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# Efficacy of maintenance treatment with methadone for opioid dependence: A meta-analytical study

BJÖRN AXEL JOHANSSON, MATS BERGLUND, ANNA LINDGREN



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The two aims of this study were to analyse the impact of methadone on outcome, and to confirm the results from previous meta-analyses by using a different methodology. The literature on randomized controlled trials (RCT) of methadone as maintenance treatment for opioid dependence was systematically reviewed. Eight studies involving 1511 patients were included. Both dichotomous and continuous variables were transformed into the standardized effect size ($d$). Homogeneity was analysed. A random effect model was used in all calculations. The combined analyses for retention, abuse and criminality were all significant: $d=0.90$, $d=0.61$, and $d=0.35$, respectively. A test of heterogeneity was significant for all three outcomes: $P<0.01$ for all comparisons. The type of study design was a significant moderator in five of nine comparisons: for retention in all three comparisons, concerning abuse in gradual detoxification vs. untreated controls and concerning criminality in placebo vs. untreated controls. In these subgroups, three of six studies were homogeneous. In one study, methadone maintenance treatment reduced abuse of illegal opioids in prisoners. We conclude that methadone maintenance treatment in opioid dependence shows positive effects on retention, opioid abuse and criminality compared with non-active controlled conditions. Type of study design could explain some of the heterogeneity found. A different meta-analytical approach made it possible to confirm effects of methadone on retention and opioid abuse from previous studies and document effect on criminality.

• *Maintenance treatment, Meta-analysis, Methadone, Opioid dependence, RCT.*

Björn Axel Johansson, M.D., Ph.D., B.Sc., Clinical Alcohol Research, University Hospital MAS, Entr. 108, SE-205 02 Malmö, Sweden, E-mail: bjorn_axel.johansson@med.lu.se; Accepted 20 September 2006.

The WHO (1) states that methadone maintenance treatment (MMT) is a major public health tool in the management of opioid dependence, and suggests that methadone should be classified as an essential drug, i.e. drugs selected with regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. During the preparation of the WHO proposal, a new, independent meta-analysis of earlier and current studies was performed (1). This article is an extension of that analysis. Our methodology differs somewhat from previous analyses (2). Both dichotomous and continuous outcome variables were transformed to the common effect measure ($d$). In a second phase, we analysed the homogeneity of the studies included. If heterogeneity was found, a moderator analysis was performed.

### *Aims*

For opioid-dependent patients, what impact does methadone have on outcome? Does a meta-analytical technique using a different approach including both dichotomous and continuous variables and a general use of the standard effect size ($d$) give similar results compared with earlier techniques?

## Sample and Methods

### *Search strategy*

A systematic search was made in Medline (1966 to July 2004), Embase, PsychINFO, PsychLITT, the Cochrane Central Register of Controlled Trials (CCTR) and in the Cochrane Database of Systematic Reviews. The following search terms were used: methadone, maintenance treatment, substance use disorders and randomized


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controlled trials (RCT). The references in published articles, reviews and meta-analyses were checked. There were no language restrictions. No systematic search was made for unpublished studies.

### *Inclusion criteria*

All studies included opioid-dependent patients according to the DSM or ICD classification systems. Only studies with duration of at least 6 weeks and with a minimum of 20 patients were included. The studies had to be randomized trials comparing methadone vs. controlled conditions.

### *Extraction procedure*

Two authors (BAJ and MB) systematically reviewed all studies. The same authors made data extraction for each study independently. A difference in opinion was resolved after discussion. A professional statistician (AL) transformed categorical data to *d*-statistics in close collaboration with the two other researchers.

### *Quality assessment*

The Swedish Council on Technology Assessment in Health Care (SBU) checklist was used (3). Each study scores from 1 to 3, with 3 representing the highest quality. The maximal score possible was 33 for individual studies and 36 for multicentre studies (3). All studies were scored by two authors (BAJ, MB). Differences in scoring were resolved by discussion.

