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Effects of Medication-Assisted Treatment (MAT) for Opioid Use Disorder on Functional Outcomes

A Systematic Review

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Preface

Over the past two decades, the U.S. Department of Defense (DoD) has invested unparalleled resources into developing effective treatments for military-related psychological health conditions. Systematic reviews are a key component in the knowledge translation process and function to translate the available research into evidence-based health care guidelines that promote optimal clinical care. Although a few government agencies, including the U.S. Department of Veterans Affairs and the Agency for Healthcare Research and Quality, have established evidence synthesis centers, there is no similar center within DoD that focuses exclusively on psychological health issues. Thus, the Southern California Evidence-based Practice Center, housed at the RAND Corporation, has been awarded a three-year contract to synthesize research on psychological health interventions important to military populations. This document is a systematic review performed during year two of this three-year project. The review will be of interest to military health policymakers and practitioners who oversee or implement Medication Assisted Treatment for opioid use disorder.

None of the authors has any conflict of interest to declare.

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Abstract

At the request of the Defense Centers of Excellence (DCoE) for Psychological Health and Traumatic Brain Injury, this systematic review (PROSPERO 2017: CRD 42017058608) synthesizes evidence on the effects of medication-assisted treatment (MAT) on functional outcomes among patients with opioid use disorder (OUD). Functional outcomes included cognitive (e.g., memory), occupational (e.g., return to work), physical (e.g., fatigue), behavioral/social (e.g., family function), and neurological (e.g., balance) function.

We searched five databases from inception to January 2017 and bibliographies of systematic reviews to identify English-language controlled trials, case control studies, and cohort comparisons of one or more groups; cross-sectional studies were excluded. Two independent reviewers screened identified literature, abstracted study-level information, and assessed the quality of included studies. Meta-analyses used the Hartung-Knapp method for random-effects models. The quality of evidence (QoE) was assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

A comprehensive search and 1,327 full-text publication screenings yielded 27 randomized controlled trials (RCTs) and ten observational studies meeting inclusion criteria. The studies reported highly diverse functional outcome measures. No RCT was rated as having low risk of bias, but several methodologically sound observational studies were identified. The statistical power to detect differences in functional outcomes was unclear in the majority of studies.

Regarding cognitive outcomes, a large observational study found that MAT users had twice the risk of injurious traffic accidents as nonusers (low QoE). Two studies reported that MAT users performed significantly worse in working memory and cognitive speed than matched controls with no history of substance use disorder (SUD) or opioid use (very low QoE). Regarding occupational outcomes, patients with OUD on MAT showed no differences from those treated without MAT. One cohort study found that fewer persons with OUD who were treated with buprenorphine reported fatigue than did persons with OUD who were untreated; other physical function outcomes either showed mixed evidence or no difference. One study showed patients taking buprenorphine or methadone scored worse in aggressive responding than did controls with no history of SUD (very low QoE); studies of other behavioral/social function outcomes either showed mixed evidence or no statistically significant difference.

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Summary

Introduction

In response to the growing epidemic of opioid misuse, federal agencies in the United States were directed to improve access to medication-assisted treatment (MAT). MAT is the use of approved medications combined with counseling, other behavioral therapies, and patient monitoring to treat opioid use disorder (OUD). Medications approved in the United States for MAT for OUD include methadone, buprenorphine, Suboxone (a combination of buprenorphine and naloxone), and naltrexone.

The Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury commissioned a systematic review of the effects of MAT for OUD on functional outcomes. These outcomes include cognitive (e.g., memory), physical (e.g., fatigue), occupational (e.g., return to work), behavioral/social (e.g., family function), and neurological (e.g., balance) function. Such outcomes are important in determining whether active-duty service members can be deployed.

Key Questions

This review was guided by the following key question (KQ) and subquestions:

1. What are the effects of MAT (using buprenorphine, buprenorphine plus naloxone, methadone, or naltrexone) for OUD on functional outcomes compared with wait-list, placebo, treatment without medication, any other comparator, or each other (e.g., buprenorphine versus naltrexone)?

a. Do the effects vary by type of medication?
b. Do the effects vary by route of administration (e.g., oral versus injection versus implant)?
c. Do the effects vary by length of treatment, follow-up time, or later cessation of MAT?
d. Do the effects vary by treatment modality (e.g., methadone clinic versus prescription medication taken at home)?

Methods

To answer the KQs, we searched PubMed, PsycINFO, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews from inception to January 2017, as well as bibliographies of existing systematic reviews to identify reports of English-language controlled trials, case-control studies, and cohort studies that compared two or more groups and reported baseline and follow-up data on functional outcomes. Cross-sectional studies were excluded, as were studies of MAT

medications not approved for use for OUD in the United States. We included two types of studies: (1) those that compared MAT-treated patients with OUD to persons with OUD who were not treated with MAT (i.e., they received another treatment, placebo, treatment as usual, or no treatment) and (2) those that compared MAT-treated patients with OUD to matched controls with no history of substance use disorder (SUD).

Two independent reviewers screened 6,292 identified citations using predetermined eligibility criteria. Because functional outcomes are most often reported as secondary outcomes in studies of substance abuse treatment, we retrieved full-text copies of all studies that assessed the efficacy of MAT for OUD and therefore potentially could meet our inclusion criteria and combed the results sections for relevant outcomes. Reviewers abstracted prespecified study-level information and assessed each included study's risk of bias (ROB); all abstracted data were checked by the project lead for accuracy.

