Impact of opioid agonist treatment on mental health in patients with opioid use disorder: a systematic review and network meta-analysis of randomized clinical trials

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**ABSTRACT**

**Background:** There is a knowledge gap in systematic reviews on the impact of opioid agonist treatments on mental health.

**Objectives:** We compared mental health outcomes between different opioid agonist treatments and placebo/waitlist, and between the different opioids themselves.

**Methods:** This meta-analysis of randomized clinical trials (RCTs) was pre-registered at PROSPERO (CRD42018109375). Embase, MEDLINE, PsychINFO, CINAHL Complete, and Web of Science were searched from inception to May 2020. RCTs were included if they compared opioid agonists with each other or with placebo/waitlist in the treatment of patients with opioid use disorder and reported at least one mental health outcome after 1-month post-baseline. Studies with psychiatric care, adjunct psychotropic medications, or unbalanced psychosocial services were excluded. The primary outcome was overall mental health symptomatology, e.g., Symptom Checklist 90 total score, between opioids and placebo/waitlist. Random effects models were used for all the meta-analyses.

**Results:** Nineteen studies were included in the narrative synthesis and 15 in the quantitative synthesis. Hydromorphone, diacetylmorphine (DAM), methadone, slow-release oral morphine, buprenorphine, and placebo/waitlist were among the included interventions. Based on the network meta-analysis for primary outcomes, buprenorphine (SMD (95% CI) = −0.61 (−1.20, −0.011)), DAM (−1.40 (−2.70, −0.23)), and methadone (−1.20 (−2.30, −0.11)) were superior to waitlist/placebo on overall mental health. Further direct pairwise meta-analysis indicated that overall mental health improved more in DAM compared to methadone (−0.23 (−0.34, −0.13)).

**Conclusions:** Opioid agonist treatments used for the treatment of opioid use disorder improve mental health independent of psychosocial services.

**Introduction**

In recent years, there has been a significant increase in illicit opioid use and opioid-related fatalities worldwide, with illicit opioids accounting for the greatest harm to the health of people who use drugs among all other substances\textsuperscript{(1)}.

In the United States, 64.3\% of adults with opioid use disorder suffer from a current comorbid mental illness\textsuperscript{(2)}.

Rates of comorbid mental disorders among patients seeking opioid agonist treatment are 20–80\% in Europe and approximately 80\% in Ontario, Canada\textsuperscript{(3,4)}. Despite these high rates of comorbidity, only around one-fourth of adults with concurrent opioid use disorder and acute mental illness receive treatment for both problems\textsuperscript{(2)}.

Regarding the currently practiced approaches that may improve mental health in people with opioid use disorder, the results of using anti-depressants for treatment of patients with comorbid major depression and opioid use disorder are inconsistent\textsuperscript{(3)}. The array of psychosocial interventions studied in the treatment of opioid use
disorder has produced mixed results (3,5). Cognitive behavioral therapy, motivational interviewing, and web-based interventions are more commonly studied as adjunctive therapies to either opioid agonist treatments or withdrawal management programs in patients with opioid use disorder. It appears that drug use and retention in treatment further improves when psychosocial interventions are used in conjunction with naltrexone in detoxification programs, as well as in opioid agonist treatment with methadone, while findings are neutral for treatment with buprenorphine (5). Mental health outcomes are understudied and rarely reported for these interventions and have produced heterogeneous results.

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 treatment strategies. Opioid agonist treatments are the mainstay and first line of treatments in opioid use disorder. Buprenorphine and methadone have been used for a long time in most parts of the world, including North America and Europe. More potent agonists like hydromorphone and diacetylmorphine have just been recently approved by Health Canada for severe opioid use disorder and urgent public health needs, while they are not among the treatment options in the USA. However, in some parts of Europe, such as Germany, diacetylmorphine has been in use for years, in addition to other opioid agonist treatment options, like dihydrocodeine and slow-release oral morphine.

Opioid agonists have a long history in the treatment of mood disorders even before anti-depressants became available on the market (6,7). 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). Based on our literature search, there have been only two systematic reviews on mental health-related outcomes in opioid agonist treatment (11,12). While both studies reported improved mental health outcomes in opioid agonist treatment, the scope of their review was limited and they were unable to distinguish between the effects of opioid agonists on mental health from the potential effects of adjunctive psychosocial interventions, because they lacked any comparison between treatment arms.

In order to further clarify the potential role of opioid agonist treatments in improving mental health in patients with opioid use disorder, we conducted a comparative assessment of mental health outcomes between opioid agonist treatments and control conditions (i.e. placebo or waitlist), in clinical trials of opioid agonist treatment. The aggregated results of direct comparisons of mental health outcomes between different opioid agonists are also provided.

Materials and methods

Protocol

The PRISMA guidelines and the latest version of the Cochrane Handbook were employed 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.

Research question and inclusion/exclusion criteria

The primary question was whether mental health outcomes improve in active opioid agonist treatment more than neutral control conditions such as placebo/waitlist, independent of psychosocial interventions, in patients with opioid use disorder. The secondary question was whether mental health outcomes differentially improve during treatment with diverse opioid agonists in patients with opioid use disorder. Randomized clinical trials were included if they compared any opioid agonists with each other or with placebo/waitlist in the 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 were excluded if patients received comprehensive psychiatric care or were randomized to adjunctive interventions such as focused psychotherapy or adjunctive psychotropic medications. Ancillary routine counseling was acceptable if it was available to all the participants in a study and was provided in the same way across all treatment arms.

Search strategy

The search strategy was developed by the lead author and discussed with an expert panel consisting of coauthors who have had substantial experience in conducting systematic reviews. The following general combination of search terms and Boolean operators were used: [names of all known opioid treatments separated by OR] AND [terms related to clinical trials separated by OR] AND [terms related to mental health outcomes separated by OR]. The exact search strategy used for each database is presented in Supplementary Table 1. On September 10, 2018, a comprehensive list of databases was searched including: EBM Reviews – Cochrane
Central Register of Controlled Trials, Embase, MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, PsychInfo, 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 opioid agonist treatments was performed to find additional full-texts. Experts in the field were also consulted. In May 2019 and May 2020, we updated our search to find any relevant newly published studies by searching the literature post September 2018 and consulting experts in the field.

**Study selection**

Four authors worked in parallel, two by two, to screen all the retrieved citations after they were calibrated for the specific inclusion/exclusion criteria using a sample of 20 challenging citations selected by the lead and senior investigators. These citations were assessed by all four authors and discussed with the lead and senior investigators to reach a consensus regarding any disparities in assessment results. Then, the retrieved citations from the systematic search stage were equally distributed in half among the two pairs of authors. In a two-stage process, authors first screened the titles/abstracts, and then screened the full-text of citations. At each stage, discrepancies in the results were resolved between the screeners after reaching a consensus with both the lead and senior investigators. 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.

