Full title: **Men and women respond differently to methadone treatment for opioid use disorder: a systematic review and meta-analysis**

Running title: **Sex differences in methadone treatment outcomes**

Authors and affiliations:

Monica Bawor;[1,2] Brittany B. Dennis;[2,3] Anuja Bhalerao;[4] Carolyn Plater;[5] Andrew Worster;[5,6] Michael Varenbut;[5] Jeff Daiter;[5] David C. Marsh;[6,7] Dipika Desai;[2] Meir Steiner;[8,9] Rebecca Anglin;[6,8] Guillaume Pare;[2,3] Lehana Thabane;[3,10] Zainab Samaan;[*3,8]

[1]MiNDS Neuroscience Graduate Program, McMaster University, Hamilton, ON

[2]Population Genomics Program, Chanchlani Research Centre, McMaster University, Hamilton, ON

[3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON

[4]Bachelor of Health Sciences Undergraduate Program, McMaster University, Hamilton, ON

[5]Ontario Addiction Treatment Centres, Ontario, Canada

[6]Department of Medicine, McMaster University, Hamilton, ON

[7]Northern Ontario School of Medicine, Sudbury, ON

[8]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON

[9]Women's Health Concerns Clinic, St. Joseph's Healthcare Hamilton, Hamilton, ON

[10]Biostatistics Unit, Centre for Evaluation of Medicine, Hamilton, ON

[*]**Corresponding Author**

Dr. Zainab Samaan, MBChB, DMMD, MSc, MRCPsych, PhD

Mood Disorders Program, St. Joseph's Healthcare, 100 West 5th Street

Hamilton, Ontario, Canada. L8N 3K7.

Tel: 905-522-1155 ext. 36372

Email: samaanz@mcmaster.ca

Declarations of interest: This work was supported by CIHR Drug Safety and Effectiveness Network (DSEN) grant (Grant number: 126639) from Ottawa, Canada and by The Chanchlani Research Centre, McMaster University in Hamilton, Canada. The funding sources have no role in the study design or reporting of the results. All authors report no conflict of interest, financial or otherwise.

ABSTRACT

Background: Opioid use disorder is a serious international concern with limited treatment success. Men and women significantly differ in their susceptibility to opioid use disorder and response to treatment and can therefore benefit from sex-specific treatment strategies. We aimed to systematically review the literature on treatment outcomes of opioid use disorder in men and women with respect to drug use behavior, health-related outcomes, and social functioning.

Methods: We searched PubMed/MEDLINE, EMBASE, PsycINFO, and CINAHL for relevant articles. Studies with human populations undergoing methadone treatment for opioid use disorder and specifically investigating sex differences were included. The systematic review protocol has been published previously.

Results: Twenty studies with 9732 participants fulfilled the review inclusion criteria, of which 18 studies were observational and 2 studies were randomized controlled trials. Results showed significant differences between men and women in alcohol use (odds ratio [OR]: 0.52; 95% confidence interval [CI]: 0.31, 0.86; p=0.01), amphetamine use (OR: 1.47; 95% CI: 1.12, 1.94; p=0.006), legal involvement (OR: 0.63; 95% CI: 0.47, 0.84; p=0.002), and employment during treatment (OR: 0.39; 95% CI: 0.21, 0.73; p=0.003). Despite these findings, the risk of bias assessment of included studies was moderate-to-high and quality of evidence was generally low.

Interpretation: Sex differences are evident in polysubstance use, legal involvement, and employment outcomes of methadone treatment for opioid use disorder. Although the quality of evidence is low, it does provide support for the development of sex-specific guidelines for effective treatment of opioid use disorder with methadone.

Systematic Review Registration: PROSPERO CRD42013006549

INTRODUCTION

Canadians are the second highest opioid analgesic consumers in the world, second only to the USA [1]. In 2012, The Canadian Medical Association Journal published a report showing that 200,000 people on average use prescription opioids regularly in Canada [2], which are increasingly becoming the most commonly used drugs of abuse [3]. Opioid prescription patterns have seen a surge of 150% over the last decade [4]. As a result, there has been an increase in the number of hospital admissions and deaths due to opioid use and overdose [5]. In addition to the collective healthcare costs, each individual untreated opioid addiction case also has a social cost of $45,000 CAN per person per year [6], a major economic cost to society.

Efforts in reducing opioid abuse have been implemented, but have yielded minimal benefit. The introduction of sustained-release Oxycontin, which has since been replaced by OxyNEO, was an attempt to minimize abuse of oxycodone products, however despite its extended-release properties, these efforts were unsuccessful in reducing opioid abuse [7]. Later, a 2012 report issued by the Ontario Public Drug Program announced that Oxycontin and OxyNEO would only be covered in special circumstances by the Ontario Drug Benefit (ODB) program in an attempt to limit its availability and eventually opioid abuse and dependence, however such efforts are yet to prove effective.

This national epidemic of excess opioid prescription for pain conditions can also be attributed to the lack of formal training and education when it comes to dealing with chronic pain and addiction [8-10]. In an effort to better manage opioid-prescribing by physicians, the National Opioid Use Guideline Group (NOUGG) developed a set of guidelines for the treatment of chronic non-cancer pain published in 2010 [11]. Although they are comprehensive, there is insufficient data to determine whether these guidelines have helped reduce the rates of opioid

prescriptions and whether there has been a consequential decrease in prescription opioid abuse and dependence.

Currently there are approximately 35,000 patients receiving substitute opioid therapy with methadone at registered addiction treatment centers in Ontario [12]. Several maintenance and detoxification treatment programs are available, including the use of methadone, buprenorphine, and naltrexone, with varying rates of outcomes in treating opioid use disorder.

Methadone is the most commonly prescribed treatment for opioid use disorder that has been available since the 1940s [13]. The literature on methadone maintenance treatment (MMT) reports effectiveness rates of 20-70% [14-17]. Treatment response in opioid use disorder is difficult to define and has been broadly described in the literature, making clinical interpretation of these studies challenging. There are no agreed criteria that characterize a treatment as a success or failure; therefore there is no accurate way to know whether treatment is working or if the healthcare resources invested in treatment are producing any benefit.

There is evidence, however, indicating that methadone treatment demonstrates a high inter-individual variability in treatment response [18], indicating that patients may have different treatment needs. Men and women especially are known to differ in multiple aspects of addiction susceptibility and behaviour including first opioid use, progression to regular use, and treatment entry [19-21]. It is also likely that men and women differ in MMT outcomes. However, these differences are not clearly described in the literature. Hence, if there are significant sex differences in treatment response, current treatment standards that offer the same clinical management of opioid use disorder for men and women may not be able to achieve optimum treatment outcomes for both sexes.

It is evident that there is a steady rise in the number of opioid users and a lack of guidelines on the sex-specific management of opioid use disorder. Here, we provide a review that summarizes the evidence on sex differences in methadone treatment outcomes. Our aim is to identify possible sex-specific patient needs that can be addressed with an individualized treatment strategy to produce better treatment outcomes, higher treatment efficacy, and lower risk of adverse events.

Study objectives

This review aims to systematically summarize the literature on sex differences in methadone treatment outcomes. We aim to:

1. Examine the differences between men and women in methadone treatment outcomes related to drug use behavior, health status, and social functioning;
2. When possible, aggregate the statistical findings in a meta-analysis to arrive at a summary estimate;
3. Critically evaluate the literature and highlight areas for future research opportunities.