### *Previous systematic reviews and meta-analyses*

#### REVIEWS

Farrell et al. (4) concluded that MMT was superior to controlled conditions for opioid abuse and criminality. The NIH Consensus Conference 1998 (5) stated that MMT diminishes opioid use, reduces transmission of HIV and hepatitis and reduces criminal activity. Ward et al. (6) reported that methadone improved health, yielded better retention, reduced heroin abuse, improved infectious-disease transmission and reduced overdose deaths. O'Connor & Fiellin (7) stated that MMT seems to be effective in promoting relapse prevention.

#### META-ANALYSIS

In the Cochrane Library, Mattick et al. (2) reported on six studies (the first six studies in Tables 1 and 2). They concluded that methadone appeared to be statistically more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use, but not statistically effective in criminal activity and mortality. Fourteen dichotomous results were included. Continuous variables were not included. The material is described in five meta-analyses: retention in treatment, morphine positive urines, self-reported heroin use, criminality and mortality. The test of heterogeneity was negative in all the analyses except retention.

Marsch (8) performed a meta-analysis on 11 studies, including three RCTs comparing methadone and untreated controls: Dole et al. (9), Gunne & Grönbladh (10) and Yancovitz et al. (11). The overall result was that MMT was effective among opioid-dependent individuals across a variety of contexts, cultural and ethnic groups, and study designs.

### *Characteristics of individual RCTs*

Table 1 shows a narrative of the eight included RCTs on methadone maintenance compared with non-active controlled conditions. Two studies (12, 13–15) were placebo-controlled, in two studies (16, 17) a gradual detoxification group was used as control and in four studies (9–11, 18) untreated controls were used. A total of 1511 subjects were included in the different studies.

### *Statistics*

We used the standardized mean difference effect size (*d*) as the measurement of outcome. Although no strict clinical interpretation of effect sizes is agreed upon, many apply the convention that 0.2 is a small but important effect, 0.5 a moderate effect and 0.8 a large effect (3). The Hedges correction (19) was used to adjust for small sample size bias. The correction factor is $1-[3/(4n-9)]$, where $n$ equals the total number of participants in the study. The effect sizes were calculated with the Comprehensive Meta Analysis Software Program (20). The program could transform means, *P* and *t*-statistics but not dichotomous variables to *d*. For categorical data, we first calculated the odds ratio,

$$OR = \frac{(x_C + 0.5)/(y_C + 0.5)}{(x_E + 0.5)/(y_E + 0.5)},$$

where 0.5 has been added to each cell in order to minimize the influence of possible zeros and small groups, according to Fleiss (21). This precautionary measure together with the Hedges correction results in a conservative handling of the calculations. The odds ratio is then transformed into *d* using

$$d = \frac{2r}{\sqrt{1 - r^2}},$$

where

$$r = \frac{\ln OR / SE(\ln OR)}{\sqrt{n_C + n_E}},$$

*Table 1.* Sample characteristics.

