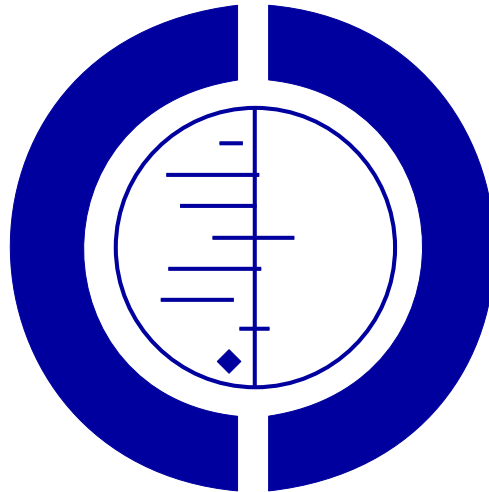


Methadone maintenance at different dosages for opioid dependence (Review)

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P



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TABLE OF CONTENTS

ABSTRACT	1
SYNOPSIS	2
BACKGROUND	2
OBJECTIVES	3
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	3
SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES	4
METHODS OF THE REVIEW	4
DESCRIPTION OF STUDIES	5
METHODOLOGICAL QUALITY	6
RESULTS	7
DISCUSSION	9
AUTHORS' CONCLUSIONS	9
ACKNOWLEDGEMENTS	10
POTENTIAL CONFLICT OF INTEREST	10
SOURCES OF SUPPORT	10
REFERENCES	10
TABLES	13
Characteristics of included studies	14
Characteristics of excluded studies	22
ADDITIONAL TABLES	23
Table 01 CPS - RR of leaving methadone maintenance treatment	23
GRAPHS	24
Comparison 01 RCT	24
Comparison 02 CPS	24
COVER SHEET	24
GRAPHS AND OTHER TABLES	25
Fig. 1. Comparison 01 RCT.	26
01 Retention rate	26
Fig. 2. Comparison 01 RCT.	28
02 Retention time (weeks)	28
Fig. 3. Comparison 01 RCT.	28
03 Opioid use (self-reported - times/week)	28
Fig. 4. Comparison 01 RCT.	29
04 Opioid use (self-reported mg/day)	29
Fig. 5. Comparison 01 RCT.	29
05 Opioid abstinence score	29
Fig. 6. Comparison 01 RCT.	30
06 Opioid abstinence at >3-4 weeks (urine based)	30
Fig. 7. Comparison 01 RCT.	31
07 Opioid withdrawal symptoms scores	31
Fig. 8. Comparison 01 RCT.	31
08 Cocaine use (self-reported - times/week)	31
Fig. 9. Comparison 01 RCT.	32
09 Cocaine abstinence at >3-4 weeks (urine-based)	32
Fig. 10. Comparison 01 RCT.	32
10 Cocaine withdrawal symptoms scores	32
Fig. 11. Comparison 01 RCT.	33
11 Side effects (at least 1)	33
Fig. 12. Comparison 01 RCT.	33
12 Criminal activity (mean nb./week)	33
Fig. 13. Comparison 01 RCT.	34

13 Money spent/day	34
Fig. 14. Comparison 02 CPS.	34
01 Overdose mortality (6 years follow-up)	34
Fig. 15. Comparison 02 CPS.	35
02 Leaving treatment (12-24 months follow-up, all studies)	35

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ABSTRACT

Background

Methadone maintenance treatment (MMT) is a long term opioid replacement therapy, effective in the management of opioid dependence. Even if MMT at high dosage is recommended for reducing illicit opioid use and promoting longer retention in treatment, at present day “the organisation and regulation of the methadone maintenance treatment varies widely”.

Objectives

To evaluate the efficacy of different dosages of MMT in modifying health and social outcomes and in promoting patients' familial, occupational and relational functioning.

Search strategy

We searched:

- MEDLINE (OVID 1966-2001)
 - EMBASE (1988-2001)
 - ERIC (1988-2001)
 - Psychinfo (1947-2001)
 - Cochrane Controlled Trials Register (CCTR) (1947-2001)
 - Register of the Cochrane Drug and Alcohol Group (CDAG) (1947-2001)
- The CDAG search strategy was applied together with a specific MESH strategy.

Further studies were searched through:

- letters to the authors
- check of references.

Selection criteria

Randomised Controlled Trials (RCT) and Controlled Prospective Studies (CPS) evaluating methadone maintenance at different dosages in the management of opioid dependence. Non-randomised trials were included when proper adjustment for confounding factors was performed at the analysis stage.

Data collection and analysis

Data Extraction was performed separately by two reviewers. Discrepancies were resolved by a third reviewer. Quality assessments of the methodology of studies were carried out using CDAG checklist.

Main results

22 studies were excluded. 21 studies were included: 11 were RCTs (2279 participants) and 10 were CPSs (3715 participants).

Outcomes: Retention rate - RCTs: High versus low doses at shorter follow-ups: RR=1.36 [1.13,1.63], and at longer ones: RR=1.62 [0.95,2.77].

Opioid use (self reported), times/w - RCTs: high versus low doses WMD= -2.00 [-4.77,0.77] high vs middle doses WMD= -1.89[-3.43, -0.35]

Opioid abstinence, (urine based) at >3-4 w - RCTs: high versus low ones: RR=1.59 [1.16,2.18] high vs middle doses RR=1.51 [0.63,3.61]

Cocaine abstinence (urine based) at >3-4 w - RCTs: high versus low doses RR=1.81 [1.15,2.85]

Overdose mortality - CPSs: high dose versus low dose at 6 years follow up: RR=0.29 [0.02-5.34] high dose vs middle dose at 6 years follow up: RR=0.38 [0.02-9.34] middle dose vs low dose at 6 years follow up: RR=0.57 [0.06-5.06]

Authors' conclusions

Methadone dosages ranging from 60 to 100 mg/day are more effective than lower dosages in retaining patients and in reducing use of heroin and cocaine during treatment. To find the optimal dose is a clinical ability, but clinician must consider these conclusions in treatment strategies.

SYNOPSIS

Synopsis pending

BACKGROUND

Opioid addiction (see CDAG module's glossary for definition) is currently defined as a "chronic, relapsing disorder" (Leshner 1997;Dole 1967); this definition, in addition to the epidemiological evidence of the drug related risks affecting the addicted population (Brettle 1991; WHO 1991; Ward 1998), has promoted the development of the "harm reduction" approach in drug addiction treatment (Brettle 1991;Ward 1998). According to this approach, treatment is aimed to increase time between relapses to heroin, to reduce intensity, frequency and length of the relapse (Leshner 1997), cocaine and polysubstance use, overdoses' risk, criminal activity, HIV, HBV and HCV infection, and to promote psychosocial adjustment (Leshner 1997;Ward 1998; Farrell 1994).

Methadone maintenance treatment (MMT) is a long term opioid replacement therapy, implying the daily administration of methadone, a long acting (24-36 h) opioid drug, and it is the more common opioid replacement therapy in USA, Europe and Australia (Ward 1998). Methadone as opioid replacement therapy was introduced by Dole and Nyswander in the 1960's (Dole 1965), as a drug meeting a number of stringent conditions: it "eliminates the euphoric appeal of heroin and the abstinence symptoms", it is "sufficiently free from toxic or dysphoric effects", it is "orally effective, long acting, medically safe, and compatible with normal performance in work and at school" (Dole 1991).

Starting from this model, MMT underwent many changes during time from its "popularisation" to the definition of different goals, such as detoxification, by means of a decrease in dosages (Ward 1998). Even if MMT at high dosage is recognised to be the best therapy in "preventing withdrawal and inducing a sufficient cross-tolerance to heroin, making average street doses non-intox-

icating" (Ward 1994a) and in reducing illicit opioid use and promoting longer retention in treatment (Ward 1998; Farrell 1994), at present day "the organisation and regulation of the methadone maintenance treatment varies widely, with explicit guidelines for programme operation in the United States and Australia and a virtual absence of structure and regulation in Britain" (Farrell 1994), except for the very recent publication of the clinical management drug misuse guidelines (Dep. of Health 1999).

The reason for such variability in the use of methadone is mainly related to the debates that crosses civil society and professional world. First of all, an agreement has not been reached about the goal of the treatment, which reflects at the moment different ideas on the model of the disease. Considering opioid addiction as an "acute disease" and detoxification as the main aim of the treatment, some professionals use MMT just as a preparation for a subsequent detoxification programme. Others consider opioid addiction as a "chronic disease" and the self-perceived well being of the patients as the main outcome, use MMT as long term treatment which allows complete social and personal rehabilitation and prevents the health damages related to drug use (McLellan 2000). The differences between this two points of view are not limited to ethical or deontological considerations, but involve interpretation of treatment outcomes: for the former a long retention in treatment is a negative outcome, whereas for the latter it is a positive one (McLellan 2002).

The debate concerns not only clinicians but also policy makers, politicians and the general population, for which the maintenance concept is related to the "prescription of a drug which causes dependence", and this idea leads to a sort of defection of the treatment, being not naturally aimed to the total recovery of the subject. This disagreement, mostly not scientific, must be taken to a more technical debate about dosage. The findings of most studies agree in indicating high dosage (>60 mg) as the more effective for the

outcomes above stated, whereas only a few authors state that low doses are effective as higher to prevent withdrawal (Wolff 1994). Moreover, a systematic review on methadone maintenance therapy versus no opioid replacement therapy for opioid dependence have been published (Mattick 2003), but the issue of differential efficacy of different dosages has not been addressed.

All these reasons suggest a need for meta-analytic and unbiased reviews addressing the above mentioned questions, and possibly clarifying which are the more protective dosages of methadone maintenance treatment (MMT) for the health of drug addicted people.

OBJECTIVES

To evaluate the efficacy and safety of different dosages of MMT for opioid dependence, in modifying health and social outcomes and in promoting patient's familial, occupational and relational functioning

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Literature was reviewed for all of the RCTs, CCTs and the prospective studies evaluating methadone maintenance at different dosages in the management of opioid dependence. Controlled Prospective Studies were included when proper adjustment for confounding factors was performed at the analysis stage.

Types of participants

Opioid addicted patients 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 study. No restriction were imposed in terms of inclusion or exclusion criteria, but studies focused on pregnancy status were excluded from the review.

Types of intervention

Comparison between two or more different dosages of MMT (also when compared with other kind of treatment or with placebo in a third arm), independently from the duration (duration was introduced as a stratification item).

Types of outcome measures

Outcome variables examined in this review were dichotomous (D) or continuous (C).

- Retention in treatment
measured by:

- time a participant remains in treatment - C

- retention rate at a given time - D

- Drug use during treatment
measured by:

- use of opioid or cocaine, based on urinalysis - D, or based on self-report - C

- Long term abstinence after treatment
measured by:

- abstinence from opioid, at a given time after the study beginning, based on urinalysis - D, or based on self-report - C

- Opioid amount used
measured by:

- the amount used per day - C
- dollars spent per day - C

- Opioid and cocaine withdrawal symptoms (based on analogical scales, self-reported - C)

- HIV, HBV and HCV seroconversion (a negative test at the beginning of the study, followed by a positive one - D)

- Risk infection behaviour
measured by:

- sharing needles and other tools, self reported - D
- sexual behaviours, self reported - D

- Work activity
measured by:

- changes in work activity (based on self reports or official documents - D)

- Criminal activity

measured by: - incarceration, reincarceration for parolees or probationers during/after the study period (based on self reports or official documents - D)

- Psychological adjustment

measured by: - level of psychological equilibrium (based on questionnaire reports, specific scales - C)

- Side effects

measured by:

- type and number of undesired pharmacological effects caused by the medication under study (based on self reports or clinical records - D, C)

- starting consumption of cocaine (based on self reports or clinical records - D, C)

- Mortality during/after the treatment (for all causes, for overdose and for acute diseases - D)

Different factors were considered as confounders and taken into account in the analysis where possible:

- age, sex, ethnicity

- education level, employment status, income
- marital status, family status
- needle sharing
- frequency of injection, route of injection
- current use of alcohol, benzodiazepine, cocaine
- HIV status
- duration of injection, age of first consumption
- previous MMT, previous MMT failure
- centre policy

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Drugs and Alcohol Group search strategy

The following sources were used:

- MEDLINE (OVID 1966-2001)
- EMBASE (1988-2001)
- ERIC (1988-2001)
- Psycinfo (1947-2001)
- Cochrane controlled trials Register (CCTR) (1947-2001)
- Register of the drug and alcohol group (CDAG) (1947-2001)

We looked for studies:

- from 1947, year of publication of the first study on the use of methadone to treat opiate withdrawal syndrome (Payte 1991)
- to December 2001
- languages: all

We applied the following strategies:

- CDAG strategy
- MESH strategy including the following terms: methadone.mp or [exp Substance-related disorders/ AND (Program evaluation/ OR Substance abuse treatment centres OR Treatment Failure/ OR Treatment outcome/ OR Drug therapy/ OR Drug Therapy, combination/ OR preventive psychiatry/ OR exp Psychotherapy/ OR Community health services/ OR Therapeutic community/ OR exp Community health Centres/ OR harm reduction.tw.)]. Editorials, reviews, commentaries, letters to the editor were included in the set.

