Impact of opioid agonists on mental health in substitution treatment for opioid use disorder:
a systematic review and Bayesian network meta-analysis of randomized clinical trials

by

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Impact of opioid agonists on mental health in substitution treatment for opioid use disorder: A systematic review and Bayesian network meta-analysis of randomized clinical trials

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Abstract

Background: Concurrent mental health problems is a major issue in opioid use disorder. As the first step in developing effective interventions, a clear understanding of factors that potentially contribute to the improvement of mental health in this population, most prominently the role of opioid medications, is required. Previous reviews did not isolate the impact of opioid agonists on mental health from those of psychosocial interventions in substitution treatment of opioid use disorder. We compared mental health outcomes between opioid medications and control conditions, i.e. placebo or waitlist, to isolate these effects.

Methods: Embase, MEDLINE, PsychInfo, CINAHL Complete, Web of Science Core Collection and RCT registries were among the systematically searched databases. RCTs were included if they compared any opioids with each other or with a placebo/waitlist in substitution treatment of patients with opioid use disorder and reported mental health outcomes using a validated measure. Individual study-level data were extracted from all available sources. Primary outcomes included difference in standardized mean score changes (SMD) for depressive symptoms and overall mental health symptomatology between opioid agonists and placebo/waitlist. Random effects model was used for both the direct pairwise meta-analysis and network meta-analysis. (Registered at https://www.crd.york.ac.uk/prospero/, CRD42018109375)

Results: Out of 6034 citations, 19 studies were included in the qualitative synthesis and 16 in the quantitative synthesis. Out of 19 studies, 18 had high overall risk of bias. Direct pairwise meta-analysis indicated that diacetylmorphine (DAM) outperformed methadone on overall mental health (SMD (CI95%)= -0.23 (-0.34, -0.13)). Buprenorphine outperformed waitlist or placebo on improvement of depressive symptoms (SMD (CI95%)= -0.95 (-1.53, -0.36)) and overall mental health (SMD (CI95%)= -0.68 (-1.33, -0.03)). Based on network meta-analysis for primary outcomes, buprenorphine (SMD (CI95%)= -0.61 (-1.20, -0.11)), DAM (SMD (CI95%)= -1.40 (-2.70, -0.23)), and methadone (SMD (CI95%)= -1.20 (-2.30, -0.11)) were superior to waitlist/placebo on overall mental health symptomatology, but none of the medications were superior to waitlist in improving depressive symptoms.

Conclusions: Opioid agonists used in substitution treatment improve overall mental health, and DAM outperforms methadone in this regard which has implications for treatment guidelines. Future trials will benefit from stricter control for sources of bias.

Lay Summary

Despite of the high prevalence of mental problems in patients with opioid use disorder, the impact of mainstay treatment approaches, i.e. substitution treatment with opioids, on mental health is poorly studied. We compared different opioids with control conditions in previous interventional studies, to better understand this impact. We systematically searched seven major databases of mental health literature as well as other potentially relevant sources. We included only interventional studies that met certain criteria. Our results show that buprenorphine, diacetylmorphine, and methadone significantly improve mental health, and diacetylmorphine has a stronger effect than methadone in this regard. These findings signify importance of medication continuation/compliance in treatment of opioid use disorder with added benefits compared to abstinence-based methods like detoxification. Beyond that, higher efficacy of diacetylmorphine to methadone implies its potential application for treatment of patients with more severe mental problems.

Preface

Ehsan Moazen Zadeh came up with the main idea of this work, which was then supported, revised, and improved by Michael Krausz as the principal supervisor. Ehsan Moazen Zadeh also designed the study, coordinated the study, contacted authors of all the included studies to collect more precise data, carried out the systematic search, monitored all screening and quality assessments, carried out all the statistical analysis, provided the first draft of the manuscript for publication in relevant journals as well as the draft of this thesis, and acted as senior reviewer in cases of disagreement between other collaborators.

An original article version of the work presented here in chapters 1-4 is already prepared for submission to relevant journals. Moazen Zadeh, E., Ziafat, K., Yazdani, K., Mamdouh, M., Wong, J., Modabbernia, A., Blanken, P., Verthein, U., Schütz, C.G., Jang, K., Akhondzadeh, S., and Krausz, R.M. (2019) Impact of opioid agonists on mental health in substitution treatment for opioid use disorder: A systematic review and Bayesian network meta-analysis of randomized clinical trials. Contribution of Ehsan Moazen Zadeh is mentioned above. Ziafat, K., Yazdani, K., Mamdouh, M., and Wong, J. helped with screening, data extraction, and quality assessments. They also reviewed and revised the manuscript before submission. Modabbernia, A. contributed to the design and methodology, and revised the manuscript before submission. Blanken, P., Verthein, U. provided essential data for some of the studies included in this review. Blanken, P., Verthein, U., Schütz, C.G. (supervisory committee member), Jang, K. (supervisory committee member), Akhondzadeh, S., and Krausz, M. (principal supervisor) provided expert consultation during the study, contributed to the interpretation of results and revised the manuscript before submission.

The UBC office of Research Ethics approval was not required for this research.

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Dedication

To those few great inspirational people who taught me to believe in myself, think critically, and always remember the true values in personal and professional life.

1 Introduction

1.1 Background and the scope of the problem

We are experiencing a significant increase in the use of opioids and opioid fatalities worldwide, with opioid-related disorders accounting for 76% of deaths associated with any drug-use disorder.[1] According to the comprehensive national reports in the US, 64.3% and 26.9% of adults with opioid use disorder suffer from mental illness and serious mental illness respectively.[2] The numbers range between 20-80% for mental disorders among patients seeking opioid substitution treatment in the Europe, and about 80% in Ontario, Canada.[3,4] This is happening while only around 1/3 of adults with concurrent opioid use disorder and mental illness receive treatments for both problems, simultaneously.[2] Furthermore, an array of psychosocial interventions studied in treatment of opioid use disorder have produced mixed results in terms of improving mental health status with a lack of consensus on an effective treatment model.[3,5] Moreover, using anti-depressants for treatment of patients with comorbid major depression and substance use disorder appears to benefit only those patients with comorbid alcohol use disorder and depression, and results for comorbid opioid use disorder are inconsistent.[3]

1.2 What we know and the gaps in knowledge

Understanding the dynamics of potential factors that contribute to the improvement of mental health in patients with opioid use disorder is essential for the development of novel effective interventions. To this end, an important factor to be studied is the role of currently available treatments, most prominently use of opioid agonist medications as the mainstay and first line of treatments in opioid use disorder. In fact, opioid agonists have a long history in the treatment of mood disorders even before anti-depressants become available on the market.[6,7] Furthermore, recent clinical studies demonstrated the efficacy of buprenorphine in improving depression and risk of suicide in patients with refractory major depression,[8] and several lines of evidence suggest the involvement of the endogenous opioid system in mood and anxiety disorders.[9,10] However, when it comes to studying opioid agonists in patients with opioid use disorder, mental health outcomes are rarely considered as primary in studies of substitution treatment, and are often not well-reported compared to other outcomes like illicit drug use or retention in treatment,[11] which has hampered our understanding of the effects of opioid agonists on mental health. Furthermore, it is worth noting that based on our literature search, there have been only two systematic reviews on mental health related outcomes in opioid substitution treatment,[11,12]

both of which focused on before-after measures of mental health in single opioid agonist medications. While both studies reported improved mental health outcomes in opioid substitution treatment, they were unable to isolate effects of opioid agonists on mental health from the potential effects of adjunct psychosocial interventions because they lacked any comparison between different opioid agonists or between these medications and placebo.

1.3 Aims and objectives

In this study, our aims were to see: 1_if the opioid agonists improve mental health in substitution treatment for opioid use disorder, independent of psychosocial interventions, 2_if any opioid agonist has a higher impact in this regard compared to other opioids. Toward these aims our objectives were to: 1_select randomized clinical trials of substitution treatment which met certain criteria that would allow us to eliminate the effects of psychosocial interventions as much as possible, 2_Compare the impact of opioid agonists on mental health with each other using direct evidence for pairwise meta-analysis, 3_Compare the impact of opioid agonists on mental health with neutral conditions, e.g. placebo/waitlist using both direct and indirect evidence for network meta-analysis.

2 Methods

2.1 Overview

The PRISMA guidelines and the latest version of the Cochrane Handbook were considered throughout the whole conduct and reporting of the study.[13] All methods (https://www.crd.york.ac.uk/prospero/, CRD42018109375) were predefined and registered before initiation of the screening phase.

2.2 Data sources and search strategy

The following general combination of search terms, Boolean operators, and search fields were used where "*" means that any extension of that word would be considered:

Title field→ [opium OR opiate* OR opioid OR heroin OR medication assisted OR substitution treatment OR maintenance treatment OR methadone OR levomethadone OR buprenorphine OR suboxone OR (morphine AND slow) OR diamorphine OR diacetylmorphine OR dihydrocodeine OR hydromorphone OR opium tincture OR tincture of opium OR methadol OR methadyl OR levomethadyl] AND

Title/Abstract field→ [trial* OR random* OR placebo] AND

All fields→ [depress* OR anxiety OR mental]

Wherever this exact combination was not possible, a more inclusive version of the search strategy was considered. The exact search strategy used to search each database is represented in Table 2.1. On September 10, 2018, a comprehensive list of databases were searched including: Ovid for EBM Reviews - Cochrane Central Register of Controlled Trials August 2018, Embase 1974 to 2018 September 07, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to September 07, 2018; EbscoHost (1968-2018) for PsychInfo and CINAHL Complete; Web of Science Core Collection; LILACS; OpenGrey; Google Scholar first 200 citations; clinicaltrials.gov and clinicaltrialsregister.eu for the completed/terminated trials registered in the recent 5 years. Finally, a hand search of reference lists from included trials as well as major systematic reviews of

substitution treatments was performed to find additional full-texts. Experts in the field were also consulted. In May 2019, we updated our search to find any relevant studies that were published after the previous search.

