions, not committed to custody of Addiction Services Agency
Interventions	Control: wait-list Treatment: 10 day methadone maintenance pre-release. Initial dose 10 mg, increasing to 35 mg at release. Continued methadone maintenance in outpatient clinic after release
Outcomes	Urinalysis (weekly for heroin, amphetamines, cocaine, barbituates and alcohol) Employment / education Reincarceration
Notes	

#### *Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

#### Gunne 1981

Methods	Two group randomised clinical trial. Randomisation: after eligibility established subjects were randomly allocated to methadone maintenance or to drug-free treatment
Participants	Geographic region: Sweden Study setting: psychiatric research centre n = 34, 23.5% female Eligibility criteria: 20-24 years, history of at least 4 years IV heroin use, withdrawal signs and positive urine on admission, a minimum of

**Gunne 1981** (Continued)

	three completed detoxifications, not arrested or serving a sentence and no dominate abuse of non-opiate drugs. Exclusion: active infectious disease	
Interventions	Control: no treatment, could not apply for the methadone program for two years Treatment: methadone maintenance treatment	
Outcomes	Illicit drug use / Urinalysis (3 x week) Criminality Vocational adjustment Health Mortality	
Notes	2 controls obtained methadone from private practitioners and were excluded	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	B - Unclear

**Newman 1979**

Methods	Double blind randomised clinical trial Randomisation: subjects randomly allocated on discharge from hospital after 2 week stabilisation on 60mg methadone to detoxification or continued maintenance	
Participants	Geographic region: Hong Kong n = 100 males Study setting: Hospital and outpatient clinic mean age = 38 years Eligibility criteria: male, 22-58 years, history of heroin dependence for at least 4 years and at least one previous treatment, current heroin dependence by three consecutive positive urine samples, voluntary application for admission (criminal justice referrals excluded), resident with fixed address, absence of past or present major psychiatric or medical illness	
Interventions	Treatment: methadone maintenance - flexible dose (average 97 mg / day) Control: detoxification from 60mg methadone at 1mg/day for 60 days, placebo thereafter	
Outcomes	Illicit drug use / Urinalysis (daily collection, analysed 2 x week for morphine only) Retention Criminal activity Mortality	
Notes		
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>

Newman 1979 (Continued)

Allocation concealment?	Unclear	B - Unclear
-------------------------	---------	-------------

**Strain 1993a**

Methods	Three group, double-blind, placebo controlled randomised controlled trial. Patients were stratified by race and sex and randomly assigned to a fixed dose schedule at admission. Treatment group assignment, stabilisation dose and dosing schedules were blind to patient and clinic staff with patient contact
Participants	Geographic region: USA Study setting: methadone treatment research clinic n = 247 mean age = 34 70% male 50% black 84% unmarried 62% unemployed Eligibility criteria: 18-50 years, history of IV opioid dependence, no chronic medical illness, absence of major mental illness, negative pregnancy test and at least three months since last treatment at the clinic
Interventions	Initial treatment of active methadone for at least 5 weeks. 15 weeks of stable dosing at 50, 20 or 0 mg per day Gradual tapering for those receiving active methadone from weeks 21-26 Individual counselling and group therapy (weekly).
Outcomes	Retention Treatment compliance Illicit drug use / Urinalysis (collected 3 x weekly, one sample selected at random for analysis for opioids, cocaine and benzodiazepines)
Notes	A subsample of 0mg patients (n=44) received an 8 week induction, reaching 0mg at 9 weeks. Data for patients in alternate 0mg treatment groups are collapsed

**Risk of bias**

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Vanichseni 1991**

Methods	Two group, open label, randomised clinical trial, with participants who applied for 45 day methadone detoxification and had at least six prior treatment episodes were randomly assigned to methadone maintenance or detoxification
Participants	Geographic region: Thailand Study setting: narcotics clinic

**Vanichseni 1991** (Continued)

	n = 240 males Eligibility criteria: heroin injectors applying for 45-day detoxification, at least 6 prior treatment episodes at the clinic	
Interventions	Treatment: methadone maintenance (flexible dose, average 74mg) Control: standard 45 day methadone detoxification	
Outcomes	Retention Illicit drug use Urinalysis (2 x week for opiates)	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	B - Unclear