Review articles, as well as all the included and excluded studies cited in the review were scanned to identify relevant studies.

Relevant editorials, commentaries, letters were reviewed to identify useful bibliography.

A search of other published or unpublished studies known or conducted by the authors of the primary studies was made to find other relevant studies.

Personal contacts with other research and review teams working in the field, as well as with authors of the included studies was made to identify other potentially relevant studies.

METHODS OF THE REVIEW

We adopted a four stages process to select studies to be included in the review:

1. Records retrieved from each database were stored on ProCite; titles were pre-screened for relevance excluding the articles not related to the subject under study, by using specific search terms or search expressions.

2. The studies not excluded above were assessed by reading the abstract. The abstract were sifted separately by two reviewers to evaluate relevance and each study was excluded according to the following criteria:

- if it was clearly not focused on opioid dependence
- if it was clearly not focused on methadone at different dosages
- if it was clearly not a RCT, a CCT or a CPS, or anyway a controlled study
- if it clearly did not present results

A study was excluded when meeting at least one of the above listed criteria.

In case of disagreement the study was included in the next step.

3. Each potentially relevant study not excluded in the previous steps was obtained and was independently assessed by two reviewers, in order to include it definitely.

4. The assessment of the internal quality of the included studies was done by two reviewers according to the CDAG's check list (Ferri 2003). The CDAG's system was used to weight the criteria used to evaluate the studies. For experimental studies (RCTs and CCTs) randomisation, allocation concealment, blinding, losses to follow-up and criteria defined as "others" (baseline comparability of the groups and absence of performance bias) were carefully examined, and a quality score was determined based on fulfillment of these criteria. For prospective studies (CPSs) population base and confounding adjustment, inclusion of all patients in the analysis and criteria defined as "others" (adequate description of the base and of the treatments) were the main characteristics examined to formulate the quality score. A threshold for exclusion was identified.

Using this system, studies were finally classified in 3 classes according to quality:

- A low risk of bias (all criteria met or one criteria partially met)
- B moderate risk of bias (a maximum of two criteria partially met)
- C high risk of bias (three or more criteria partially met or at least one criteria not met)

Any disagreement has been resolved by a third reviewer.

According to quality, data extraction from included studies and quantitative analysis was performed by two reviewers independently. A standardized checklist was used for data extraction. Disagreement was dealt with by the third reviewer, acting as a mediator.

The authors of studies which needed integration of results were contacted, and the reference put into the "Awaiting assessment" section. Two of them (D'Ippoliti 1998; Torrens 1996) provided the requested integrations, allowing the inclusion of the data in the metaanalysis.

For Controlled Prospective Studies, which needed a proper adjustment for confounding factors to be included in the review, the absolute number of subjects in the numerator of occurrence measures given by authors in the papers were unadjusted, and only presented RRs were adjusted for confounding. To fill RevMan tables, which need absolute number of subjects of numerator and denominator measures to provide figures, "adjusted numbers" of numerators were then re-calculated as follows: absolute number of subjects in the numerator of the control group were kept fixed and "adjusted numbers" of subjects with the occurrence under study in the treatment group were re-calculated as product of the adjusted RRs by the absolute numbers of the control group. The fictitious adjusted numbers of events in the intervention group so obtained were put in the tables together with the initial number of subjects in the control group to compare the effects among the studies.

Some CPSs studies did not present data useful for the inclusion in the metaanalysis (Caglehorn 1991; Caglehorn 1994; Caglehorn 1996; Gaughwin 1998; Gossop 2001; Maddux 1997): they mainly used Cox regression statistical analysis, providing a RR of leaving treatment according to a continue increase in methadone dose. For these studies, data were extracted converting the provided measures in RRs at specific dosages (30 mg, 60 mg, 90 mg/day); they were summarized in the Additional Table 01.

We used the RevMan software for the analysis. RCTs and CPSs were analysed separately.

For each study finally included the main results were reported in a table, in which methadone use was presented in classes of dosage, in order to pool together arms subjects with similar exposition to methadone. An evaluation by length of follow-up was made for retention rate. To standardized the outcomes measured with time scales, days were converted into weeks. The different withdrawal symptoms point scales were converted into a standardized 75-point scale, in order to make possible comparison among the studies.

For RCTs, included results were grouped into the following methadone dosages: 1-39 mg/day, 40-59 mg/day; 60-109 mg/day, >110 mg/day.

For CPSs, because of a slight overlapping among the categories presented in the studies, results were presented for the outcome "leaving treatment" grouped into three broad groups: low dose, middle dose, high dose. In fact, Del Rio 1997 provided RRs comparing 15-40 mg/day, 45-60 mg/day and 65-110 mg/

day; D'Ippoliti 1998 compared <30 mg/day, 30-59 mg/day and >=60 mg/day; Torrens 1996 compared <=80 mg/day and >80 mg/day. For the outcome "mortality" the categories of the only study included (Van Ameijden 1999) were maintained: 5-55 mg/day, 55-70 mg/day, >75 mg/day.

A standardized effect size was calculated for each study, based on the outcomes reported. Where possible, relative risk and 95% confidence intervals were calculated through a fixed effects model, and for continuous outcomes a weighted mean difference between groups was presented. To assess for statistical heterogeneity, a test of homogeneity was performed.

In order to assess the effect of the low quality studies on the synthetic results, all included studies were submitted to a sensitivity analysis, either including or excluding the class C ones.

Results were integrated from the meta-analytic review into a discussion taking into account other relevant publications. Convergence between the meta-analysis results and the narrative review was taken to indicate strong evidence of the effect.

DESCRIPTION OF STUDIES

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

Excluded studies

Twenty-two studies were excluded from the review.

Three were RCTs; the study by Havassy (Havassy 1984) was excluded because the randomization process failed, and there was inadequate control of confounding variables to use it as a CCT. The study by Panell (Panell 1977) and the study by Strain (Strain 1993b) presented secondary analysis of subsamples of the original trials (Ling 1996 and Strain 1993a), included in the review. In the study by Saxon (Saxon 1996), the comparison was made between contingency and non-contingency approaches and not between doses.

All the other excluded studies were CPSs; they were mainly excluded because of inadequate control of confounding variables, except for the studies by Caglehorn (Caglehorn 1993a; Caglehorn 1993b) which presented a secondary analysis of the original study (Caglehorn 1991), included in the review. The study by Hartel (Hartel 1998) used a retrospective ascertainment of the exposure; Langendam (Langendam 2000a) did not evaluate the effect of methadone dosage in the multivariate analysis, whilst the study by Stine (Stine 1992) evaluated the effects of different contingency approaches and not of methadone dosages.

Included studies

In total, 21 STUDIES (26 reports) were included in the review.

- Study design

Eleven studies were RCTs, ten were CPSs; six of them did not present data useful for the inclusion in the meta-analysis, because of the statistical model used for the analysis; however, they provided results which can be presented in a narrative way.

- Length of follow-up

RCTs: range 7-52 weeks

CPSs: range 1-10 years

- Setting

USA (11 RCTs, 1 CPS)

Australia (4 CPSs)

UK (1 CPS)

Switzerland (1 CPS)

The Netherlands (1 CPS)

Spain (1 CPS)

Italy (1 CPS)

- Comparisons

Among RCTs, five studies compared buprenorphine and methadone treatment, and at least two arms had different methadone dosages with 643 subjects involved (Johnson 1992; Kosten-Oliveto 1993; Ling 1996; Schottenfeld 1997). One study compared levomethadyl acetate and two different methadone dosages with 430 subjects involved (Ling 1976), and one study compared levomethadyl acetate, buprenorphine and two different methadone dosages with 220 subjects involved (Johnson 2000). Three studies with 559 subjects involved (Goldstein 1973; Strain 1993a; Strain 1999) were focused on the comparison of different dosages of methadone. In the study by Rhoades, 142 subjects involved (Rhoades 1998), subjects were randomly assigned to two methadone dosages and to two or five visits per week, no results were however useful for the inclusion in the meta-analysis. The remaining study (Preston 2000) evaluated interventions based on contingent vouchers, and two methadone dosages, combined in different ways: for our analysis we used the groups which received non-contingent vouchers, which involve 285 subjects.

RCTs (see "comparison and data" for the outcomes): eleven studies and 2279 subjects.

Comparison 1: 60-109 mg/day vs 1-39 mg/day (at 17-26 weeks) (Johnson 1992; Johnson 2000; Kosten-Oliveto 1993; Ling 1996; Schottenfeld 1997)

Comparison 2: 60-109 mg/day vs 1-39 mg/day (at 52 weeks) (Ling 1996)

Comparison 3: 60-109 mg/day vs 40-59 mg/day (at 7-13 weeks) (Ling 1976; Preston 2000)

Comparison 4: 60-109 mg/day vs 40-59 mg/day (at 27-40 weeks) (Goldstein 1973; Ling 1976; Strain 1999)

Comparison 5: 40-59 mg/day vs 1-39 mg/day (at 20 weeks) (Strain 1993a)

Comparison 6: >110 mg/day vs 40-59 mg/day (at 27 weeks) (Goldstein 1973)

Comparison 7: >110 mg/day vs 60-109 mg/day (at 27 weeks) (Goldstein 1973)

CPSs, outcome "mortality", one study and 498 subjects (Van Ameijden 1999):

Comparison 1: >75 mg/day vs 5-55 mg/day

Comparison 2: >75 mg/day vs 55-70 mg/day

Comparison 3: 55-70 mg/day vs 5-55 mg/day

CPSs, outcome "leaving treatment", three studies and 1202 subjects (D'Ippoliti 1998; Del Rio 1997; Torrens 1996):

Comparison 1: high dose vs middle dose

Comparison 2: middle dose vs low dose

Comparison 3: high dose vs low dose

Details on the comparison groups are available in the Characteristics of Included Studies tables.

- Outcomes

All included studies were assessed to determine whether they provided data for the outcomes measure of interest, including retention in treatment, heroin and cocaine use by urinalysis, self-reported heroin and cocaine use, long-term abstinence, withdrawal symptoms, amount of drug used per day, criminal activity, HIV, HBV and HCV sero-conversion, overdose and all-causes mortality. After reviewing the studies, it was realized that it was not possible to include urine results for heroin and cocaine use when these were not reported at an individual level; most part of the studies provided in fact proportions of positive tests calculated as the number of positive tests divided by the total of number of tests carried out, and using tests instead of subjects as a unit of analysis: this procedure violates the hypothesis of independence among observations (Ferri 2003). Only two studies, showing results at an individual level (percent of patients abstinent), could be included in the meta-analysis (Johnson 2000; Schottenfeld 1997). Authors will be contacted in order to provide urine data at a individual level.

Among CPSs, three studies (D'Ippoliti 1998; Del Rio 1997; Torrens 1996) were focused on risk of leaving treatment as outcome, whilst one study evaluated the effect of dosages on mortality rate (Van Ameijden 1999).

METHODOLOGICAL QUALITY

RCTs

Of the eleven RCTs included in this review, nine were conducted under double blind conditions (Johnson 1992; Johnson 2000; Kosten-Oliveto 1993; Ling 1976; Ling 1996; Preston 2000; Schottenfeld 1997; Strain 1993a; Strain 1999), and two under single blind conditions (Goldstein 1973; Rhoades 1998). In order to maintain the double-blind approach, it was generally used a double-dummy procedure: for example, comparing methadone with

buprenorphine, patients were given both an oral solution and a sublingual preparation.

Only one of the eleven studies (Strain 1999) described in detail a method of allocation concealment, which was adequate: assignments were sealed in numbered envelopes, and dose codes were entered into a database accessible only to pharmacy staff and selected research assistants with no patients contact. All the other studies did not describe allocation concealment procedures 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.

Five of the eleven studies described the randomisation process (Strain 1999; Schottenfeld 1997; Preston 2000; Ling 1996; Johnson 2000); all the others mentioned it without any description.

The characteristics of the patients and the inclusion and exclusion criteria were generally well defined in all the studies. Similarity of the treatment groups at the start of the trial was generally good, except for two studies (Rhoades 1998; Johnson 1992).

The completion of the follow-ups was generally quite high, or it was used an intention to treat analysis. The number of participants varied between 116 subjects (Schottenfeld 1997) up to 430 subjects (Ling 1996).