| Studies | *n* | Design | Participants | Quality scores |
|---|---|---|---|---|
| Dole et al., 1969, New York, USA (9) | 28 | RCT. Open study. 50-week trial. The control group consisted of patients on waiting list. 10-day MMT before release. | Mean age 32 years. 100% male. All subjects had abused heroin for at least 10 years and had five or more previous convictions. | 20 |
| Newman & Whitehill, 1979, Hong Kong, China (12) | 100 | RCT. Double blind. 156-week trial. The control group consisted of patients detoxified from methadone and thereafter transferred to placebo. | Age 22–58 years. 100% male. All subjects had been addicted to heroin for at least 4 years and with at least one previous treatment period. | 24 |
| Gunne & Grönbladh, 1981, Uppsala, Sweden (10) | 34 | RCT. Open study. 104-week trial. The control group consisted of non-treated patients. | Mean age 23 years. 65% male in the experimental group, 88% male in the control group. All subjects had abused heroin IV for at least 7 years and had completed three detoxifications. | 21 |
| Yancovitz et al., 1991, New York, USA (11) | 301 | RCT. 64-week trial. The control group consisted of patients with frequent contact on waiting list for MMT. | Mean age 35 years. 79% male. Mean 15 years of regular IV drug use. | 26 |
| Vanichseni et al., 1991, Bangkok, Thailand (17) | 240 | RCT. Open study. 6-week trial. The control group consisted of patients under gradual detoxification from methadone during 45 days. | 83% younger than 35 years. 100% male with at least six previous treatment episodes. | 24 |
| Strain et al., 1993a, 1993b, 1994, Baltimore, USA (13–15) | 95 (247) | RCT. Double blind. 26-week trial. Three-group trial: methadone 50 mg, 20 mg, and 0 mg/day, respectively. | Mean age 34 years. Male 70%. Mean 8 years of opioid use . 28% on parole or probation. | 26 |
| Sees et al., 2000, San Francisco, USA (16) | 179 | RCT. 26-week trial. The control group consisted of patients under gradual detoxification from methadone during 180 days. | Mean age 40 years. 59% male. Mean 17 years of heroin abuse. | 28 |
| Dolan et al., 2003, Sydney, Australia (18) | 382 | RCT. Prison-based MMT. 17-week trial. The control group consisted of patients on a waiting list. | Mean age 27 years. 100% male. Mean age at first injection 17 years. Five previous imprisonments. | 26 |

MMT, methadone maintenance treatment; IV, intravenous.



$$SE(\ln OR) = \sqrt{\frac{1}{x_C + 0.5} + \frac{1}{y_C + 0.5} + \frac{1}{x_E + 0.5} + \frac{1}{y_E + 0.5}}$$

and

$$SE(d) = \sigma = \sqrt{\frac{n_K + n_E}{n_K \times n_E} + \frac{(\ln OR / SE(\ln OR))^2}{2(n_K + n_E - 1)}},$$

according to Shadish & Haddock (22).

The different meta-analytical calculations were also tested for homogeneity with the Comprehensive Meta Analysis Software Program (20). A random effect model was used in all calculations. If heterogeneity was present ($P<0.05$), the different study designs were studied as moderators with a variance analysis (ANOVA) from the same statistical programme (20).

The material was also analysed using only studies with sufficient power. A medium effect-size of 0.50 needs at least 23 subjects in each group to achieve a power of 0.80 at a level of significance of 0.05 (24). The sample was also analysed for dichotomous outcomes only.

## Results

### *Included studies*

Of the eight studies that fulfilled the inclusion criteria and that were included in the analysis, four (6, 9, 11, 13–15) were published in the US, one (10) in Sweden, one (17) in Thailand, one (12) in China and one (18) in Australia, so four continents were represented. One study was published per decade in the 1960s (9), 1970s (12) and 1980s (10). Three studies (11, 13–15, 17) were published in the 1990s and two studies (16, 18) were published between 2000 and 2003 (Table 1).

### *Issues of extraction*

Data from extraction procedures are presented in Table 2. Some of the extracted data have to be commented upon. Retention: In Dole's study, MMT attendants were compared with controls that regularly reported to a probation officer (9). In the Yankovich paper on methadone vs. waiting list followed by MMT, the length of stay in MMT is used (11). Abuse: In the Vanichseni's study, 34/120 in the MMT group vs. 64/120 in the control group had only positive urines (17). In the study by Strain et al., the differences between the 50-mg and 0-mg groups on opioid positive urines were

*Table 2.* Outcome of methadone maintenance compared with randomized controlled studies with non-methadone controls in opioid dependence.