Meta-analyses were conducted using the Hartung-Knapp method for random-effects models when sufficient data were available. Continuous outcomes were expressed as standard mean differences (SMDs), and categorical outcomes were expressed as relative ratios (RRs) together with the 95-percent confidence intervals (CIs). The overall quality of evidence (QoE) was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation approach, and we differentiated high, moderate, low, and very low confidence in summary results (conclusions).

Results

Despite a comprehensive literature search that identified 1,327 publications that were scrutinized as full text, only 37 studies (27 randomized controlled trials [RCTs] and ten observational studies reported in 41 articles) met inclusion criteria. No RCT was rated as having low ROB, primarily because of lack of participant blinding, high attrition rate, and lack of reporting of the method of randomization and allocation concealment. Several observational studies with low ROB were identified.

The studies reported on a large number of highly diverse functional outcome measures, including verbal memory, attention, insomnia, fatigue, and criminal activity. Functional measures were primary outcomes in only six of the RCTs; it is unclear if the other trials, which were statistically powered to detect differences in illicit use of opioids or treatment retention, had adequate power to detect differences in functional effects.

KQ 1: Effects of MAT on Functional Outcomes

We found that although MAT patients performed significantly better on some functional outcomes than persons with OUD who did not receive MAT, they performed worse on several cognitive measures than did matched "healthy" controls with no history of SUD or opioid use.

Because of the limited number of studies identified and the moderate-to-high ROB of many of them, QoE is low or very low for all evidence statements.

Cognitive Function

Individuals with OUD using MAT versus healthy controls with no history of SUD.

A very large observational study conducted in France found that persons prescribed MAT had twice the risk of injurious traffic accidents than nonusers (low QoE). A cohort study measuring working memory found that OUD patients using either buprenorphine or methadone scored significantly worse than did matched controls with no history of SUD or opioid use (very low QoE). Another cohort study measured cognitive speed and found that OUD patients who used either buprenorphine or methadone scored significantly worse than did controls with no history of SUD or opioid use (very low QoE).

Two studies reported that MAT patients performed no worse than healthy controls in verbal memory tasks. One cohort study reported a difference in verbal memory favoring methadone patients, while another cohort study found no difference between methadone patients and healthy controls (very low QoE). Both studies found no difference between OUD patients taking buprenorphine and healthy controls (low QoE).

Two cohort studies showed no significant difference in attention between MAT-treated OUD patients and healthy controls with no history of SUD or opioid use (low QoE).

Individuals with OUD who were treated with MAT versus individuals with OUD not treated with MAT.

No studies that met our inclusion criteria compared cognitive outcomes between persons with OUD who were treated with MAT to persons with OUD who were not treated with MAT medications.

Occupational Function

Individuals with OUD who were treated with MAT versus individuals with OUD not treated with MAT.

Three RCTs and two observational studies that measured employment outcomes found no difference between MAT patients and persons with OUD treated for substance abuse without MAT (very low QoE).

Physical Function

Individuals with OUD who were treated with MAT versus controls with no history of SUD.

We identified no studies that reported physical function that met our inclusion criteria.

Individuals with OUD who were treated with MAT versus individuals with OUD not treated with MAT.

In one cohort study, a significantly lower percentage of patients with OUD who received buprenorphine reported fatigue than did untreated persons with OUD, while there was no difference in the rate of fatigue between persons with OUD who received methadone and these controls (very low QoE).

A meta-analysis of four RCTs found no difference in the percentage reporting insomnia between participants receiving MAT and those receiving a placebo (RR 1.02; CI 0.61, 1.71; moderate QoE). A methadone cohort study also reported no difference in insomnia (very low QoE).

One RCT comparing methadone versus a non-MAT intervention reported no difference in mean ASI medical scores. A cohort study comparing buprenorphine treatment with syringe exchange also reported no difference for this measure (very low QoE).

Behavioral/Social Function

Individuals with OUD who were treated with MAT versus controls with no history of SUD.

One small cohort study reported aggression outcomes; an RCT that randomized OUD patients to either buprenorphine or methadone found that individuals receiving either treatment scored significantly worse on aggressive responding than did controls with no history of SUD (very low QoE).

Individuals with OUD who were treated with MAT versus individuals with OUD not treated with MAT.

Studies reporting on crime (classified as a dysfunctional outcome) showed mixed results. Two RCTs reported that OUD patients on methadone spent fewer days engaged in criminal activity than those randomized to a placebo or wait-list (SMD –0.57; CI –1.00, –0.13; low QoE). However, a meta-analysis of RCTs that reported the percentage arrested or incarcerated found no statistically significant difference between patients randomized to MAT and those not randomized to MAT (RR 0.75; CI 0.46, 1.23; low QoE). An RCT and a cohort study that used a scale assessing illegal activities reported significantly better scores for OUD patients treated with MAT than for participants provided with psychosocially enhanced detox or syringe exchange. Another RCT and another cohort study reported no statistically significant difference for the mean number of charges or the mean number of arrests between MAT-treated patients and those not receiving treatment (all very low QoE).

One RCT reported no significant differences in mean family or psychiatric function scores between MAT and placebo groups; a cohort study also reported no statistically significant differences in a psychiatric function score (very low QoE).

Neurological Function

No studies that compared OUD patients who received MAT to those without MAT or that compared OUD patients who received MAT to controls with no history of SUD reported on neurological outcomes (e.g., hyporeflexia, balance, coordination).

KQ 1a: Effects by Type of Medication

Sixteen studies compared the effects of different MAT medications; of these, ten compared buprenorphine to methadone.