According to these criteria, five RCTs (Strain 1999; Schottenfeld 1997; Preston 2000; Ling 1996; Johnson 2000) were evaluated as high quality studies (class A), five (Goldstein 1973; Ling 1976; Kosten-Oliveto 1993; Strain 1993a; Johnson 1992) as moderate quality studies (class B), and one (Rhoades 1998) as low quality study (class C). To perform sensitivity analysis it was considered in this case not necessary, because the low quality class study did not provide useful data for the tables, and all the other studies had high or moderate quality.

CPSs

Of ten CPSs included in this review, four provided data on retention by classes of methadone dosage (D'Ippoliti 1998; Del Rio 1997; Torrens 1996; Van Ameijden 1999), whilst, as mentioned in the Methods section, six provided a measure of risk according to a continuous increase of methadone dose. All the studies provided an adequate description of the population base, clear inclusion and exclusion criteria. The number of participants varied between 111 (Del Rio 1997) up to 721 (D'Ippoliti 1998).

For outcomes such as retention or leaving treatment, it was not proper to evaluate losses to follow-up as a criteria to discriminate high and low quality studies. The adjustment for confounding variables was the main criteria used to judge the quality of the CPS studies. Because of poor adjustment, two of them (Del Rio 1997; Gossop 2001) were classified as low quality studies (class C), whilst all the others were judged as moderate quality studies (class B). It was in fact impossible to exclude residual confounding. Sensitivity analysis was performed in order to evaluate the effect

of low quality studies on the main outcome (treatment retention). Keeping the low quality study in the review did not significantly change the results, so it were kept on.

RESULTS

• Treatment retention

RCTs

Retention in treatment has been studied through relative measures of retention and time in treatment, according to the type of indicator found in the included papers.

Retention rates

As presented in the Methods section, 22 arms of 10 Randomised controlled trials has been classified, according to the used range of dose, in 4 groups of exposure: 1-39 mg/day, 40-59 mg/day, 60-109 mg-day and 110+ mg/day. These four arms were stratified in 2 different follow-up periods. absolute values of retention rates ranged from 20% (low dose, medium follow-up; Johnson 1992) to 96% (medium dose, short follow-up; Ling 1976).

High doses, ranging from 60 to 109 mg/day, showed better retention rates than low doses (1-39 mg/day) both in shorter follow-ups (RR=1.36 [1.13,1.63]) (five studies, 247 patients in the treatment arm and 249 patients in the control one, Johnson 1992; Johnson 2000; Kosten-Oliveto 1993; Ling 1996; Schottenfeld 1997), and in longer ones (RR=1.62[0.95,2.77]) (one study, 75 patients in the treatment arm, Ling 1996). Retention rates ranges from 20% (low doses; Johnson 1992) to 70.9% (high doses; Johnson 2000). High doses compared with medium doses (40-59 mg/day) seemed to show differences in effectiveness only for follow-ups longer than 27 weeks (RR=1.23 [1.05,1.45]) (three studies, 277 patients in the treatment arm and 283 controls, Goldstein 1973; Ling 1976; Strain 1999), whereas for shorter follow-up no differences has been evidenced (two studies, 173 patients in the treatment arm and 174 controls, Ling 1976; Preston 2000).

Only one study compared medium doses with low doses, and the RR of 1.26 [0.91,1.75] appeared to be affected by random error (Strain 1993a, 84 patients in the treatment arm and 82 controls). Very high doses appeared to be more effective compared with medium doses (RR=1.67 [1.05,2.66]) (Goldstein 1973, 40 patients in the treatment arm and 40 controls) but not with high doses (RR=0.96 [0.69,1.34]) (Goldstein 1973).

The dose relationship in retention rates in the only study with more than 2 arms (Goldstein 1973) show the following results at 27 weeks follow-up: very high doses 62.5%, high doses 62.0% medium doses 37.0%, with a significant effect of very high and high doses vs middle ones, but without significance from very high doses and high ones.

Retention time

Four RCTs (Johnson 2000; Kosten-Oliveto 1993; Preston 2000; Rhoades 1998) presented results on retention as time function.

Length of retention were expressed as means and standard deviations in a specific arm, as they were reported in the article, and ranged from 12.6 weeks (high dose arm, Preston 2000) to 19.6 weeks (high dose arm, Schottenfeld 1997). Whereas high compared to medium did not show differences (WMD=-0.30 weeks [-0.77,0.17] (Preston 2000, 31 patients in the treatment arm and 28 controls), high doses seemed to be more effective when compared with low doses (WMD=3.54 weeks [2.19,4.89]) (three study, 118 patients in the treatment arm and 119 controls, Johnson 2000; Kosten-Oliveto 1993; Rhoades 1998).

CPSs

Height of ten Controlled Prospective Studies included data on retention in the papers. Three of them showed data useful to be included in the metaanalysis (D'Ippoliti 1998; Del Rio 1997; Torrens 1996), whereas results from the others are presented in the Additional Table 01. Seven studies analysed retention as the risk of leaving treatment, while one as the risk of staying in treatment. Results from observational studies seems to confirm those from randomised trials: high doses are always protective for leaving treatment, but in the study of Del Rio 1997. For studies included in metaanalysis, relative risks ranged from 0.68 [0.51-0.89] for high vs middle dose (two studies, 191 patients in the treatment arm and 423 controls, D'Ippoliti 1998; Del Rio 1997) to 0.35 [0.27,0.45] for high dose compared to low dose (three studies, 317 patients in the treatment arm, 396 controls, D'Ippoliti 1998; Del Rio 1997; Torrens 1996). For studies presented in the additional Table 01, RR of leaving treatment at different times from starting varies from 0.56 to 0.40 for medium doses treatments compared to low doses, and from 0 to 0.28 for high doses compared to low doses (all comparisons are statistically significant). The study of Maddux 1997 considered the risk of retention instead of the probability of leaving; higher doses treatments show a statistically significant RR of 2.32 to be retained at 1 year, when compared to low doses maintenance. Medium dose vs low dose show a statistically significant RR of 1.66 at 1 year follow-up.

- Heroin use

RCTs

The relationship between methadone dose and use of heroin is reported by 3 RCTs and 1 included CPS, in 5 different ways. Two studies (Preston 2000; Johnson 2000) reported the mean number of times/week of use of heroin: high dose compared to low dose reduce the use of heroin as far as 2 times/week (Johnson 2000, 55 patients in the treatment as well in the control arm); high dose vs medium dose reduce also the amount of heroin consumed (Preston 2000, 31 patients in the treatment arm, 28 controls) and increase the number of periods of opioid abstinence longer than 3 weeks (Preston 2000; Johnson 2000; Kosten-Oliveto 1993; Schottenfeld 1997); the result is statistically significant for high compared to low doses (RR=1.59 [1.16,2.18]) (three studies, 118 patients in the treatment arm, 119 controls, Johnson 2000; Kosten-Oliveto 1993; Schottenfeld 1997). One RCT (Ling 1996, 75 patients in

the treatment as well in the control arm) uses a specific abstinence score, based on number of weeks of abstinence, showing its increase using high vs low doses.

CPSs

Only one of the included CPS reported results on use of heroin (Gossop 2001), showing a RR of 0.98 [0.97,0.98] for the reduction in use of heroin for each mg increase of average methadone dose.

- Opioid withdrawal symptoms

RCTs

Two studies addressed the question on the role of methadone dose in reducing withdrawal symptoms (Preston 2000; Kosten-Oliveto 1993). The increase of dose seems to reduce the symptoms of withdrawal, but the results are not statistically significant, either in the comparison high vs medium dose (Preston 2000, 31 patients in the treatment group, 28 controls), or in the high vs low dose (Kosten-Oliveto 1993, 35 patients in the treatment group, 34 controls).

- Cocaine use

RCTs

Three studies addressed the question on relationship between the dosages of the methadone treatment and the use of cocaine. Results from one of them are based on self reported frequency of use (Kosten-Oliveto 1993), and it suggests a non significant excess of use of cocaine among subjects treated with higher doses compared with subjects treated with lower doses (29 patients in the treatment arm, 30 controls). Two studies used the frequency of abstinence period longer than 3 weeks, based on urine analysis, and the pooled results showed that high dose increase the probability to stay abstinent from cocaine, compared with low dose (RR=1.81 [1.15,2.85]) (Johnson 2000; Schottenfeld 1997, 83 patients in the treatment arm, 85 controls). One study reported a high proportion of positive tests for cocaine in patients treated with higher methadone doses (Rhoades 1998); it was based on urinalysis and not on individuals and could not be used in the metaanalysis, as explained in the Cochrane Drug and Alcohol module (Ferri 2003).

- Cocaine withdrawal symptoms

RCTs

No effect of methadone doses has been showed by the only study addressing this question (Kosten-Oliveto 1993, 29 patients in the treatment arm and 30 controls).

- Side effects

RCTs

No significant differences are evident for side effects, included in COSTART list (FDA 1985), for high doses compared to low (Johnson 2000, 55 patients in the treatment as well in the control arm).

- Criminal activity

RCTs

No significant differences are evident for mean number of criminal activities in the comparison between high dose and medium dose in the only study focusing on this outcome (Preston 2000, 31 patients in the treatment arm, 28 controls).

- Money spent

RCTs

Subjects under treatment with higher doses appears to spent less money for illicit drugs than those under treatment with medium dosages (Preston 2000, 31 patients in the treatment group, 28 controls).

- Mortality

CPSs

Only one CPS studied the outcome mortality, and in spite of the high number of subjects involved in the study, the results are not statistically significant (Van Ameijden 1999, 498 patients); nevertheless, all contrasts between dosages showed protective effect for higher dosages, with a clear suggestion of a dose response relationship.

DISCUSSION

This review is based on 11 RCTs and on 10 CPSs, included after a careful assessment of scientific validity. Its main result is that methadone maintenance is a dose-dependent treatment. The higher doses of methadone are associated with better retention in treatment, less heroin use during treatment and lower withdrawal symptoms, until around 100 mg/day, after that the reliability of evidence is lower. The effect of dose on risk of death and on criminal activities can not be reliably assessed because the only study addressing these objectives have not sufficient power to obtain significant results. The probability to stay abstinent from cocaine is higher with high doses of methadone, compared with low doses. No side effects are evident from studies. No more socially relevant outcomes nor infectious diseases risks has been searched by the studies included in the review.

The effectiveness of higher doses of methadone in promoting retention, reducing heroin and promote abstinence from cocaine is consistent within included studies and with pharmacokinetic observations (Ward 1998; Hiltunen 1999). The excess of cocaine use in treatment with higher doses reported by Oliveto (Kosten-Oliveto 1993) can be an effect of chance. Cocaine can be used by methadone maintained patients for different reasons, including antagonism of opioid sedative effects, searching for euphoria independent from methadone “blockade” and to suppress opioid withdrawal. The risk of increasing use of cocaine during methadone maintenance treatment reported by some authors (Tennant 1995; Stine 1991) can be an effect of the underdosing of methadone and

higher doses of this medicament should stop use, as showed by this review. Nevertheless the risk of cocaine use in methadone maintenance can be taken carefully into consideration in the choice of patient treatment given that non effective treatments are available nowadays to contrast cocaine use (Lima 2003a; Lima 2003b; Soares 2003).

The use of higher doses of methadone for the aim of retain patients and stop their use of heroin seems to be effective; however the professional community showed some resistance in accepting such a treatment modality (D’Aunno 1999; Farrell 1994; Baillie 1992; Ward 1994b). This is to a certain extent driven by ideological assumption about the nature of opioid addiction (Rawson 1991), but partly is due to the management of the treatment by the staff: in general the patient and the staff determine together methadone dosages (Langendam 2000b), and sometimes the patient asks for lower doses, sufficient to contrast withdrawal symptoms but not to neutralise heroin euphoric effects. The availability of systematic reviews on evidence of effectiveness may contribute to the implementation of higher doses treatments.

The low number of studies aimed at studying the influence of methadone dosage in mortality is not surprising; although death is the outcome that can better act as a global indicator of success of treatment, nevertheless death is fortunately a seldom event, even in a high risk population like drug users, and to reach the needed statistical power to study mortality requires big RCTs or long follow-up periods. Observational studies appears to be less complex to carry out for the assessment of the relationship between treatment and mortality, as the study included in our review (Van Ameijden 1999).

This review takes into consideration observational studies together of randomised trials. All studies have been critically appraised using the Cochrane Drug and Alcohol Group methodology (Ferri 2003), and randomised and observational studies have been analysed separately, to avoid bias. In conclusion of the review, we can affirm that observational studies showed results which are consistent with those from randomised studies, and they add a relevant outcome not assumed by RCTs, the risk of death.

AUTHORS’ CONCLUSIONS

Implications for practice

The results of the review support the conclusion that methadone dosages ranging from 60 to 100 mg/day are more effective than lower dosages in retaining patients and in reducing use of heroin and cocaine during treatment. To find the optimal dose is a clinical ability, but clinician must consider these conclusions in treatment strategies. The most important side effect is the risk of increase the use of cocaine, which therefore needs to be carefully surveyed by clinicians.