Table 2.1 Specific search strategies used for each database

Database	**Search Strategy**
Ovid	(opium or opiate$ or opioid or heroin or medication assisted or substitution treatment or maintenance treatment or methadone or levomethadone or buprenorphine or suboxone or (morphine and slow) or diamorphine or diacetylmorphine or dihydrocodeine or hydromorphone or opium tincture or tincture of opium or methadol or methadyl or levomethadyl).ti. and (trial$ or random$ or placebo$).ab. and (depress$ or anxiety or mental or psychiatric).tw.
EbscoHost	(TI(opium OR opiate* OR opioid OR heroin OR medication assisted OR substitution treatment OR maintenance treatment OR methadone OR levomethadone OR buprenorphine OR suboxone OR (morphine AND slow) OR diamorphine OR diacetylmorphine OR dihydrocodeine OR hydromorphone OR opium tincture OR tincture of opium OR methadol OR methadyl OR levomethadyl) AND AB(trial* OR random* OR placebo*) AND TX(depress* OR anxiety OR mental OR psychiatric))
Web of Science Core Collection	TI=(opium OR opiate* OR opioid OR heroin OR medication assisted OR substitution treatment OR maintenance treatment OR methadone OR levomethadone OR buprenorphine OR suboxone OR (morphine AND slow) OR diamorphine OR diacetylmorphine OR dihydrocodeine OR hydromorphone OR opium tincture OR tincture of opium OR methadol OR methadyl OR levomethadyl) AND TS=(trial* OR random* OR placebo*) AND TS=(depress* OR anxiety OR mental OR psychiatric)

Database	Search Strategy
LILACS	Title, abstract, subject: (opium OR opiate* OR opioid OR heroin OR "medication assisted" OR "substitution treatment" OR "maintenance treatment" OR methadone OR levomethadone OR buprenorphine OR suboxone OR (morphine AND slow) OR diamorphine OR diacetylmorphine OR dihydrocodeine OR hydromorphone OR "opium tincture" OR "tincture of opium" OR methadol OR methadyl OR levomethadyl) AND (trial* OR random* OR placebo*) AND (depress* OR anxiety OR mental OR psychiatric)
OpenGrey	(Opium OR opiate* OR opioid OR heroin OR "medication assisted" OR "substitution treatment" OR "maintenance treatment" OR methadone OR levomethadone OR buprenorphine OR suboxone OR "slow-release morphine" OR diamorphine OR diacetylmorphine OR dihydrocodeine OR hydromorphone OR "opium tincture" OR "tincture of opium" OR methadol OR methadyl OR levomethadyl) AND (trial* OR random* OR placebo*) AND (depress* OR anxiety OR mental OR psychiatric)
Google Scholar	(opioid OR heroin OR "medication assisted" OR "substitution treatment" OR methadone OR buprenorphine) AND (trial OR randomized) AND (depressive OR depression OR anxiety OR mental)

Database	Search Strategy
clinicaltrials.gov	*Filters:* _Interventional studies (clinical trials), _completed or terminated, _first posted from Sep10, 2013 *Search:* condition→ opioid; other terms→ Opium OR heroin OR "medication assisted" OR "substitution treatment" OR "maintenance treatment" OR methadone OR levomethadone OR buprenorphine OR suboxone OR "slow-release morphine" OR diamorphine OR diacetylmorphine OR dihydrocodeine OR hydromorphone OR methadol OR methadyl OR levomethadyl
European Union Register of Clinical Trials	*Filters:* _completed or prematurely ended, _first posted from Sep10, 2013 *Search:* terms→ opioid OR opiate OR opium OR heroin OR "medication assisted" OR "substitution treatment" OR "maintenance treatment" OR methadone OR levomethadone OR buprenorphine OR suboxone OR "slow-release morphine" OR diamorphine OR diacetylmorphine OR dihydrocodeine OR hydromorphone OR methadol OR methadyl OR levomethadyl

2.3 Study selection and inclusion/exclusion criteria

Four authors, all of whom were UBC students, worked in parallel, two by two, to screen all the retrieved citations after they were trained and calibrated for the specific inclusion/exclusion criteria by Moazen Zadeh, E., using a sample of 20 challenging citations that were assessed by all the four authors and discussed with the lead investigator (Moazen Zadeh, E.) to reach a consensus. In accordance with objective 1 of the study, randomized clinical trials were included if they compared any opioid agonists with each other or with a placebo/waitlist in substitution treatment of patients with opioid use disorder and reported at least one mental health outcome using a validated measurement tool on a span of more

than 1 month post-baseline. Studies with comprehensive psychiatric interventions other than opioid agonists, or those primarily focused on adjunctive interventions such as psychotherapy or adjunctive medications were excluded. Ancillary routine psychological counselling was acceptable if it was available to all the participants in a study and was provided in a similar way across all treatment arms. Conference abstracts, thesis reports, and registries of clinical trials were also included if enough data could be collected, either through the reports themselves or by contacting the authors.

2.4 Data Extraction

The four authors involved in screening, carried out data extraction on a primary sample of 4 studies, where results were compared, discussed, and calibrated amongst them and the lead investigator (Moazen Zadeh, E.). Afterwards, the four authors worked in parallel, two by two, extracting data from all studies. Final results were compared, and in cases of discrepancy, a consensus was reached after discussion with the lead investigator. Relevant data were extracted from the included studies using excel sheets prepared by the lead investigator with predefined columns including: title, name of authors, study design, main diagnosis and diagnostic criteria, concurrent psychiatric conditions, use of other substances beside opioids, details of main interventions/medications including type/dose/frequency, details of any ancillary interventions or services such as routine counselling, duration of the study, duration of the illness, age, gender, inpatient/outpatient setting, any potentially important conflict of interest, any differences in baseline characteristics between treatment arms, methods of analysis such as Intention to Treat (ITT) or Per Protocol, number of patients assigned versus numbers of patients who finished the study and those who were analyzed for each mental health outcome. For each mental health outcome, the following details were recorded: primary or secondary, scale of measurement, baseline values as well as all follow-up values, timepoint for each measurement, and any summary measures of change provided by the authors plus statistical tests used.

2.5 Quality assessment

Lead investigator (Moazen Zadeh, E.) assessed the quality of all studies. In addition, four authors carried out quality assessment on a primary sample of 5 studies independently, where results were compared, discussed, and calibrated amongst them and the lead investigator. Afterwards, the 4 authors worked in parallel two by two assessing the quality of all studies. Final results were compared, and in cases of discrepancy, a consensus was reached after discussion with the lead investigator. The recently

released comprehensive Risk of Bias Tool version 2 (ROB2) from Cochrane Collaboration, which evaluates each outcome for 6 domains of potential bias as well the overall risk of bias, was used for quality assessment of single studies.[14] Bias is defined as a deviation from truth or systematic error, which can lead to underestimation or overestimation of true intervention effect. In cases of similarity among the assessment results for the different outcomes of a single study, a single assessment result was reported for that study.

2.6 Outcomes and measures

In accordance with objective #3, primary outcomes included standardized mean difference in score changes from baseline to endpoint between opioid agonists and placebo/waitlist for depressive symptoms and overall mental health symptomatology as the most commonly reported mental symptom and outcome respectively in clinical trials of opioid substitution treatment estimated through network meta-analysis (NMA). In accordance with objective #2, secondary outcomes included standardized mean difference in score changes between different opioid agonists for any measures of mental health estimated through direct pairwise meta-analysis. Data from similar measures of mental health were combined, i.e. scores from depression subscale of Symptom Checklist-90 (SCL-90) as well as shorter versions, Beck Depression Inventory (BDI), or Self Rating Depression Scale;[15,16] total scores/global severity index from SCL-90 as well as shorter versions, Brief Symptom Inventory (BSI), or Kessler psychological distress scale (K10);[17-19] composite scores of psychiatric status on Addiction Severity Index (ASI) or European ASI;[20] and mental health quality of life measured by Short Form Health Survey-36 (SF36) or Lancashire Quality of Life Profile (LQOLP).[21,22] Validity, reliability, and level of correlation of similar measures are discussed elsewhere.[15-22]

2.7 Data analysis and synthesis

Standardized mean differences (SMD) and standard errors (SE) estimated through pairwise meta-analysis were used as the input for network meta-analysis. An estimated intervention effect, i.e. SMD, was considered significant if the 95% confidence interval around the SMD did not overlap the value of zero. Data from injecting, inhaling, and oral administration of medications or from different doses of a single medication were combined for the studies that included more than one administration route or dosing strategy.

For the direct pairwise meta-analysis, all outcomes from all studies were brought to a standardized scale, regardless of whether there was a single study on a specific comparison or multiple studies available. For each outcome of interest, if there was more than one study with usable data for analysis on a specific pairwise comparison between 2 medications, meta-analysis was carried out for that comparison and data from other comparisons for the same outcome was also represented. Comprehensive Meta-analysis v2.0 was utilized for this purpose, using a random effects model. Measures of heterogeneity were reported including Q statistic for assessment of significance of heterogeneity, the I^2 to evaluate the proportion of total variability attributable to heterogeneity, and Tau^2 for the extent of heterogeneity. Funnel plots were presented if there were enough number of studies to make the assessment of publication bias feasible. Sensitivity analysis was considered based on the results of risk of bias assessment.

For the network meta-analysis (NMA), outcomes with enough number of studies directly comparing medications and also including at least one study comparing an active medication with a placebo/waitlist were considered for NMA. An online free version of R package GeMTC for Bayesian NMA (https://gemtc.drugis.org/) by Markov Chain Monte Carlo was used with all the codes accessible from the website. Contrast-based NMA was considered rather than arm-based analysis, as the data available from some of the studies was only in the format of difference in effect size between the treatment arms. Random effects method was used rather than fixed effects in order to account for the heterogeneity among studies and potential inconsistencies throughout the network; however, results from both methods were presented. Normal likelihood and standardized mean difference (SMD) link were assumed . Number of chains were set at 4, burn-in iterations at 5000, inference iterations at 20000, and thinning factor at 10. Convergence diagnostics, measures of model fit, and leverage-residual deviance plots were used to decide if the final model was appropriate. Node-splitting analysis of consistency was not applicable as there was no closed loop in the model network. Rank probabilities plot and effect estimates were used to compare the medications with placebo/waitlist. Extensive explanation of the terminology used in this section, as well as comparison of general concepts of NMA with direct pairwise met-analysis can be found on the provider website (https://gemtc.drugis.org/manual) or in relevant textbooks.