**Yancovitz 1991**

Methods	Two group randomised clinical trial, with opioid dependent participants on waiting-lists for comprehensive methadone maintenance programs who were randomised to either the interim methadone program or wait list with frequent contact	
Participants	Geographic region: USA n = 301 Study setting: interim methadone clinic 79.4% male 10% White 35% Black 55% Hispanic Eligibility criteria: wait list for comprehensive methadone maintenance program	
Interventions	Control: wait-list with frequent contact Treatment: "interim" methadone maintenance; standard physical exam on admission, flexible dosing 5 days a week, pick up on weekends from another site, minimal counselling, referral to community agencies	
Outcomes	Urinalysis (2 x weekly for heroin and cocaine) Entry into conventional treatment	
Notes	For the first 3 months of the study there were three experimental groups; interim methadone, wait-list with frequent contact and bi-weekly urinalysis, and the wait-list with no contact. Recruitment slowed which resulted in the protocol being changed two experimental groups; interim methadone and wait-list with frequent contact. The wait-list then only lasted one month at which time the participants were switched to a methadone program. Data from the initial discontinued minimal contact group is not include in the analysis	

Yancovitz 1991 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

**Characteristics of excluded studies** [ordered by study ID]

Study	Reason for exclusion
Bale 1980	The authors planned to conduct a randomised controlled trial comparing methadone maintenance, therapeutic communities and detoxification programs. Ethical and practical problems prevented random assignment and the study therefore does not meet inclusion criteria for this review

## DATA AND ANALYSES

### Comparison 1. Methadone maintenance treatment vs no methadone maintenance treatment

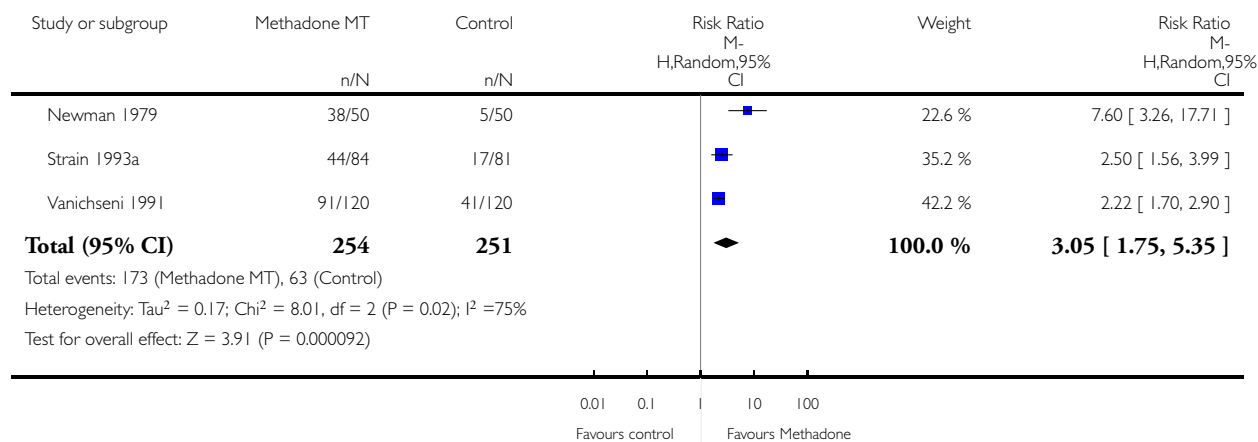
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Retention in treatment	3	505	Risk Ratio (M-H, Random, 95% CI)	3.05 [1.75, 5.35]
2 Morphine positive urines	2	409	Risk Difference (M-H, Random, 95% CI)	-0.32 [-0.40, -0.23]
3 Self reported heroin use	3	230	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.23, 0.44]
4 Criminal activity	3	363	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.12, 1.25]
5 Mortality	3	435	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.06, 4.23]

#### Analysis 1.1. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 1 Retention in treatment.

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs no methadone maintenance treatment