Implications for research

The main implications for research concern open questions and methodological errors of studies.

There are many questions that remain without answer:

- there are some major outcomes for which data are absent or unsatisfactory: the effect of methadone dose in mortality reduction is the most important one. In general social outcomes are seldom addressed by researchers, and we do not have reliable answer to the question if there is the same dose-response relationship, as found for retention and use of heroin, for criminality or social adjustment;
- cocaine use during methadone maintenance is a major problem, and no effective medication is available; further research on effective treatments is needed, either pharmacological or not;
- both higher dosages and psycho-social interventions associated to methadone are able to improve outcomes, but the interaction between these two treatments modalities is unknown;
- one of the open questions is if different characteristics of patients can determine different needs as regards methadone effective doses. Some authors suggest that patients with less severe dependence can be successfully treated with doses lower than 50mg per day (Ward 1994b), but no studies addressed at the moment such a question.

On the methodological point of view, main problems which should be avoided in further research on methadone dosages are:

- the heterogeneity of outcome indicators: to aid comparison between studies, which is the main objective of the science, and to simplify synthesis of results, each author should make effort to adopt both outcome indicators and categorisation of outcomes already adopted by other studies. The editors of scientific journal, scientific societies and all the scientific community, should

promote the use of standards in reporting results (CONSORT 2001);

- the control of confounding remain the major methodological reason for the exclusion of observational studies. Given that non-randomised trials are essential to study rare outcomes, such as mortality, and to address questions on effectiveness of treatments, researchers should play a major effort to improve the study design particularly in confounding adjustment.

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POTENTIAL CONFLICT OF INTEREST

None

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- *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Caplehorn 1991
Methods	CPS quality class: B
Participants	238 individuals with a history of opiate addiction and current illicit opiate use confirmed by urinalysis, entering methadone maintenance treatment at two clinics in Sydney, Australia, between February 1986 and August 1987.
Interventions	Methadone maintenance at different dosages, measured by maximum daily dose.
Outcomes	Time in treatment. Socio-demographic and methadone dose data were extracted from clinical records.
Notes	No data suitable for inclusion in the tables. Cox regression model. RR of leaving treatment per different dosages (<60, 60-79, >80 mg/day).
Allocation concealment	D

Study	Caplehorn 1994
Methods	CPS quality class: B
Participants	307 individuals with a history of addiction to illicit opioids admitted into methadone maintenance in the Parramatta programme before 1 July 1979. Study period ended 1 January 1991. New South Wales, Australia.
Interventions	Methadone maintenance at different dosages, measured by maximum daily dose.
Outcomes	Time in treatment. Socio-demographic data, methadone treatment history, methadone dose data were extracted from clinical records. Subjects who had died prior to the end of the study period were identified checking the NSW Registry of Births Deaths and Marriages.
Notes	No data suitable for inclusion in the tables. Cox regression model. RR of leaving treatment per each mg increase in daily methadone dose.
Allocation concealment	D

Study	Caplehorn 1996
Methods	CPS quality class: B
Participants	280 heroin addicts entering 10 methadone programs operated by independent, private physicians between 1989 and 1992. Sydney, Australia.
Interventions	Methadone maintenance at different dosages, measured by maximum daily dose.
Outcomes	Time in treatment. Socio-demographic data, methadone treatment history, methadone dose data were extracted from clinical records.
Notes	No data suitable for inclusion in the tables. Cox regression model. RR of leaving treatment (maximum dose 100 mg/day vs maximum dose 50 mg/day).
Allocation concealment	D

Characteristics of included studies (Continued)

Study	D'Ippoliti 1998
Methods	CPS quality class: B
Participants	721 drug users entering methadone maintenance in the first 6 months of 1995. Lazio Region, Italy.
Interventions	Methadone maintenance at different dosages: - <30mg (n=113) - 30-59 mg (n=384) - >= 60 mg (n=158)
Outcomes	Treatment retention at 1 year follow-up. RRs adjusted by main confounders.
Notes	Baseline group for RR: <30 mg/day.
Allocation concealment	D

Study	Del Rio 1997
Methods	CPS quality class: C
Participants	111 adults patients attending a methadone treatment programme in Geneva, Switzerland between February 1991 and January 1995. Inclusion criteria: age of over 18 years, a history of addiction to opiates for more than 2 years and 2 previous drug rehabilitation attempts.
Interventions	Methadone maintenance at different dosages: - 15-40 mg/day (n=39) - 45-60 mg/day (n=39) - 65-110 mg/day (n=33)
Outcomes	Treatment retention at 18 months. Programme failures included dropouts, imprisonment, administrative discharge, death for a condition contracted while in program. Programme successes included patients still in the program at the end of follow-up, transfers to other doctors after stabilization, termination of program agreed with the physician, imprisonment for an offence committed before entering the program. All patients were followed until they quit the programme or until 31 July 1995, whichever came first.
Notes	Prevalent subjects. Only few confounding factors are taken into account. Baseline group for RH: 65-110 mg/day.
Allocation concealment	D

Study	Gaughwin 1998
Methods	CPS quality class: B
Participants	229 participants randomly sampled from the 1239 drug addicted people enrolled for the first time in the methadone program between January 1981 and June 1991, plus for 40 HIV positive participants who enrolled in the program during the same period. Adelaide, Australia.
Interventions	Methadone maintenance at different dosages, measured by maximum daily dose.
Outcomes	Treatment retention. Time spent on initial program.
Notes	No data suitable for inclusion in the tables. Cox regression model. RR of treatment retention per increase in maximum dose of methadone.
Allocation concealment	D

Characteristics of included studies (Continued)

Study	Goldstein 1973
Methods	RCT - Single blind, randomized clinical trial. quality class: B
Participants	120 patients enrolled from the East Valley Clinic and Santa Clara County Methadone Program, Stanford, California. Study period not specified.
Interventions	For the first 9 weeks (phase I) all patients were treated identically: the induction dose (30 mg/day) was repeated for 2 days, then 10 mg/day increase were administered daily reaching the stabilization dose (80 mg/day). From week 10th to 16th (phase II) increases or decreases of dose were administered to the intervention groups for which the stabilization doses were 160 and 40 mg/day. From week 17th to 27th (phase III) subjects were maintained at the stabilization dose: - 160 mg/day (n=40) - 80 mg/day (n=40) - 40 mg/day (n=40)
Outcomes	Treatment retention at 27 weeks (10 weeks treatment). Self reported withdrawal symptoms. Use of drugs measured by urine samples collected on a random basis, one day in five on the average, and analyzed using thin-layer chromatography technique.
Notes	
Allocation concealment	B
Study	Gossop 2001
Methods	CPS quality class: C
Participants	Random stratified sample of 351 patients selected among subjects with complete methadone dosage data in the NTORS National UK Cohort between March and July 1995.
Interventions	Methadone Maintenance (n=240) and Methadone Reduction (n=111).
Outcomes	Treatment retention. Self reported regular heroin use (more than once a week) at 2 years from the beginning of the treatment.
Notes	No data suitable for inclusion in the tables. ITT analysis. OR of heroin use per each mg of increase in methadone dose.
Allocation concealment	D
Study	Johnson 1992
Methods	RCT - Randomized, double blind, double-dummy clinical trial. quality class: B
Participants	162 unpaid volunteers enrolled between September 1988 and November 1989. 53 subjects treated with buprenorphine, 109 subjects treated with methadone. Inclusion criteria: 21-50 years old, self-reported length of present addiction of at least 4 months, two or more episodes of heroin use per day, self reported daily value of heroin use of \$50 or greater, self reported withdrawal symptoms, three consecutively collected daily urines, at least two of which positive for opioids, no current methadone treatment. No acute or chronic medical or psychiatric illnesses, no pregnancy. Baltimore, USA.
Interventions	Patients were assigned to one of three treatment groups: - 20 mg methadone/day (n=55) - 60 mg methadone/day (n=54) - 8 mg buprenorphine/day (n=53) 180-day study: 17 weeks of induction/maintenance phase, then detoxification.

Characteristics of included studies (Continued)

High dose was accomplished by administering 20 mg as the first dose, then 10 mg increase were administered daily. For low dose induction: 20 mg as first dose, followed by 30 mg for 4 days, 25 mg for 4 days and then 20 mg daily.

Patients received treatment with both oral and sublingual doses daily.

Counseling for relapse prevention was offered but not mandatory.

Outcomes	Outcomes measured at 17 weeks from the beginning of the treatment. Retention time in treatment. Opioids and cocaine use: measured by urine samples collected three times a week. Drug abstinence measured by monday urine samples. Urine samples assayed in triplicate using radioimmunoassay and twice with enzyme-multiplied immunotechnique. Metabolite level for positivity: 300ng/ml.
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Notes

Allocation concealment B

Study Johnson 2000

Methods	RCT - Double blind, single-site, controlled study, with stratified randomization. quality class: A
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Participants	220 patients aged 21-55 years with a diagnosis of opioid dependence according to DSM IV, no serious medical or psychiatric illnesses requiring long-term medication, recent opioid use on toxicologic screening, negative serum pregnancy test. 55 patients in each treatment group. Enrollment period: January 1996 - November 1997. Baltimore, USA.
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Interventions	Four treatment groups: - levomethadyl acetate, 75-115 mg, 3 times a week (n=55) - buprenorphine, 16-32 mg, 3 times a week (n=55) - methadone, 60-100 mg daily (n=55) - methadone 20 mg daily (n=55) Induction phase: weeks 1 and 2. Maintenance phase: weeks 3 to 17. Patients assigned to high dose MM started with 20 mg, with 10 mg increases administered daily until the dose reached 60 mg. Low dose MM patients continued to receive 20 mg daily.
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Outcomes	Treatment retention at 17 weeks. Opioid and cocaine use measured by urine specimens collected 3 times a week and analysed by enzyme multiplied immunoassay technique (cut off: 300 ng/ml). Degree of continuous abstinence from opioid or cocaine use, defined by at least 12 consecutive opioid or cocaine-free urine specimens. Side effects of treatment. Self-reported opioid use.
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Notes	ITT analysis. Missing samples were considered positive for purposes of analysis.
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Allocation concealment B

Study Kosten-Oliveto 1993

Methods	RCT - 24 weeks, double blind, double dummy, randomized clinical trial. quality class: B
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Participants	140 patients meeting DSM-III-R criteria for opioid dependence, with at least a 1-year history of opioid abuse, prior treatment, positive urine screen for opioids and naloxone-precipitated opioid withdrawal symptoms. New Haven - Connecticut, USA. Study period not specified.
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Interventions	Patients were randomly assigned to one of four treatment groups: - buprenorphine 2 mg/day (n=28) - buprenorphine 6 mg/day (n=28) - methadone 35 mg/day (n=34) - methadone 65 mg/day (n=35)
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Characteristics of included studies (Continued)

Patients received both an oral and sublingual vehicle, one of which contained the active compound. All medications were given under nursing supervision once daily, and the dosage was started at 2 mg of buprenorphine or 35 mg of methadone daily, and gradually increased to 6 mg of buprenorphine or 65 mg of methadone during the first 2 weeks. Doses were maintained stable for a period of 17 weeks. subsequently, patients underwent a gradual reduction in dose over 4-5 weeks.

Over the study period, patients were treated with relapse-prevention group therapy.

Outcomes	Treatment retention. Self reported drug use. Opioid withdrawal symptoms. Drug use, measured by urine samples collected weekly, randomly on Monday or Tuesday, and tested using the Abbott Diagnostic radioimmunoassay drug detection system (cut off: 200 ng/ml). Opioid withdrawal symptoms were self-reported on a weekly basis, evaluated by a 25-items opioid withdrawal rating form and rated on a 75-point scale. Cocaine withdrawal symptoms were self-reported on a weekly basis and rated on a 24-point scale.
Notes	No ITT analysis. 15 patients of the original sample were excluded because they completed less than 3 weeks in the study. For the cocaine study, 110 patients were included in the analysis (reported cocaine use, at least 20% of urines positive for cocaine).
Allocation concealment	B

Study **Ling 1976**

Methods	RCT - 40 weeks (280 days) double blind, randomized clinical trial. quality class: B
Participants	430 subjects, meeting Food and Drug Administration criteria for admission to methadone maintenance, aged 18-60 years, no major psychiatric or medical illnesses, no current alcoholism, no pending criminal charges. Veteran Administration Hospitals, USA, April 1973 - March 1975.
Interventions	Patients were randomly assigned to one of three groups: - methadone 50 mg/day (n=146) - methadone 100 mg/day (n=142) - levomethadyl acetate 80 mg/day (n=142) Methadyl acetate group received active medication on Monday, Wednesday, Friday, with placebo on all other days. The first dose was 30 mg in all three groups, incremented by 10 mg on each succeeding Monday until the patient achieved his target dose. All doses were dispensed double-blind.
Outcomes	Treatment retention. Drug use, measured by urine samples collected weekly using a random testing sequence supplied centrally. Safety (side effects).
Notes	All patients were male (veterans). High attrition rate (58%).
Allocation concealment	B

Study **Ling 1996**

Methods	RCT - Double blind, randomized, controlled trial. quality class: A
Participants	225 patients, aged 18-65 years, in good general health, meeting DSM-III-R criteria for opioid dependence and the FDA criteria for methadone maintenance treatment, not currently enrolled in a methadone maintenance program. Exclusion criteria: acute medical conditions, dependence to other drugs, pregnancy. October 1990 - September 1992. Los Angeles, California, USA.