METHODS

This review has been registered with PROSPERO (ID: CRD42013006549) and the detailed methods of this review have been previously reported in a protocol [22]. Briefly, the review included observational studies and randomized controlled trials (RCTs) that focused on sex differences in patients undergoing methadone treatment for opioid use disorder. We searched PubMed/MEDLINE, EMBASE, PsycINFO, and CINAHL databases from inception to August 11, 2014 for relevant articles. The search was limited to human adult populations. Two authors (MB and AB) independently reviewed articles at each stage of the screening process and any

disagreements were resolved by consensus or by including a third author (ZS). We extracted data in duplicate using a pilot-tested data extraction form. We assessed risk of bias using an adapted version of the Newcastle-Ottawa Scale (NOS) [23] for observational studies and the Cochrane Collaboration's tool for RCTs [24]. We used a random effects model for the summary estimate, assuming heterogeneity between studies. We used a pooled odds ratio (OR) for dichotomous outcomes and mean difference was used for continuous outcomes. We performed analyses using Review Manager 5.1 and present summary measures with corresponding 95% confidence intervals (CI) and p-values. This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (refer to Fig. S1 for completed PRISMA checklist) [25].

RESULTS

Study selection

We included 20 studies with 9732 participants in the review (see Fig. 1 for flow diagram of systematic search). The strength of agreement between the two independent raters was high for title (Kappa: 0.823; 95% CI: 0.736, 0.910), abstract (Kappa: 0.898; 95% CI: 0.760, 1.000), and full-text (Kappa: 0.834; 95% CI: 0.615, 1.000) screens.

Study characteristics

Studies included were cohort studies (n=18) and RCTs (n=2). Studies were conducted in the USA (n=16), Israel (n=2), Spain (n=1), and Sweden (n=1). The sample size for each study varied from 53 to 2683 participants, and all studies reported a greater percentage of male participants. Ethnicity among study samples varied greatly; Caucasian/White, African-American/Black, and

Mexican-American/Latino were the most frequently reported ethnicities. Detailed characteristics of included studies are presented in Table 1.

Risk of bias assessment

Using the NOS for risk of bias assessment of observational studies, we evaluated selection bias, performance bias, detection bias, and information bias for 18 studies. We used the Cochrane Collaborations' tool to assess the risk of bias among two RCTs [26, 27]. Generally, the risk of bias was moderate-to-high for observational studies (Table 2) and low for RCTs (Table 3).

Sex differences in MMT outcomes

We tested the differences between men and women for outcomes related to drug use behavior, health status, and social functioning while in methadone treatment for opioid addiction.

1. ***Drug use***

Polysubstance use

In total, 11 studies looked at polysubstance use during treatment between men and women. We performed a separate meta-analysis for each substance reported, including alcohol, amphetamines, benzodiazepines, cannabis, and cocaine.

Of the seven studies examining alcohol use during methadone treatment, three were included in a meta-analysis [28-30] of 809 men and 701 women. The pooled results demonstrate that the odds of self-reporting alcohol use while on methadone treatment were significantly lower among women compared to men (OR: 0.52, CI: 0.31, 0.86, p=0.01) (Table 4). Heterogeneity was significant among these studies (I^2=77%; p=0.01) (Fig. 2).

Two studies [31, 32] evaluating amphetamine use through urine toxicology were combined in a meta-analysis of 2691 men and 462 women. The odds of amphetamine use while on methadone treatment were significantly greater among women compared to men (OR: 1.47; 95% CI: 1.12, 1.94; p=0.006) (Fig. 3). No significant differences were seen between men and women in the use of other substances (see Figs. S2-S5 in Supplementary Material for respective forest plots of opioid, cannabis, cocaine, and benzodiazepine use), methadone maintenance dose at 6-12 months in treatment (Fig. S6), or treatment retention (Fig. S7).

2. Health status

As per the protocol [22], we had planned to analyze health outcomes including methadone related adverse events, current health status, and psychological status. Data on health and psychological status varied significantly in design and outcome definitions, therefore these outcomes were unsuitable for a meta-analysis. Also, adverse events were not assessed in any of the included studies and a meta-analysis was not possible.

3. Social functioning

Legal involvement

Six studies assessed sex differences in legal involvement and criminal behavior, two of which were suitable for a meta-analysis (674 men and 592 women) [28, 29]. Women were less likely to report arrests or legal supervision (including probation or parole) during treatment compared to men (OR: 0.63; 95% CI: 0.47, 0.84; p=0.002) (Table 4; Fig. 4).

Employment

Of the eight studies assessing employment status, five were suitable for pooling in a meta-analysis [28-30, 33, 34]. Women (n=1030) were less likely to be employed compared to men (n=1291) (OR: 0.39; 95% CI: 0.21, 0.73; p=0.003) (Table 4; Fig. 5).

No significant sex differences were found in marital status (married or common-law) between men (n=1100) and women (n=878) during methadone treatment, as seen in a meta-analysis pooling results from four studies [28-30, 33] (Table 4; Fig. S8). Studies measuring sexual risk behavior had highly variable outcome definitions thereby precluding determination of whether sex differences were present for this outcome using a meta-analysis.

4. Long-term prognosis

Of the included studies, six assessed outcomes of long-term treatment prognosis. Specific cohorts of methadone patients were followed longitudinally or identified retrospectively with follow-up time periods ranging from 1-25 years after treatment completion. Many of these studies reported data on several treatment-related outcomes including illicit opioid use (n=5), legal involvement (n=2), employment (n=2), and mortality (n=3). Due to the large differences in follow-up time points, a meta-analysis for the above outcomes was not suitable, however we provide a brief summary of findings.

Illicit opioid use

Jimenez-Trevino et al. [35] investigated sex differences in an aging cohort of past methadone patients. They found that 25 years after treatment completion, the percentage of men using heroin was significantly greater than that of women (32.5% vs. 0%; p=0.038). The remaining four studies report no significant sex differences in illicit opioid use when measured as the percentage of participants reporting any or daily opioid use within the four weeks prior to follow-up [28], in the previous year prior to follow-up [34, 36], or when measured using urine toxicology at one year of follow-up [37].

Legal involvement

Both Marsh & Simpson [37] and Savage & Simpson [36] studied sex differences in criminal behavior or legal involvement at one year after discharge from methadone treatment. Marsh & Simpson found that the percentage of participants reporting lifetime arrests or incarceration at follow-up was significantly greater among men (30% vs. 12%; $p<0.05$) [37]. Similarly, Savage & Simpson found that a greater percentage of men reported ever being in jail over three days on legal charges during the first year after treatment compared to women (27 vs. 15%; $p<0.05$) [36].

Employment

Employment status was assessed at one year follow-up by Marsh & Simpson [37] and Savage & Simpson [36]. The percentage of men reporting greater than six months of employment at one year after treatment discharge was significantly greater than that of women (51% vs. 31%; $p<0.05$) [37]. A significantly greater percentage of men also reported any employment of one month or more during the first year after treatment compared to women (68% vs. 41%; $p<0.05$) [36].

Mortality

Two of the three studies assessing mortality [38, 39] examined death rates at one year of follow-up. Pooled results demonstrate that the number of deaths at one year after treatment did not differ significantly between men (n=581) and women (n=353) (Table 4; Fig. S9). Additionally, the third study by Jimenez-Trevino that followed an aging cohort of past methadone patients for 25 years also found no significant difference in mortality rates between men and women at 25 year follow-up [35].

DISCUSSION

Since methadone treatment was introduced to North America in the late 1940s, its services have generally been geared towards men. The question of sex differences in methadone treatment became of interest in the 1980s, as evidenced by the multiple studies published in the following 20 years. However since then, research in this area has remained relatively stagnant. The number of treatment-seeking women opioid users is growing dramatically; it is believed that this growth is in response to the increased rates of opioid prescriptions, which make opioids more accessible and easier to abuse. This surge has not only raised concerns regarding treatment services for men and women, it has also brought to our attention the possibility that men and women differ in many aspects of the addiction profile and will therefore benefit from treatment that accommodates these differences.

Summary of evidence

In this review, we have aimed to gather the existing literature on sex differences in methadone maintenance treatment outcomes in an effort to understand the factors that influence treatment for men and women individually. Through an extensive investigation of the literature, we were able to perform a systematic review and meta-analysis to achieve a comprehensive overview of past and current literature in this field. To our knowledge, a review on sex differences combining this number of outcomes in methadone treatment has never been completed, therefore we believe that this review will provide the necessary evidence to guide future treatment strategies and clinical guidelines.