The quality of evidence for the network met-analysis was also assessed by the lead author using guidelines defined by Salanti et al.,[23] based on the GRADE guidelines for assessment of quality of evidence and overall rating of confidence in the estimates.[24]

3 Results

3.1 Included studies

After removing duplicate citations, 2983 citations were screened for title and abstract out of which 167 citations remained for further assessment. Finally, 22 studies met inclusion criteria and remained for data-extraction, but only 19 were included for qualitative synthesis because enough data were not received from authors of three studies (Figure 1).[25-27] Summary of these can be found in Table 3.1. Furthermore, only 16 studies were included in quantitative synthesis as outcome data from two studies were not sufficient for such analysis,[28-31] and similar measures to Haight et al.,[32] were not available from other studies in order to be combined for quantitative synthesis.

3.2 Quality assessment

Except for one study with Low Risk of bias in all the ROB2 indicated domains,[33,34] all studies had Some Concerns or High Risk of bias in multiple assessment domains, which resulted in an overall High Risk of bias for those studies (Table 3.2). The Randomization Process domain had the highest frequency of Low Risk studies, while the two domains concerning Deviations from Intended Interventions had the highest frequency of High Risk studies (Table 3.2).

3.3 Publication bias

In this study, publication bias was not assessed due to the low number of studies in each pairwise comparison according to Cochrane's recommendation of the availability of around 10 trials on each pairwise comparison for a meaningful interpretation of publication bias.[13,35] By definition, publication bias refers to a systematic bias in the probability of studies getting published and subsequently included in a review based on the significance and direction of their results.

Figure 3.1 Flow diagram of screened and included studies

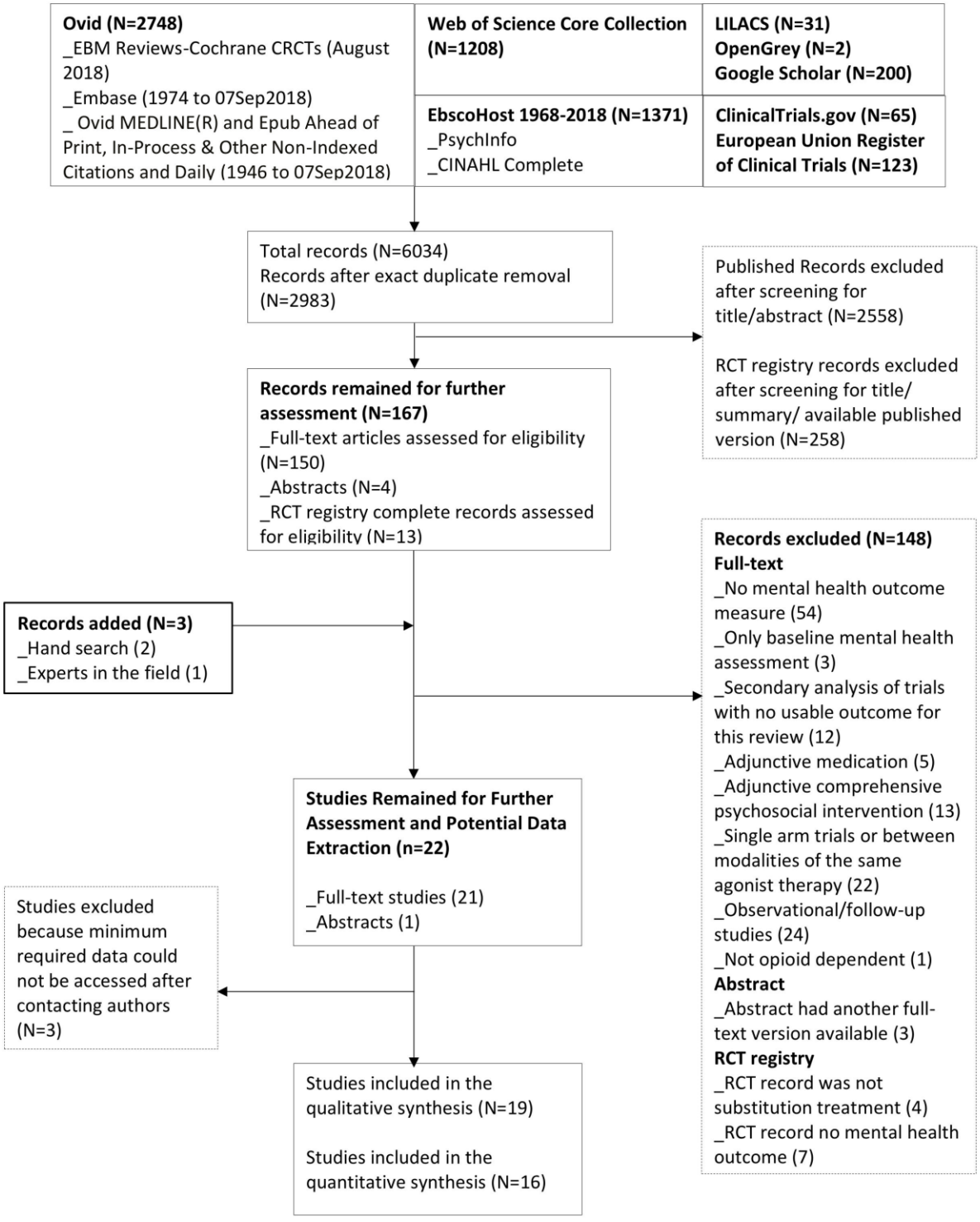


Table 3.1 Summary of studies included in this review

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Oviedo-Joekes et al. (2016)[33] Oviedo-Joekes et al. (2015)[34]	Severe opioid use disorder based on DSM-V (Chronic opioid-dependence with current injection opioid use and previous experience of substitution treatment)	Mean (SD) days of use in previous month for HDM and DAM arms respectively: Crack cocaine→ 11.25 (12.97), 9.41 (12.46)	Patients had to be in poor physical health or psychosocial functioning as measured by MAP	HDM: 45.17 (10.19); DAM: 43.50 (9.03)	HDM: 67%; DAM= 71.6%	DAM: injectable/up to 3 doses per day/up to 400 mg per dose/up to 1000 mg per day/average dose of 454.0 mg per day HDM: injectable/up to 3 doses per day/up to 400 mg per dose/up to 1000 mg per day after conversion to equivalent doses of DAM (1:2-2.2 ratio)/average dose of 212.6 mg per day	DAM: 76 out of 102 patients received oral methadone (mean 23.64mg per day) HDM: 81 out of 100 patients received oral methadone (mean 24.58mg per day) Participants had access to addiction counselors, social workers, and allied health professionals.	6 months

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Van den Brink et al. (2003)[36]	Opioid dependence based on DSM-IV	Average number of days of drug use during the past month for heroin and methadone arms respectively: Cocaine→ 15.2-15.5, 15.2-18.0; Amphetamines→ 0.1-0.9, 0.1-1.2	Percent of patients with concurrent conditions for heroin (injecting-inhaling) and methadone (arm1-arm2) arms respectively: HIV→ 3.9-13.3%, 9.9-13.3%; Any DSM-IV diagnosis→ 28.2-31.6%, 27.7-34.0%	Heroin (injecting-inhaling): 39.2-40.0; Methadone (arm1-arm2): 38.0-39.6	Heroin (injecting-inhaling): 78.6-82.9%; Methadone (arm1-arm2): 79.1-81.6%	Heroin: injecting-inhaling/ mean 57 mg of methadone and 540 mg of heroin per day/once per day and 2.1 times per day respectively Methadone: methadone arms combined/ once per day/average dose of 67-71 mg per day	All patients had access to standard medical and psychosocial services.	12 months
March et al. (2006)[40]	Opiate dependence based on ICD-10.	No specific information	Percent of patients with concurrent conditions for DAM and methadone arms respectively: HIV→ 38.7%, 41.9%; HCV→93.5 %, 93.5%; HBV→ 3.2%, 3.2%	DAM: 37.0 (5.8); Methadone: 37.3 (5.2)	DAM: 83.9%; Methadone: 96.8%	DAM: intravenous heroine and oral methadone/twice and once per day/ average 274.5 mg per day and 42.6 mg per day respectively Methadone: oral/ once per day/average 105 mg per day	All participants had access to social resources, as well as psychiatric, psychotherapeutic, and medical treatments for concomitant disease.	9 months

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Reimer et al., (2011)[41] Karow et al. (2010)[42] Hassen et al. (2007)[43]	Opioid dependence based on ICD-10.	Mean (SD) days of use in previous month for heroin and methadone arms respectively: Alcohol→ 11.8 (11.4), 13.8 (12.6); Cocaine→ 22.3 (10.0), 22.2 (10.0); Benzodiazepines→ 16.2 (11.6), 16.5 (11.6)	Percent of patients with concurrent conditions for heroin and methadone arms respectively: HIV→ 8.9%, 9.5%; HCV→ 85.6%, 87.7%; HBV→ 64.4%, 68.1%	Heroin: 36.2 (6.7); Methadone: 36.6 (6.8)	Heroin: 80%; Methado: 79.8%	Heroin: average of 442 mg per day with an additional 8 mg of methadone per day Methadone: average of 99 mg per day	For all participants, psychosocial care was provided including case management, and either integrated case management and motivational interviews or drug counselling and psychoeducation	12 months
Oviedo-Joekes et al. (2009)[44]	Opioid dependence based on DSM-IV	Mean (SD) days of use in previous month for DAM and methadone arms respectively: Cocaine powder→ 5.4 (9.7), 4.1 (7.7); Crack cocaine→ 15.1 (13.2), 12.7 (13.3)	For DAM and methadone arms respectively: HIV→ 9.6%, 10.8%; HCV→ 64.3%, 62.2%	DAM: 39.7 (7.6); Methadone: 39.3 (9.4)	DAM: 63.5%; Methadone: 58.6%	DAM: injecting/ 2 times per day/average of 392.3 mg per day when the drug was prescribed alone (365.5 mg if accompanied by 34.0 mg methadone) Methadone: oral/ once per day/average of 96.0 mg per day	A range of psychosocial and primary care services was offered to all participants.	12 months