Characteristics of included studies (Continued)

Interventions	Patients were randomly assigned to one of three groups: - buprenorphine 8 mg/day (n=75) - methadone 30 mg/day (n=75) - methadone 80 mg/day (n=75) Each patient received both an oral and sublingual form of medication, only one of which was active. For patients assigned to 80 mg methadone/day, the dose was increased by 5 mg daily until the 80 mg dose was reached.
Outcomes	Treatment retention at 26 and 52 weeks. Use of drugs, measured by urine samples collected three times a week on Monday, Wednesday and Friday and analyzed for opioids in the form of morphine by fluorescence polarization immunoassay (FPI) using the Abbott Diagnostic TDX System (Irving, Texas) (cut off: 300 mg/ml). Opioid withdrawal symptoms.
Notes	
Allocation concealment	B
Study	Maddux 1997
Methods	CPS quality class: B
Participants	610 chronic opioid users admitted to methadone maintenance program located in San Antonio - Texas, USA, during the years 1989-1991.
Interventions	Methadone maintenance at different dosages. The physician tended to regulate the dose according to needs expressed by patients. The starting dose was 30 mg, increased by 10 mg daily until the stabilization dose. Till the 3rd month continued heroin use led to dose increase, after the 3rd month it led to program probation with the requirement of negative urine test for 3 months. A positive test then led to involuntary withdrawal and discharge.
Outcomes	Treatment retention at 1 year follow-up. Data were collected by interview with subjects at the time of the admission, by review of clinical record 1 year after admission, and by follow-up interviews as soon as possible after the first anniversary of admission. Urine specimens were collected once per month on randomly selected days and screened by enzyme immunoassay; positive tests were confirmed by thin-layer chromatography.
Notes	No data suitable for inclusion in the tables. OR of increase in retention per 10 mg increase in methadone dose.
Allocation concealment	D
Study	Preston 2000
Methods	RCT - Double blind, randomized controlled trial. quality class: A
Participants	285 patients admitted to methadone maintenance program at the Archway Clinic - Baltimore, USA. Inclusion criteria: age 18-65 years, history of drug use by injection, qualified for methadone maintenance according to Food and Drug Administration guidelines, no current dependence on alcohol or benzodiazepines, at least 3 of 15 urine specimens collected during a 5 week baseline positive for heroin, no major medical or psychiatric illnesses. Study period not specified.
Interventions	Throughout the study (5 weeks baseline + 8 weeks intervention) all patients received daily methadone maintenance and weekly counseling. Patients were randomly assigned to one of four groups: - methadone 50 mg/day and contingent voucher for opiate-negative urine specimens (n=29) - methadone 70 mg/day (n=31) - methadone 70 mg/day and contingent voucher (n=32) - methadone 50 mg/day (n=28)

Characteristics of included studies (Continued)

Dose was stabilized at 50 mg within the first week of treatment and held constant through the 5 weeks baseline. Dose increases were given as 60 mg on days 1 through 3 and 70 mg on day 4 of the intervention. Dose assignment was blinded to patients, treatment and research staff.

Outcomes	Treatment retention at 13 weeks. Opiate and cocaine use, measured by urine specimens collected three times a week and analysed using enzyme multiplied immunoassay technique (cut off: 300 ng/ml). A self reported drug use questionnaire was administered immediately after urine specimens collection. Lifestyle changes (criminal activity and drug use during previous week) and craving questionnaire were administered once a week (Wednesday).
Notes	Only comparison standard and dose increase groups (non contingent) were taken into account in the review.
Allocation concealment	B

Study	Rhoades 1998
Methods	RCT - Single blind randomised trial. quality class: C
Participants	142 patients aged 18-50 years, meeting DSM-III-R criteria for opioid dependence, in good physical and psychiatric health. Houston-Texas, USA. Study period not specified.
Interventions	Subjects were randomly assigned to 50 or 80 mg of methadone per day and to 2 or 5 visits per week. Study phases were: intake, stabilization, 24 weeks treatment. Subjects received about \$14.00 per week for research elements as well as bus or parking tokens. Before and after the HIV testing, proper counseling was provided.
Outcomes	Treatment retention at 24 weeks, drug use, craving. Administered questionnaires: - structured clinical interview for DSM-III-R - Addiction Severity Index - Hamilton Depression/Anxiety - Beck Depression Inventory - Profile of Mood States - Medication Side Effects Questionnaire - Drug History - Desire to Use Drugs Inventory Urine samples were split with half retained for retesting in a certified on-site laboratory. Qualitative testing was by Syva EMIT System and the tox-lab thin layer chromatographic system.
Notes	Single blind. Attrition bias. 123 subjects out of 142 began the stabilization period, but 16 did not complete it. Out of 107 subjects entering treatment phase, only 71 completed the 24 week study (analysis sample). No ITT analysis.
Allocation concealment	B

Study	Schottenfeld 1997
Methods	RCT - Double blind randomized clinical trial. quality class: A
Participants	116 subjects meeting FDA criteria for methadone maintenance treatment, fulfilling DSM-III R criteria for both opioids and cocaine dependence, and having an opiate positive urine toxicology test at baseline. A naloxone challenge test was used to verify current physiologic opioid dependence in subjects with no history of methadone maintenance. New Haven, Connecticut. January 1991 - July 1993.
Interventions	Subjects were randomly assigned to one of four treatment groups: - 65 mg methadone/day (n=28) - 20 mg methadone/day (n=30) - 12 mg buprenorphine/day (n=29) - 4 mg buprenorphine/day (n=29)

Characteristics of included studies (Continued)

	After 2 weeks of induction, subjects were maintained at their full maintenance dose for 22 weeks. Subjects participated in a 1-hour weekly group counseling session.
Outcomes	Retention in treatment at 24 weeks. Opioid use and cocaine use, assessed by urine samples obtained twice a week during the first 9 months of the study and thrice weekly between September 1991 and July 1993. Samples were tested with Abbott Tdx system (cut off: 200 ng/ml for opioids, 300 ng/ml for cocaine). Weekly self-report ratings of drug use were collected by the Weekly Drug Use Inventory.
Notes	At the conclusion of the study, 16 of initial 132 subjects randomly assigned to the treatments were deemed ineligible because they did not satisfy the eligibility criteria regarding cocaine dependence or abuse (4 subjects from each of the 4 maintenance treatments). At the end of the study, differences in retention among the 4 maintenance groups were not statistically significant; differences in retention for the initially enrolled sample of 132 individuals were statistically significant.
Allocation concealment	B
Study	Strain 1993a
Methods	RCT - Randomized, double blind, placebo-controlled study. quality class: B
Participants	247 patients aged 18-50 years, with a history of intravenous opioid dependence, no chronic medical or psychiatric illnesses, a negative pregnancy test for women, and at least 3 months since the last treatment. September 1988 - July 1990. Baltimore, USA.
Interventions	6 months short-term methadone treatment program (182 days). All participants received a minimum of 35 days of active methadone (stable or decreasing) during the first 5 weeks of treatment and then 15 weeks of stable doses at: - 50 mg (n=84) - 20 mg (n=82) - detoxification group: 0 mg/day (n=81). During weeks 21 through 26, the methadone dose was gradually tapered. Individual counseling and group therapy were offered. Treatment group assignment, stabilization doses and dosing schedules were double-blind for all patients and the clinic staff who had patient contact.
Outcomes	Treatment retention at 20 weeks. Opioid and cocaine use through week 20, measured by urine samples collected 3 times a week. Samples were tested on site using EMIT (cut off: 300 microg/ml); one sample each week was randomly selected to be sent to an outside laboratory for thin-layer chromatography analysis.
Notes	ITT analysis.
Allocation concealment	B
Study	Strain 1999
Methods	RCT - 40-weeks randomized, double blind clinical trial. quality class: A
Participants	192 patients aged >18 years, with at least 2 previous detoxication attempts or a single MMT, current intravenous opioid dependence, no chronic medical or psychiatric illnesses, negative pregnancy test, at least 1 month since the patient's last treatment at the clinic. June 1992 - October 1995. Baltimore, USA.
Interventions	Patients were admitted to one of two methadone dose schedules: - 40 to 50 mg/day (n=97) - 80 to 100 mg/day (n=95), with concurrent counselling. Group assignment and methadone dosing were double-blind for patients and staff. During the first week all participants received 30 mg of methadone daily. Over the subsequent 5 weeks, patients in the high dose condition had dose increases of 10 mg per week, and patients in the moderate dose condition had dose increases of 2 mg per week. Beginning in week 6 patients achieved the stabilization dosages (80 mg and 40 mg). Through week 8 to 30 patients were eligible to receive

Characteristics of included studies (Continued)

	double-blind dose increases (based on opioid use) and decreases (request of the patient or consecutive opioid negative samples). through week 31 to 40, dose was tapered at a rate of 10% per week.
Outcomes	Treatment retention. Self-reported illicit opioid use. Use of drugs measured by urine samples collected twice weekly and tested using enzyme-multiplied immunoassay technique (cut off: 300 microg/ml).
Notes	ITT analysis.
Allocation concealment	A

Study **Torrens 1996**

Methods	CPS quality class: B
Participants	370 heroin addicts meeting DSM-III-R criteria for opioid dependence, admitted for the first time to a methadone maintenance treatment program at the Centro de Atencion y Seguimiento between March 1991 and December 1994. Barcelona, Spain.
Interventions	Methadone maintenance at different dosages: - <=80 mg/day (n=244) - > 80 mg/day (n=126) Low-threshold treatment not abstinence-oriented. Patients are not aware of the methadone dose dispensed. High-dose policy (no upper limit) and no restriction on long-term treatment (no time limit).
Outcomes	Treatment retention at 2 years follow-up. Medical records were used to obtain data regarding patients. Heroin and cocaine use was monitored by urinalyses carried out weekly.
Notes	Baseline group for RR: >80 mg/day.
Allocation concealment	D

Study **Van Ameijden 1999**

Methods	CPS quality class: B
Participants	498 injecting drug users with a Dutch nationality, enrolled for the Amsterdam Cohort Study via methadone maintenance programs and a sexually transmitted diseases clinic. Enrollment started in 1985; follow-up: April 1989 - May 1995.
Interventions	Methadone maintenance at different dosages: - 5-55 mg/day - 55-70 mg/day - >75 mg/day
Outcomes	All cause mortality, overdose mortality. Vital status was determined using local and national population registries, and causes of death were verified and completed using hospital records, data from the drug department and postmortem examinations. Follow-up was undertaken every 4 months.
Notes	
Allocation concealment	D

Characteristics of excluded studies

Characteristics of excluded studies (Continued)

Blaney 1999	CPS. Naturalistic approach: patients were not randomly assigned to a given dose level. No confounding adjustment at the analysis stage.
Borg 1999	CPS. No confounding adjustment.
Brown	CPS. Random samples of subjects extracted from different treatment programs. No random allocation of treatments, no confounding adjustment at the analysis stage.
Caplehorn 1993a	CPS. Secondary analysis of the original study (Caplehorn 1991, included).
Caplehorn 1993b	CPS. Secondary analysis of a subsample of the original study (Caplehorn 1991, included).
De Leon 1995	CPS. Inadequate control for confounding factors: only employment status is included in the multivariate regression model.
Handal 1976	CPS. Selection bias; no confounding adjustment at the analysis stage.
Hartel 1998	Retrospective ascertainment of exposure.
Havassy 1984	RCT. Randomization failed. Inadequate control of confounding variables.
Joe 1991	CPS. The multivariate regression model containing methadone dosage has been performed without main confounders (included in others models without dosage).
Langendam 2000a	CPS. The effect of methadone dosage on overdose mortality was not evaluated in multivariate analysis.
Maxwell 1999	CPS. No confounding adjustment at the analysis stage.
McGlothlin 1981	CPS. Selection bias; no confounding adjustment at the analysis stage.
Mino 1998	CPS. Inadequate control of confounding factors. The final multivariate model does not contain all the variables related to the outcome in the univariate analysis.
Panell 1977	RCT. Analysis of a subsample of the national study (Ling 1976, included).
Saxon 1996	RCT. Comparison is made between different contingency counseling approaches and non-contingency ones.
Schut 1973	CPS. Selection bias; no control of confounding variables at the analysis stage.
Seow 1980	CPS. No measures adjusted for confounding variables are presented.
Siassi 1977a	CPS. Selection bias; no confounding adjustment at the analysis stage.
Siassi 1977b	CPS. Selection bias. No confounding adjustment. at the analysis stage.
Stine 1992	CPS. Evaluation of the effect of 2 contingency management programs on cocaine abuse. Methadone dose was lowered in response to cocaine-positive urines and raised in response to abstinence. Exposure variables are approaches, not dosages.
Strain 1993b	RCT. Secondary analysis of a subsample of the original study (Strain 1993a, included).
Williams 1970	CPS. No measurement of attrition. Separate evaluation of low and high dosage groups. No effect measures at the analysis stage. No control of confounding variables.