A meta-analysis of three RCTs that compared the effects of buprenorphine treatment on fatigue to that of methadone showed a significantly lower prevalence of fatigue in buprenorphine patients than in methadone patients (RR 0.62; CI 0.41, 0.95; moderate QoE). In absolute terms, 52 fewer buprenorphine patients per 1,000 reported fatigue compared with methadone patients.

Three RCTs that focused on cognitive function compared the effects of buprenorphine to methadone; no statistically significant differences in memory, cognitive speed and flexibility, attention, or vision were reported between treatments, with the exception of a small study where buprenorphine patients performed better than did methadone patients in vision tracking (low QoE for memory and attention because of high ROB and imprecision; very low QoE for cognitive speed, cognitive flexibility, and vision because of high ROB, imprecision, and lack of replication).

A meta-analysis of three RCTs reporting on insomnia found no statistical difference between buprenorphine and methadone groups (low QoE). Two RCTs reporting on pain perception found no significant difference between buprenorphine and methadone groups (low QoE). The only RCT of Suboxone versus methadone that reported functional outcomes found no significant difference in pain-rating scores at six months (very low QoE). One RCT of methadone versus naltrexone found no significant difference in the mean number of days patients engaged in illegal activity (very low QoE). A large nationally representative observational study found no differences in the increase in the proportion of participants who were employed and the number of arrests in the past 30 days among patients who received extended-release naltrexone administered by injection, oral naltrexone, Suboxone, or psychosocial treatment without medication (very low QoE).

KQ 1b: Effects by Route of Administration

We identified three RCTs that directly compared routes of administration of the same medication that reported on functional outcomes (physical and social function). None reported significant differences on these outcomes.

One RCT found no difference in risk of insomnia between oral Suboxone and Suboxone implant, and one RCT found no difference in effect on social function between methadone administered orally and by injection (very low QoE). Two RCTs found no difference in effects on mental health or physical health between methadone administered orally and that administered by injection (very low QoE). One large nationally representative observational study reported no differences in percentage employed or arrested during treatment among patients receiving Suboxone, oral naltrexone, injection naltrexone, or non-MAT treatment (very low QoE).

KQ 1c: Effects by Length of Treatment, Follow-Up, and Later Cessation

Three studies followed MAT patients longitudinally but none found an interaction effect of intervention by time on the reported results (ASI family component and psychiatric component) (very low QoE).

One RCT and one cohort study reported no statistically significant effect of length of treatment by treatment group on memory, attention, medical score, or legal score (very low QoE). A meta-regression across studies found no indication that RCTs with longer follow-up differed in effects on sleep (insomnia) or legal outcomes (arrests).

We identified only one study that addressed the question of how and when functional outcome effects change after cessation of MAT. The study compared MAT patients who remained in treatment to former patients no longer on MAT. Current MAT patients were significantly more likely to be not working in the past 30 days than former patients. The difference between current and former MAT treatment groups in terms of the percentage arrested in the past 30 days was not statistically significant (very low QoE).

KQ 1d: Effects by Treatment Modality

In the United States, methadone is traditionally dispensed under supervision at a methadone clinic, while buprenorphine is prescribed by a physician and can be distributed at a pharmacy. These two drugs are compared in KQ 1a. The results of studies that compared different modalities using the same medication are presented in the next section.

One cohort study with low ROB reported fewer nondrug-related crimes were committed by OUD patients prescribed methadone from a general practitioner's office than by those dispensed methadone at a traditional methadone clinic (very low QoE).

One RCT reported no differences in ASI psychiatric, legal, employment, or medical scores between a group take-home methadone program with twice a week distribution versus twice per month; however, the statistical power to detect differences in these functional outcomes is unknown (very low QoE).

Discussion

Some studies found significant effects in favor of MAT regarding the amount of criminal activity or legal status compared with persons with OUD not receiving MAT. In several studies, MAT patients performed significantly worse than matched controls with no history of SUD or opioid use on measures of aggression, working memory, and cognitive speed. However, it is unclear if the observed differences are because of MAT or because of long-term use of opioids in general. Although healthy controls are usually matched to patients on demographic and other characteristics, these individuals clearly differ in substance abuse history and may differ in unreported psychological, psychiatric, and family history characteristics that contribute to poor function. Quality of evidence for most outcomes was low or very low.

It is unclear in many instances if participants met standards required for military deployment. No studies were conducted on active-duty service members or reported performance on specific occupational tasks. No studies reported the current or former occupations of participants, and applicability of the outcome measures to successful military deployment was not discussed in any study.

Conclusions

Making clinical and policy recommendations is beyond the scope of the systematic review; the goal of this report was to summarize, synthesize, and assess the quality of the existing evidence. Despite an exhaustive and systematic search, the small number of studies that report on outcomes of interest and the weaknesses in the body of evidence prevent any strong conclusions about the effects of MAT on functional outcomes or differences in effects among medication types, route of administration, treatment modality, or length of treatment.