**Data extraction**

Four authors carried out data extraction on a primary sample of four studies, where results were compared, discussed, and calibrated amongst them and the lead investigator. Afterward, the four authors worked in parallel pairs to extract data from all studies. Final results were compared, and in cases of discrepancy, a consensus was reached after discussion with the lead and senior investigators. Relevant data were extracted from the included studies using excel sheets with predefined columns, including those mentioned in Table 1 as well as details of analytical methods and reported statistics. For each mental health outcome, we recorded: primary or secondary, the scale of measurement, baseline and follow-up values, the timeline of measurements, and any summary measures reported, in addition to the statistical tests that were used.

**Risk of bias assessment**

Four authors conducted a risk of bias assessment on a primary sample of five studies, in which results were compared, discussed, and calibrated amongst them and the lead investigator. This was followed by the two pairs of authors working in parallel and assessing the risk of bias in all studies. Final results were compared, and in cases of discrepancy, a consensus was reached after discussion with the lead and senior investigators. The recently released comprehensive Cochrane Risk of Bias Tool version 2 (RoB2), which evaluates each outcome for six domains of potential bias, as well overall risk of bias, was used for the assessment of single studies (44). In cases of similarity among the assessment results for the different outcomes of a single study, a single assessment result was reported for the whole study.

**Outcomes, synthesis strategy, and measures**

Primary outcomes included the standardized mean difference in score changes from baseline to endpoint between opioid agonists and placebo/waitlist for depressive symptoms and overall mental health symptomatology. Secondary outcomes included the standardized mean difference in score changes among different opioid agonists for any measure of mental health. A narrative synthesis was carried out by putting together studies on direct comparison of each specific pair of treatments, e.g. methadone and buprenorphine. Characteristics of those studies, as well as the reported mental health outcomes were used for this synthesis. The quantitative synthesis was carried out in two stages: assessing primary outcomes using network meta-analysis, and direct pairwise meta-analyses for secondary outcomes.

For the quantitative synthesis only, data from the following measures of mental health were combined: depression subscale of Symptom Checklist-90 (SCL-90) as well as shorter versions, Beck Depression Inventory (BDI), or Self Rating Depression Scale (45,46); total scores/global severity index from SCL-90, as well as shorter versions, Brief Symptom Inventory (BSI), or Kessler psychological distress scale (K10) (47–49); composite scores of psychiatric status on Addiction Severity Index (ASI) or European ASI (50); and mental health quality of life measured by Short Form Health Survey-36 (SF36) or Lancashire Quality of Life Profile (LQOLP) (51,52).

The SCL-90 consists of nine subscales, including somatization, obsessive compulsion, interpersonal
Table 1. Summary of studies included in the systematic review of mental health outcomes in opioid agonist treatment.

| Study                          | Inclusion Criteria          | Other Drug Use                  | Concurrent Conditions                                                                 | Age, mean | Male Sex, % | Main Interventions                                                                 | Ancillary Services                      | Duration | Scales and mental health outcomes | Results |
|-------------------------------|----------------------------|--------------------------------|---------------------------------------|-----------|-------------|----------------------------------------|----------------------------------------|----------|----------------------------------|---------|
| Oviedo-Joekes et al. (14)     | Severe opioid use disorder (DSM-V) | Crack cocaine                  | Patients had to be in poor physical health or psychosocial functioning                  | HDM: 45.17; DAM: 43.50 | HDM: 67%; DAM = 71.6% | DAM: injectable/average 454.0 mg daily plus 23.64 mg methadone daily DAM: injectable/after conversion to equivalent doses of DAM/average 212.6 mg daily plus 24.58 mg methadone daily | Addiction counselors, social workers, and allied health professionals | 6 months | _SCL-90/depressive symptoms _SCL-90/overall mental health _EuroASI/psychiatric status _MAP/psychological health | _NS     |
| Oviedo-Joekes et al. (15)     |                            |                                |                                       |           |             |                                        |                                        |          |                                  |         |
| Van den Brink et al. (16)     | Opioid dependence (DSM-IV)  | Cocaine; Amphetamines          | Patients had poor physical or mental health or poor social functioning                  | 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/average 540 mg of heroin and 57 mg of methadone daily Methadone: oral methadone arms combined/average 67–71 mg daily | Standard medical and psychosocial services | 12 months | _SCL-90/depressive symptoms _SCL-90/overall mental health _EuroASI/psychiatric status | _Favors Heroin _NS |
| March et al. (17)              | Opiate dependence (ICD-10)  | No specific information         | HN; HCV; HBV                                                                          | DAM: 37.0; Methadone: 37.3 | DAM: 83.9%; Methadone: 96.8% | DAM: intravenous/average 274.5 mg daily with 42.6 mg daily oral methadone Methadone: oral/average 105 mg daily | Legal problem solving and arranging invalidity benefit, housing, and other social resources, as well as psychiatric, psychotherapeutic, and medical treatments for concomitant disease | 9 months | _SCL-90/overall mental health _ASI/psychiatric status _SF-12/mental health quality of life | _NS |

(Continued)
| Study                  | Inclusion Criteria | Other Drug Use                  | Concurrent Conditions | Age, mean | Male Sex, % | Main Interventions                                                                 | Ancillary Services                                           | Duration | Scales and mental health outcomes                                      | Results       |
|-----------------------|--------------------|---------------------------------|-----------------------|-----------|-------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------|----------|------------------------------------------------------------------------|---------------|
| Reimer et al. (18)    | Opioid dependence  | Alcohol; Cocaine; Benzodiazepines | HIV; HCV; HBV         | Heroin: 36.2; Methadone: 36.6 | Heroin: 80%; Methadone: 79.8% | Heroin: injectable/average 442 mg daily with an additional 8 mg daily oral methadone Methadone: oral/average 99 mg daily | Psychosocial care including case management, and either integrated case management and motivational interviews or drug counseling and psychoeducation | 12 months | _SCL-90/overall mental health_                              | _Favors Heroin |
| Karow et al. (19)     | Opioid dependence  | Alcohol; Cocaine; Benzodiazepines | HIV; HCV; HBV         | Heroin: 36.2; Methadone: 36.6 | Heroin: 80%; Methadone: 79.8% | Heroin: injectable/average 442 mg daily with an additional 8 mg daily oral methadone Methadone: oral/average 99 mg daily | Psychosocial care including case management, and either integrated case management and motivational interviews or drug counseling and psychoeducation | 12 months | _EuroASI/psychiatric status_                      | _Favors Heroin |
| Hassen et al. (20)    | Opioid dependence  | Alcohol; Cocaine; Benzodiazepines | HIV; HCV; HBV         | Heroin: 36.2; Methadone: 36.6 | Heroin: 80%; Methadone: 79.8% | Heroin: injectable/average 442 mg daily with an additional 8 mg daily oral methadone Methadone: oral/average 99 mg daily | Psychosocial care including case management, and either integrated case management and motivational interviews or drug counseling and psychoeducation | 12 months | _EuroASI/psychiatric status_                      | _Favors Heroin |
| Oviedo-Joekes et al.  | Opioid dependence  | Alcohol; Cocaine; Benzodiazepines | HIV; HCV; HBV         | Heroin: 36.2; Methadone: 36.6 | Heroin: 80%; Methadone: 79.8% | Heroin: injectable/average 442 mg daily with an additional 8 mg daily oral methadone Methadone: oral/average 99 mg daily | Psychosocial care including case management, and either integrated case management and motivational interviews or drug counseling and psychoeducation | 12 months | _EuroASI/psychiatric status_                      | _Favors Heroin |
| Demaret et al. (22)   | Opioid dependence  | Alcohol; Cocaine; Benzodiazepines | HIV; HCV; HBV         | Heroin: 36.2; Methadone: 36.6 | Heroin: 80%; Methadone: 79.8% | Heroin: injectable/average 442 mg daily with an additional 8 mg daily oral methadone Methadone: oral/average 99 mg daily | Psychosocial care including case management, and either integrated case management and motivational interviews or drug counseling and psychoeducation | 12 months | _EuroASI/psychiatric status_                      | _Favors Heroin |