Our review combined results from 20 studies that assessed a number of outcomes and we were able to determine the treatment-related factors that vary significantly between men and women to be polysubstance use, legal involvement, and employment. Women were less likely than men to use alcohol, report arrests or legal supervision, and be employed during treatment.

However, women were more likely to use amphetamines during treatment compared to men (see Fig. 6 for a visual representation of these sex differences).

Implications

This review has highlighted how men and women differ in their response to methadone treatment by incorporating an extensive list of outcomes used to describe treatment response. This information can be used to develop a comprehensive sex-specific and patient-centered service model that integrates medical care, other substance use treatment programs, counseling, mental health services, and employment needs. The current Methadone Maintenance Treatment Program Standards and Clinical Guidelines [40] place emphasis on treating concurrent mental and physical disorders through regular assessments and screening conducted by a primary care physician, however, specific strategies are not outlined. Additionally, recommendations for treating alcohol dependence among MMT patients are vaguely described. The guidelines also make no mention of employment services or strategies for reducing criminal activity during treatment. It has already been established that improvements in medical care and mental health services, as well as lower rates of polysubstance use, reductions in criminal activity, and employment services utilization are associated with better treatment outcomes [41]. With information provided by this review, we have been able to define specific patient needs for men and women and treatments can be specifically tailored to target these areas (Table 5).

Data from this review can be used to inform patients, healthcare providers, and health policy makers, all of which can work together to develop individualized sex-specific treatment strategies. These findings can be developed into a set of guidelines and disseminated to healthcare professionals so that they can incorporate this information into their daily practice. This will also be a useful opportunity to update the current best practice guidelines for

methadone treatment, as they do not adequately reflect the current population and are not based on rigorous methodological evidence.

Quality of evidence

In order to ascertain our confidence in these findings, we performed an assessment of risk of bias and overall quality of evidence. We found that the majority of these studies were at a moderate-to-high risk for bias, most often due to small or unrepresentative sample sizes, failure to adjust for confounders, and lack of objective outcome assessment. The overall quality of evidence was very low-to-moderate, which is most likely due to the observational nature of the included studies, as they are inherently prone to bias, but also to the differences in outcome measurement between studies, allowing for a high level of variation and heterogeneity in some cases.

Due to the fact that some studies were performed over three decades ago, the standards for scientific methodology were different compared to the methods used in research today. In many cases, potential confounding variables were not controlled for in the analyses, which may have otherwise changed the significance of the observed associations. For example, methadone dose is likely to be associated with Body Mass Index (BMI), which is known to be typically higher among men, however the studies assessing differences in methadone dose between men and women (Camacho et al. [42] and Peles & Adelson [31]) failed to adjust their analyses with this variable. Additionally, the nature of observational studies, especially in the field of psychiatry, causes most assessments to rely heavily on self-reported data that can be highly subjective. Patients with addiction may have difficulty recalling their patterns of drug use, potentially introducing recall bias into the analyses, or may withhold information by choice. Although it can be difficult to obtain objective measurements of the outcomes of interest, the credibility of this data is still brought into question.

Many of the meta-analysis findings had high levels of heterogeneity, and this is most probably due to the difference in durations of outcome measurement among studies. Studies measured specific outcomes at different points throughout treatment, including within the first month in treatment, six months in treatment, or one year in treatment. It is expected that outcomes will be more accurate with increasing time in treatment. For example, Peles & Adelson [31] measured cocaine use within one month of admission and they found that women were more likely to use cocaine during treatment. In comparison, Schilling et al. [30] measured cocaine use within the previous six months of treatment using aggregated urine screens; their results indicated that women were less likely to use cocaine during treatment. These two opposing studies rendered the association between men and women insignificant when in fact, the latter study may be a more accurate representation of the true effect.

There is a also a large variation in years of publication of these studies; the majority of studies were conducted several decades ago and when combined with more current studies, this may yield variability in results due to different outcome definitions and measurements or perhaps due to the changing demographic of this population.

Limitations

The main issue with the current literature on methadone treatment outcomes is that there is no common definition or measurement for treatment response. Treatment response can be defined objectively as relapse measured through urine toxicology or as retention in treatment, however these are not standardized definitions. Furthermore, what constitutes good or poor treatment response has not been defined and remains unclear. We included a comprehensive list of outcomes that depict response to treatment in an effort to acquire an overarching description of response.

The number of studies in this area of research is minimal thereby precluding large meta-analyses. As well, the differences in outcome measurements made it impossible to combine all studies and several studies were not included in the meta-analyses [35-37, 43-47]. As a result, each of the individual meta-analyses per outcome in this review contained, at most, five studies, thus making the summary statistic limited and should be interpreted with caution. With the addition of one study, the associations may lose significance or change direction in some cases, or vice versa, therefore the results should be interpreted cautiously.

It is also possible that the differences seen between men and women in this review may actually be a representation of the general population, not specific to methadone patients. For instance, the association between men and criminal behavior (including arrests, incarcerations, probation, and parole) is seen among the general population of men [48] and, therefore, may not be directly attributed to methadone treatment. Nonetheless, this remains an important factor when considering treatment options for men who may be at risk of legal difficulty and termination of treatment prematurely and, therefore, a shorter treatment regimen may be a more feasible option for men with legal challenges.

Future directions

Most importantly, an improvement to the quality of studies' methodology and reporting standards following the appropriate guidelines of CONSORT or one of its extensions in the field of addiction literature are essential. It would also be highly beneficial for studies on addiction to incorporate the concept of the minimum core dataset. This is a standard list of variables that must be extracted at a minimum and reported in every study in a specified field of research in order to be publishable; such factors include age, sex, ethnicity, drug dose, and objective measurements, etc. This would enhance the quality of data and minimize heterogeneity when attempting to

combine the results in meta-analyses thereby reducing heterogeneity and increasing our confidence in the estimates and overall generalizability of the review results.

Conclusions

Based on the current review results, we concluded that sex differences in methadone treatment outcomes exist and should be taken into consideration in the management of opioid use disorders. Although the variation in methodological quality, outcome measurements, and sample sizes poses methodological challenges, the patterns demonstrated in this review can provide useful guidance for sex-specific treatment strategies. It is our hope that these findings can be helpful in improving both the treatment for patients with opioid use disorder and the overall field of research in opioid addiction.