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Abbreviations

AIDS	acquired immune deficiency syndrome
CI	confidence interval
CNS	central nervous system
DCoE	Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury
DoD	U.S. Department of Defense
DR2	decision and reaction test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
FDA	U.S. Food and Drug Administration
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HR	hazard ration
ITT	intention-to-treat
KEEP	Key Extended Entry Program
KQ	key question
MAP	Maudsley Addiction Profile
MAT	Medication-Assisted Treatment (for opioid use disorder)
MCQ	Memory Complaint Questionnaire
MD	mean difference
MMT	methadone maintenance therapy
NR	not reported
OMT	opioid maintenance treatment
OR	odds ratio
OUD	opioid use disorder
PASAT	Paced Auditory Serial Addition Task
PSAP	Point Subtraction Aggression Paradigm
PVT	peripheral vision test
QOE	quality of evidence
RCT	randomized controlled trial
RD	risk difference
RE	random effect
ROB	risk of bias
RR	relative ratio
RST3	reactive stress tolerance test
RWT	Regensburg Word Fluency Test
SAMHSA	U.S. Substance Abuse and Mental Health Services Administration

SD	standard deviation
SEP	syringe-exchange program
SF-36	36-Item Short-Form Survey
SMD	standard mean difference
SUD	substance use disorder
TAP	Test for Attentional Performance
TAU	treatment as usual
TMT-A	Trail-Making Test A
VA	U.S. Department of Veterans Affairs
VLMT	Verbal Learning and Memory Test
WMS-III	Wechsler Memory Scale, Third Edition
XR-NTX	extended-release naltrexone

1. Introduction

Opioids are a class of drugs that includes the illicit drug heroin as well as the prescription pain relievers oxycodone, hydrocodone, codeine, morphine, and fentanyl (National Institute on Drug Abuse, undated). The misuse of these drugs has increased tremendously during the past 15 years. In 2014, 586,000 Americans had a substance use disorder (SUD) involving heroin, and 1.9 million had an SUD involving a prescription pain reliever (Substance Abuse and Mental Health Services Administration and Center for Behavioral Health Statistics and Quality, 2015). The same year, more than 28,000 people died of opioid overdose, an increase of more than 400 percent since 1999 (Rudd et al., 2016). According to a retrospective cohort analysis of data from 2008 through 2010 (Jones, 2013), 80 percent of new heroin users in the United States started out misusing prescription painkillers.

A study of almost 2,600 U.S. soldiers that had returned from deployment to Iraq or Afghanistan found that 44 percent had chronic pain and 15.1 percent regularly used opioids (Toblin et al., 2014). These rates are much higher than the estimates of 26 and 4 percent, respectively, for the general civilian population (Toblin et al., 2014). Drug overdose deaths more than doubled among active-duty personnel between 2006 and 2011 (Headquarters, Department of the Army, 2012). Prescription medications (most commonly oxycodone) were involved in 68 percent of those deaths.

Medication-Assisted Treatment (MAT) is the use of medications combined with counseling, other behavioral therapies, and patient monitoring to treat opioid use disorder. Medications approved in the United States for MAT include methadone, buprenorphine, a combination of buprenorphine and naloxone marketed as Suboxone, and naltrexone.

In response to the growing epidemic of opioid misuse, former President Barack Obama issued an Executive Memorandum in October 2015 (The White House, 2015) directing all federal agencies to improve access to MAT. Federal agencies that directly provide health care services, contract to provide health care services, reimburse for health care services, or facilitate access to health benefits were directed to identify any barriers individuals with opioid use disorder would encounter in accessing MAT and to submit an action plan to address the barriers. The U.S. Department of Defense (DoD), which provides health care services through TRICARE, is one such federal agency. The current DoD/U.S. Department of Veterans Affairs (VA) Clinical Practice Guideline for the Management of Substance Use Disorders strongly recommends the use of opioid agonists for MAT, either methadone in an Opioid Treatment Program or Suboxone through physician office-based opioid treatment (VA, 2015). In pregnant women, buprenorphine alone is recommended. The guideline strongly recommends extended-release injectable naltrexone, an opioid antagonist, for patients for whom treatment with an opioid agonist is contraindicated.

The DoD/VA recommendations were based on a systematic review of SUD treatment focused on effects on consumption of opioids and other drugs, adherence to treatment, and adverse events. The recommendations were also based on the balance of desirable and undesirable medication effects, values and preferences of patients, and DoD mission readiness; however, "functional outcomes" that may be related to occupational performance were not addressed by the systematic review. Neurocognitive ability is a key determinant of functional outcomes. Memory, reaction time, cognitive processing speed, and vigilance are measures of neurocognitive ability that affect problem solving, skill acquisition, occupational performance, and social function. Such outcomes are important in determining whether active-duty service members can be deployed. Currently, active-duty service members taking methadone for MAT are ineligible for deployment.

Medications used in MAT are described in the next paragraph. Appendix A shows the U.S. Food and Drug Administration (FDA) warnings regarding adverse events.

Methadone was developed in the 1940s and first introduced as a treatment for heroin addicts in the United States in the 1960s (Mattick et al., 2009). The FDA regulated the use of methadone for opioid dependent patients in 1972 (Ball and Ross, 1991). Methadone is administered orally, most often as a liquid. Diskette, powder, and tablet forms are also available (World Health Organization, 2009). Methadone must be prescribed by a physician and administered in a specialized clinic. Patients are typically initiated at low dosages, with the first dose between 10 and 20 milligrams (mg). The FDA limits the first dose to 30 mg for the first treatment day (World Health Organization, 2009). After, no regulations limit the maximum daily dose of methadone. However, doses typically range from 60 mg to 120 mg (American Society of Addiction Medicine, 2015). Recommended duration of treatment is at least one year, although treatment may be maintained for many years. Supplemental psychosocial support may be recommended depending on the individual's situation.