Outcome: 1 Retention in treatment



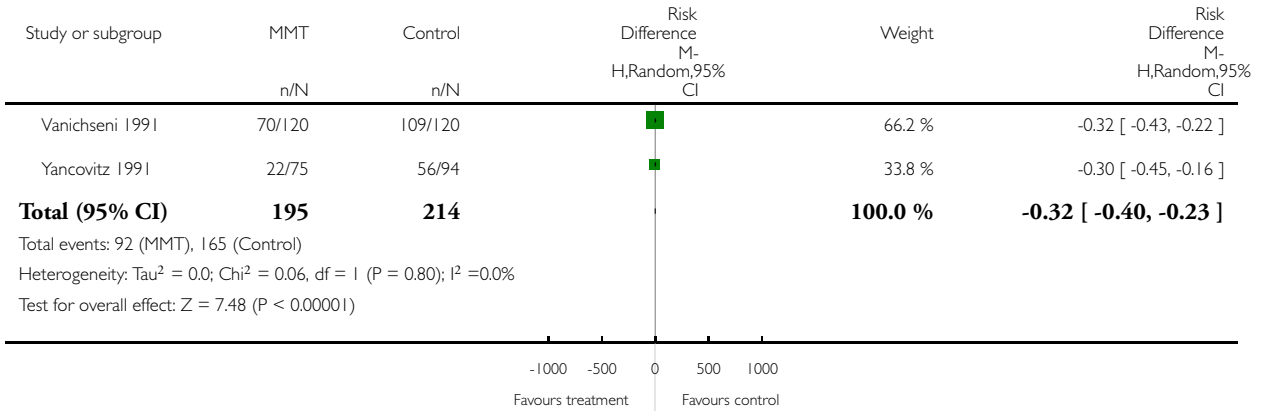


**Analysis 1.2. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 2 Morphine positive urines.**

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs no methadone maintenance treatment

Outcome: 2 Morphine positive urines

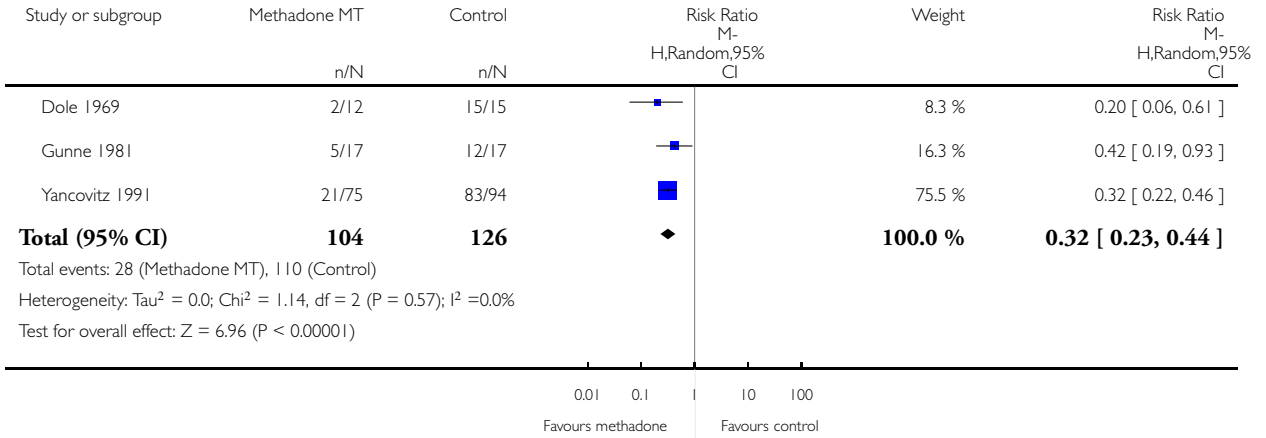


**Analysis 1.3. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 3 Self reported heroin use.**

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs no methadone maintenance treatment