REFERENCES

1. INCB: **Estimated world requirements for 2012 - statistics for 2010. Statistical information on narcotic drugs data.** In. New York, USA: United Nations; 2011.
2. Webster PC: **Medically induced opioid addiction reaching alarming levels**. In: *Cmaj. Volume 184*, edn. Canada; 2012: 285-286.
3. Fischer B, Rehm J, Goldman B, Popova S: **Non-medical use of prescription opioids and public health in Canada: an urgent call for research and interventions development**. *Can J Public Health* 2008, **99**(3):182-184.
4. Manchikanti L, Helm S, 2nd, Fellows B, Janata JW, Pampati V, Grider JS, Boswell MV: **Opioid epidemic in the United States**. *Pain Physician* 2012, **15**(3 Suppl):ES9-38.
5. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2012. New York, NY; 2010 [cited 2014 July 29]. Available from: http://www.unodc.org/unodc/en/data-and-analysis/WDR-2010.html.
6. Wall R, Rehm J, Fischer B, Brands B, Gliksman L, Stewart J, Medved W, Blake J: **Social costs of untreated opioid dependence**. *J Urban Health* 2000, **77**(4):688-722.
7. Rischitelli DG, Karbowicz SH: **Safety and efficacy of controlled-release oxycodone: a systematic literature review**. *Pharmacotherapy* 2002, **22**(7):898-904.
8. Mezei L, Murinson BB: **Pain education in North American medical schools**. *J Pain* 2011, **12**(12):1199-1208.
9. Drayer RA, Henderson J, Reidenberg M: **Barriers to better pain control in hospitalized patients**. *Journal of Pain and Symptom Management* 1999, **17**(6):434-440.
10. Isaacson JH, Fleming M, Kraus M, Kahn R, Mundt M: **A national survey of training in substance use disorders in residency programs**. *J Stud Alcohol* 2000, **61**(6):912-915.
11. National Opioid Use Guideline Group (NOUGG). Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. Canada; 2010 [cited 2014 August 14].
12. Centre for Addiction and Mental Health (CAMH). Mentla Health and Addiction Information: Methadone. Toronto, ON; 2010 [cited 2014 July 29]. Available from: http://www.camh.ca/en/hospital/health_information/a_z_mental_health_and_addiction_information/methadone/Pages/methadone.aspx
13. Fischer B: **Prescriptions, power and politics: the turbulent history of methadone maintenance in Canada**. *J Public Health Policy* 2000, **21**(2):187-210.
14. Dutta R, Roy S: **Mechanism(s) involved in opioid drug abuse modulation of HAND**. *Curr HIV Res* 2012, **10**(5):469-477.
15. Eap CB, Buclin T, Baumann P: **Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence**. *Clin Pharmacokinet* 2002, **41**(14):1153-1193.
16. Mattick RP, Breen C, Kimber J, Davoli M: **Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence**. *Cochrane Database Syst Rev* 2009(3):CD002209.
17. Oviedo-Joekes E, Guh D, Brissette S, Marchand K, Marsh D, Chettiar J, Nosyk B, Krausz M, Anis A, Schechter MT: **Effectiveness of diacetylmorphine versus methadone for the treatment of opioid dependence in women**. *Drug & Alcohol Dependence* 2010, **111**(1-2):50-57.

18. Li Y, Kantelip JP, Gerritsen-van Schieveen P, Davani S: **Interindividual variability of methadone response: impact of genetic polymorphism**. *Mol Diagn Ther* 2008, **12**(2):109-124.
19. Anglin MD, Hser YI, McGlothlin WH: **Sex differences in addict careers. 2. Becoming addicted**. *Am J Drug Alcohol Abuse* 1987, **13**(1-2):59-71.
20. Hser YI, Anglin MD, McGlothlin W: **Sex differences in addict careers. 1. Initiation of use**. *Am J Drug Alcohol Abuse* 1987, **13**(1-2):33-57.
21. Hser YI, Anglin MD, Booth MW: **Sex differences in addict careers. 3. Addiction**. *Am J Drug Alcohol Abuse* 1987, **13**(3):231-251.
22. Bawor M, Dennis BB, Anglin R, Steiner M, Thabane L, Samaan Z: **Sex differences in outcomes of methadone maintenance treatment for opioid addiction: a systematic review protocol**. *Systematic Reviews* 2014, **3**(1):45.
23. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, Tugwell P: **The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses**. In.; 2000.
24. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA: **The Cochrane Collaboration's tool for assessing risk of bias in randomised trials**. *Bmj* 2011, **343**:d5928.
25. Moher D, Liberati A, Tetzlaff J, Altman DG: **Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement**. *PLoS Med* 2009, **6**(7):e1000097.
26. Jones HE, Fitzgerald H, Johnson RE: **Males and females differ in response to opioid agonist medications**. *American Journal on Addictions* 2005, **14**(3):223-233.
27. Schottenfeld RS, Pakes JR, Kosten TR: **Prognostic factors in Buprenorphine- versus methadone-maintained patients**. *Journal of Nervous & Mental Disease* 1998, **186**(1):35-43.
28. Anglin MD, Hser Y-I, Booth MW: **Sex Differences in Addict Careers. 4. Treatment**. *The American Journal of Drug and Alcohol Abuse* 1987, **13**(3):253-280.
29. Hser YI, Anglin MD, Liu Y: **A survival analysis of gender and ethnic differences in responsiveness to methadone maintenance treatment**. *Int J Addict* 1990, **25**(11a):1295-1315.
30. Schilling RF, el-Bassel N, Schinke SP, Nichols S, Botvin GJ, Orlandi MA: **Sexual behavior, attitudes toward safer sex, and gender among a cohort of 244 recovering i.v. drug users**. *Int J Addict* 1991, **26**(8):859-877.
31. Peles E, Adelson M: **Gender differences and pregnant women in a methadone maintenance treatment (MMT) clinic**. *Journal of Addictive Diseases* 2006, **25**(2):39-45.
32. Schiff M, Levit S, Moreno RC: **Retention and illicit drug use among methadone patients in Israel: a gender comparison**. In: *Addict Behav. Volume 32*, edn. England; 2007: 2108-2119.
33. Brown LS, Jr., Alterman AI, Rutherford MJ, Cacciola JS, Zaballero AR: **Addiction Severity Index scores of four racial/ethnic and gender groups of methadone maintenance patients**. *J Subst Abuse* 1993, **5**(3):269-279.
34. Grella CE, Lovinger K: **Gender differences in physical and mental health outcomes among an aging cohort of individuals with a history of heroin dependence**. *Addictive Behaviors* 2012, **37**(3):306-312.

35. Jimenez-Trevino L, Saiz PA, Garcia-Portilla MP, Diaz-Mesa EM, Sanchez-Lasheras F, Buron P, Casares MJ, Marina P, Gutierrez E, Bobes J: **A 25-year follow-up of patients admitted to methadone treatment for the first time: mortality and gender differences**. *Addictive Behaviors* 2011, **36**(12):1184-1190.
36. Savage LJ, Simpson DD: **Posttreatment outcomes of sex and ethnic groups treated in methadone maintenance during 1969-1972**. *J Psychedelic Drugs* 1980, **12**(1):55-64.
37. Marsh KL, Simpson DD: **Sex Differences in Opioid Addiction Careers**. *The American Journal of Drug and Alcohol Abuse* 1986, **12**(4):309-329.
38. Chatham LR, Hiller ML, Rowan-Szal GA, Joe GW, Simpson DD: **Gender differences at admission and follow-up in a sample of methadone maintenance clients**. *Substance Use and Misuse* 1999, **34**(8):1137-1165.
39. Webber MP, Schoenbaum EE, Gourevitch MN, Buono D, Klein RS: **A prospective study of HIV disease progression in female and male drug users**. *Aids* 1999, **13**(2):257-262.
40. College of Physicians and Surgeons of Ontario. **Methadone Maintenance Treatment. Program Standards and Clinical Guidelines.** Toronto, ON; 2011 [cited 2014 July 29]. Available from: http://www.cpso.on.ca/uploadedFiles/members/MMT-Guidelines.pdf.
41. Health Canada. **Literature Review - Methadone Maintenance Treatment.** Canada; 2002 [cited 2014 July 21]. Available from: http://www.hc-sc.gc.ca/hc-ps/pubs/adp-apd/methadone/index-eng.php.
42. Camacho LM, Bartholomew NG, Joe GW, Cloud MA, Simpson DD: **Gender, cocaine and during-treatment HIV risk reduction among injection opioid users in methadone maintenance**. *Drug and Alcohol Dependence* 1996, **41**(1):1-7.
43. Haug NA, Sorensen JL, Lollo ND, Gruber VA, Delucchi KL, Hall SM: **Gender differences among HIV-positive methadone maintenance patients enrolled in a medication adherence trial**. *AIDS Care* 2005, **17**(8):1022-1029.
44. Mulvaney FD, Brown Jr LS, Alterman AI, Sage RE, Cnaan A, Cacciola J, Rutherford M: **Methadone-maintenance outcomes for Hispanic and African–American men and women**. *Drug and Alcohol Dependence* 1999, **54**(1):11-18.
45. Rutherford MJ, Cacciola JS, Alterman AI, Cook TG: **Social competence in opiate-addicted individuals: gender differences, relationship to psychiatric diagnoses, and treatment response**. *Addict Behav* 1997, **22**(3):419-425.
46. Steer RA, Kotzker E: **Affective changes in male and female methadone patients**. *Drug and Alcohol Dependence* 1980, **5**(2):115-122.
47. Stenbacka M, Leifman A, Romelsjo A: **The impact of methadone treatment on registered convictions and arrests in HIV-positive and HIV-negative men and women with one or more treatment periods**. *Drug Alcohol Rev* 2003, **22**(1):27-34.
48. Heidensohn F, Gelsthorpe L: **Gender and crime**: Oxford University Press; 2012.