(Continued)
| Study                        | Inclusion Criteria | Other Drug Use | Concurrent Conditions | Age, mean | Male Sex, % | Main Interventions                                                                 | Ancillary Services                                                                 | Duration | Scales and mental health outcomes                                                                 | Results |
|------------------------------|--------------------|----------------|-----------------------|-----------|-------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------|--------------------------------------------------------------------------------------------------|---------|
| Metrebian et al. (23)        | Opioid dependence  | Alcohol; Crack cocaine; Illicit benzodiazepines Alcohol dependence or regular abuse of benzodiazepines was exclusion criteria | Patients were excluded if they had significant and active medical or psychiatric conditions. | Heroin: 37.5; Methadone (injecting-oral): 37–37.2 | Heroin: 86%; Methadone: 67% | Heroin: injecting/average of 399 mg daily plus 42 mg oral methadone Methadone: injecting average 128 mg daily plus 31 mg supplementary oral, or optimized oral alone mean 107 mg daily | Monthly reviews with a study medical officer, psychologist for individual CBT-based therapy, other ancillary services | 6 months | SF-36/overall mental health quality of life                                                      | _NS     |
| Strang et al. (24)           |                    |                |                       |           |             |                                                                                    |                                                                                      |          |                                                                                                  |         |
| Lintzeris et al. (25)        |                    |                |                       |           |             |                                                                                    |                                                                                      |          |                                                                                                  |         |
| Eder et al. (26)             | Opioid dependence  | Multi-substance dependence was exclusion criteria | No specific information. | SROM: 29.5; Methadone: 27.9 | SROM: 84.4%; Methadone: 90.6% | SROM: oral/average 680 mg daily Methadone: oral/average 85 mg daily Standardized 30-minute psychosocial counseling sessions on a twice-weekly basis | No information.                                                                      | 14 weeks, (7 weeks before cross-over) | BDI/depressive symptoms | _Favors Morphine                                                                                   |         |
| Winklbaur et al. (27)        |                    |                |                       |           |             |                                                                                    |                                                                                      |          |                                                                                                  |         |
| Verthein et al. (28)         | Opioid dependence  | Cocaine        | HIV; Syphilis; HBV; HCV | Total ITT sample: 38.1 | Total ITT sample: 81.5% | SROM: oral/average 791 mg daily Methadone: oral/average 103 mg daily | No information.                                                                      | 22 weeks (11 weeks before cross-over) | SCL-27/overall mental health | _Favors Morphine                                                                                   |         |
| Beck et al. (29)             |                    |                |                       |           |             |                                                                                    |                                                                                      |          | SCL-27/depressive symptoms SCL-27/dysthymic symptoms SCL-27/vegetative symptoms SCL-27/agoraphobic symptoms SCL-27/sociophobic symptoms SCL-27/symptoms of mistrust |         |

(Continued)
| Study | Inclusion Criteria | Other Drug Use | Concurrent Conditions | Age, mean | Male Sex, % | Main Interventions | Ancillary Services | Duration | Scales and mental health outcomes | Results |
|-------|--------------------|----------------|-----------------------|-----------|-------------|-------------------|-------------------|----------|-------------------------------|---------|
| Roberton et al. (30) | Opioid dependence (local procedures) | Alcohol; Cocaine or crack; Amphetamines or MDMA; Cannabis; Benzodiazepines | HIV; HBV; HCV | 80% of dihydrocodeine and 90% of methadone group were 16–35 y | Dihydrocodeine: 72% Methadone: 71% | Dihydrocodeine oral/equivalent dose to methadone (30 mg dihydrocodeine equal to 2.5 mg methadone) Methadone: 40–150 mg daily | No information. | 36 months | _MAP/psychological health | _NS |
| Strain et al. (31) | Intravenous opioid dependence (Documented previous treatment or legal involvement, a positive urine sample, and physical examination) | Alcohol; Cocaine; Marijuana; sedatives-hypnotics | Patients were excluded if they had chronic medical or major mental illnesses. | 0 mg: 33.4; 20 mg: 33.1; 50 mg: 34.6 | 0 mg: 72%; 20 mg: 67%; 50 mg: 70% | Methadone 0 mg daily Methadone 20 mg daily Methadone 50 mg daily Initially stabilized at 25 mg, then titrated to target dose. Target stable doses from week 6–20 (15 weeks). | Individual counselor, weekly group therapy focused on relapse prevention, and on-site medical services | 20 weeks | _BDI/depressive symptoms | _NS |
| Study | Inclusion Criteria | Other Drug Use | Concurrent Conditions | Age, mean | Male Sex, % | Main Interventions | Ancillary Services | Duration | Scales and mental health outcomes | Results |
|-------|--------------------|----------------|-----------------------|-----------|-------------|-------------------|-------------------|----------|-----------------------------------|---------|
| Pani et al. (34) | Opioid \(\text{dependence (DSM-IV)}\) | | Patients were excluded if they were currently using antiepileptics, disulfiram or neuroleptics. | Buprenorphine: 28; Methadone: 28 | Buprenorphine: 92.1%; Methadone: 79.4% | Buprenorphine: oral/8 mg daily plus placebo; Methadone: oral/60 mg daily plus placebo | Weekly individual counseling session on addiction, health, psychological, relational, and legal-related issues | 6 months | _GAF/psychosocial functioning_  | _NS_ |
| Strain et al. (35) | Opioid \(\text{dependence (DSM-III-R)}\) | Alcohol; Cocaine; Sedative-hypnotics | Patients were excluded if they had chronic medical or major mental illnesses. | Buprenorphine: 32.2; Methadone: 32.8 | Buprenorphine: 68%; Methadone: 74% | Buprenorphine: oral/sublingual/average 8.9 mg daily; Methadone: average 54 mg daily | Individual counseling, and weekly group therapy, focused on relapse prevention; on-site medical services | 16 weeks | _SCL-90/overall mental health_ | _NS_ |
| Dean et al. (37) | Opioid \(\text{dependence (DSM-IV)}\) | Alcohol; Cocaine; Amphetamine; Cannabis; Tobacco; Tranquilizers | Patients were excluded if they were using disulfiram, anticonvulsant, or antipsychotic medications. | Buprenorphine: 29.2; Methadone: 29.8 | Buprenorphine: 63%; Methadone: 61% | Buprenorphine: oral/mean 8.6 mg daily; Methadone: oral/mean 50.1 mg daily | No information. | 13 weeks | _SCL-90/overall mental health_  | _NS_ |
| Neri et al. (39) | Opioid \(\text{dependence (DSM-IV)}\) | Codependence of alcohol, amphetamines, cannabinoids and benzodiazepines was exclusion criteria | No specific information. | Buprenorphine: 24; Methadone: 27 | Buprenorphine: 87%; Methadone: 90% | Methadone: oral/medium 100 mg daily; Buprenorphine: sublingual/mean 30.40 mg daily | No information. | 12 months | _SCL-90/overall mental health_  | _NS_ |