ADDITIONAL TABLES

Table 01 CPS - RR of leaving methadone maintenance treatment

Study	RR - 30 mg/ day	RR - 60 mg/ day	RR - 90 mg/ day	p
Caplehorn 1991 (1.2 years follow-up)	1	0.40 (0.21,0.61)	0.13 (0.05,0.34)	
Caplehorn 1994 (3 years follow-up)	1	0.56	0.12	<0.05
Caplehorn 1996 (0.4-1.66 years follow-up)	1 (50 mg)		0.28 (0.17,0.47)	
Gaughwin 1998 (0-10 years follow-up)	1	0.40	0.00	<0.01

Methadone maintenance at different dosages for opioid dependence (Review)

23

GRAPHS

Comparison 01 RCT

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Retention rate			Relative Risk (Fixed) 95% CI	Subtotals only
02 Retention time (weeks)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
03 Opioid use (self-reported - times/week)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
04 Opioid use (self-reported mg/day)	1	59	Weighted Mean Difference (Fixed) 95% CI	-0.31 [-0.70, 0.08]
05 Opioid abstinence score	1	150	Weighted Mean Difference (Fixed) 95% CI	24.80 [8.91, 40.69]
06 Opioid abstinence at >3-4 weeks (urine based)			Relative Risk (Fixed) 95% CI	Subtotals only
07 Opioid withdrawal symptoms scores			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
08 Cocaine use (self-reported - times/week)	1	59	Weighted Mean Difference (Fixed) 95% CI	0.80 [-0.88, 2.48]
09 Cocaine abstinence at >3-4 weeks (urine-based)	2	168	Relative Risk (Fixed) 95% CI	1.81 [1.15, 2.85]
10 Cocaine withdrawal symptoms scores	1	59	Weighted Mean Difference (Fixed) 95% CI	0.00 [-2.12, 2.12]
11 Side effects (at least 1)	1	110	Relative Risk (Fixed) 95% CI	1.14 [0.74, 1.75]
12 Criminal activity (mean nb./week)	1	59	Weighted Mean Difference (Fixed) 95% CI	0.05 [-0.03, 0.13]
13 Money spent/day	1	59	Weighted Mean Difference (Fixed) 95% CI	-2.00 [-4.74, 0.74]

Comparison 02 CPS

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Overdose mortality (6 years follow-up)			Relative Risk (Fixed) 95% CI	Subtotals only
02 Leaving treatment (12-24 months follow-up, all studies)			Relative Risk (Fixed) 95% CI	Subtotals only

COVER SHEET

Title	Methadone maintenance at different dosages for opioid dependence
Authors	Faggiano F, Vigna-Taglianti F, Versino E, Lemma P
Contribution of author(s)	FF, PL and EV conceptualised the review; FV-T and EV performed the literature searches and organised papers collection. FF, FV-T and EV reviewed the papers and coded data from the papers for meta-analysis. FF wrote results, discussion and conclusions sections. FV-T wrote methods, description of studies and methodological quality of included studies sections. EV provided comments and participated to the completion of the report.
Issue protocol first published	2000/3

Review first published	2003/3
Date of most recent amendment	03 February 2005
Date of most recent SUBSTANTIVE amendment	02 May 2003
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

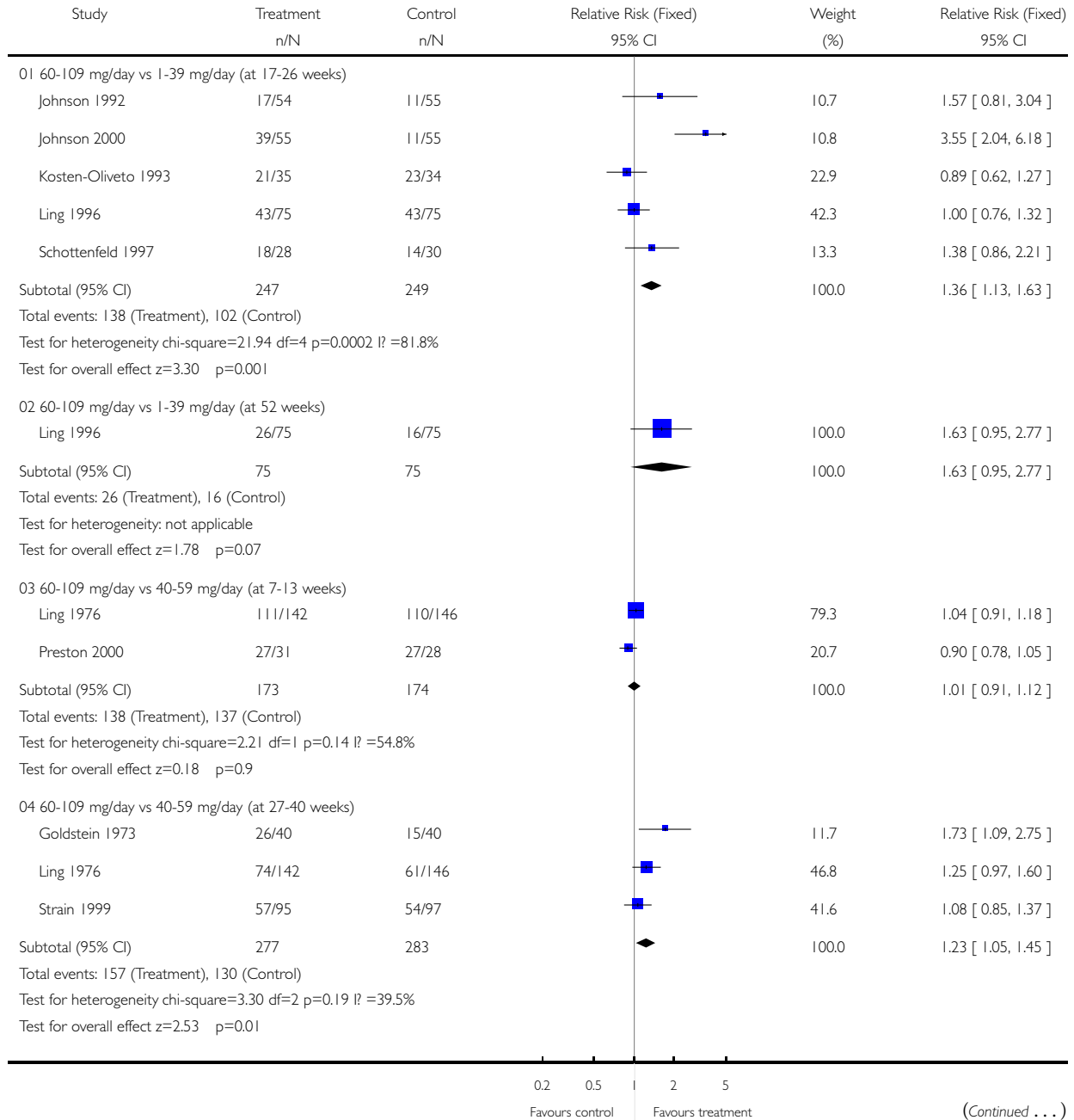
Fig. 1. Comparison 01 RCT

01.01 Retention rate

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 01 Retention rate



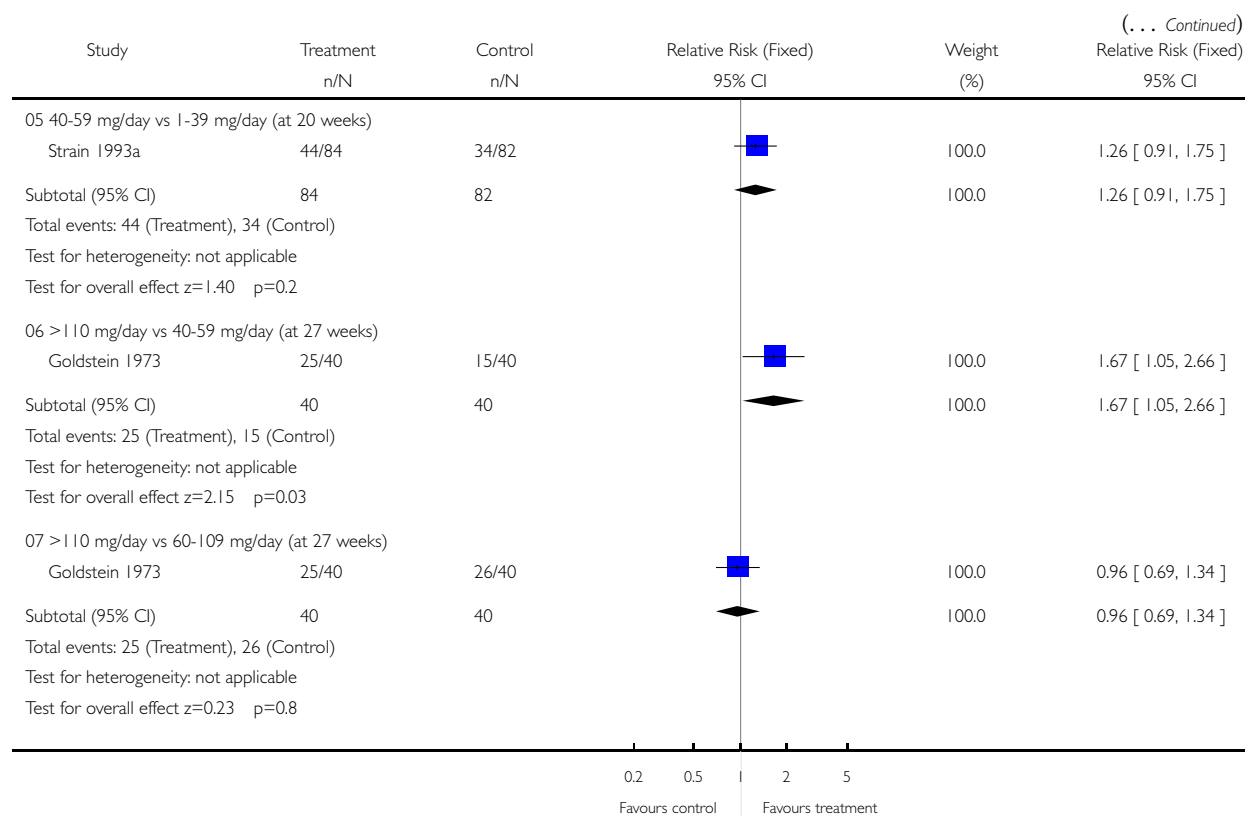


Fig. 2. Comparison 01 RCT

01.02 Retention time (weeks)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 02 Retention time (weeks)

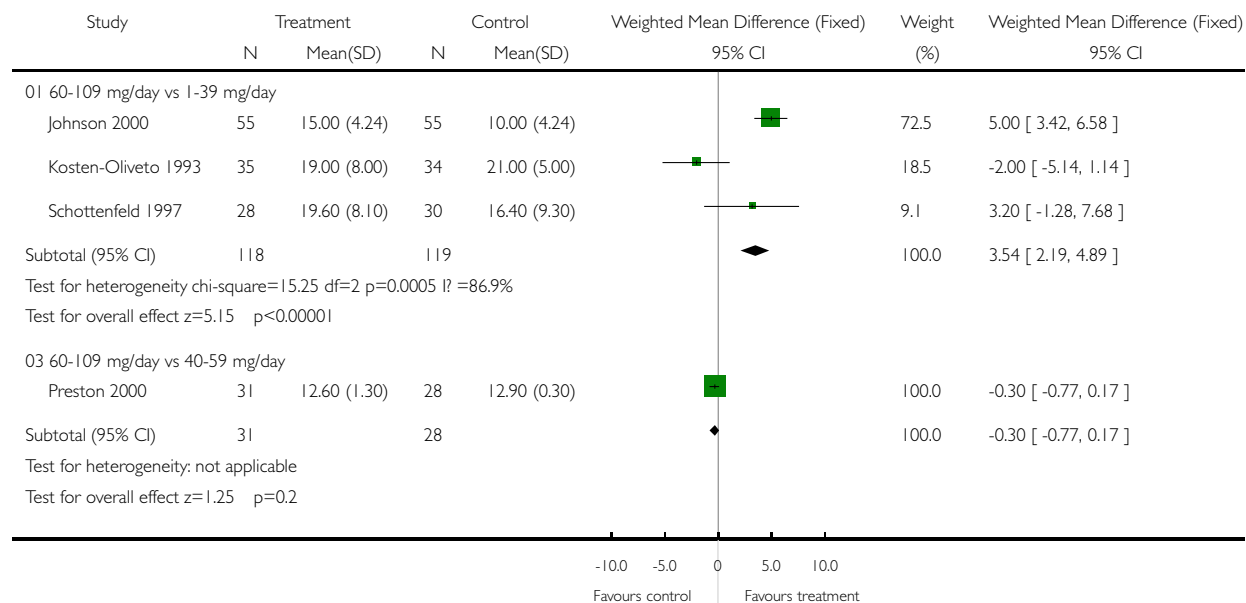


Fig. 3. Comparison 01 RCT

01.03 Opioid use (self-reported - times/week)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 03 Opioid use (self-reported - times/week)