SUPPORTING INFORMATION – LEGEND

Figure S1. Completed PRISMA Checklist

Figure S2. Self-reported illicit opioid use during first year post-treatment

Figure S3. Cannabis use over the last six months measured using urine toxicology

Figure S4. Cocaine use over the last six months measured using urine toxicology

Figure S5. Benzodiazepine use over the last six months measured using urine toxicology

Figure S6. Mean methadone dose after 6-12 months in treatment (mg/day)

Figure S7. Number of subjects with 12-20 months of treatment retention

Figure S8. Number of subjects currently married or living with spouse

Figure S9. Number of deaths reported at one year after treatment completion

Figure 1. Flow diagram for included studies

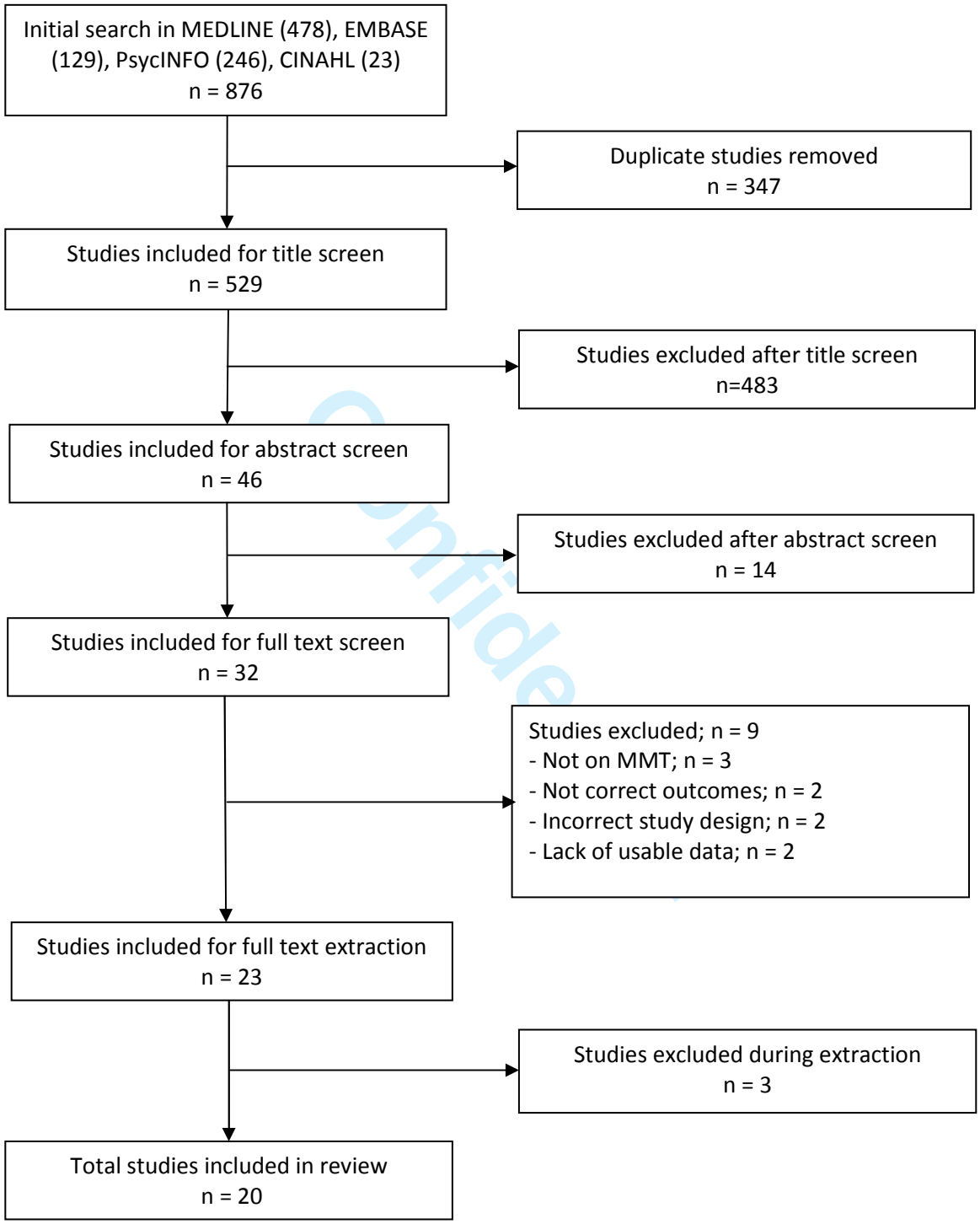


Table 1. Characteristics of included studies

Author (Year)	Place of publication	Study design	Total sample size; n	Sample size; n (%)	Age; mean [SD]	Ethnicity (%)	Outcomes Measured
Anglin (1987)	Los Angeles, USA	Cohort	546	M: 282 (51.7) W: 264 (48.4)	M: 33.6 W: 30.4	Anglos (77.7%) Chicanos (22.3%)	• Illicit opioid use • Treatment retention • Polysubstance use • Legal involvement • Marital status • Employment • Long-term prognosis
Brown (1993)	Brooklyn, USA	Cohort	468	M: 291 (62.2) W: 177 (37.8)	M: 37.7 W: 35.8	Black (55.6%) Hispanic (44.4%)	• Illicit opioid use • Polysubstance use • Health status • Psychological status • Legal involvement • Marital status • Employment
Camacho (1996)	Fort Worth, USA	Cohort	326	M: 223 (68.0) W: 103 (32.0)	M: 38.0 W: 34.0	Black (16%) Mexican American (45%) White (36%) Other (4%)	• Methadone dose • Sexual risk behavior
Chatham (1999)	Fort Worth, USA	Cohort	405	M: 279 (64.1) W: 126 (31.1)	M: 37.6 W: 34.4	Mexican American (43%) Caucasian (36%) African American (16%)	• Illicit opioid use • Treatment retention • Polysubstance use • Health status • Psychological status • Legal involvement • Sexual risk behavior • Marital status • Employment
Grella (2012)	Los Angeles, USA	Cohort	343	M: 191 (55.7) W: 152 (44.3)	M: 58.3 (4.9) W: 55.0 (4.1)	White (71.1%) Hispanic (26.8%) Other (2.0%)	• Health status • Psychological status • Employment • Long-term prognosis
Haug (2005)	San	Secondary	78	M: 42 (53.9)	M: 42.9 (7.95)	Caucasian (35%)	• Illicit opioid use