| Study | *n* | Weeks | Design | Outcome measures: Retention | Opioid abuse | Criminality | Others | |
|---|---|---|---|---|---|---|---|---|
| Dole et al., 1969 (9) | 28 (32) | 50 | 1) Methadone, 35 mg/day; 2) untreated control | 1) 9/12; 2) 1/16 | Subjective: 1) 0/12; 2) 15/15 | Reincarceration: 1) 3/12; 2) 15/16 | Employment or school: 1) 50%; 2) 0% | Amphetamine/cocaine: 1) 25%; 2) No data. Barbiturates: 1) 25%; 2) No data. Alcohol: 1) 25%; 2) No data |
| Newman & Whitehill, 1979 (12) | 100 | 156 | 1) Methadone, 97 mg/day; 2) placebo | 1) 28/50; 2) 1/50 | Persistent heroin use: 1) 5/22; 2) 31/49 | Conviction rate/100 man-months enrolment:* 1) 1.4; 2) 3.2 | Annual mortality rate: 1) 2%; 2) 0.7% | – |
| Gunne & Grönbladh, 1981 (10) | 34 | 104 | 1) Methadone (no dose reported); 2) untreated control | – | Drug free: 1) 12/17; 2) 1/17 | In prison after 2 years: 1) 0/17; 2) 2/17 | Annual mortality rate: 1) 0%; 2) 6% | Rehabilitated: 1) 76%; 2) 6% |
| Yancovitz et al., 1991 (11) | 301 | 64 | 1) Methadone, 80 mg/day; 2) untreated control | 1) 54/75; 2) 53/94 | Positive urines (1 month): 1) 22/75; 2) 56/94 | Jail: 1) 2/149; 2) 1/152 | Annual mortality rate: 1) 0%; 2) 1% | Cocaine positive urines: 1) 68%; 2) 70%. Methadone (non-prescribed): 1) 1%; 2) 39% |
| Vanichseni et al., 1991 (17) | 240 | 6 | 1) Methadone, 74 mg/day; 2) Methadone, 58 mg/day (gradual detoxification 45 days) | 1) 91/120; 2) 41/120 | Positive urines (all samples): 1) 34/120; 2) 64/120 | – | – | – |
| Strain et al., 1993a, 1993b, 1994 (13–15) | 95 (165), (247) | 26 | 1) Methadone, 50 mg/day; [2) Methadone, 20 mg/day)]; 3) Methadone, 0 mg/day | Week 20: 1) 44/84; [2) 34/82)]; 3) 17/81 | Number of positive urines/individuals†, $n=95$. During 20 weeks: 1) Significant, less than 3. | Legal status† (from ASI, composite score) $n=95$. Week 20: 1) 0.11; [2) 0.18)]; 3) 0.14 | WSC, 50 mg, $<0$ mg. BDI, No group differences. DAQ, no group differences | BZD positive urines, $n=247$, Week 20: No group differences. Cocaine positive urines, $n=247$, Week 20: 1) 53%; [2) 62%)]; 3) 67% |
| Sees et al., 2000 (16) | 179 | 26 | 1) Methadone 86 mg/day; 2) Methadone 85 mg/day (gradual detoxification 180 days) | 1) 86%; 2) 20%. Data extracted from graph | Heroin use:† 1) <2). Group × time, Significant differences | Legal status† (from ASI, composite score): 1) $0.05 \pm 0.13$; 2) $0.13 \pm 0.19$ | HIV risk behaviours. No group differences. Psychosocial functioning. No group differences | Cocaine use: No group differences. Alcohol use: No group differences |
| Dolan et al., 2003 (18) | 382 | 17 | 1) Methadone 60 mg/day; 2) untreated controls (waiting list) | – | Hair analysis month 4 $n=235$: 1) 27%; 2) 42%. Mean number of times heroin injected† $n=253$: 1) 1.3; 2) 8.5. t = 4.1 | – | Shared syringes, Follow-up, 4 months: 1) 20%; 2) 54% | HIV prevalence: Zero at both baseline and follow up. HCV incidence at follow up (for 32 treated and 35 controls HCV-negative at baseline): 1) 4/32; 2) 4/35 |