(Continued)
| Study | Inclusion Criteria | Other Drug Use | Concurrent Conditions | Age, mean | Male Sex, % | Main Interventions | Ancillary Services | Duration | Scales and mental health outcomes | Results |
|-------|--------------------|----------------|-----------------------|-----------|------------|-------------------|-------------------|----------|-----------------------------------|---------|
| Krook et al. (40) | Opioid dependence (DSM-IV) | All patients were polysubstance dependent. Most commonly used substances: benzodiazepines and cannabis | No specific information. | Buprenorphine: 38; Placebo: 38 | Buprenorphine: 65.5%; Placebo: 67% | Buprenorphine: sublingual/16 mg daily Placebo: sublingual | No additional psychosocial treatment or support was provided. | 12 weeks | _SCL-5/overall mental health_ | _NS_ |
| Dunlop et al. (41) | Opioid dependence (DSM-IV) | Alcohol; Amphetamine; Tobacco | 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; Waitlist: 37.7 | Buprenorphine/ naloxone: 60%; Waitlist: 52% | Buprenorphine- Naloxone: oral/average 21.0–22.7 mg daily Waitlist: access to methadone or buprenorphine maintenance treatment on request | No specific additional services provided. | 12 weeks | _K10/overall mental health_ _SF-12/overall mental health quality of life_ | _Favors_ Buprenorphine | Buprenorphine |
| Streck et al. (42) | Opioid use disorder (DSM-V) | Cocaine Dependence on sedative-hypnotics or alcohol was exclusion criteria | Participants had to be clear of unstable psychiatric or medical illness that could interfere with consent or participation. | Buprenorphine: 33.6; Waitlist: 35.7 | Buprenorphine: 60%; Waitlist: 56% | Buprenorphine: sublingual/self-administered daily Waitlist: no medication | No psychological counseling or social support provided. | 12 weeks | _BAI/anxiety_ _BDI-II/depression_ _BS/overall mental health_ _BS/interpersonal sensitivity_ _BS/amplity_ _BS/obsessive-compulsive symptoms_ _BS/paranoid ideation_ _ASL/psychiatric status_ | _Favors_ Buprenorphine | Buprenorphine |

(Continued)
| Study | Inclusion Criteria | Other Drug Use | Concurrent Conditions | Age, mean | Male Sex, % | Main Interventions | Ancillary Services | Duration | Scales and mental health outcomes | Results |
|-------|--------------------|----------------|-----------------------|----------|------------|-------------------|-------------------|----------|----------------------------------|---------|
| Haight et al. (43) | Moderate or severe opioid use disorder (DSM-V) | Alcohol; Cocaine; Amphetamine/metamphetamine; Cannabinoids; Benzodiazepines; Tobacco | Back pain; HCV; Depression; Anxiety; Insomnia | Buprenorphine (300/100-300/300): 39.3 – 40.4; Placebo: 39.2 | Buprenorphine: 67.08%; Placebo: 65% | RBP300/100: injection/300 mg month 1 and month 2; 100 mg monthly afterward. RBP300/300: injection/600 mg monthly. Placebo1: injection/matched RBP300/100. Placebo2: injection/matched RBP300/300. | Loperamide and non-opioid medications to alleviate opioid withdrawal symptoms; weekly individual drug counseling | 24 weeks | C-SSRS/suicide ideation _NS | NS |

ASI/EuroASI, Addiction Severity Index/European version; BAL, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; C-SSRS, Columbia Suicide Severity Rating Scale; DAM, Diacetylmorphine; DSM-IV/V, Diagnostic and Statistical Manual of Mental Disorders version IV/V; GAF, Global Assessment of Functioning; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HDM, Hydromorphone; HIV, Human Immunodeficiency Virus; ICD-10, International Classification of Diseases version 10; K10, Kessler psychological distress scale; LQOLP, Lancashire Quality of Life Profile; MAP, Maudsley Addiction Profile; NS, not significant; QOL, Quality of Life; SCL-90/27/5, Symptom Checklist 90/27/5; SD, Standard Deviation; SF-12/36, Short Form survey for quality of life 12/36 item; SRDS, Self-Rating Depression Scale; SROM, Slow-Release Oral Morphine; STAI, Sate-Trait Anxiety Inventory
sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychotism. The BSI consists of the same nine subscales, similar to SCL-90. The K10 is a measure of overall psychological distress. The ASI measures the severity of problems in seven functional domains, including physical health, employment/support status, alcohol use, drug use, legal status, family/social functioning, and psychiatric symptoms. The SF-36 has 36 items on eight subscales of physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health, all of which converge on either of the two mental or physical health composite domains. The LQOLP has nine domains of living situation, family, social relationships, leisure activities, work/education, finances, personal safety, health, and religion, resulting in several scores including a composite mental health quality of life score.

The Beck depression inventory and self-rating depression measure depressive symptoms. The SCL-90, BSI, and ASI are more commonly used in studies of substance use disorder in general, and opioid use disorder in particular. Meanwhile, all the mentioned scales have acceptable validity and reliability, as well as considerable inter-scale correlation in specific domains of interest that are used for meta-analysis in this review. The Validity, reliability, and level of correlation of similar measures can be found elsewhere (45–52).

**Statistical analysis**

All the analyses were preplanned. Data from injecting, inhaling, and oral administration of opioid agonists or from different doses of a single opioid agonist were combined for the studies that included more than one administration route or dosing.

For the network meta-analysis (NMA), standardized mean differences (SMD) and standard errors (SE) that were estimated for each single study on each included mental health outcome were used as the input. 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 conducted. Random effects method was used rather than fixed-effect 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 identity link function 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 were used to check for the effect of starting values and proper mixing of chains. Leverage-residual deviance plots were used to decide if the final model was appropriate and measures of model fit such as Deviance Information Criterion (DIC) were reported. 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 opioid agonists with placebo/waitlist.

The quality of evidence for the network meta-analysis was also assessed using guidelines defined by Salanti et al. (53), based on the GRADE guidelines for the assessment of the quality of evidence and overall rating of confidence in the estimates (54).