	Francisco, USA	data analysis		W: 36 (46.2)	W: 45.5 (7.62)	African American (32%) Latino (12%) Other (12%)	• Polysubstance use • Health status • Psychological status
Hser (1990)	Los Angeles, USA	Cohort	720	M: 392 (54.4) W: 328 (45.6)	M: 33.4 W: 30.2	Anglo (74.2%) Chicano (25.8%)	• Illicit opioid use • Treatment retention • Polysubstance use • Legal involvement • Marital status • Employment
Jimenez-Trevino (2011)	Oviedo, Spain	Cohort	53	M: 41 (77.4) W: 12 (22.6)	M: 51.2 (10.1) W: 49.8 (3.8)	NR	• Long-term prognosis
Jones (2005)	Baltimore, USA	RCT	55	M: 36 (65.5) W: 19 (34.5)	M: 37.3 (1.2) W: 35.0 (1.5)	White (46%) Non-white (54%)	• Illicit opioid use • Treatment retention
Marsh (1986)	Fort Worth, USA	Cohort	175	M: 91 (52.0) W: 84 (48.0)	M: 26.8 W: 24.6	Black (52%) White (48%)	• Long-term prognosis
Mulvaney (1999)	Philadelphia, USA	Cohort	548	M: 343 (63.0) W: 205 (37.0)	NR	Black (58%) Hispanics (42%)	• Illicit opioid use • Polysubstance use • Health status • Psychological status • Legal involvement • Marital status • Employment
Peles (2006)	Tel-Aviv, Israel	Cohort	470	M: 339 (72.1) W: 131 (27.9)	M: 37.3 (8.3) W: 34.5 (7.5)	Mainly Isreali	• Illicit opioid use • Treatment retention • Polysubstance use • Methadone dose
Rutherford (1997)	Philadelphia, USA	Cohort	72	M: 44 (61.1) W: 28 (38.9)	M: 39.7 W: 35.2	White (51.4%) Black (45.8%)	• Employment
Savage (1980)	Forth Worth, USA	Cohort	1483	M: 1151 (77.6) W: 332 (22.4)	M: 27.4 W: 25.9	Black (46.2) White (31.6%) Puerto Rican (9.8%) Mexican American (12.4%)	• Long-term prognosis
Schiff (2007)	Jerusalem, Israel	Secondary data analysis	2683	M: 2352 (87.7) W: 331 (12.3)	NR	Mainly Israeli	• Illicit opioid use • Treatment retention • Polysubstance use
Schilling (1991)	New York	Cohort	244	M: 135 (55.0)	M: 38.9 (8.8)	White (22%)	• Illicit opioid use

	City, USA			W: 109 (45.0)	W: 34.5 (5.8)	Black (54%) Hispanic (23%) Other 1%	• Treatment retention • Polysubstance use • Sexual risk behavior • Marital status • Employment
Schottenfeld (1998)	West Haven, USA	RCT	58	M: 39 (67.2) W: 19 (32.8)	M: 33 W: 33.4	White (75.9%)	• Illicit opioid use • Treatment retention • Polysubstance use
Steer (1980)	Philadelphia, USA	Cohort	150	M: 107 (71.3) W: 43 (28.7)	NR	Black (70%) White (30%)	• Psychological status
Stenbacka (2003)	Stockholm, Sweden	Cohort	331	M: 233 (70.4) W: 98 (29.6)	NR	Swedish	• Legal involvement
Webber (1999)	Bronx, USA	Cohort	524	M: 302 (58.0) W: 222 (42.0)	Median (Min-Max) M: 37.1 (21.6-66.0) W: 34.7 (19.9-66.1)	Hispanic (63%) Black (23%) White (14%)	• Illicit opioid use

M = men; W = women; NR = Not reported; SD = standard deviation

		SELECTION BIAS	PERFORMANCE BIAS		DETECTION BIAS		INFORMATION BIAS		
Author, Last name	Year	Is the **source population** representative?	Is the **sample size** adequate and is there sufficient **power**?	Did the study adjust for **confounders**?	Did the study use appropriate **statistics** for outcome of interest?	Is there little **missing data** and was it handled appropriately?	Are the **methods or outcome measurements** explicitly stated and is it appropriate?	Is there an **objective assessment** of outcomes?	Total (out of 21)
Anglin	1987	2	1	1	2	1	1	1	9
Brown	1993	1	1	1	2	2	2	1	10
Camacho	1996	2	2	1	2	2	3	1	13
Chatham	1999	2	2	1	2	2	3	3	15
Grella	2012	1	2	1	1	1	2	1	9
Haug	2005	1	1	1	2	2	3	3	13
Hser	1990	2	2	1	2	2	1	0	10
Jimenez-Trevino	2011	1	1	1	2	0	2	1	8
Marsh	1986	1	1	1	1	2	1	0	7
Mulvaney	1999	2	2	1	2	2	2	2	13
Peles	2006	2	1	1	2	1	3	2	12
Rutherford	1997	1	1	1	2	1	2	0	8
Savage	1980	2	2	1	1	2	1	0	9
Schiff	2007	2	2	1	2	1	1	3	12
Schilling	1991	1	1	1	2	2	2	0	9
Steer	1980	2	1	2	3	2	2	0	12
Stenbacka	2003	2	2	1	2	1	3	3	14
Webber	1999	1	2	2	2	2	2	2	13

0 = Definitely no; 1 = Mostly no; 2 = Mostly yes; 3 = Definitely yes

Author, Last name	Year	1. Was the **allocation sequence generated** adequately?	2. Was allocation **concealed** adequately?	3. Was **knowledge of intervention** adequately prevented?	4. Were **incomplete data** adequately addressed?	5. Are reports of the study free of **selective outcome reporting**?	6. Was the study free of other problems that could put it at **high risk of bias**?
Jones	2005	1	1	1	1	1	1
Schottenfield	1998	1	1	1	1	1	1

1 = Low risk of bias

Outcome	No. of studies	Subjects; n		Pooled OR or SMD (95% CI)	I^2 %	Summary of sex differences	GRADE quality of evidence
		M	W				
Illicit opioid use							
Cohort studies	3	976	814	0.81 (0.50, 1.31) p=0.39	82 p=0.003	--	very low[1,2]
RCTs	3	75	38	1.39 (0.61, 3.19) p=0.44	0 P=0.72	--	moderate[3]
Treatment retention	3	1010	585	1.01 (0.62, 1.63) p=0.97	77 p=0.01	--	low
Polysubstance use							
Cannabis use	2	2691	462	0.85 (0.67, 1.08) p=0.18	0 p=0.67	--	low
Alcohol use	3	809	701	0.52 (0.31, 0.86) p=0.01	77 p=0.01	Women less likely to use alcohol	moderate[1,2,6]
Cocaine use	3	2826	571	1.07 (0.64, 1.78) p=0.80	76 p=0.01	--	very low[2,4,7]
Amphetamine use	2	2691	462	1.47 (1.12, 1.94) p=0.006	0 p=0.96	Women more likely to use amphetamines	low
Benzodiazepine use	2	2691	462	0.94 (0.70, 1.27) P=0.70	44 P=0.18	--	low
Methadone dose (maintenance)	2	562	234	-2.38 (-5.67, 0.91) p=0.16	0 p=0.82	--	low
Mortality	2	581	353	1.61 (0.60, 4.33) p=0.35	83 p=0.02	--	low
Legal involvement	2	674	592	0.63 (0.47, 0.84) p=0.002	39 p=0.20	Women less likely to report arrests or legal supervision	moderate[1,2]
Marital status	4	1100	878	0.96 (0.75, 1.21) p=0.71	0 P=0.53	--	low
Employment	5	1291	1030	0.39 (0.21, 0.73) p=0.003	91 p<0.0001	Women less likely to be employed	moderate[1,2,4,5]

M = men; W = women; OR = odds ratio; SMD = standardized mean difference; CI = confidence interval; RCT = randomized controlled trial

[1] Differences in outcome definition and measurement among studies

[2] Studies did not adjust for relevant treatment-related confounders (i.e. methadone dose, opioid use, other medications, etc.)