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Demaret et al. (2015)[45]	Opioid dependence for the past 5 years (No specific diagnostic criteria mentioned)	Percent of patients using drugs in the past month for DAM and methadone arms respectively: Alcohol ≥5 glasses on a drinking day→ 25%, 32%; Cocaine→ 39%, 53%; Benzodiazepines→ 50%, 34%	Poor physical or mental health was an inclusion criteria.	DAM: 43 (6); Methadone: 42 (7)	DAM: 83%; Methadone: 92%	DAM: mean 2.3 times per day/mean dose of 573 mg per day (additional daily dose of methadone 20 mg) Methadone: once per day/average dose of 77 (±21) mg per day	All participants were offered psychosocial services.	12 months
Metrebian et al. (2014)[37] Strang et al. (2010)[38] Lintzeris et al. (2006)[39]	Opioid dependence based on DSM-IV.	Percent of patients using drugs for heroin and methadone arms respectively: Alcohol→ 44.2%, 50-57.1%; Crack cocaine→ 79.1%, 69.1-73.8%; Illicit benzodiazepines→ 30.2%, 31-42.9%	Patients were excluded if they had significant and active medical (e.g. hepatic failure) or psychiatric conditions (e.g. active psychosis, severe affective disorder), alcohol dependence or regular abuse of benzodiazepines.	Heroin: 37.5 (6.6); Methadone (injecting-oral): 37 (7.0)-37.2 (5.9)	Heroin: 86%; Methadone: 67%	Heroin: injecting/ twice per day/ mean 399 mg/optional oral methadone Methadone: injecting/<200mg once per day oral/average of 31 mg, /mean of 107mg, 80-300mg/ once daily	All patients had monthly reviews with a study medical officer, access to a psychologist for individual CBT-based therapy, access to other ancillary services (e.g. group programs) available at each site on a voluntary basis.	6 months

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Eder et al. (2005)[46] Winklbaur et al. (2008)[47]	Opioid dependence based on DSM-IV	No specific information. (Patients were excluded if they had multi-substance dependence)	No specific information.	SROM: 29.5 (7.5); Methadone: 27.9 (5.6)	SROM: 84.4%; Methadone: 90.6%	SROM: oral capsules/average dose of 680mg per day Methadone: oral solution/average dose of 85mg per day	All patients had access to standardized 30-minute psychosocial counselling sessions on a twice-weekly basis	14 weeks, (7 weeks before cross-over)
Verthein et al. (2014)[48] Beck et al. (2014)[49]	Opioid dependence based on ICD-10 or DSM-IV.	Percent of patients using drugs in whole sample: Cocaine→48.2%	Percent of patients in whole sample: HIV→ 3.6%, Syphilis→ 0.4%, HBV→ 57.4%, HCV→ 57.5%	Total ITT sample: 38.1 (7.6)	Total ITT sample: 81.5%	SROM: once per day/mean dose of 791 mg per day Methadone: oral /once per day/mean dose of 103 mg per day	No information.	22 weeks (11 weeks before cross-over)
Robertson et al. (2006)[28]	Opioid dependence based on local procedures (No specific criteria mentioned)	Percent of patients using drugs for dihydrocodeine and methadone groups respectively: Alcohol→ 17%, 26%; Cocaine or crack→ 18%, 19%; Amphetamines or MDMA→ 22%, 18%; Cannabis→ 66%, 71%; Benzodiazepines→ 78%, 77%	Percent of patients for dihydrocodeine and methadone arms respectively: HIV→ 1%, 0%; HBV→ 2%, 4%; HCV→ 9%, 8%	16-55 years old for both groups, 80% of dihydrocodeine and 90% of methadone group were 16-35.	Dihydrocodeine: 72%; Methadone: 71%	Dihydrocodeine: equivalent dose to methadone in form of 30mg-60mg tablets/twice per day Methadone: 40-150mg per day	No information.	36 months

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Strain et al. (1993a)[29] Strain et al. (1993b)[30] Strain et al. (1998)[31]	Intravenous opioid dependence based on documentation of previous treatment for opioid dependence or legal involvement secondary to opioid use, a urine sample positive for opioids, and physical examination consistent with acute and chronic needle use.	Percent of patients using drugs for methadone 0mg, 20mg, and 50mg doses respectively: Alcohol→ 25%, 22%, 23%; Cocaine→ 43%, 55%, 45%; Marijuana→ 5%, 4%, 7%; sedatives-hypnotics→ 9%, 10%, 13%	Patients were excluded if they had chronic medical or major mental illnesses.	0mg: 33.4 (5.6); 20mg: 33.1 (5.7); 50mg: 34.6 (6.4)	0mg: 72%; 20mg: 67%; 50mg: 70%	Methadone (0mg): once per day Methadone (20mg): once per day Methadone (50mg): once per day	All patients were assigned an individual counselor, given weekly group therapy which focused on relapse prevention, and provided on-site medical services.	20 weeks
Pani et al. (2000)[50]	Opioid dependence based on DSM-IV	No specific information. (Patients were excluded if they had a current diagnosis of alcohol or hypnotic-sedative dependence based on DSM-IV)	Patients were excluded if they were currently using antiepileptics, disulfiram or neuroleptics.	Buprenorphine: 28 (4); Methadone: 28 (5)	Buprenorphine: 92.1%; Methadone: 79.4%	Buprenorphine: tablets/once per day/stable dose of 8 mg per day Methadone: syrup/once per day/stable dose of 60mg per day All patients received placebo.	All participants were involved in weekly individual counselling session on addiction, health, psychological, relational, and legal-related issues.	6 months

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Strain et al. (1996)[52] Strain et al. (1994)[53]	Opioid dependence based on DSM-III-R (History of at least 1 year of intravenous opioid dependence; no prior methadone treatment episode longer than 21 days; no prior history of buprenorphine treatment)	Percent of patients using drugs for buprenorphine and methadone arms respectively: Alcohol→ 62%, 54%; Cocaine→ 64%, 69%; Sedative-hypnotics→ 12%, 11%	Patients were excluded if they had chronic medical or major mental illnesses.	Buprenorphine: 32.2 (5.5); Methadone: 32.8 (6.1)	Buprenorphine: 68%; Methadone: 74%	Buprenorphine: both oral and sublingual medications at each administration, one of which was active/once per day/2,4,6,8mg (during first 4 days (induction)) and stabilized at 8mg per day/average dose of 8.9mg Methadone: both oral and sublingual medications at each administration, one of which was active/once per day/20, 30, 40, 50mg (during first 4 days (induction)) and stabilized at 50mg per day/average dose of 54mg	All patients received individual counselling, and weekly group therapy, focused on relapse prevention; on-site medical services were also available.	16 weeks

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Dean et al. (2004)[54] Mattick et al. (2003)[55]	Opioid dependence based on DSM-IV (Opioid substitution treatment in the month preceding the study was an exclusion criteria)	Mean (SD) frequency of drug use per day for buprenorphine and methadone arms respectively: Alcohol (n drinks)→ 0.7 (1.7), 0.7 (2.0); Cocaine (rate)→ 0.1 (0.3), 0.2 (0.9); Amphetamine (rate)→ 0.02 (0.1), 0.02 (0.2); Cannabis (n joints)→ 2.5 (5.7), 2.9 (5.9); Tobacco (n cigarettes)→ 22 (11.7), 20 (11.7); Tranquilizers (n tablets)→ 1.9 (7.3), 0.8 (2.7)	Patients were excluded if they were using disulfiram, anticonvulsant, or antipsychotic medications.	Buprenorphine: 29.2 (7.53); Methadone: 29.8 (7.78)	Buprenorphine: 63%; Methadone: 61%	Buprenorphine: daily dose mean SD 8.6 (4.1), dose range of 2-32mg per day in weeks 1-6, starting week 7-13 trice weekly doses with double dose Methadone: daily dose mean SD 50.1 (24.3), range 20-150/ single-day or alternate day dosing was allowed depending on individual needs	No information.	13 weeks
Neri et al. (2005)[51]	Opioid dependence based on DSM-IV	No specific information. (Patients were excluded if they had codependence of alcohol, amphetamines, cannabinoids and benzodiazepines; however sporadic use with less than a month with less than a month with negative urine screen at recruitment was acceptable)	No specific information.	Buprenorphine: 24 (5); Methadone: 27 (6)	Buprenorphine: 87%; Methadone: 90%	Methadone: oral syrup/medium dose of 100 mg per day Buprenorphine: sublingual/final dose of 30.40 (2.8) mg per day	No information.	12 months

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Krook et al. (2002)[56]	Opioid dependence based on DSM-IV	All patients were polysubstance dependent, with the most commonly used substances at baseline being benzodiazepines and cannabis.	No specific information.	Buprenorphine: 38 (range 26-49); Placebo: 38 (range 29-53)	Buprenorphine: 65.5%; Placebo: 67%	Buprenorphine: sublingual tablets/16 mg per day Placebo: sublingual tablets	No additional control or psychosocial treatment or support was provided.	12 weeks
Dunlop et al. (2017)[57]	Opioid dependence based on DSM-IV (Opioid agonist treatment in the previous month, or more than two weeks of consecutive opioid agonist treatment in the previous 3 months was an exclusion criteria)	Days of drug use in previous month for Buprenorphine/naloxone and waitlist arms respectively: Alcohol→ 4.6 (8.8), 2.3 (3.9); Amphetamine→ 2.0 (3.6), 0.5 (0.7); Tobacco→ 26.9 (5.6), 26.9 (5.6) (Participants were excluded if they had current substance dependence to alcohol, benzodiazepines, amphetamines or cocaine)	Participants were ineligible if they had concurrent major medical or psychiatric conditions where immediate opioid agonist treatment and/or other treatments were clinically indicated.	Buprenorphine/naloxone: 36.1 (7.3); Waitlist: 37.7 (9.0)	Buprenorphine/naloxone: 60%; Waitlist: 52%	Buprenorphine-Naloxone: target dose of 16-24 mg/once daily average dose of 21.0 (5.8 (SD)) mg at week 4, 22.3 (5.0 (SD)) mg at week 8, and 22.7 (5.7 (SD)) mg at week 12 Waitlist: participants were given access to methadone or buprenorphine maintenance treatment on request	No specific additional services provided.	12 weeks