For the direct pairwise meta-analysis, pooled estimates of SMDs were provided alongside SEs. Comprehensive Meta-analysis v2.0 was utilized for this purpose, using random effects models. Measures of heterogeneity were reported including Q statistic for assessing the 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 studies to make the assessment of small-study effects, including publication bias, feasible. The symmetry of funnel plots does not eliminate the possibility of publication bias, but the asymmetry of plots warrants further scrutiny. By definition, publication bias refers to a systematic bias in the probability of studies getting published based on the significance and direction of their results. Sensitivity analysis was considered if there were more than one study with low risk of bias on a specific outcome. Pooled estimates for these low-risk/high-risk studies would be compared with the combination of low-risk/high-risk studies.

**Results**

**Study selection and overview**

After duplicate removal, 2983 citations were screened (Figure 1). Twenty-two studies initially met the inclusion criteria, but only 19 were included in this review because sufficient data were not received from the authors of three studies (55–57). Furthermore, only 15 studies were included in the quantitative synthesis since outcomes from two of the studies were not reported with adequate details (30–33), and similar measures to the ones used in studies by Haight et al. (43), and Strain et al. (35,36), were not available from other studies in order to be included for quantitative synthesis.

Table 1 represents study characteristics and any mental health outcomes reported in 19 included studies. Table 2 represents the risk of bias assessment for the 19 included studies. The results of the meta-analysis are reported in Table 3, as well as Figure 2–5.
Overall, 2983 unique citations were screened and 19 studies were finally included in this systematic review, out of which 15 were used in the quantitative synthesis.

Figure 1. PRISMA flow diagram of studies assessed for systematic review of clinical trials of opioid agonist treatment.
Table 2. Risk of Bias Assessment for mental health outcomes in clinical trials of opioid agonist treatment.

| Treatment          | Study                          | Randomization Process | Deviations from Intended Interventions | Deviations from Intended Interventions | Missing Outcome Data | Measurement of the Outcome | Selection of the Reported Results | Overall |
|--------------------|--------------------------------|-----------------------|----------------------------------------|----------------------------------------|----------------------|-----------------------------|----------------------------------|---------|
| DAM-HDM            | Oviedo-Joekes et al. (14)      | Low Risk              | Low Risk                               | Low Risk                               | Low Risk             | Low Risk                    | Low Risk                         | Low Risk |
|                    | Oviedo-Joekes et al. (15)      |                       |                                        |                                        |                      |                             |                                  |         |
| DAM-Methadone      | Van den Brink et al. (16)      | Low Risk              | Some Concerns                          | High Risk                              | High Risk            | Low Risk                    | Some Concerns                    | High Risk |
|                    | March et al. (17)              | Low Risk              | Some Concerns                          | High Risk                              | High Risk            | Some Concerns               | Some Concerns                    | High Risk |
|                    | Reimer et al. (18)             | Low Risk              | Some Concerns                          | High Risk                              | High Risk            | Low Risk                    | Some Concerns                    | High Risk |
|                    | Karow et al. (19)              | Low Risk              | Some Concerns                          | High Risk                              | High Risk            | Some Concerns               | Some Concerns                    | High Risk |
|                    | Hassen et al. (20)             | Low Risk              | Some Concerns                          | High Risk                              | High Risk            | Some Concerns               | Some Concerns                    | High Risk |
|                    | Oviedo-Joekes et al. (21)      | Some Concerns         | High Risk                              | High Risk                              | Low Risk             | Low Risk                    | Some Concerns                    | High Risk |
|                    | Demaret et al. (22)            | Low Risk              | High Risk                              | Low Risk                               | Low Risk             | Low Risk                    | Some Concerns                    | High Risk |
|                    | Metrebian et al. (23)          | Low Risk              | High Risk                              | Low Risk                               | Low Risk             | Low Risk                    | Some Concerns                    | High Risk |
|                    | Strang et al. (24)             | Low Risk              | High Risk                              | High Risk                              | Low Risk             | Low Risk                    | Some Concerns                    | High Risk |
|                    | Lintzeris et al. (25)          | Low Risk              | High Risk                              | High Risk                              | Low Risk             | Low Risk                    | Some Concerns                    | High Risk |
| SROM-Methadone     | Eder et al. (26)               | Low Risk              | High Risk                              | Low Risk                               | High Risk            | Low Risk                    | Some Concerns                    | High Risk |
|                    | Winklaur et al. (27)           |                       |                                        |                                        |                      |                             |                                  |         |
|                    | Verthein et al. (28)           | Some Concerns         | Low Risk                               | Low Risk                               | Some Concerns        | High Risk                    | Some Concerns                    | High Risk |
|                    | Beck et al. (29)               |                       |                                        |                                        |                      |                             |                                  |         |
| DHC-Methadone      | Robertson et al. (30)          | Some Concerns         | High Risk                              | High Risk                              | High Risk            | Low Risk                    | Some Concerns                    | High Risk |
| Methadone Dose 50/20- Dose 0 | Strain et al. (31)            | Some Concerns         | High Risk                              | High Risk                              | High Risk            | Low Risk                    | Some Concerns                    | High Risk |
|                    | Strain et al. (32)             |                       |                                        |                                        |                      |                             |                                  |         |
|                    | Strain et al. (33)             |                       |                                        |                                        |                      |                             |                                  |         |
| Buprenorphine-Methadone | Pani et al. (34)             | Some Concerns         | High Risk                              | High Risk                              | High Risk            | Low Risk                    | Some Concerns                    | High Risk |
|                    | Strain et al. (35)             | Some Concerns         | High Risk                              | High Risk                              | High Risk            | Low Risk                    | Some Concerns                    | High Risk |
|                    | Strain et al. (36)             |                       |                                        |                                        |                      |                             |                                  |         |
|                    | Dean et al. (37)               | Low Risk              | Low Risk                               | High Risk                              | Low Risk             | Low Risk                    | Low Risk                         | High Risk |
|                    | Mattick et al. (38)            |                       |                                        |                                        |                      |                             |                                  |         |
|                    | Neri et al. (39)               | Some Concerns         | High Risk                              | High Risk                              | High Risk            | Low Risk                    | Some Concerns                    | High Risk |
| Buprenorphine-Waitlist/Placebo | Krook et al. (40)             | Low Risk              | Some Concerns                          | High Risk                              | Low Risk             | Low Risk                    | Some Concerns                    | High Risk |
|                    | Dunlop et al. (41)             | Low Risk              | Some Concerns                          | High Risk                              | Low Risk             | Low Risk                    | Some Concerns                    | High Risk |
|                    | Streck et al. (42)             | Low Risk              | Some Concerns                          | High Risk                              | Low Risk             | Low Risk                    | Some Concerns                    | High Risk |
|                    | Haight et al. (43)             | Low Risk              | Some Concerns                          | High Risk                              | Low Risk             | Low Risk                    | Some Concerns                    | High Risk |

DAM, Diacetylmorphine; HDM, Hydromorphone; SROM, Slow-Release Oral Morphine
### Table 3. Summary of findings from network meta-analysis and GRADE assessment for mental health outcomes in opioid agonist treatment.