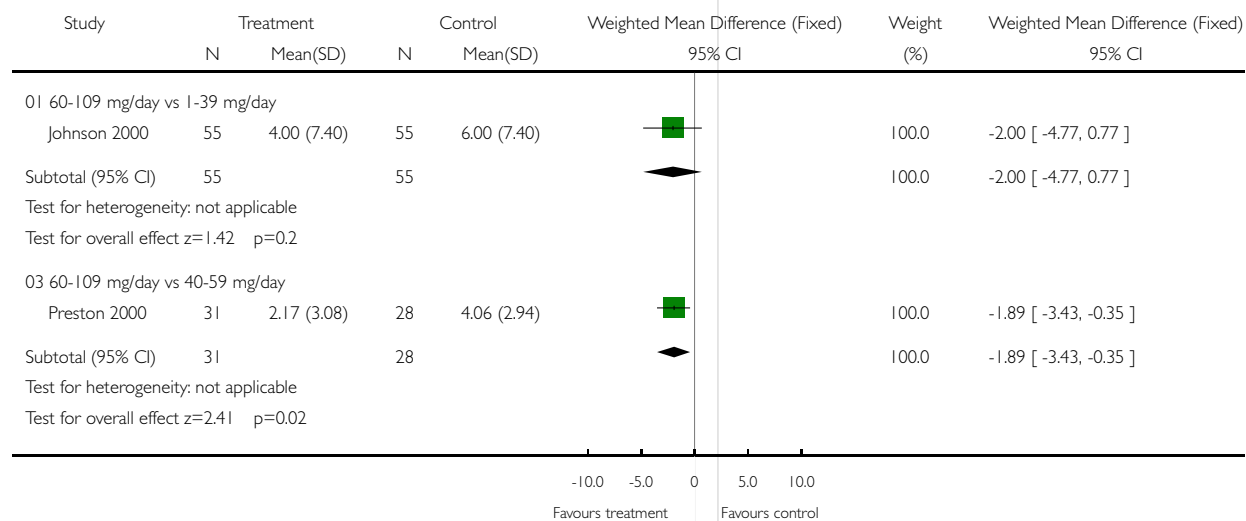


Fig. 4. Comparison 01 RCT

01.04 Opioid use (self-reported mg/day)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 04 Opioid use (self-reported mg/day)

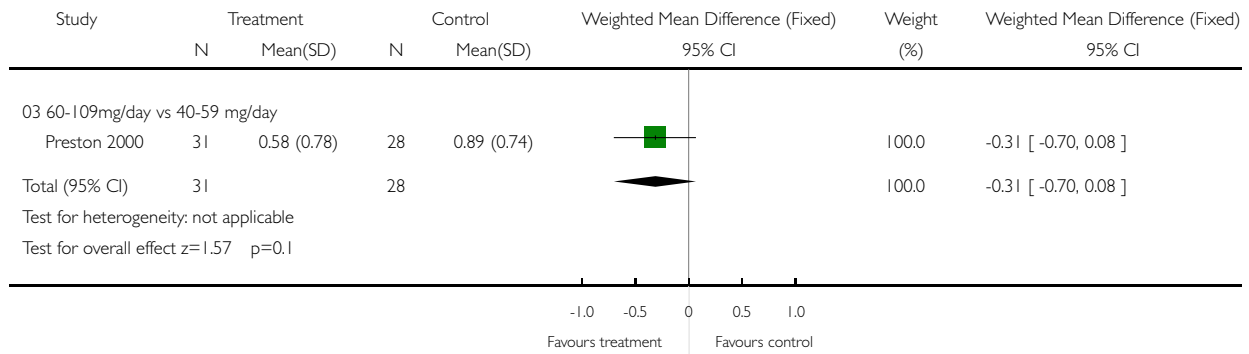


Fig. 5. Comparison 01 RCT

01.05 Opioid abstinence score

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 05 Opioid abstinence score

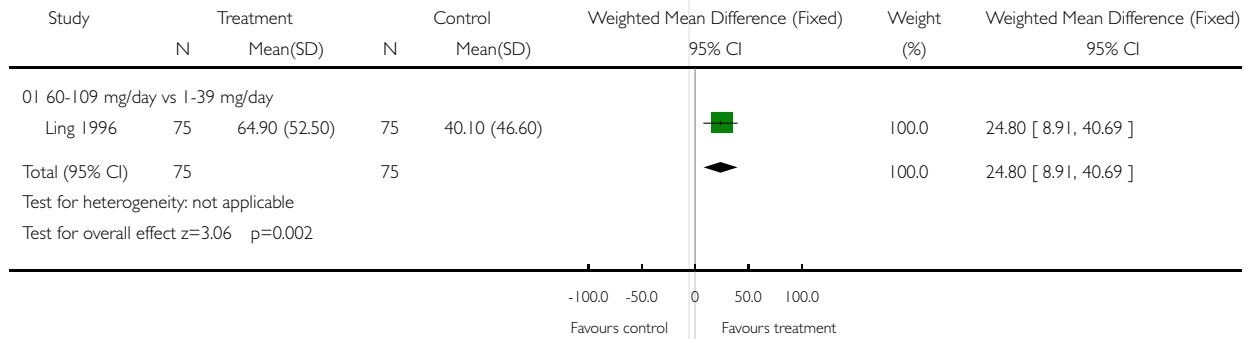


Fig. 6. Comparison 01 RCT

01.06 Opioid abstinence at >3-4 weeks (urine based)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 06 Opioid abstinence at >3-4 weeks (urine based)

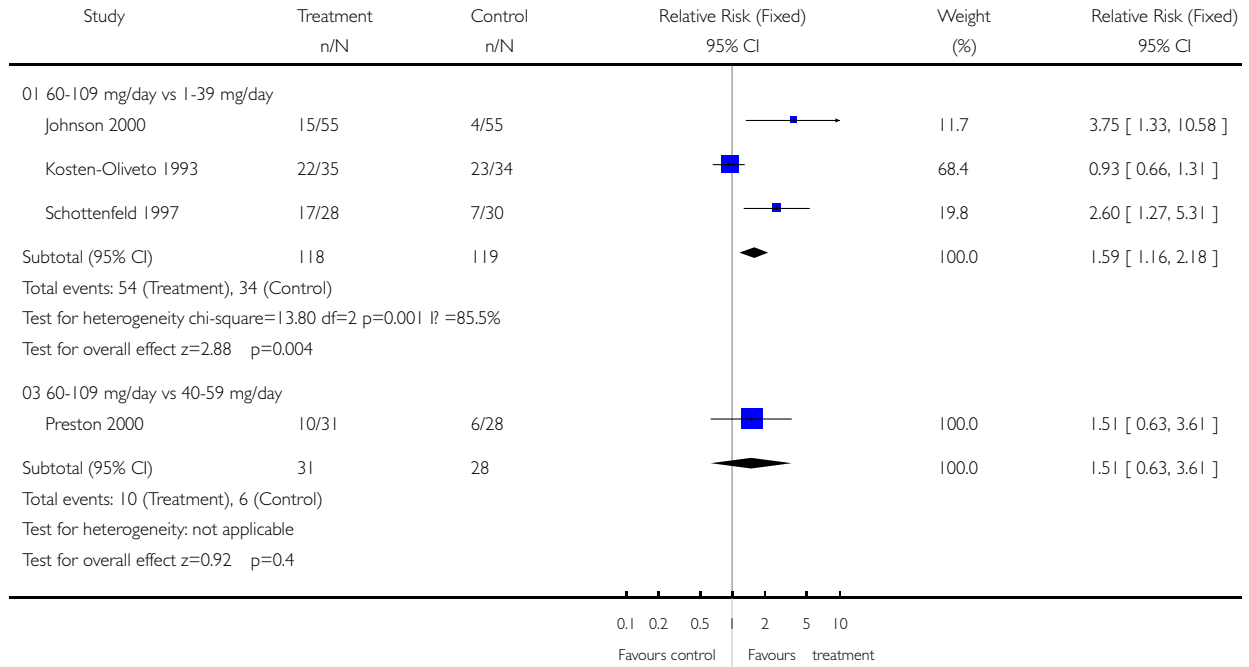


Fig. 7. Comparison 01 RCT

01.07 Opioid withdrawal symptoms scores

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 07 Opioid withdrawal symptoms scores

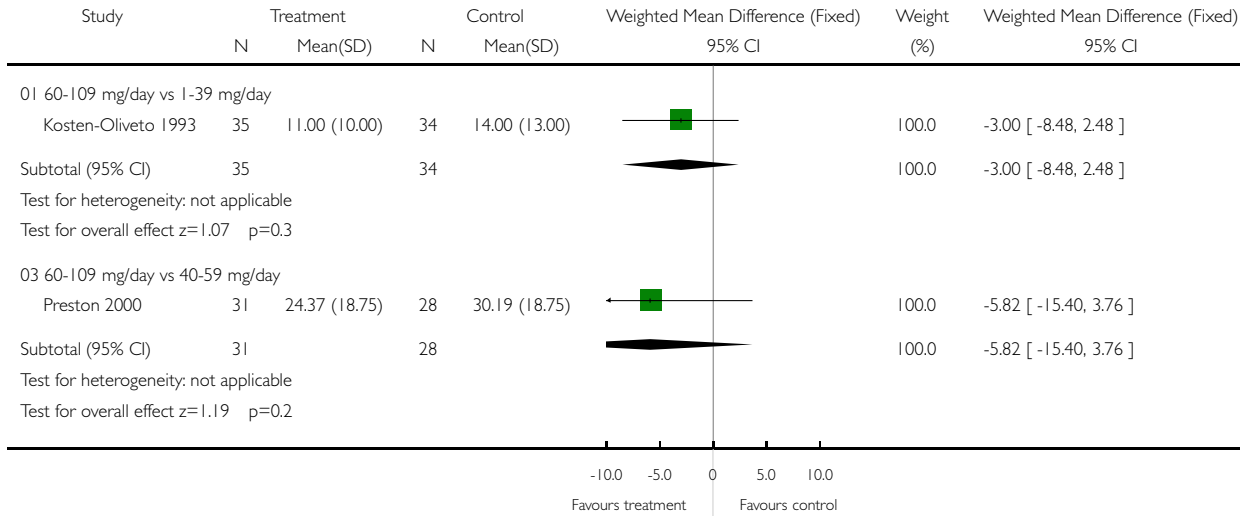


Fig. 8. Comparison 01 RCT

01.08 Cocaine use (self-reported - times/week)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 08 Cocaine use (self-reported - times/week)

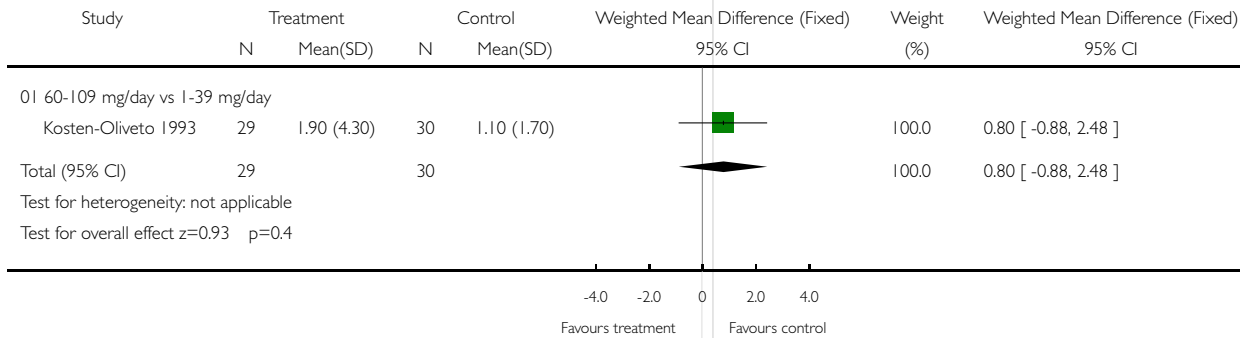


Fig. 9. Comparison 01 RCT

01.09 Cocaine abstinence at >3-4 weeks (urine-based)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 09 Cocaine abstinence at >3-4 weeks (urine-based)