Buprenorphine for opioid addiction was approved by the Drug Addiction Act of 2000 and by the FDA in 2002 (U.S. Department of Health and Human Services, 2005). Buprenorphine is a partial agonist opioid drug receptor modulator that can be prescribed alone or in conjunction with naloxone, an antagonist of the mu-opioid receptor. The combination of the two drugs is marketed as Suboxone. Buprenorphine can be prescribed only by physicians who have received specialized training or are certified in addiction medicine or psychiatry. No specific requirements regulate pharmacies that fill and dispense buprenorphine (U.S. Department of Health and Human Services, 2015); however, it is recommended that the first dose be administered in a setting where medical staff can observe the patient (McNicholas, 2004). Buprenorphine is most often administered either as a pill or sublingually. When administered with naloxone, the ratio of buprenorphine to naloxone is 4 to 1 (U.S. Department of Health and Human Services, revised 2012). The American Society for Addiction Medicine recommends that heroin patients receive their first buprenorphine dose within six to 12 hours after their last heroin dose and other opioid-dependent patients receive their first dose 24 to 72 hours after their last opioid dose. Duration of

buprenorphine maintenance treatment can range from a few months to many years. A buprenorphine implant was approved by the FDA in 2016.

Naltrexone was developed in 1963 and approved in 1984 by the FDA for the treatment of opioid dependence (U.S. Department of Health and Human Services, 2009). Naltrexone is an opioid antagonist, which means that patients undergoing naltrexone treatment should abstain from all opioids from seven to ten days before initiation through the completion of treatment. Extended-release naltrexone (XR-NTX) can be ordered by a physician, physician assistant, or nurse practitioner (U.S. Department of Health and Human Services, 2015). In the United States, naltrexone can be administered orally or intramuscularly. For oral administration, dosages are usually 50 mg per day or 100 mg three times per week supplemented with a 150 mg dose once per week for oral naltrexone. For intramuscular administration, a dose of 380 mg is typically administered every month (American Society of Addiction Medicine, 2015). Duration of treatment depends on the patient's symptoms and condition (American Society of Addiction Medicine, 2015). Supplemental treatment—such as counseling, therapy, or social support programs—is recommended during treatment (U.S. Department of Health and Human Services, 2015). Naltrexone is also available in an implant form in Australia and some European countries; however, it is not approved by the FDA for use in the United States.

This systematic review aims to synthesize estimates of the effects of MAT for opioid use disorder (OUD) on functional outcomes including cognitive (e.g., memory), occupational (e.g., return to work), physical (e.g., fatigue), behavioral/social (e.g., family function), and neurological (e.g., balance) functions.

We assess whether effects differ by type of medication, route of administration (e.g., injection or oral), length of treatment, and modality.

The following question and subquestions guide this systematic review:

1. What are the effects of MAT (using buprenorphine, buprenorphine plus naloxone, methadone, or naltrexone) on functional outcomes compared with wait-list, placebo, treatment without medication, any other comparator, or one another (e.g., buprenorphine versus naltrexone)?
    a. Do the effects vary by type of medication?
    b. Do the effects vary by route of administration (e.g., oral versus injection versus implant)?
    c. Do the effects vary by length of treatment, follow-up time, or later cessation of MAT?
    d. Do the effects vary by treatment modality (e.g., methadone clinic versus prescription medication taken at home)?

2. Methods

Literature Search

We searched PubMed, PsycINFO, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews for English-language studies of the effects of MAT for OUD. The search strategy was developed by a senior librarian in RAND's Knowledge Services that was informed by search results of prior feasibility scans conducted for this project and existing systematic reviews on the topic. The search string is presented in Appendix B. Because functional outcomes are often reported as secondary outcomes (substance use measures are frequently primary outcomes), we did not restrict the literature search to citations referencing functional outcomes. Instead, we retrieved and screened full texts of trials and observational studies of the MAT interventions to determine whether relevant outcomes were reported in the publication. Prior systematic reviews on MAT were reference-mined for possibly relevant studies.

Eligibility Criteria

The inclusion and exclusion criteria are summarized in the following PICOTSS (participants, interventions, comparators, outcomes, timing, settings, and study design) framework.

- Participants
  - Studies of male and female participants, 18 years of age or older, were eligible for inclusion. Studies of pregnant women were excluded.
- Interventions
  - Studies evaluating methadone, buprenorphine, buprenorphine plus naloxone (Suboxone), or naltrexone for MAT for OUD were eligible, regardless of route of administration. Studies evaluating MAT interventions not approved in the United States, such as slow-release morphine or heroin, were excluded. Studies of opioid detox only, without maintenance, were excluded.
- Comparators
  - Studies that compared MAT with treatment of OUD without medications, with wait-list control, with no-treatment, or with other active treatments were included, as were head-to-head studies of MAT comparing medications, settings, and route of administration. Studies that compared MAT patients to matched controls with no history of SUD or opioid use were also eligible.

- Outcomes
  - Studies were required to report functional outcomes, including cognitive processing (e.g., memory, reaction time, attention, vigilance), occupational function (e.g., return to work), physical function, behavioral/social function (criminal activity, arrests, family function), or neurological function. Studies were required to assess outcomes in all participants or screen for the presence or absence of events in all included participants; studies reporting individual adverse events only for selected patients (e.g., reasons for dropping out of the study) were excluded.
- Timing
  - Studies could involve any treatment duration referred to as "maintenance," and any follow-up period was eligible.
- Settings
  - Studies were limited to outpatient settings (i.e., methadone clinic or doctor's office). Studies conducted in hospitals (inpatient), and residential rehabilitation facilities were excluded. MAT studies that began in prison and followed patients after release, through an outpatient phase, were eligible.
- Study design
  - Studies were limited to controlled trials, with or without random assignment, and observational studies (cohort or case-control) that compare two or more groups and report baseline and follow-up measures. Cross-sectional studies were excluded.