| Outcome and geometry of the network | Pairwise comparison with waitlist or waitlist/placebo as the reference | Random-effects model, SMD (95%CI) | Fixed-effect model, SMD (95%CI) | Certainty of evidence | Interpretation of findings |
|-----------------------------------|-------------------------------------------------|---------------------------------|---------------------------------|------------------------|--------------------------|
| **Depressive symptoms**<br>(7 RCTs, 962 participants) | **HDM** (Indirect evidence only) | −0.23 (−7.90, 7.50) | −0.70 (−1.40, 0.04) | Very Low | Insufficient evidence |
| | **DAM** (Indirect evidence only) | −0.36 (−6.70, 5.80) | −0.86 (−1.50, −0.17) | Very Low | Insufficient evidence |
| **Waitlist/Methadone** | **Methadone** (Indirect evidence only) | −0.036 (−5.20, 5.20) | −0.65 (−1.30, 0.011) | Very Low | Insufficient evidence |
| **Overall mental health symptomatology**<br>(10 RCTs, 1947 participants) | **Buprenorphine** (Direct evidence only) | −0.98 (−5.70, 3.50) | −0.95 (−1.50, −0.37) | Low | Insufficient evidence |
| | **HDM (Indirect evidence only)** | −1.20 (−2.80, 0.19) | −1.20 (−1.90, −0.42) | Very Low | Probably Superior |
| | **DAM (Indirect evidence only)** | −1.40 (−2.70, −0.23) | −1.30 (−2.0, −0.63) | Low or Very Low | Probably Superior |
| **Waitlist/Placebo** | **Methadone (Indirect evidence only)** | −1.20 (−2.30, −0.11) | −1.10 (−1.80, −0.40) | Low or Very Low | Probably Superior |
| | **SROM (Indirect evidence only)** | −1.30 (−2.80, 0.030) | −1.20 (−2.00, −0.49) | Very Low | Probably Superior |
| | **Buprenorphine (Direct evidence only)** | −0.61 (−1.20, −0.11) | −0.54 (−0.83, −0.26) | Low | Probably Superior |

CI, Confidence Interval; DAM, Diacetylmorphine; HDM, Hydromorphone; SMD, Standardized Mean Difference; SROM, Slow-Release Oral Morphine.
Figure 2. Meta-analysis of depressive symptoms in clinical trials of opioid agonist treatment. Buprenorphine was significantly more effective than waitlist (random effect size = −0.949, error = 0.298, p value = 0.001). Other comparisons showed no significant difference. Bupr., buprenorphine; DAM, diacetylmorphine; HDM, hydromorphone; Meth., methadone; Wait., waitlist.
Figure 3. Meta-analysis of overall mental health symptomatology in clinical trials of opioid agonist treatment. DAM and buprenorphine were significantly more effective than methadone (random effect size = −0.233, error = 0.052, p value <0.001) and waitlist/placebo (random effect size = −0.680, error = 0.332, p-value = 0.040), respectively. Other comparisons showed no significant difference. Bupr., buprenorphine; DAM, diacetylmorphine; HDM, hydromorphone; Meth., methadone; Plac., placebo; SROM, slow-release oral morphine; Wait., waitlist.

| Model | Study name | Std diff in means | Standard error | Lower limit | Upper limit | Z-Value | p-Value | DAM | HDM |
|-------|-------------|-------------------|----------------|-------------|-------------|---------|---------|------|------|
| Fixed | Oweido-Jokes (2016) | −0.154 | 0.145 | −0.437 | 0.129 | −1.006 | 0.297 | 97 95 |
| Random | | −0.154 | 0.145 | −0.437 | 0.129 | −1.006 | 0.297 |

| Heterogeneity | Q-value | df (Q) | P-value | I-squared | Tau squared |
|---------------|---------|--------|---------|-----------|-------------|
| Fixed | 0.000 | 0 | 1.000 | 0.000 | 0.000 |
| Random | 0.000 | 0 | 1.000 | 0.000 | 0.000 |

```
Favours DAM  Favours HDM
```

| Model | Study name | Std diff in means | Standard error | Lower limit | Upper limit | Z-Value | p-Value | DAM | Meth. |
|-------|-------------|-------------------|----------------|-------------|-------------|---------|---------|------|-------|
| Fixed | Van den Broek et al. (2003) | −0.279 | 0.106 | −0.486 | 0.109 | −2.785 | 0.006 | 197 | 215 |
| Random | March et al. (2006) | 0.029 | 0.254 | 0.507 | 0.585 | 0.101 | 0.919 | 27 23 |
| Fixed | Remer et al. (2011) | −0.216 | 0.105 | −0.330 | 0.120 | −3.175 | 0.006 | 346 | 462 |
| Random | Demarco et al. (2015) | −0.371 | 0.235 | −0.587 | 0.113 | −1.608 | 0.108 | 36 38 |

| Heterogeneity | Q-value | df (Q) | P-value | I-squared | Tau squared |
|---------------|---------|--------|---------|-----------|-------------|
| Fixed | 1.005 | 3 | 0.881 | 0.000 | 0.000 |
| Random | 0.000 | 0 | 1.000 | 0.000 | 0.000 |

```
Favours DAM  Favours Meth.
```

| Model | Study name | Std diff in means | Standard error | Lower limit | Upper limit | Z-Value | p-Value | SROM | Meth. |
|-------|-------------|-------------------|----------------|-------------|-------------|---------|---------|------|-------|
| Fixed | Vachon et al. (2015) | −0.124 | 0.129 | −0.377 | 0.129 | −0.963 | 0.335 | 123 | 118 |
| Random | | −0.124 | 0.129 | −0.377 | 0.129 | −0.963 | 0.335 |

| Heterogeneity | Q-value | df (Q) | P-value | I-squared | Tau squared |
|---------------|---------|--------|---------|-----------|-------------|
| Fixed | 0.000 | 0 | 1.000 | 0.000 | 0.000 |
| Random | 0.000 | 0 | 1.000 | 0.000 | 0.000 |

```
Favours SROM  Favours Meth.
```

| Model | Study name | Std diff in means | Standard error | Lower limit | Upper limit | Z-Value | p-Value | Bupr. | Meth. |
|-------|-------------|-------------------|----------------|-------------|-------------|---------|---------|-------|-------|
| Fixed | Pani et al. (2000) | 0.553 | 0.324 | −0.081 | 0.660 | 1.186 | 1.709 | 0.088 | 18 22 |
| Random | | 0.553 | 0.324 | −0.081 | 0.660 | 1.186 | 1.709 | 0.088 |

| Heterogeneity | Q-value | df (Q) | P-value | I-squared | Tau squared |
|---------------|---------|--------|---------|-----------|-------------|
| Fixed | 0.000 | 0 | 1.000 | 0.000 | 0.000 |
| Random | 0.000 | 0 | 1.000 | 0.000 | 0.000 |

```
Favours Bupr.  Favours Meth.
```

| Model | Study name | Std diff in means | Standard error | Lower limit | Upper limit | Z-Value | p-Value | Wait./Plac. | Meth. |
|-------|-------------|-------------------|----------------|-------------|-------------|---------|---------|-----------|-------|
| Fixed | Krook et al. (2002) | −0.169 | 0.301 | −0.458 | 0.231 | −0.611 | 0.417 | 51 51 |
| Random | Dorlop et al. (2017) | −1.272 | 0.310 | −1.879 | 0.594 | −4.410 | 0.000 | 25 25 |
| Fixed | Streck et al. (2016) | −0.700 | 0.291 | −1.004 | 0.203 | −2.403 | 0.016 | 25 25 |
| Random | | −0.545 | 0.146 | −0.691 | 0.143 | −3.726 | 0.000 |

| Heterogeneity | Q-value | df (Q) | P-value | I-squared | Tau squared |
|---------------|---------|--------|---------|-----------|-------------|
| Fixed | 0.000 | 2 | 0.009 | 78.688 | 0.258 |
| Random | 0.000 | 2 | 0.009 | 78.688 | 0.258 |

```
Favours Bupr.  Favours Wait./Plac.
```
Risk of bias