[3] Small sample sizes and wide confidence intervals across studies

[4] Inadequate statistical measures and some missing data

[5] Significant association at p<0.01

[6] Significant association at p<0.05
[7] High variability in estimates of effect across studies

Fig 2

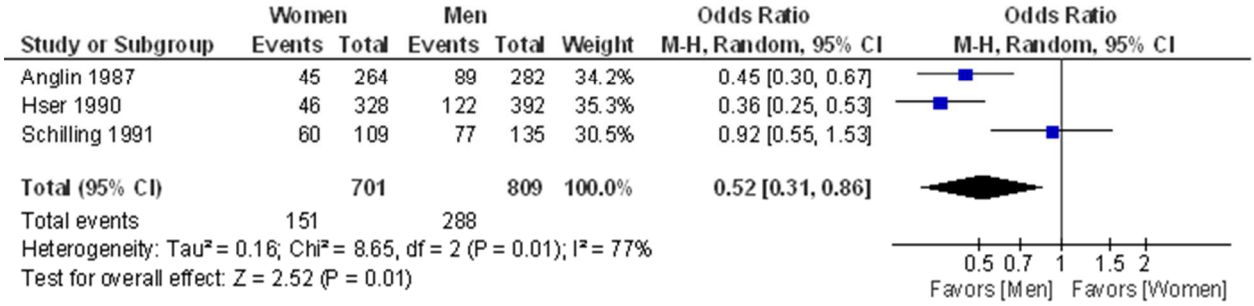


Fig 3

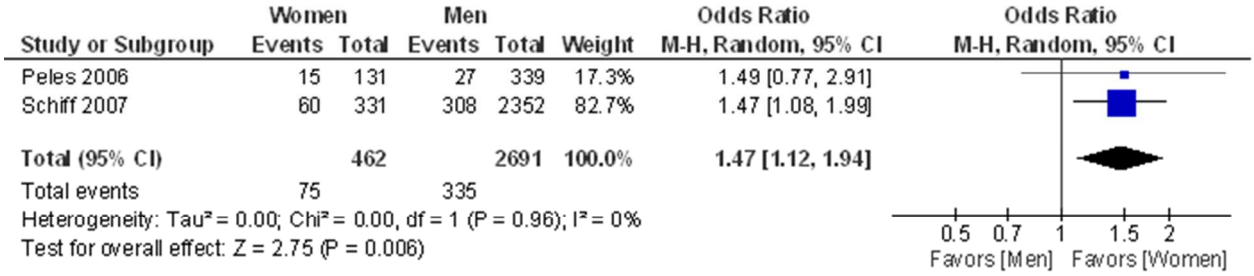


Fig 4

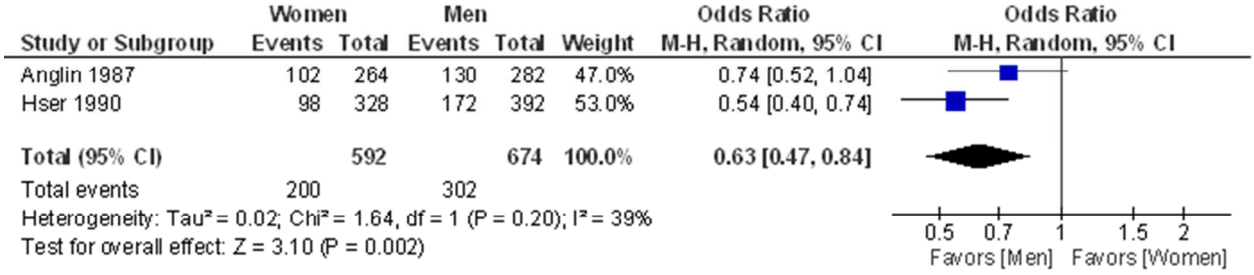
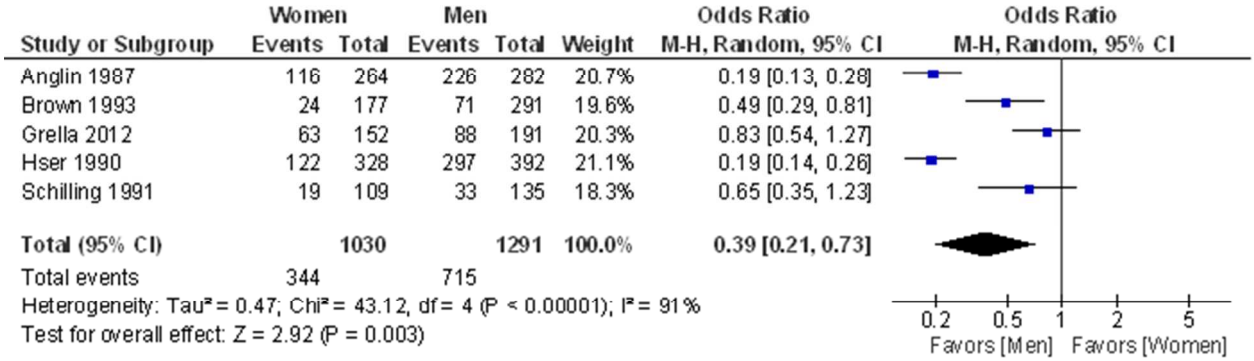


Fig 5



#	Outcome	Men	Women
1	Illicit opioid use		
2	Treatment retention		
3	Alcohol use	OR: 0.52 (95% CI: 0.31, 0.86)	
4	Amphetamine use	OR: 1.47 (95% CI: 1.12, 1.94)	
5	Benzodiazepine use		
6	Cannabis use		
7	Cocaine use		
8	Methadone dose		
9	Legal involvement	OR: 0.63 (95% CI: 0.47, 0.84)	
10	Employment	OR: 0.39 (95% CI: 0.21, 0.73)	
11	Marital status		
12	Long-term mortality		

Legend

	No sex differences
	Women more likely than men
	Women less likely than men

Clinical recommendations	
Men	**Women**
Alcohol use	***Amphetamine use***
• Psychosocial treatment (individual or group)such as cognitive-behavioral therapy • Behavioral incentive programs of abstinence • Support groups • Educational programs • Medications (Antabuse, disulfiriam) • Management of withdrawal symptoms • Routine breath alcohol monitoring or other available laboratory screening (e.g EtG)	• Psychosocial treatment (individual or group) such as cognitive-behavioral therapy • Behavioral incentive programs of abstinence • Support groups • Educational programs • Management of withdrawal symptoms • Routine and random urine drug screens
Legal involvement	***Employment***
• Psychosocial therapy • Increased employment services utilization • Regular criminal background investigations	• Interview and job skills training • Regular workshops on resume writing, maintaining a job, money management • Community engagement • In-field temporary job experience • Individual or group vocational counseling

Supplementary Information (online only)

Figure S1. Completed PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	In protocol
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	In protocol
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	In protocol
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	In protocol

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	In protocol
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	In protocol
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	In protocol
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 + Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6 + Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7 + Tables 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-13 + Table 4 + Figs. 2-9 + Figs. S2-S10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-13 + Table 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7 + Tables 2 and 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure S2. Cohort and randomized controlled studies measuring illicit opioid use during treatment