ASI, Addiction Severity Index; WSC, Withdrawal Symptom Checklist; BDI, Beck Depression Index; DAQ, Dose Adequacy Questionnaire; BZD, Benzodiazepines; HIV, Human Immunodeficiency Virus; HCV, Hepatitis C Virus.
*Not used in meta-analysis.
†Continuous variables for meta-analyses.
[ ] Data not used in calculations.

significant on the 5% level (13–15). Criminality: In the study by Strain et al. (13–15), the distribution of the mean ASI criminality composite score was approximated according to literature.

### *Types of outcome*

Our technique made it possible to include most of the available studies (seven of eight; references 9–17) in three separate meta-analyses. In all studies, opioid abuse was used as an outcome. Six of seven studies (9–16) evaluated retention and five of seven criminality. A total of 18 results—14 dichotomous and four continuous variables—were included in the meta-analysis. The outcome measures were sub-classified according to type of control group: gradual detoxification, placebo and untreated controls, respectively. Outcome measures for retention, opioid abuse and criminality are presented as meta-analyses in Figs. 1–3.

Other outcomes not analysed in the meta-analyses but mentioned in Table 2 were: mortality (three), employment or school (one), psychosocial functioning (one), rehabilitation (one), ASI (two), depressive symptoms (one), withdrawal symptoms (one), dose adequacy (one), shared syringes (one), HIV prevalence (one), HCV incidence (one), HIV-risk behaviour (one), methadone (non-prescribed) abuse (one), amphetamine/cocaine abuse (four), barbiturate abuse (one), benzodiazepine abuse (one), and alcohol abuse (two).

In the study by Strain et al. (13–15), the 20-mg/day methadone group was excluded from the analysis. Dolan et al. (18) present a study performed inside an Australian prison, where 382 opioid-dependent prisoners were randomized either to a prison-based MMT or to a waiting list. The study is presented separately.

### *Meta-analyses*

The results of the meta-analyses for retention, opioid abuse and criminality are presented in Figs. 1–3. The combined analyses, expressed in standard mean differences ($d$), were all significant: $d=0.90$, $d=0.61$ and $d=0.35$, respectively. Test for heterogeneity was significant for all three analyses, but in the subgroups, three of seven analyses were homogeneous.

Type of study design was a significant moderator in five of nine comparisons.

All three comparisons were significant for retention, detoxification vs. untreated controls for abuse, and detoxification vs. untreated controls for criminality.

In the study by Dolan et al. (18) with incarcerated opioid-dependent subjects, objective and subjective measures of opioid use were significantly reduced in the methadone group compared with waiting list controls—$d=0.30$ (CI 95% 0.04–0.56), and $d=0.53$ (CI 95% 0.27–0.79), respectively. This study is excluded from the meta-analysis because of its special population and setting.

Gunne & Grönbladh (10) reported an annual mortality rate of 6% in the control group, while Newman & Whitehill (12) and Yancovitz et al. (11) reported annual mortality rates of 0.7% and 1% respectively. We regarded