Except for one study with a Low Risk of bias in all the RoB2 indicated domains (14,15), all studies had Some Concerns or a High Risk of bias in multiple assessment domains, which resulted in an overall High Risk of bias for those studies (Table 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 2). In this review, small study effects were not assessed due to the low number of studies in each pairwise comparison for a meaningful interpretation of small-study effects in a particular publication bias (13,58).

Narrative synthesis

Hydromorphone-diacetylmorphine

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 1) (14,15). Oral methadone and counseling services were available to all participants. No significant differences were reported in

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**Figure 4.** Meta-analysis of addiction severity index in clinical trials of opioid agonist treatment. DAM was significantly more effective than methadone (random effect size = −0.189, error = 0.086, p value = 0.028). Other comparisons showed no significant difference. Bupr., buprenorphine; DAM, diacetylmorphine; HDM, hydromorphone; Meth., methadone; Wait., waitlist.
the 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 (Table 1).

**Diacetylmorphine-methadone**
Six studies compared injectable heroin (DAM) with oral methadone, while in two of those studies inhalable heroin and injectable methadone were provided as well (Table 1) (16,23–25). In all studies, patients were provided with psychosocial care, and those in the heroin treatment group had access to optional oral methadone. Most patients had a history of relapse following prior methadone treatments and were patients with polydrug use. Patients in four studies had poor physical/psychosocial health conditions or high levels of serious comorbid medical conditions like HIV and HCV (16–21). The duration of studies varied from 6 months to 12 months. While two studies mainly reported no significant differences between the two treatments on various mental health scales (16–18,23), four studies reported superiority of DAM on some scales, particularly overall mental health (Table 1) (16,18,21,22).

**Dihydrocodeine-methadone**
Only one study was included comparing oral dihydrocodeine and oral methadone in patients with opioid
dependence (Table 1) (30). The majority of patients were using other comorbid substances at baseline. The prevalence of serious comorbid conditions was low in the sample. No significant difference was reported in the improvement of psychological health after 36 months of therapy (Table 1).

**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 (26,27), while cocaine use and HBV/HCV was reported for half of the sample at baseline in the other study (28,29). Standardized psychosocial counseling was provided in one study (26), while it was not reported by the other study (28). 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 1). Assessment of heterogeneity was not feasible as there were insufficient data for meta-analysis on the overlapping outcomes between the two studies.

**Methadone dose 0-methadone dose 20/50**

One included study compared three different doses of oral methadone, i.e. 0 mg, 20 mg, and 50 mg, in patients with intravenous opioid dependence, who did not have chronic medical illness or major psychiatric comorbidities (Table 1) (31). Counseling services were available to all participants. No significant difference was reported in the improvement of depressive symptoms among the three different dosing groups after 20 weeks of therapy.

**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 (34,39), and had moderate to high prevalence of using other substances in the other two studies (35–38). In three of the studies, patients also had to have no history of disulfiram, antipsychotic, or anticonvulsant use, or history of major mental illness, including schizophrenia (34,35,37). 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 (34), as well as psychological problems in the past 30 days, measured at baseline and follow-up visits (35). One study reported the superiority of buprenorphine to methadone in improving depressive symptoms (Table 1) (39).

**Buprenorphine-waitlist/placebo**

Four studies compared oral buprenorphine, depot buprenorphine, and buprenorphine/naloxone with either placebo (two studies) or waitlist (two studies) (Table 1) in patients with opioid use disorder, who were explicitly opioid agonist treatment-free in the 1–3 months prior to beginning the study. In one study (40), all patients were polysubstance dependent, while in the other three studies, patients with other substance use disorders or major psychiatric comorbidities were excluded and prevalence of other substance use was reported at baseline (41–43). Weekly individual drug counseling appears to be the only psychosocial care provided in one of the studies (43). No significant difference was reported between buprenorphine and placebo, during the 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 the 12 weeks of treatment in all mental health outcomes, including but not limited to overall mental health, mental health quality of life, anxiety, and depressive symptoms (Table 1).

**Quantitative synthesis**

**Network meta-analysis**

Based on the availability of data, NMA was applied for depressive symptoms and overall mental health symptomatology outcomes. For depression, seven RCTs were included. As represented by the thickness of the connecting lines in the geometry of the network in Table 3, there was one study for HDM-DAM, three studies for methadone-DAM, two studies for methadone-buprenorphine, and one study for buprenorphine-waitlist. As represented by the size of the nodes, methadone has the most number of participants, followed by DAM, buprenorphine, HDM, and waitlist, respectively. 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 opioid agonists compared with waitlist/placebo for reducing depressive symptoms, the effect sizes were statistically significant only for DAM and buprenorphine in the fixed-effect model, and not significant for any of the opioid agonists in the random-effects model. For overall mental health, 10 RCTs were included. As represented by the thickness of the connecting lines in the geometry of the network in Table 3, there was one
study for HDM-DAM, one study for SROM-methadone, four studies for methadone-DAM, one study for methadone-buprenorphine, and four studies for buprenorphine-waitlist/placebo. As represented by the size of the nodes in the geometry of the network in Table 4, buprenorphine has the most number of participants, followed by methadone, DAM, SROM, waitlist/placebo, and HDM. 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-effect model (DIC = 20.9) and the random-effects model (DIC = 20.2). The effect estimates (Table 3) showed significant effects for all opioid agonists 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 buprenorphine. Finally, based on the GRADE guidelines, for all pairwise comparisons between opioid agonists and placebo/waitlist, confidence in effect estimates of depressive symptoms and overall mental health was either low or very low (Table 3).