Study	Inclusion/exclusion Criteria	Other Drug Use at Baseline	Concurrent Conditions	Age, Mean (SD if reported)	Male Sex, (%)	Main Interventions	Ancillary services	Duration
Streck et al. (2018)[58]	Opioid use disorder DSM-V	Percent of patients using drugs in previous month for buprenorphine and waitlist arms respectively: Cocaine→28%, 32%. (Participants were excluded if they were physically dependent on sedative-hypnotics or alcohol)	Participants had to be clear of unstable psychiatric (active psychosis) or medical (acute cardiovascular disease) illness that could interfere with participation.	Buprenorphine: 33.6 (10.0); Waitlist: 35.7 (10.7)	Buprenorphine: 60%; Waitlist: 56%	Buprenorphine: sublingual tablets/ self-administered daily Waitlist: no medication	No psychological counselling or social support provided.	12 weeks
Haight et al. (2019)[32]	Moderate or severe opioid use disorder based on DSM-V (Medication-assisted treatment for opioid use disorder in the 3 month prior to start of the study was an exclusion criteria)	Percent of patients using drugs for buprenorphine combined and placebo combined arms respectively: Alcohol→ 79.2%, 81%; Cocaine→ 43.06%, 42%; Amphetamine/metamphetamine→ 20.29%, 19.0%; Cannabinoids→ 51.48%, 53.0%; Benzodiazepines→ 11.14%, 13.0%; Tobacco→ 92.33%, 93% Patients were excluded if they had concurrent non-opioid substance use disorder.	Percent of patients with concurrent conditions for buprenorphine combined and placebo combined arms respectively: HCV→ 13.61%, 10%; Depression → 12.38%; 13%; Anxiety→ 9.16%, 10%;	Buprenorphine (300/100-300/300): 39.3 (11.0)-40.4 (11.2); Placebo: 39.2 (11.0)	Buprenorphine: 67.08%; Placebo: 65%	RBP300/100: injection/300 mg on days 1 and 29; 100 mg monthly from day 57. RBP300/300: injection/600 mg/ monthly from day 1. Placebo1: matched RBP300/100. Placebo2: injectionsmatched RBP300/300.	Participants could receive loperamide and non-opioid medications to alleviate opioid withdrawal symptoms. All participants received weekly individual drug counselling.	24 weeks

Table 3.2 Risk of bias assessment for mental health outcomes

	Study	Randomization Process	Deviations from Intended Interventions (Effect of Assignment to Intervention)	Deviations from Intended Interventions (Effect of Adhering to Intervention)	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Results	Overall
DAM-HDM	Oviedo-Joekes et al. (2016)[33] Oviedo-Joekes et al. (2015)[34]	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
DAM-Methadone	Van den Brink et al. (2003)[36]	Low Risk	Some Concerns	High Risk	High Risk	High Risk	Some Concerns	High Risk
	March et al. (2006)[40]	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Some Concerns	High Risk
	Reimer et al., (2011)[41] Karow et al. (2010)[42] Hassen et al. (2007)[43]	Low Risk	High Risk	High Risk	Low Risk	High Risk	Some Concerns	High Risk
	Oviedo-Joekes et al. (2009)[44]	Some Concerns	High Risk	High Risk	High Risk	Low Risk	Some Concerns	High Risk
	Demaret et al. (2015)[45]	Low Risk	High Risk	High Risk	Low Risk	High Risk	Some Concerns	High Risk
	Metrebian et al. (2014)[37] Strang et al. (2010)[38] Lintzeris et al. (2006)[39]	Low Risk	High Risk	High Risk	High Risk	High Risk	Low Risk	High Risk

	Study	Randomization Process	Deviations from Intended Interventions (Effect of Assignment to Intervention)	Deviations from Intended Interventions (Effect of Adhering to Intervention)	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Results	Overall
SROM-Methadone	Eder et al. (2005)[46] Winklbaur et al. (2008)[47]	Low Risk	High Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
	Verthein et al. (2014)[48] Beck et al. (2014)[49]	Some Concerns	Low Risk	Low Risk	Some Concerns	High Risk	Some Concerns	High Risk
DHC-Methadone	Robertson et al. (2006)[28]	Some Concerns	High Risk	High Risk	High Risk	High Risk	Some Concerns	High Risk
Methadone Dose 50/20-Dose 0	Strain et al. (1993a)[29] Strain et al. (1993b)[30] Strain et al. (1998)[31]	Some Concerns	High Risk	High Risk	High Risk	Low Risk	Some Concerns	High Risk
Buprenorphine-Methadone	Pani et al. (2000)[50]	Some Concerns	High Risk	High Risk	High Risk	Low Risk	Some Concerns	High Risk
	Strain et al. (1996)[52] Strain et al. (1994)[53]	Some Concerns	High Risk	High Risk	High Risk	Low Risk	Some Concerns	High Risk
	Dean et al. (2004)[54] Mattick et al. (2003)[55]	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	High Risk
	Neri et al. (2005)[51]	Some Concerns	High Risk	High Risk	High Risk	High Risk	Some Concerns	High Risk

	Study	Randomization Process	Deviations from Intended Interventions (Effect of Assignment to Intervention)	Deviations from Intended Interventions (Effect of Adhering to Intervention)	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Results	Overall
Buprenorphine-Waitlist/Placebo	Krook et al. (2002)[56]	Low Risk	Some Concerns	High Risk	Low Risk	High Risk	Some Concerns	High Risk
	Dunlop et al. (2017)[57]	Low Risk	High Risk	High Risk	High Risk	High Risk	Low Risk	High Risk
	Streck et al. (2018)[58]	Some Concerns	Some Concerns	High Risk	Low Risk	High Risk	Low Risk	High Risk
	Haight et al. (2019)[32]	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	High Risk

3.4 Narrative synthesis

For the pairwise comparison of hydromorphone (HDM)-diacetylmorphine (DAM), only one study was included comparing injectable HDM with injectable DAM in patients with severe opioid use disorder and poor physical/psychosocial conditions, most of whom had a history of relapse after previous methadone treatments (Table 3.1).[33,34] Oral methadone and counselling services were available to all participants. No significant difference was reported in improvement of mental health outcomes, i.e. depressive symptoms and overall mental health changes were similar between the two treatments after 6 months of therapy.

For the pairwise comparison of DAM-methadone, overall, six studies compared injectable heroin (DAM) with oral methadone, while in 2 of the studies inhalable heroin and injectable methadone were provided as well (Table 3.1).[36-39] In all studies, patients were provided with psychosocial care, and those in the heroin treatment had access to optional oral methadone. Patients mostly had a history of relapse after methadone treatments and were polydrug users, except for one study, where such relevant information was not reported for the participants but it was common in the local area the trial was conducted.[40] Patients in 4 studies had poor physical/psychosocial health conditions or high levels of serious comorbid medical conditions like HIV and HCV.[36,40-44] Duration of studies varied from 6 to 12 months. While 2 studies mainly reported no significant differences between the two treatments on various mental health scales,[36,37,40,41] 4 studies reported superiority of DAM on some scales particularly overall mental health measured by SCL-90.[36,41,44,45] Heterogeneity indexes demonstrated a low level of between study variance (Tau^2) and inconsistency (I^2) for depressive symptoms, almost zero variance and inconsistency for overall mental health measured by SCL-90, low variance and moderate inconsistency for psychiatric status measured by ASI, and zero variance and inconsistency for mental health quality of life (Figures 2-5).

For the pairwise comparison of dihydrocodeine-methadone, only one study was included comparing oral dihydrocodeine and oral methadone in patients with opioid dependence (Table 3.1).[28] Majority of patients were using other comorbid substances at baseline, as well. Prevalence of serious comorbid conditions were low in the sample. No significant difference was reported in the improvement of psychological health measured by Maudsley Addiction Profile (MAP) after 36 months of therapy.

For the pairwise comparison of slow-release oral morphine (SROM)-methadone, two studies compared SROM with oral methadone in patients with opioid dependence. Polysubstance dependence was an exclusion criteria in one study with no information on serious comorbid conditions,[46,47] while cocaine use and HBV/HCV was reported in half of the sample at baseline in the other study.[48,49] Standardized psychosocial counseling was provided in one study,[46] while no relevant information was provided by the other report.[48] After 14-22 weeks of treatment, SROM was superior to methadone on almost all measures of mental health including depressive symptoms, anxiety symptoms, overall mental health, and different subscales of SCL-27 (Table 3.1). Assessment of heterogeneity was not feasible as there were insufficient data for meta-analysis on the overlapping outcomes between the two studies.

For the pairwise comparison of methadone dose 0-dose 25/50, only one included study compared 3 different doses of oral methadone, i.e. 0mg, 20mg, and 50mg, in patients with intravenous opioid dependence, who did not have chronic medical illness or major psychiatric comorbidities (Table 3.1).[29] Counselling services were available to all participants. No significant difference was reported in improvement of depressive symptoms among the 3 different dosing groups after 20 weeks of therapy. The fixed-dose of methadone in this study was not consistent with current flexible-dose treatment guidelines and was well below the reported average methadone dose in other trials that were included in our review.