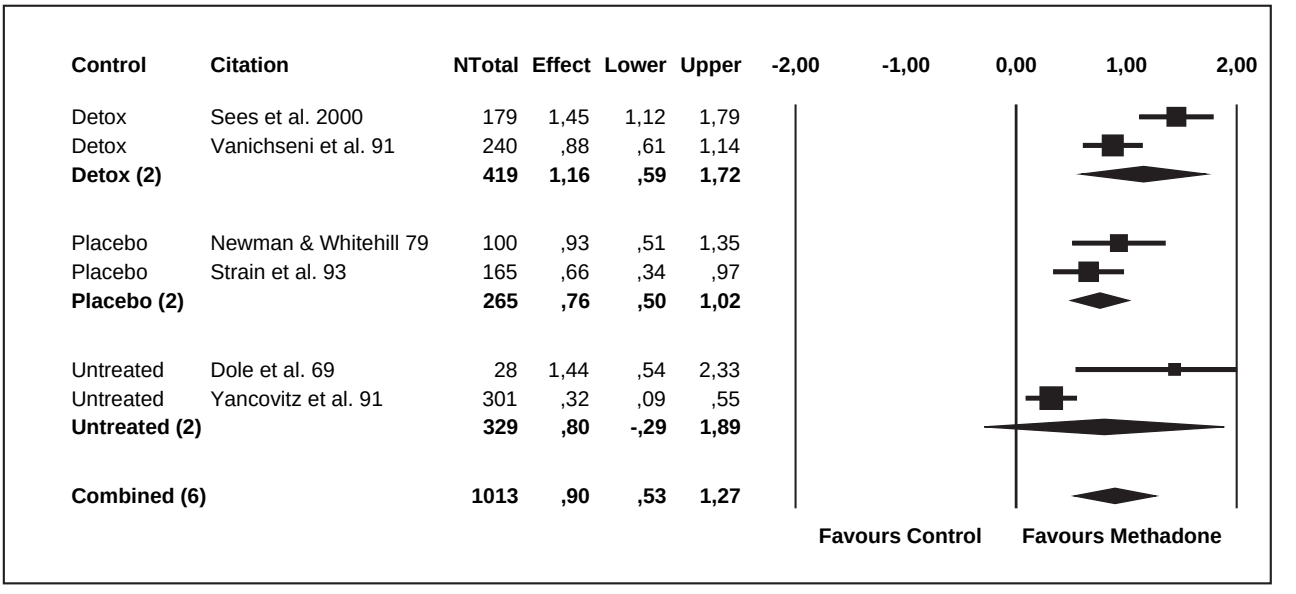


*Fig. 1.* Standardized mean differences and 95% confidence intervals. Methadone vs. non-active control related to different study design. Outcome measure: retention. Test of heterogeneity—detoxification: $Q=7.1$, df $=1$, $P=0.01$, placebo: $Q=1.1$, df $=1$, $P=0.30$, untreated: $Q=6.2$, df $=1$, $P=0.01$, combined: $Q=35.6$, df $=5$, $P=0.01$. ANOVA analyses—detoxification vs. placebo: $Q=4.4$, df $=1.0$, $P=0.04$, detoxification vs. untreated: $Q=21.3$, df $=1.0$, $P=0.01$, placebo vs. untreated: $Q=4.6$, df $=1.0$, $P=0.03$.