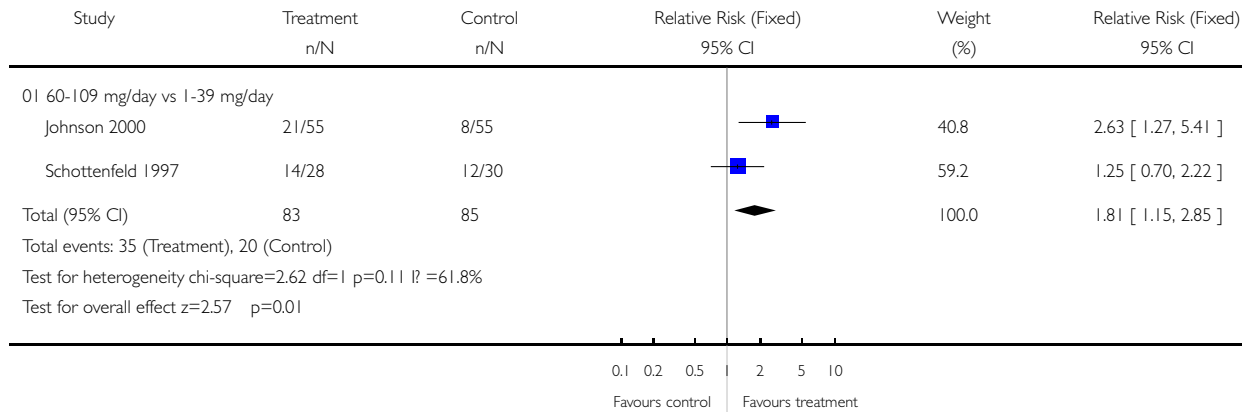


Fig. 10. Comparison 01 RCT

01.10 Cocaine withdrawal symptoms scores

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 10 Cocaine withdrawal symptoms scores

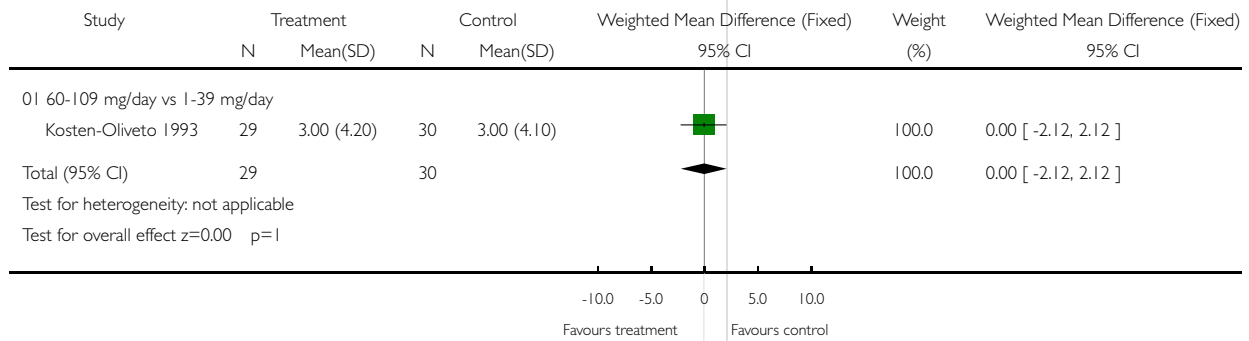


Fig. 11. Comparison 01 RCT

01.11 Side effects (at least 1)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 11 Side effects (at least 1)

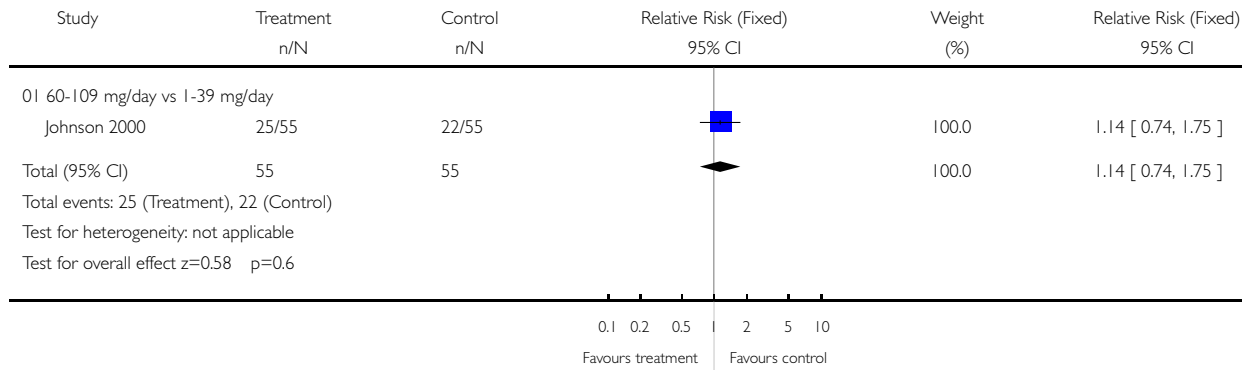


Fig. 12. Comparison 01 RCT

01.12 Criminal activity (mean nb./week)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 12 Criminal activity (mean nb./week)

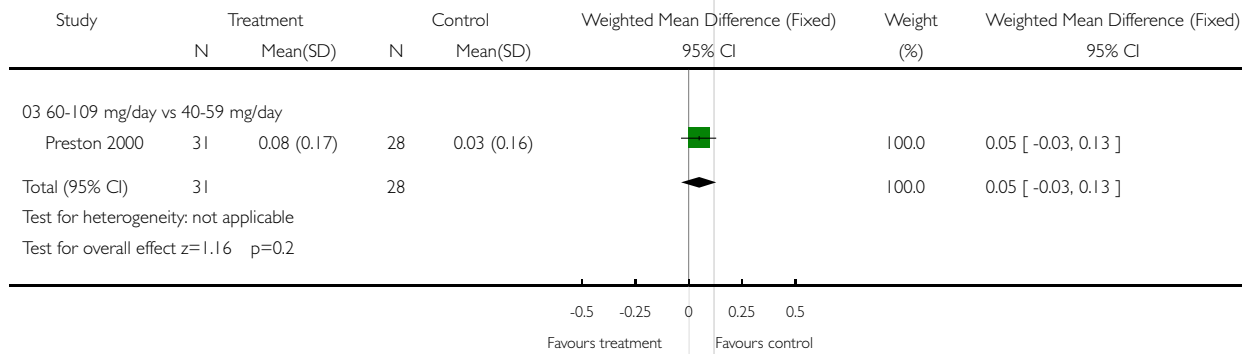


Fig. 13. Comparison 01 RCT

01.13 Money spent/day

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 01 RCT

Outcome: 13 Money spent/day

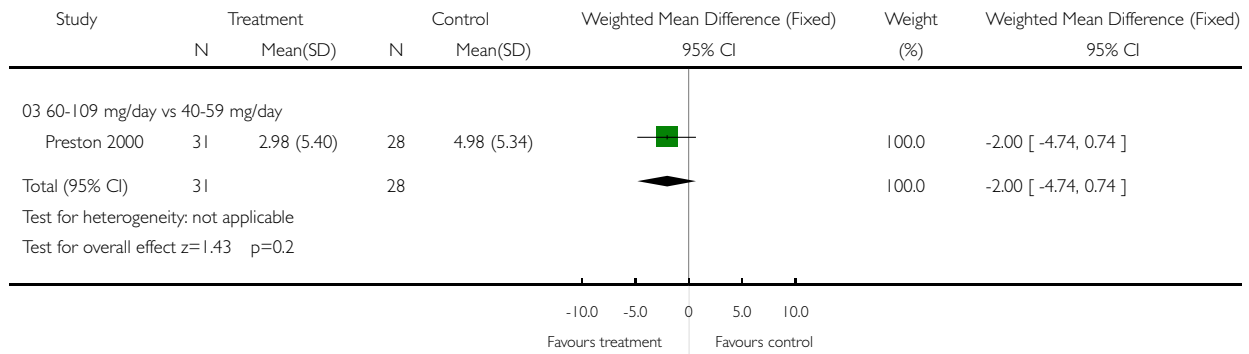


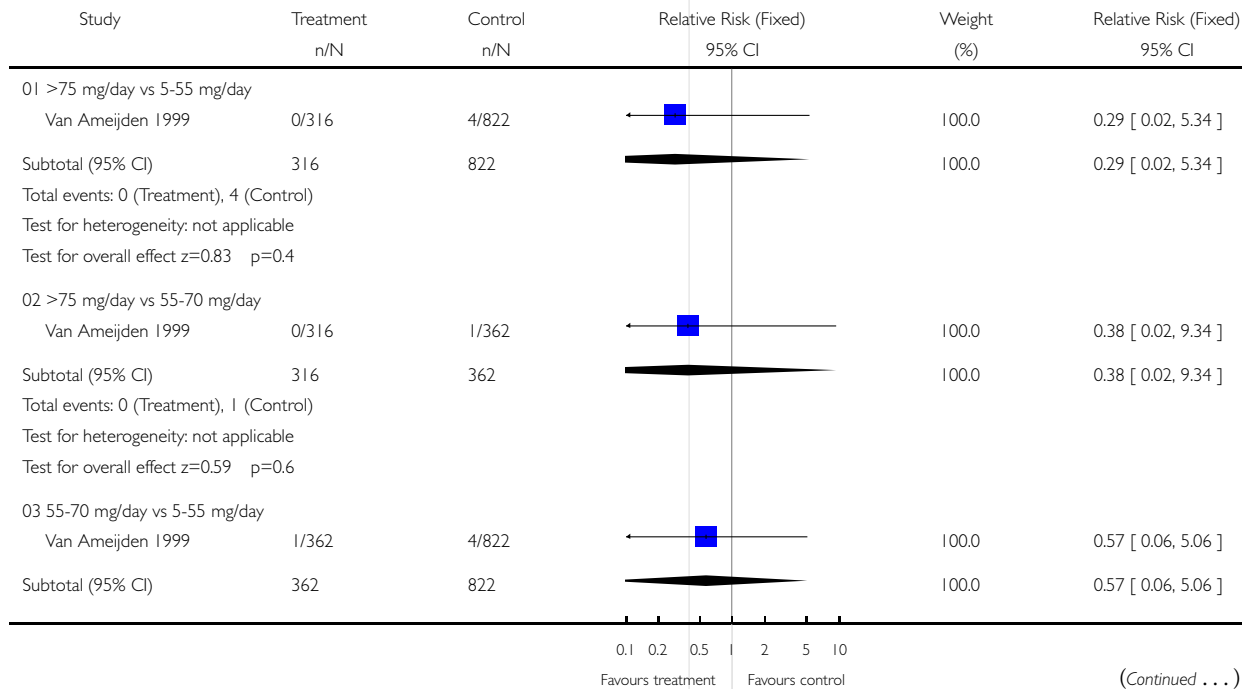
Fig. 14. Comparison 02 CPS

02.01 Overdose mortality (6 years follow-up)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 02 CPS

Outcome: 01 Overdose mortality (6 years follow-up)



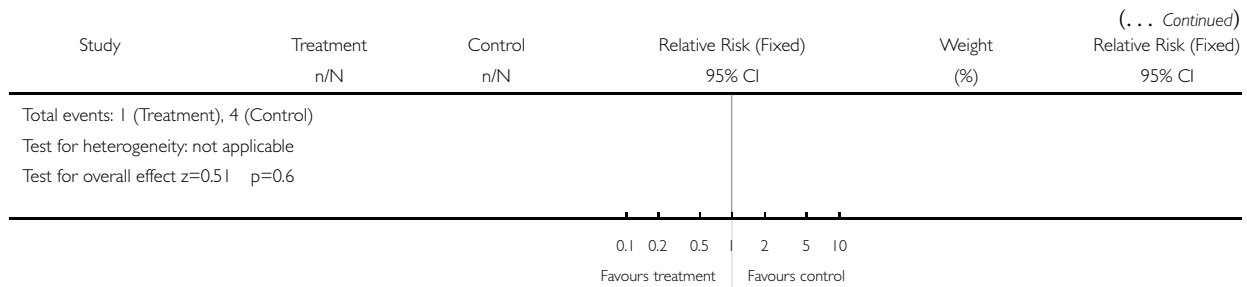


Fig. 15. Comparison 02 CPS

02.02 Leaving treatment (12-24 months follow-up, all studies)

Review: Methadone maintenance at different dosages for opioid dependence

Comparison: 02 CPS

Outcome: 02 Leaving treatment (12-24 months follow-up, all studies)