Inclusion Screening

Following a pilot session to ensure similar interpretation of the inclusion and exclusion criteria, two reviewers independently screened titles and abstracts of retrieved citations. Citations judged as potentially eligible by one or both reviewers were obtained as full text.

Full-text publications were screened against inclusion and exclusion criteria by two independent reviewers; disagreements were resolved through discussion within the review team with the project lead making the final decision. Reasons for exclusion at each stage were recorded in an electronic database.

Data Extraction

Data-collection forms were designed by the project lead with input from the project team and tested on three randomly selected studies. Forms were modified accordingly, and a final pilot on a random selection of studies was conducted to ensure agreement of interpretation. Two reviewers independently abstracted categorical study-level data using database software designed for systematic reviews, and discrepancies were resolved through discussion at weekly review team meetings. Qualitative information was abstracted by one reviewer and checked by the project lead. Two reviewers abstracted all outcome data; to ensure quality, the data extraction

accuracy was checked by the project lead and a statistician.

Information extracted from individual studies included the following:

- study ID and year
- participants: gender, age, race/ethnicity, years of opioid use, and population description
- interventions: medication used, dosage, route of administration, and any behavioral approach (e.g., cognitive behavioral therapy, substance abuse counseling, 12 step)
- comparators: type and description of comparator (e.g., wait-list control, treatment without medication, substance-abuse counseling plus placebo, and matched controls with no history of SUD, or head-to-head trials of MAT types/dosages)
- outcomes: functional domain, method of measurement, metric of data expression (e.g., means, proportions) and corresponding results (e.g., effect estimate, precision), and functional adverse events (e.g., insomnia) for all follow-ups
- timing: time-points of outcome assessment and duration of intervention
- setting: country and clinical setting/treatment modality where medication was administered
- study design: inclusion and exclusion criteria, sample size, and items relevant to risk of bias (ROB) assessment.

When two or more publications appeared to be reporting on the same study, participant descriptions were compared to identify studies with multiple publications and companion papers. All publications that contributed unique data to an included study were included for data extraction. All analyses were conducted at the study level; publications reporting on the same outcomes for the same participants entered the analyses only once, so participants were not counted multiple times in the findings. The review is based on data published in peer-reviewed scientific journals and did not include conference abstracts or dissertations.

Outcome data were based on intention-to-treat (ITT) analyses reported in the included studies. In the absence of ITT data, we used the number randomized as the denominator for count data and the number of participants at follow-up for means and proportions.

Risk of Bias

Reviewers extracted information on selection bias, performance bias, detection bias, attrition bias, and reporting bias of the included studies. The first five included studies were rated in dual; kappa for the ROB for these five studies was 0.82. The remaining studies were reviewed by one researcher and then reviewed for accuracy by the project leader. For controlled trials, we used the Cochrane Risk of Bias tool (Higgins and Green, 2011), which assesses the following sources of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), completeness of reporting outcome data (attrition bias), and selective outcome reporting (reporting bias). For the observational studies, we examined the representativeness of the MAT patients, the baseline similarity of the compared groups, efforts to match groups or use consecutive patients, how outcomes were obtained (official records, direct observation, or self-

report), and whether potential confounders were adjusted for. The full ROB instruments are included as Appendix C.

To determine study-limitation evaluations for the quality of evidence assessment and for potential sensitivity analyses, the project lead categorized each study as having overall low, moderate, or high ROB. We used the following methodology, based on the most important items from the Higgins and Green handbook:

- *Low ROB*: Comparable groups are initially assembled and maintained throughout the study with at least 80-percent follow-up at one year; reliable, valid measurement is used and applied equally to all groups; interventions are clearly described; all important outcomes are considered; appropriate attention is given to confounders in analysis; ITT analysis is used for trials.
- *Moderate ROB*: One or more of the following issues is found in the study: Some, but not major, differences between groups exist at follow-up; measurement instruments are acceptable but not ideal, although are generally applied equally; some, but not all, important outcomes are considered; some, but not all, potential confounders are accounted for in analyses. ITT analysis is used for trials.
- *High ROB*: One or more of the following "fatal flaws" is found in the study: Initially assembled groups are not comparable or maintained throughout the study, unreliable or invalid measurements are used or applied unequally across groups, key confounders are given little to no attention in analyses, and ITT analysis is not used.

Data Synthesis

The purpose of the systematic review was to synthesize the evidence of MAT for opioid use disorder on functional outcomes. We differentiated cognitive function, occupational function, physical function, behavioral/social function, and neurological function.

Effects in studies using categorical variables were summarized as relative ratios (RRs) together with their 95-percent confidence intervals (CIs) comparing treatment and control group results. Effects estimates for studies using continuous variables were computed as mean differences (MDs) between the treatment and comparison groups. Where more than one study was available that reported on the outcome of interest and studies did not use the same assessment scale, we computed standard mean differences (SMDs) to allow comparisons across studies that used different measures.

When sufficient data were available and clinical diversity was acceptable, we conducted meta-analysis to pool results across included randomized controlled trials (RCTs) for the outcomes of interest. To avoid population heterogeneity, we conducted separate analyses comparing (1) persons with OUD on MAT to persons with OUD not on MAT and (2) MAT patients to controls with no history of SUD or opioid use. We used the Hartung-Knapp-Sidik-Jonkman method for our random-effects meta-analysis (Hartung, 1999; Hartung and Knapp, 2001; Sidik and Jonkman, 2006). This approach is preferred when the number of studies to be pooled is small and when there is evidence of heterogeneity (IntHout, Ioannidis, Borm, 2014). It

has been shown that the error rates are more robust than with the DerSimonian and Laird method (Sánchez-Meca and Marin-Martinez, 2008). We report the I-squared statistic as a measure of between-study heterogeneity. Meta-analyses used the longest follow-up point where studies reported on multiple data points (data for all follow-ups are displayed in the evidence table in Appendix D).