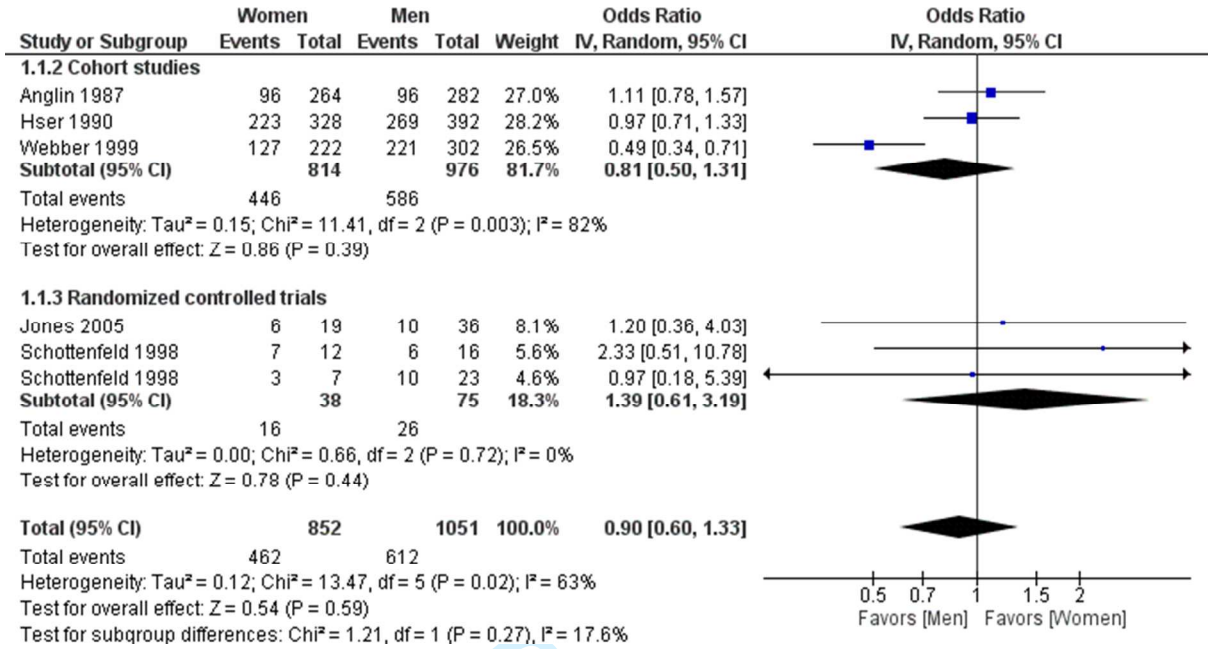


Figure S3. Number of subjects with 12-20 months of treatment retention

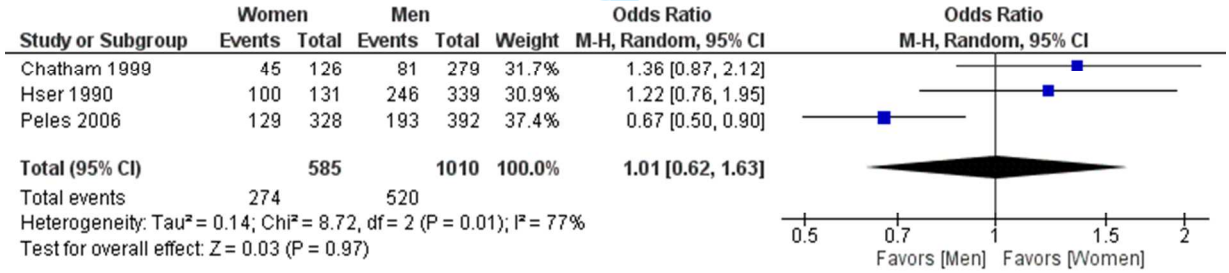


Figure S4. Cannabis use over the last six months measured using urine toxicology

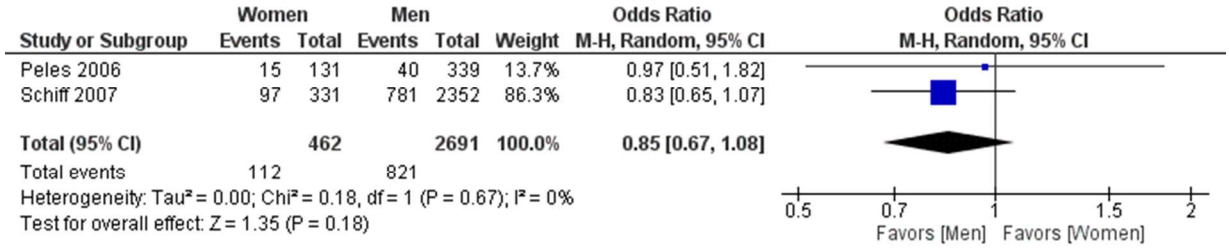


Figure S5. Cocaine use over the last six months measured using urine toxicology

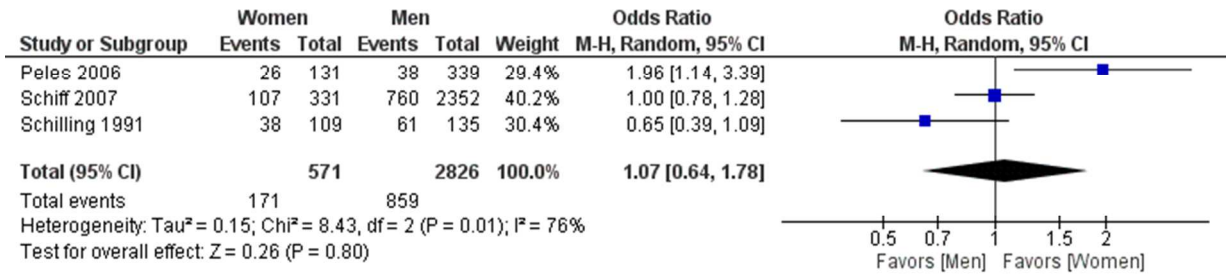


Figure S6. Benzodiazepine use over the last six months measured using urine toxicology

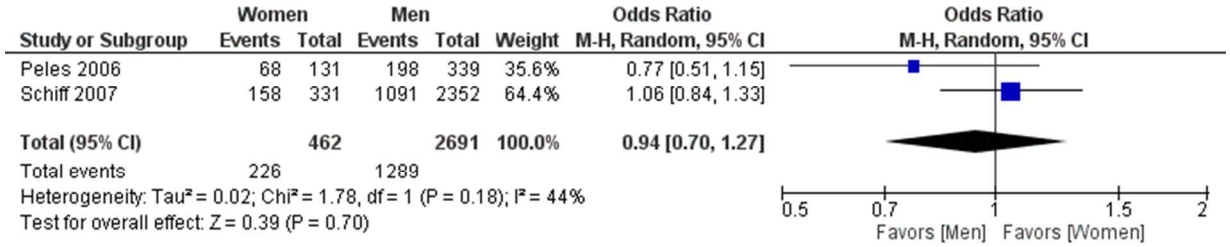


Figure S7. Mean methadone dose after 6-12 months in treatment (mg/day)

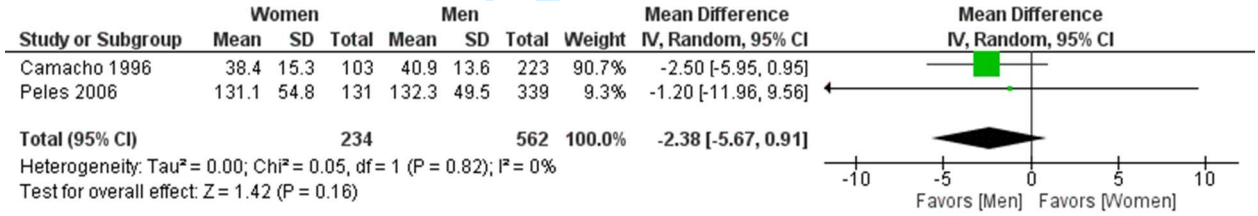


Figure S8. Number of subjects currently married or living with spouse

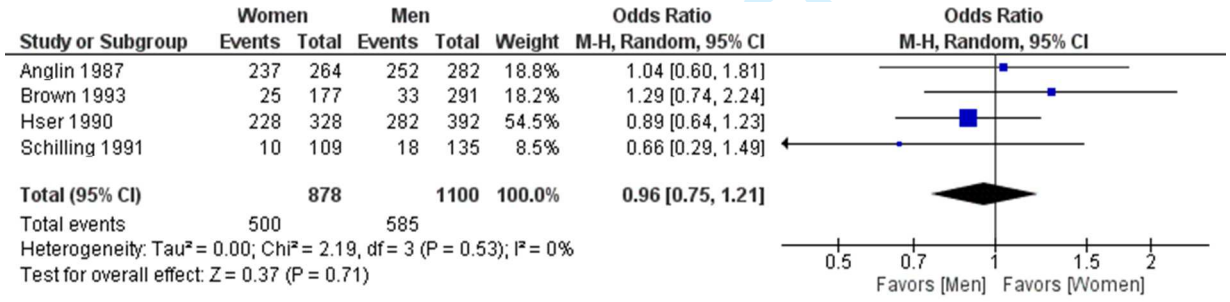


Figure S9. Number of deaths reported at one year after treatment completion