Outcome: 3 Self reported heroin use

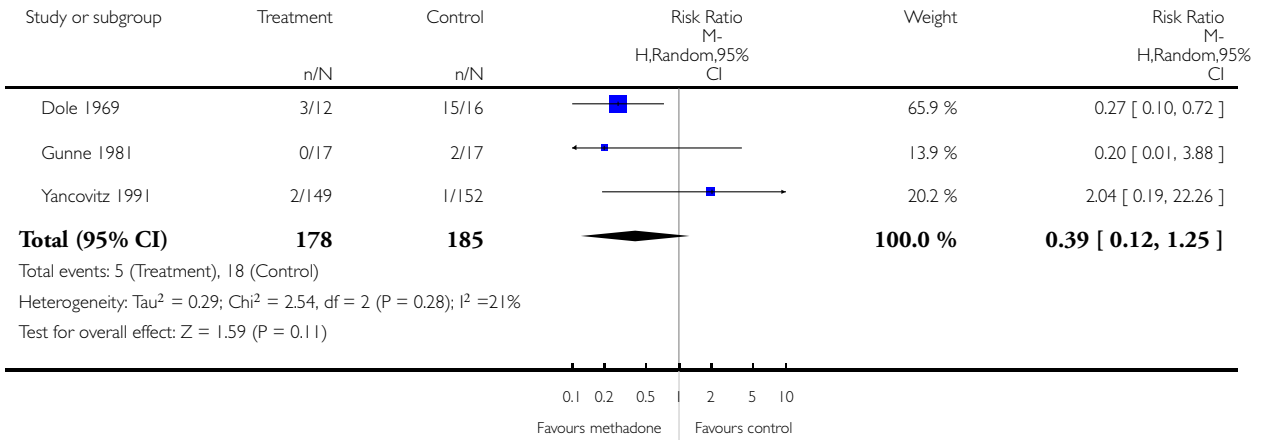


**Analysis 1.4. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 4 Criminal activity.**

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs no methadone maintenance treatment

Outcome: 4 Criminal activity

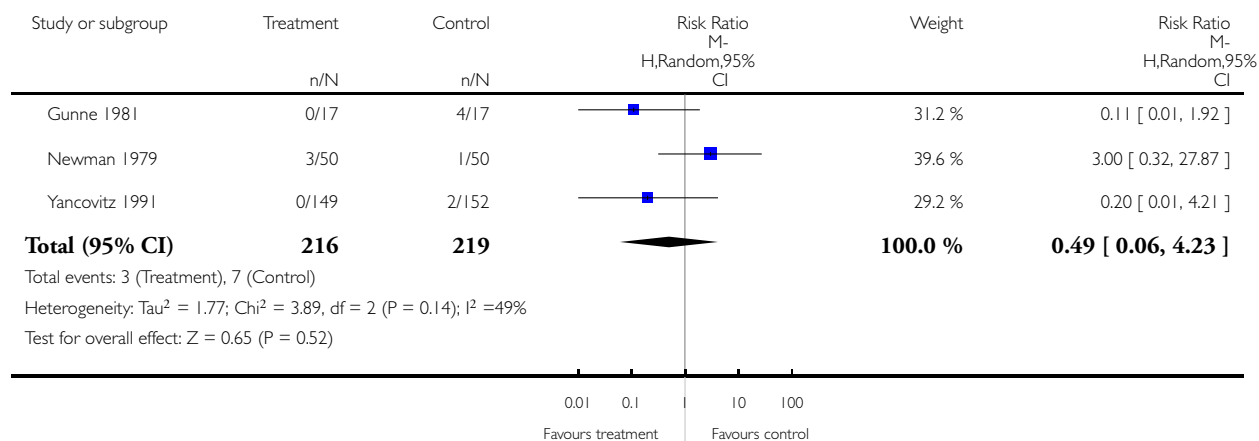


## Analysis 1.5. Comparison 1 Methadone maintenance treatment vs no methadone maintenance treatment, Outcome 5 Mortality.

Review: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence

Comparison: 1 Methadone maintenance treatment vs no methadone maintenance treatment

Outcome: 5 Mortality



## WHAT'S NEW

Last assessed as up-to-date: 23 February 2003.

Date	Event	Description
26 March 2008	Amended	Converted to new review format.

## HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 4, 2002

Date	Event	Description
24 February 2003	New citation required and conclusions have changed	Substantive amendment

## CONTRIBUTIONS OF AUTHORS

Contributions: Richard P Mattick, Jo Klimber and Courtney Breen reviewed the papers, with Courtney Breen and Richard P. Mattick coding data from the papers for meta-analysis.

Richard P. Mattick conceptualised the review and Courtney Breen 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.

## DECLARATIONS OF INTEREST

None.

## SOURCES OF SUPPORT

### Internal sources

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

### External sources

- Commonwealth Department of Health and Aged Care, Canberra, Australia.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Metabolic Detoxication, Drug; Methadone [\*therapeutic use]; Narcotics [\*therapeutic use]; Opioid-Related Disorders [\*rehabilitation]; Randomized Controlled Trials as Topic

## MeSH check words

Humans