Quality of Evidence

The quality of evidence was assessed for major outcomes using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach (Balshem et al., 2011). Namely, the body of evidence was assessed based on the following dimensions: study limitations (low, medium, or high), consistency (consistent, inconsistent, or unknown), directness (direct or indirect), and precision (precise or imprecise) (Egger et al., 1997).

Per the GRADE system, if RCTs are identified that respond to a particular question, the quality of evidence is initially rated as high and then downgraded when results are primarily based on studies with substantial limitations; when results are inconsistent across individual studies or in the presence of substantial heterogeneity in pooled analyses; when the result is based on only a single study without replication in an independent research study; when conclusions are based on indirect evidence (e.g., effects bases on meta-regressions across studies in the absence of head-to-head comparisons); and when pooled results are imprecise estimates of the treatment effect (CIs are wide, spanning effect sizes with different clinical conclusions.

We differentiated four levels of the quality of evidence:

- *High* indicates that the review authors are very confident that the effect estimate lies close to the true effect for a given outcome, as the body of evidence has few or no deficiencies. As such, the reviewers believe the findings are stable. That is, further research is very unlikely to change confidence in the effect estimate.
- *Moderate* indicates that the review authors are moderately confident that the effect estimate lies close to the true effect for a given outcome, as the body of evidence has some deficiencies. As such, the reviewers believe that the findings are likely to be stable, but further research may change confidence in the effect estimate and may even change the estimate.
- *Low* indicates that the review authors have limited confidence that the effect estimate lies close to the true effect for a given outcome, as the body of evidence has major or numerous (or both) deficiencies. As such, the reviewers believe that additional evidence is needed before concluding either that the findings are stable or that the effect estimate lies close to the true effect.
- *Very low* indicates that the review authors have very little confidence that the effect estimate lies close to the true effect for a given outcome, as the body of evidence has very major deficiencies. As such, the true effect is likely to be substantially different from the estimated effect; thus, any estimate of effect is very uncertain.