For the pairwise comparison of methadone-buprenorphine, four studies compared oral methadone with oral buprenorphine in patients with opioid dependence, who had to have no other substance dependence in two of the studies,[50,51] and had moderate to high prevalence of using other substances in the other two studies.[52-55] In three studies, patients also had to have no history of disulfiram, antipsychotic, or anti-convulsant use, or history of major mental illness including schizophrenia.[50,52,54] During the 3-6 months of therapy, there was no significant difference between methadone and buprenorphine in an array of mental health outcomes, while two studies reported superiority of methadone in improving depressive, obsessive compulsive, and phobic anxiety symptoms,[50] as well as psychological problems in the past 30 days measured at baseline and follow-up visits.[52] One study reported superiority of buprenorphine to methadone in improving depressive symptoms.[51] Heterogeneity indexes demonstrated a high level of between-study variance (Tau^2) and inconsistency (I^2) for depressive symptoms (Figure 2).

For the pairwise comparison of buprenorphine-waitlist/placebo, four studies compared oral buprenorphine, depot buprenorphine, and buprenorphine/naloxone with either placebo (2 studies) or waitlist controls (2 studies) (Table 3.1) in patients with opioid use disorder, who were explicitly substitution treatment-free within 1-3months prior to beginning the study. In one study,[56] all patients were polysubstance dependent with no information provided regarding serious medical comorbidities, while in the other 3 studies patients with other substance use disorders or major psychiatric comorbidities were excluded and prevalence of other substance use was reported at baseline.[32,57,58] Weekly individual drug counselling appears to be the only psychosocial care provided in one of the studies.[32] No significant difference was reported between buprenorphine and placebo during 12-24 weeks of treatment, in improving overall mental health, number of anxiety/depression episodes in the past month, or incidence of suicide ideation/attempt. Buprenorphine was superior to waitlist during 12 weeks of treatment in all mental health outcomes including overall mental health measured by K10 and BSI, mental health quality of life, anxiety/depressive/obsessive-compulsive/phobic anxiety symptoms, and psychiatric status measured by ASI. Heterogeneity indexes demonstrated a moderate level of between study variance (Tau^2) but high inconsistency (I^2) for overall mental health (Figure 3).