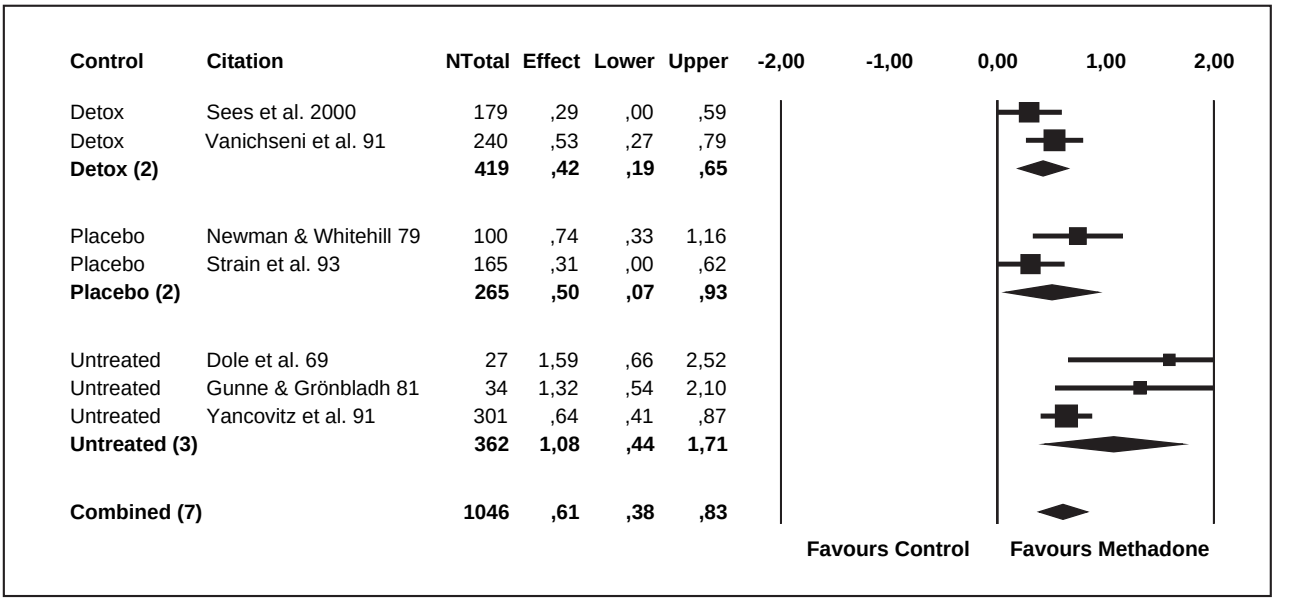


*Fig. 2*. Standardized mean differences and 95% confidence intervals. Methadone vs. non-active control related to different study design. Outcome measure: abuse. Test of heterogeneity—detoxification: $Q=1.4$, df $=1$, $P=0.24$, placebo: $Q=2.9$, df $=1$, $P=0.09$, untreated: $Q=6.5$, df $=2$, $P=0.04$, combined: $Q=16.1$, df $=6$, $P=0.01$. ANOVA analyses—detoxification vs. placebo $Q=0.1$, df $=1.0$, $P=0.81$, detoxification vs. untreated $Q=4.8$, df $=1.0$, $P=0.03$, placebo vs. untreated $Q=2.9$, df $=1.0$, $P=0.09$.

the differences between the mortality rates as being too large to enable a formal meta-analysis.

### *Analysis of adequately powered studies only*

The studies of Dole et al. (9) and Gunne & Grönbladh (10) were excluded because of low power. The findings of the analysis of the remaining studies were similar to our main results.

### *Analysis of dichotomous outcome variables only*

When only dichotomous outcome variables were used, similar results were found as in the complete analysis.

## Discussion

### *Main results*

The main results of this paper are that methadone increases retention in treatment and reduces opioid