**Direct pairwise meta-analyses**

In the direct pairwise comparisons, a meta-analysis was applied for depression (Figure 2), overall mental health symptomatology (Figure 3), ASI psychiatric section (Figure 4), and mental health quality of life (Figure 5). For depression, there was a trend toward the higher effect of diacetylmorphine compared with methadone based on the results of two studies with a low level of between-study variance (τ²) and inconsistency (I²) (Figure 2b), and a significantly higher effect of buprenorphine compared with waitlist based on the results of one study (Figure 2d). Comparison of buprenorphine and methadone using three studies with a high level of between-study variance and inconsistency (Figure 2c), and DAM with HDM, using one study (Figure 2a), did not show any significant difference. For overall mental health symptomatology, DAM was significantly more effective than methadone based on the results of four studies with low variance and moderate inconsistency (Figure 4b). Comparisons of DAM with HDM (Figure 4a), and buprenorphine with waitlist (Figure 4c), with one study for each comparison, did not show any significant difference. For the quality of life mental health section, buprenorphine was significantly more effective than waitlist based on the results of one study (Figure 5c). Comparisons of DAM with methadone, using two studies with zero variance and inconsistency (Figure 5a), and SROM with methadone, using one study (Figure 5b), did not show any significant difference. Sensitivity analysis was not applicable as only one study had an overall low risk of bias.

**Discussion**

From the 19 studies included in this review, 15 studies were used in the quantitative analyses, out of which 14 had a high overall risk of bias. Network meta-analysis showed that buprenorphine, DAM, and methadone were superior to waitlist/placebo in improving overall mental health symptomatology. No treatment was superior to placebo in improving depressive symptoms, according to the network meta-analysis. Direct pairwise meta-analyses showed that overall mental health symptomatology improved more in DAM than methadone, and the same was true for psychiatric status. Depressive symptoms improved more in buprenorphine than waitlist or placebo, and the same was true for overall mental health symptomatology as well as mental health quality of life. The results of all other direct pairwise comparisons were not significant.

Previous systematic reviews did not report comparative outcomes and instead focused on longitudinal changes in measures of mental health (11,12). Feelemeyer et al. (12) only included cohort studies from specific countries, while Fingleton et al. (11) included both cohorts and clinical trials from any country. Both studies reported improved mental health for most opioid agonists, but in many of the included studies, opioid agonist treatment was provided in conjunction with psychosocial interventions, which makes it hard to conclude that the effects seen were solely attributable to the opioid agonists. In our study, we were able to provide an improved picture of the potential impact of opioid agonist treatments on mental health, by crossing-out the effects of psychosocial interventions as much as possible. The importance of our findings is several folds; besides the robust literature published on the superiority of drug use outcomes and retention in opioid agonist treatment compared with abstinence-based methods...
like detoxification, the superiority of opioid agonists to placebo/waitlist on mental health outcomes further emphasizes opioid agonist treatment continuation/adherence as an essential part of the treatment approach. Beyond that, higher improvement of mental health during treatment with some opioid agonists over others in this review, e.g. DAM compared to methadone, alongside their previously reported superior effectiveness on drug use outcomes, implies their potential added benefits for the treatment of patients with more severe opioid use disorder or with higher comorbidities. This is in line with suggestions from previous original research (59). Clinicians, in particular, may want to encourage patients to seek long-term opioid agonist treatment rather than abstinence-based methods, wherever possible, explaining that it may help with their psychological well-being. Physicians should also be more open to providing potent opioid agonist treatment options, like DAM, if it is available and if patients meet the clinical criteria for receiving the treatment. Last but not least, the current state of available evidence on mental health outcomes in RCTs of opioid agonist treatment implies the necessity of more attention to the psychiatric assessments of these patients, and the integration of addiction psychiatry services to the current treatment systems, as well as training of addiction physicians for assessment of psychiatric comorbidities (60).

Previous comprehensive reviews rated the risk of bias as medium or low for some of the studies included in this review, using an older version of the Cochrane risk of bias tool and focusing on retention in treatment and adverse events as the outcomes of interest (61). In this review, we assessed mental health as a subjective outcome using the extensively revised and more comprehensive new version of the Cochrane risk of bias tool, which explains lower ratings for risk of bias in our study, compared to previous reviews. It would be inherently very hard to completely eliminate some of the sources of bias in future studies, such as blinding for comparison of opioid agonists with physiologically different effects, e.g. buprenorphine and methadone, because an experienced patient recognizes differential treatment effects. Meanwhile, some major considerations are well applicable to most of future studies. These include but are not limited to 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.

**Limitation**

This review was subject to some limitations. First, many of the RCTs of opioid agonist treatment that would be otherwise eligible did not measure or report any mental health outcomes to be included in this review. In this regard, our findings should be interpreted with caution. Second, in most studies, the exact quantity and quality of utilized psychosocial services were not reported. Meanwhile, we should note that all these trials were randomized, with baseline characteristics similar among the trial arms in each study, and any routine psychosocial service was similarly available to all participants. Third, except for one study, all the included studies had a high risk of bias. Fourth, we could not formally assess the publication bias due to an insufficient number of studies for each pairwise comparison. Meanwhile, in the majority of the included studies, mental health outcomes were among the secondary outcomes, and consequently less prone to influence the publication status. Fifth, we did not investigate the dose–response relationship between opioid agonist treatment and mental health outcomes, which needs to be further investigated at the individual patient-level data in future RCTs. Sixth, the role of gender, age, comorbid physical pain, and other potentially relevant variables were not investigated in the association of opioid agonist treatment with mental health improvement. Meanwhile, given that baseline characteristics, such as the physical or mental health status, were comparable between the treatment groups in each study alleviates this concern. It is unclear how much of the limitations mentioned above could have potentially skewed the results, since they are mainly related to an insufficiency of evidence, except for the third limitation, which may have favored the primary treatment of interest in those studies with a high risk of bias.

**Conclusion**

Overall, it appears that mental health symptomatology tends to improve in treatments with major opioid agonists, after accounting for the potential role of psychosocial interventions, and this improvement favors DAM-assisted treatment in comparison to methadone. The true clinical significance of these findings remains to be delineated in a well-defined target population, for example in patients with comorbid severe opioid use disorder and clinical depression. Future studies may further explore the impact of opioid dosage and treatment duration on mental health outcomes at the individual patient-level data. Recommendations for future research
mainly concern the design and conduct of clinical trials of opioid agonist treatment, rather than further reviews.

**Author contributions**

EMZ had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. EMZ contributed to the conceptualization, designed the study, coordinated the study, carried out the statistical analyses, provided the first draft, and acted as co-senior reviewer in cases of disagreement. KZ, KY, MM, and JW carried out screening, data extraction, and quality assessment. They also revised the manuscript for important intellectual content. AM contributed to the design, provided methodological guidance, and revised the manuscript for important intellectual content. PB and UV provided essential data for some of the studies included in this review. PB, UV, CS, KJ, SA, and MK provided consultation during the study, contributed to the interpretation of results and revised the manuscript for important intellectual content. MK conceptualized the study, contributed to the design, helped with coordination of the study, and acted as co-senior reviewer in cases of disagreement.

**Data availability**

All data supporting the findings of this study are available from the corresponding author, EMZ, upon reasonable request.

**Disclosure of interest**

EMZ, KZ, KY, MM, JW, AM, KJ, CS, SA, and RMK declare no competing interests. PB received grants from The Dutch Ministry of Health, Welfare and Sports (VWS), during the conduct of the study. UV received speaker’s honoraria from Mundipharma GmbH and traveling expenses from Camurus GmbH and Mundipharma GmbH.

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