Figure 3.2 Meta-analysis of depressive symptoms

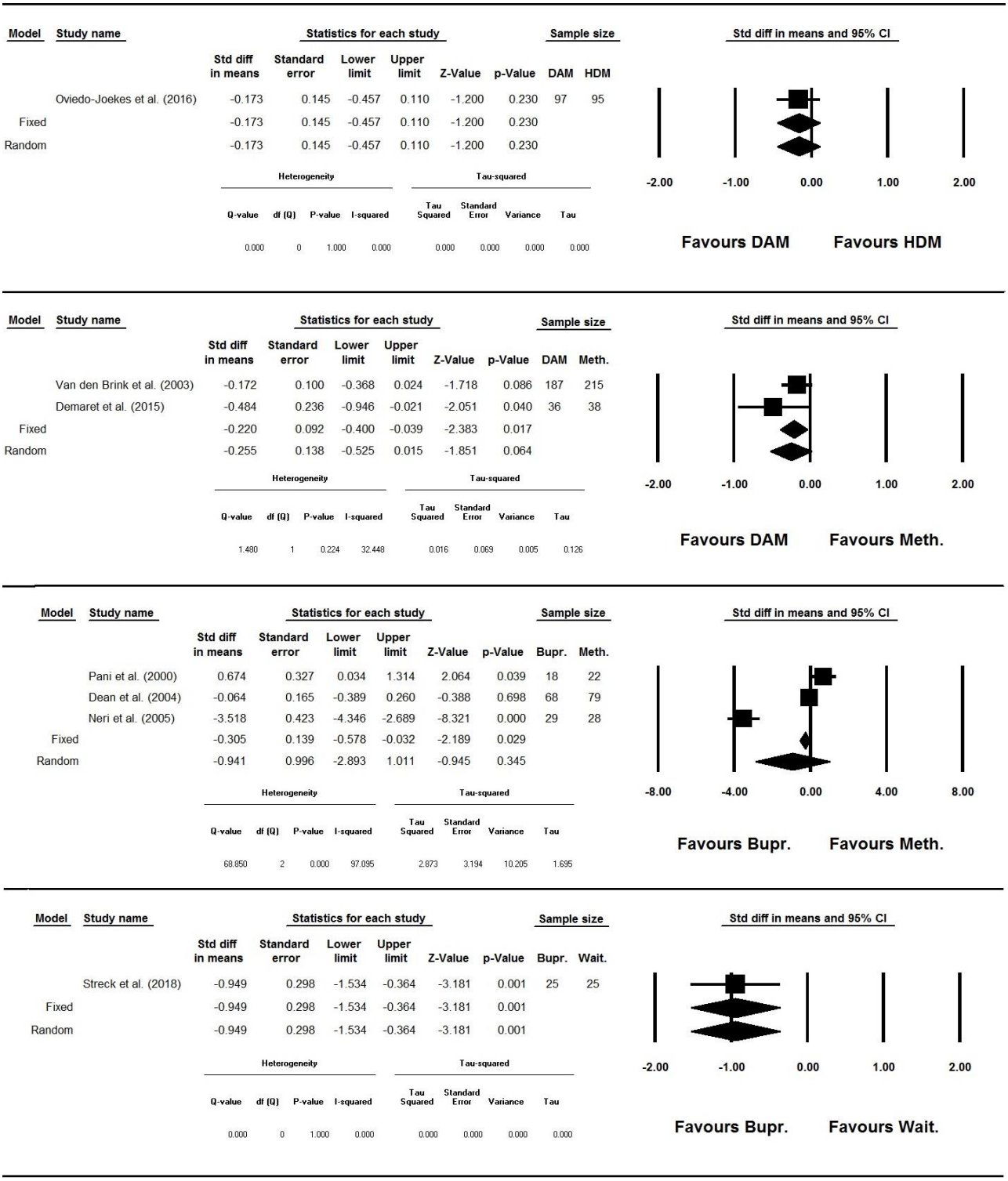


Figure 3.3 Meta-analysis of overall mental health symptomatology

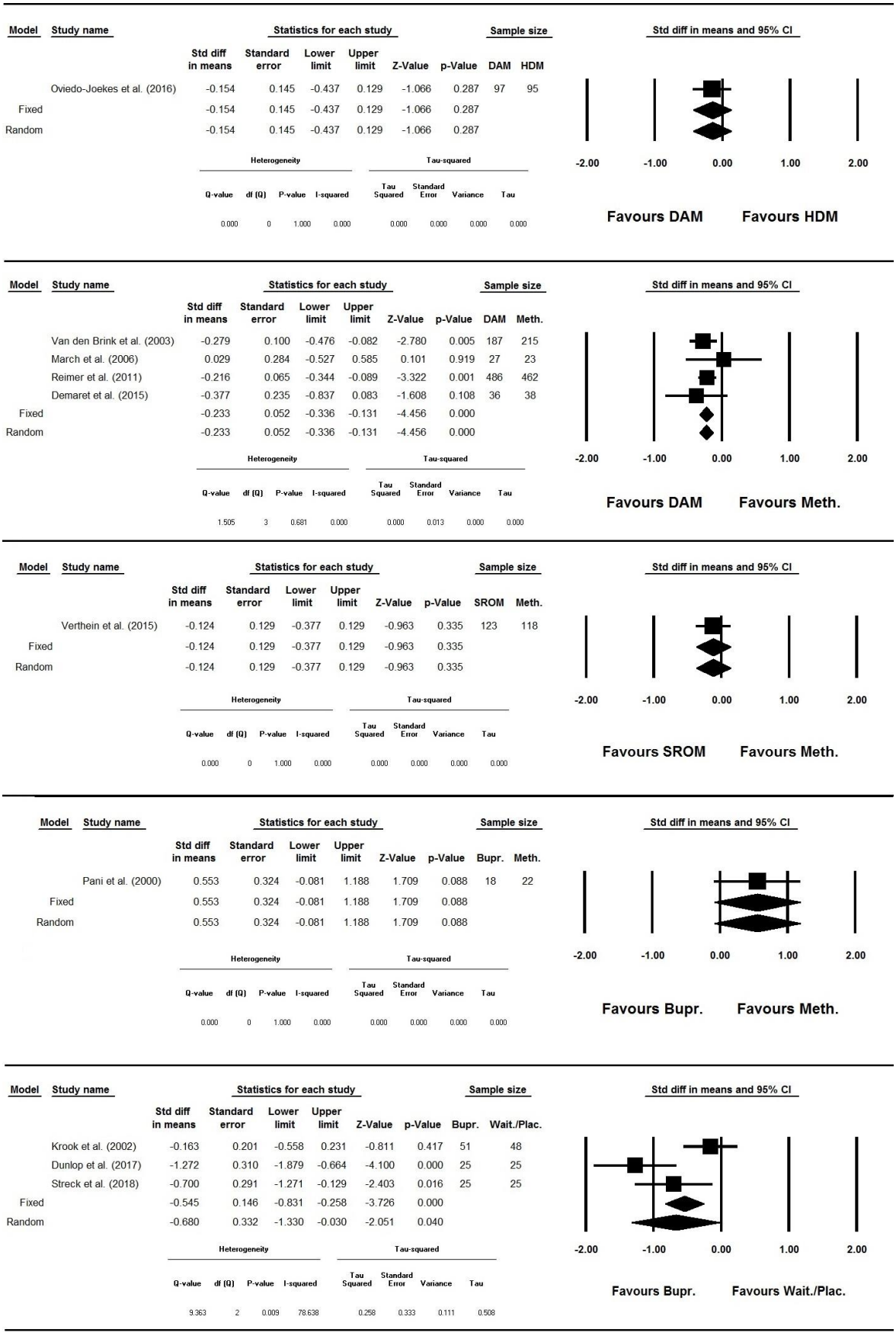


Figure 3.4 Meta-analysis of ASI Psychiatric Status section

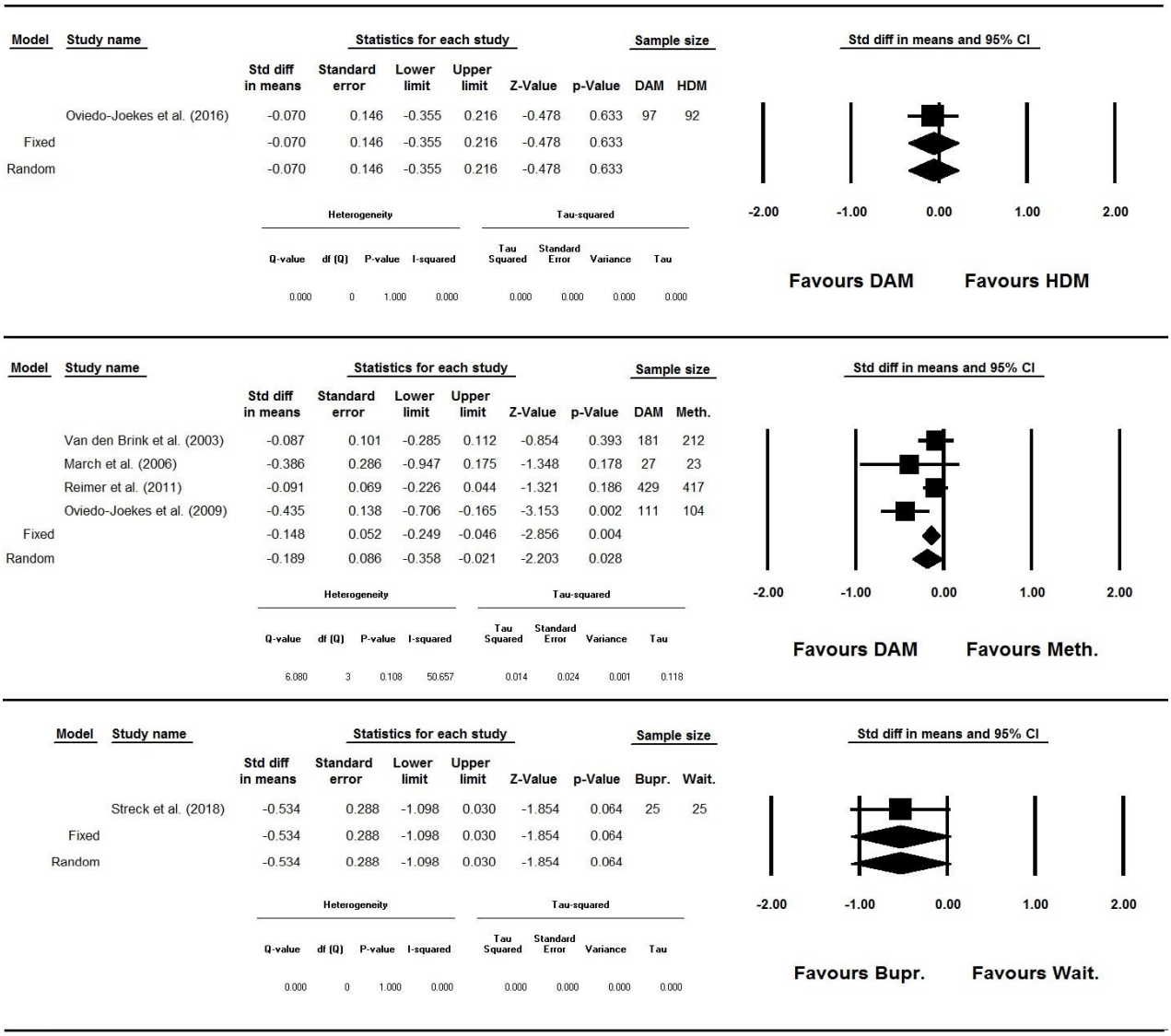
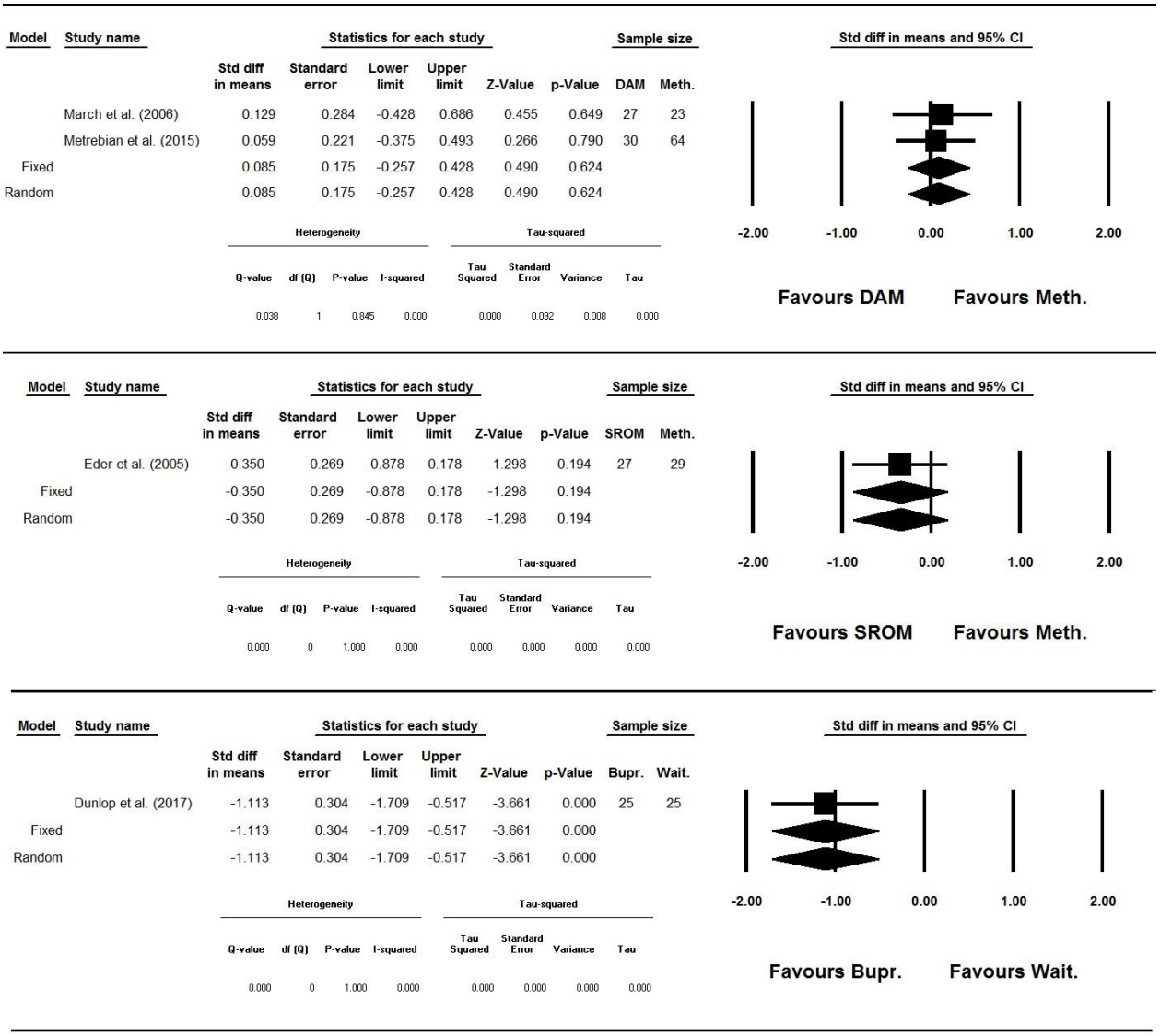


Figure 3.5 Meta-analysis of Mental Health section in Quality of Life



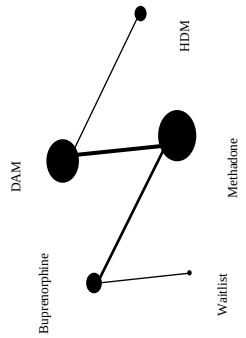
3.5 Quantitative synthesis

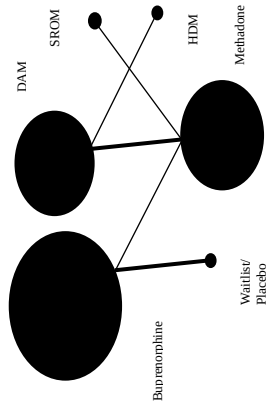
In the direct pairwise comparisons, meta-analysis was applied for depression (Figure 2), overall mental health symptomatology (Figure 3), ASI Psychiatric Status section (Figure 4), and Quality of Life Mental Health section (Figure 5). For depression, there was a trend towards higher effect of diacetylmorphine compared with methadone based on the results of two studies, and significantly higher effect of buprenorphine compared with waitlist based on the results of 1 study. Comparison of DAM with HDM and buprenorphine with methadone were not significant. For overall mental health symptomatology, DAM was significantly more effective than methadone based on the results of 4 studies, and buprenorphine was significantly more effective than placebo/waitlist based on the results of 3 studies. Comparisons of DAM with HDM, buprenorphine with methadone, and SROM with methadone were not significant. For ASI Psychiatric Status section, DAM was significantly more effective than methadone based on the results of 4 studies. Comparisons of DAM with HDM, and buprenorphine with waitlist were not significant. For Quality of Life Mental Health section, buprenorphine was significantly more effective than waitlist based on the results of 1 study. Comparisons of DAM with methadone, and SROM with methadone were not significant. Sensitivity analysis was not applicable as only 1 study had an overall low risk of bias.