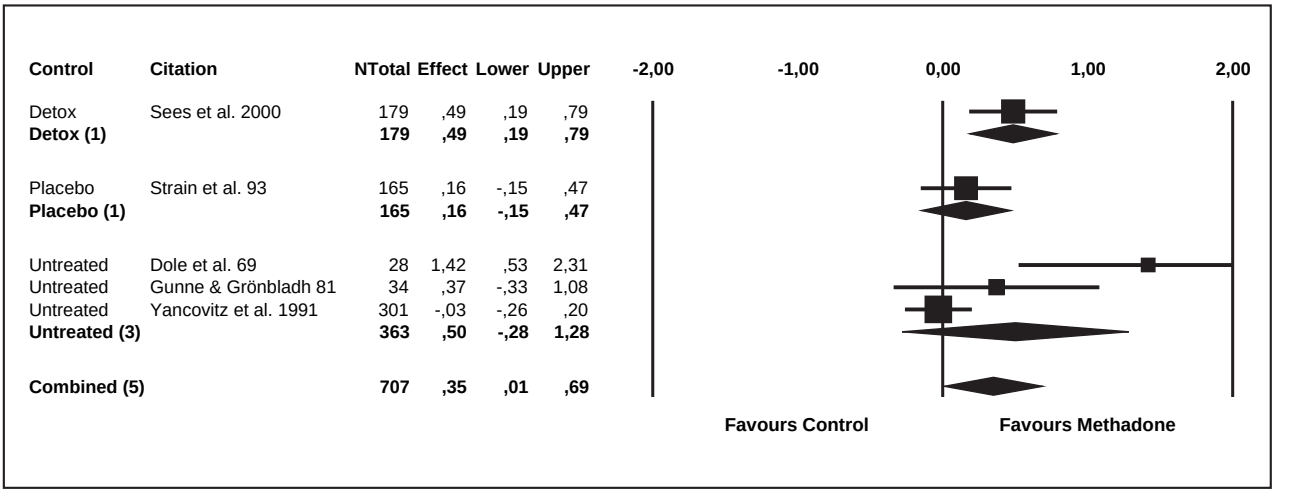


*Fig. 3*. Standardized mean differences and 95% confidence intervals. Methadone vs. non-active control related to different study design. Outcome measure: criminality. Test of heterogeneity—untreated: $Q=11.1$, df $=2.0$, $P=0.003$, combined: $Q=18.8$, df $=4.0$, $P=0.001$. ANOVA analyses—detoxification vs. placebo $Q=2.2$, df $=1.0$, $P=0.14$, detoxification vs. untreated $Q=4.5$, df $=1.0$, $P=0.03$, placebo vs. untreated $Q=0.13$, df $=1.0$, $P=0.73$.

abuse and criminality compared with controlled conditions in outpatients, and reduces opioid abuse in prisoners. The type of design had influence on the effect sizes. The results are generally comparable with previous meta-analyses (2) even if the techniques were different.

### *Dichotomous vs. continuous variables*

The transformation of dichotomous variables into the standard mean effect (*d*) has been criticized by Poikolainen (23), who also argued that continuous variables tend to yield higher d-values than dichotomous ones. However, the meta-analysis by Moyer et al. (24) successfully used a similar approach to ours and thereby managed to include a larger proportion of studies than in previous meta-analyses (25). In the present meta-analysis, continuous outcomes were reported in two studies (13–16) with four separate results. Their d-values are at the same magnitude as the *d*-values from the dichotomous variables and so did not support the arguments of Poikolainen (23).

### *Small study biases*

The inclusion of studies with a small number of subjects could influence the power of the meta-analysis (24). In our analysis, we have corrected for the influence of small sample sizes using the Hedges correction (19), both for the independent studies and in the meta-analysis, indicating a conservative approach. Separate analysis without underpowered studies (9, 10) and continuous variables did not change the main results.

### *Similarities and differences compared with Mattick et al. (2)*

One difference between the present study and that of Mattick et al. (2) was that we included two more studies: Sees et al. (16) and Dolan et al. (18). We transformed both dichotomous and continuous variables into a common effect measure (*d*), while Mattick and collaborators (2) included dichotomous variables only. With this approach we could include two more results compared with Mattick et al. (2), criminality from Strain et al. (13–15) and from Sees et al. (16). We also made a moderator analysis using the type of study design as moderator, which explained some of the heterogeneity (Figs. 1–3). We did not perform a meta-analysis on mortality because mortality rates in the control groups differed more than five-fold between the different studies. Mattick et al. (2) reported homogeneity in four of five meta-analyses. The difference between their meta-analysis and ours was that they used fewer studies and thus had less power to discover heterogeneity. There were also a few differences on extractions that however did not influence on the main result.

## Conclusion

MMT in opioid dependence shows robust effects for retention, opioid abuse and criminality compared with non-active controlled conditions. In one study, MMT reduced abuse of illegal opioids in prison.

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Björn Axel Johansson, M.D., Ph.D., B.Sc., Clinical Alcohol Research, Malmö University Hospital, Lund University, Lund, Sweden.
Mats Berglund, M.D., Ph.D., Clinical Alcohol Research, Malmö University Hospital, Lund University, Lund, Sweden.
Anna Lindgren, Ph.D., Department of Mathematical Statistics, Centre for Mathematical Sciences, Lund University, Lund, Sweden.