In the final analysis, based on the availability of data, NMA was applied for depressive symptoms and overall mental health symptomatology outcomes. For depression, both fixed and random effects models had an acceptable level of convergence based on trace and density plots as well as Potential Scale Reduction Factor (PSRF) values equal to 1.00, but the model fit improved substantially from the fixed effect model (DIC=78.2) to the random effects model (DIC=14.2). Although effect estimates (Table 3) showed higher point estimate effect sizes for all medications compared with waitlist/placebo for decreasing depressive symptoms, the effect sizes were not significant based on random effects model. For overall mental health, both fixed and random effects models had an acceptable level of convergence based on trace and density plots, as well as PSRF values equal to 1.00, and the model fit was comparable between the fixed effects model (DIC=20.9) and the random effects model (DIC=20.2). The effect estimates (Table 3) showed significant effects for all medications in improving overall mental health symptomatology compared to waitlist/placebo in the fixed effect model, and a significant effect for buprenorphine, diacetylmorphine, and methadone in the random effects model, where the highest point estimate effect size was for diacetylmorphine followed by methadone and buprenor-

phine. Finally, based on GRADE guidelines, for all pairwise comparisons between substitution medications and placebo/waitlist, confidence in effect estimates of depressive symptoms and overall mental health was either low or very low (Table 3).

Table 3.3 Summary of findings from Network Meta-analysis and GRADE assessment

Outcome and geometry of the network	**Pairwise comparison**	**Random effects model, SMD (95%CI)**	**Fixed effects model, SMD (95%CI)**	**Certainty of evidence**	**Interpretation of findings**
Depressive symptoms (7 RCTs, 962 participants) 	**HDM- Waitlist (Indirect evidence only)**	-0.23 (-7.90, 7.50)	-0.70 (-1.40, 0.04)	Very Low Study limitations, indirectness, imprecision	Probably Superior
	DAM- Waitlist (Indirect evidence only)	-0.36 (-6.70, 5.80)	-0.86 (-1.50, -0.17)	Very Low Study limitations, indirectness, imprecision	Probably Superior
	Methadone- Waitlist (Indirect evidence only)	-0.036 (-5.20, 5.20)	-0.65 (-1.30, 0.011)	Very Low Study limitations, indirectness, imprecision	Probably Superior
	Buprenorphine-Waitlist (Direct evidence only)	-0.98 (-5.70, 3.50)	-0.95 (-1.50, -0.37)	Low Study limitations, imprecision	Probably Superior

Outcome and geometry of the network	Pairwise comparison	Random effects model, SMD (95%CI)	Fixed effects model, SMD (95%CI)	Certainty of evidence	Interpretation of findings
Overall mental health symptomatology (10 RCTs, 1947 participants) 	**HDM-Waitlist/Placebo (Indirect evidence only)**	-1.20 (-2.80, 0.19)	-1.20 (-1.90, -0.42)	Very Low Study limitations, indirectness, imprecision	Probably Superior
	DAM-Waitlist/Placebo (Indirect evidence only)	-1.40 (-2.70, -0.23)	-1.30 (-2.0, -0.63)	Low or Very Low Study limitations, indirectness	Probably Superior
	Methadone-Waitlist/Placebo (Indirect evidence only)	-1.20 (-2.30, -0.11)	-1.10 (-1.80, -0.40)	Low or Very Low Study limitations, indirectness	Probably Superior
	SROM-Waitlist/Placebo (Indirect evidence only)	-1.30 (-2.80, 0.030)	-1.20 (-2.00, -0.49)	Very Low Study limitations, indirectness, imprecision	Probably Superior
	Buprenorphine-Waitlist/Placebo (Direct evidence only)	-0.61 (-1.20, -0.11)	-0.54 (-0.83, -0.26)	Low Study limitations, inconsistency	Probably Superior

4 Discussion

4.1 Summary of findings

Our findings showed that the 19 included studies were highly variable in terms of severity of substance use disorder and comorbidities, while some specific pairwise comparisons like the methadone-DAM studies were more consistent in their findings and the heterogeneity was not significant. Out of 19 studies, 18 had an overall high risk of bias. The results of direct pairwise meta-analyses indicated that DAM outperformed methadone in the improvement of overall mental health and psychiatric status. Furthermore, buprenorphine outperformed waitlist or placebo in the improvement of depressive symptoms, overall mental health, and mental health quality of life. Other direct pairwise comparisons were not significant. Based on the results of network meta-analysis, buprenorphine, DAM, and methadone were superior to waitlist/placebo in the improvement of overall mental health. None of the medications were superior to waitlist in the improvement of depressive symptoms. In cases where the results were not significant in NMA, the low number of studies was the main culprit. This was implied by the large mean effect sizes and consistency of findings.

4.2 Importance and implications

Previous systematic reviews did not report comparative outcomes and instead focused on longitudinal changes in measures of mental health.[11,12] Feelemyer et al.,[12] only included cohort studies from specific countries while Fingleton et al.[11] included both cohorts and clinical trials from all countries. Both studies reported improved mental health for most medications, but in many of the included studies, medication treatment was provided in conjunction with psychosocial interventions, which makes it hard to conclude that the effects seen were mainly from the medications. In our study, we were able to provide a higher level of evidence for this hypothesis using meta-analysis and network meta-analysis to compare medications with each other and placebo/waitlist, thus eliminating the effects of psychosocial interventions as much as possible. The importance of studying comparative efficacy of opioid agonists on mental health outcomes is several folds; superiority of opioid agonists to placebo/waitlist signifies medication continuation/compliance as an essential part of the treatment approach with added benefits compared to abstinence methods like detoxification. Beyond that, higher efficacy of some opioid agonists over others in improving mental health, hereby DAM to methadone, implies their potential application for treatment of patients with higher psychiatric comorbidities. This also

has implications for treatment guidelines, medication approval, and availability of those medications in various countries. For example, as we already know, DAM is not available as a treatment option in many countries around the world. Last but not least, it implies the importance of integration of addiction psychiatry services to the current treatment systems, as well as training of addiction physicians for assessment of psychiatric comorbidities and tailoring treatment plans to the patients' specific needs.[59]

4.3 Justification and potential mechanisms of action

Potential mechanisms of actions of opioids in improvement of mental health is not well-investigated or reported, compared to the numerous studies on opioid receptor system in craving and withdrawal. Meanwhile, hereby we hypothesize potential pathways through which opioid agonists may improve mental health. In the first place, improved mental health may be an indirect result of less withdrawal or craving, improved sense of well-being, higher quality of life, and more satisfaction-with-life when patients are receiving substitution treatment compared to illicit drugs or the relative abstinence state in waitlist or placebo conditions.[29,32,56,57,60] Beyond this, there is a high prevalence of pain problems among patients participating in substitution treatment,[61,62] and pain is associated with psychiatric comorbidities and depressive symptoms in this population.[61-63] Opioid substitution treatment is the backbone of pain management in these patients,[64] which may help improve psychiatric symptomatology as a results of pain improvement. These aforementioned indirect mechanisms may also well-explain the higher efficacy of DAM compared with methadone in improving mental health, as DAM is a more potent opioid agonist with well-documented superior treatment outcomes.[40-45] Beside the potential indirect effects, direct involvement of the endogenous opioid system in mood and anxiety disorders is discussed in comprehensive reviews,[9,10] and evidence suggests the interaction of opioids with the dopamine system in the treatment of neuropsychiatric conditions other than substance use disorders.[65,66] These later evidence have provided implications for novel clinical applications of opioids.

4.4 Limitations

Implications of our findings are subject to some limitations. First, many of the eligible studies including some well-designed and strong clinical trials did not measure or report any mental health outcomes to be included in this review,[67,68] and from those that were initially included we could not collect enough information from authors of all studies. As a result, we ended up with a single study for some

of the pairwise comparisons, and an open loop in the network meta-analysis which made assessment of heterogeneity and consistency inapplicable, respectively. The low number of studies also rendered findings from NMA not significant in case of overall mental health symptomatology for HDM and SROM despite their large mean effect sizes. Second, in most studies, the quantity and quality of utilized psychosocial interventions were not reported. Third, except for one study, all the included studies had a high overall risk of bias, which rendered sensitivity analysis inapplicable. Previous comprehensive reviews rated risk of bias as medium or low for some of the studies included in this review, using an older version of Cochrane risk of bias tool and focusing on retention in treatment and adverse events.[69] In this review, we assessed mental health as a subjective outcome using the extensively revised and more comprehensive new version of Cochrane risk of bias tool, which together explain lower ratings for risk of bias compared to previous reviews. Fourth, we could not formally assess publication bias due to the low number of studies. Meanwhile, in the majority of included studies, mental health outcomes were among the secondary outcomes, and consequently less prone to influence the publication status.

Despite of the limitations mentioned above, for the specific pairwise comparison of DAM with methadone, there were 2 or more clinical trials on all outcomes with considerable overall sample size and negligible heterogeneity. We should also note that all of these trials were randomized, with baseline characteristics mostly similar among the trial arms in each study, and any psychosocial intervention similarly available to all participants. Moreover, in terms of overall mental health symptomatology assessed by NMA, the low level of confidence in the findings was mainly attributable to the open loops and the limited number of trials. It is important to note that because of the nature of the substance use problem, characteristics of the studied population, and the guidelines for substitution treatment, some sources of bias and lower confidence levels in the evidence from clinical trials are inevitable. Beyond that, conduct of further placebo-controlled studies are not ethically justifiable, meaning that waitlist controlled trials are the only alternative.

4.5 Conclusions

Overall, our findings show that major opioid agonists used in substitution treatment improve mental health, and DAM outperforms methadone in this regard, while further high quality data is required to both reproduce these findings and reliably distinguish the effects of other opioid agonists on the im-

provement of mental health. Future studies may explore the idea of whether patients with higher psychiatric comorbidity may benefit more from certain opioid agonists. Furthermore, recommendations for future research mainly concern design and conduct of future clinical trials of substitution treatment rather than further reviews in the field. In particular, our understanding of the benefits of opioid substitution treatment with respect to mental health outcomes will substantially improve if future studies assess a broad range of psychopathologies as primary outcomes, report their findings in greater details, and reduce the risk of bias through instituting a stricter protocol. Major considerations include double-dummy blinding, planning and reporting analysis methods in advance, dealing with missing data properly and applying intention to treat analysis, clarity in reporting mental health outcomes, and documenting and reporting quantity and quality of ancillary services.

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