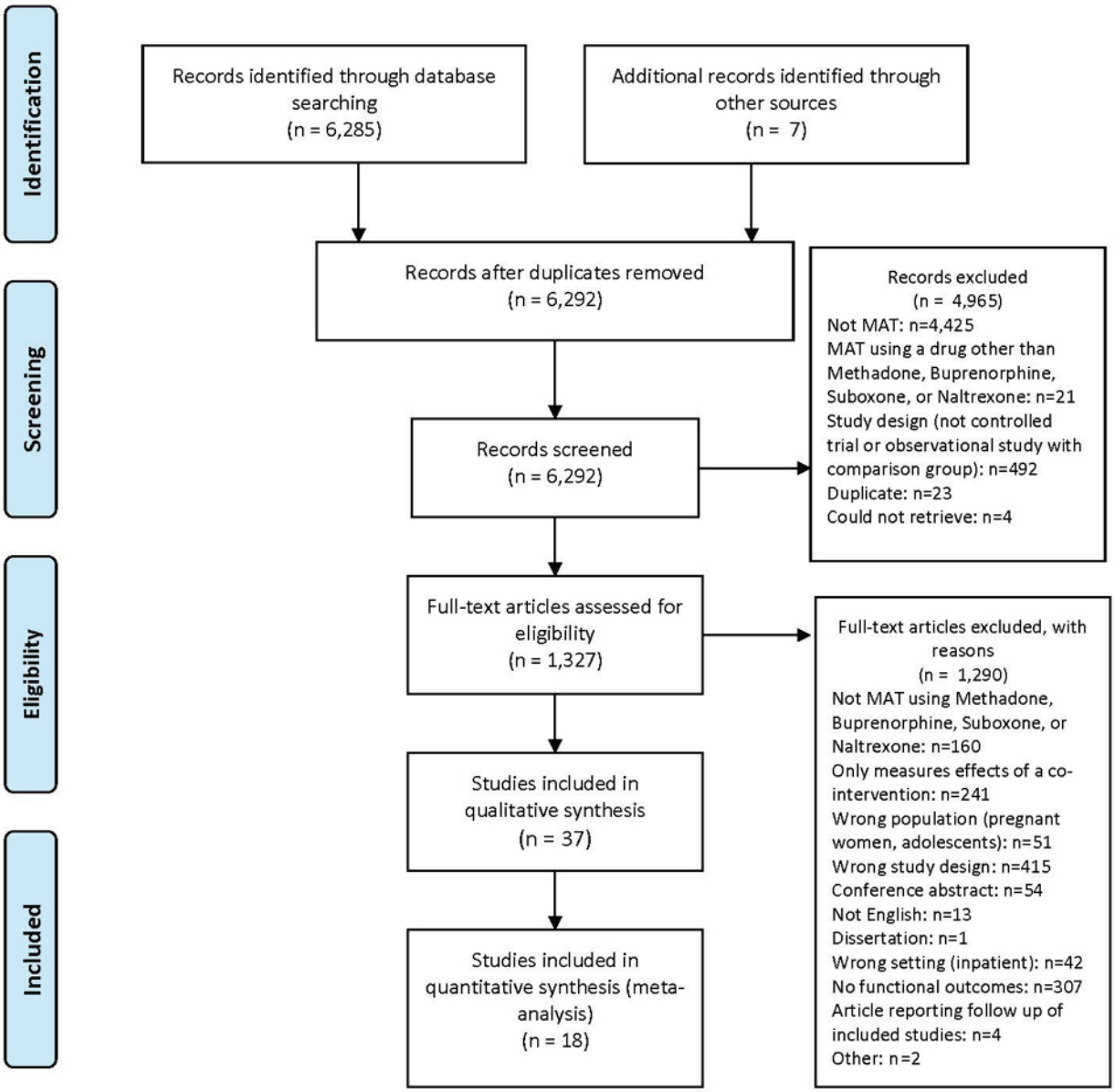
3. Results

Search Results

A total of 6,292 citations were identified for review through electronic literature searches and reference-mining of relevant systematic reviews (see Figure 3.1). Two trained reviewers excluded 4,965 citations before full-text review. The primary reason for exclusion was that the study did not assess MAT (*n* = 4,425) for OUD; these articles may have studied the use of MAT for other purposes (e.g., treatment of alcohol abuse, detoxification). Studies were also excluded if they studied a MAT medication not approved by the FDA (*n* = 21) or used study designs (*n* = 492) outside the scope of this review. Medications included in this review were limited to methadone, buprenorphine, Suboxone, and naltrexone. Study designs in this review included controlled trials and observational studies with at least one comparison group that reported baseline and follow-up data. Cross-sectional studies were excluded. Additionally, 23 duplicate articles were excluded, and four articles could not be retrieved using their citations.

Full-text review was also conducted by two independent reviewers. Based on the full-text review of 1,327 articles, 1,290 articles were excluded and 37 articles were included in the final analysis. Articles were excluded if they reported on MAT studies using a medication outside the scope of this review (*n* = 160), only measured the effects of a co-intervention such as counseling (*n* = 241), did not report any functional outcomes (*n* = 307), or used out-of-scope study designs (*n* = 415). Fifty-one articles reported on populations beyond the scope of this review (e.g., adolescents and pregnant women), 42 articles were excluded for setting (inpatient or residential), 13 were not published in English, 54 were conference abstracts, one was a dissertation, and two were excluded for other reasons. Appendix E lists excluded publications with reasons for exclusion. Four articles reported follow-up data on the 37 included studies; these data were abstracted and included in our analyses.

Figure 3.1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Article Flow Diagram



Description of Included Studies

Design

Twenty-seven controlled trials, four case-control studies, and six cohort comparisons reporting baseline and follow-up data were included. Sample size for controlled trials ranged from 32 to 585 participants enrolled. Observational studies ranged from an open-label

nonrandomized study that enrolled 38 participants to a case-control study of all injurious traffic accidents in a French government database (*n* = 72,685).

Setting

The vast majority of studies were conducted in North America (19) or Europe (16). One study was conducted in Australia and another in Asia.

Fourteen studies were conducted at methadone clinics, nine were conducted at other substance abuse treatment centers, three were conducted at VA facilities, and seven were conducted at physician offices. There were six studies of "take-home" medications, administered either as an implant or as take-home methadone. In seven studies, MAT was initiated in prison, and patients were followed up after release. These numbers are not mutually exclusive, as head-to-head studies of MAT could be conducted in more than one setting; for example, methadone might be distributed at a methadone clinic, while in the same study, buprenorphine might be distributed at a physician's office located in an outpatient clinic. Setting was unclear or not reported in eight studies; several of these studies assessed methadone, which can be assumed to have been administered under supervision at a methadone clinic.

Participants

The mean age of participants ranged from 24.4 (standard deviation [SD] 3.6) years to 44.4 (SD 9.2) years. Four studies enrolled only men, one study enrolled only women, and four studies did not report gender composition. The remaining studies ranged from 6.5 to 46.3 percent women. Racial composition was infrequently reported. Mean length of pre-intervention opioid use ranged from 2.0 to 17.7 years in controlled trials; the majority of trials required *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) diagnosis for eligibility.

Interventions

The 37 studies included a total of 58 MAT arms: 34 methadone arms, 16 buprenorphine arms, five Suboxone arms, and seven naltrexone arms. The numbers do not add to 58, as two studies had MAT arms that grouped two medications together: one observational study of auto accidents in France grouped drivers taking prescription methadone or buprenorphine together, while an observational study of cognitive ability grouped patients on Suboxone with those on buprenorphine alone. Route of administration was oral (e.g., liquid methadone or sublingual buprenorphine) in 44 arms; three additional arms used injectable methadone; and five arms studied buprenorphine, Suboxone, or naltrexone administered via an implant that continuously supplied the medication for at least one month. Route of administration was not reported for six arms.

In controlled trials, the length of treatment at follow-up ranged from one to 36 months; the mean was 7.2 months (SD 7.0 months).

Comparators

Eleven of the 27 controlled trials were head-to-head trials of MAT that did not include a non-MAT comparison group. In addition, two of the ten observational studies did not have a non-MAT comparison. Six studies had a placebo group, six had a group that received counseling or psychosocial treatment only, three had matched, untreated persons with OUD, and three studies compared MAT patients to a matched control group with no history of SUD or opioid use. The following comparison groups were each included in one study: a syringe-exchange program (SEP), residential therapeutic community, and wait-list. One observational study assessed whether persons prescribed methadone or buprenorphine had a higher frequency of injurious traffic accidents than persons not on those medications. Another cohort study compared patients who had dropped out of methadone treatment to those who had stayed enrolled for several years. Finally, one study followed opioid-dependent prisoners who were randomized to either methadone or no treatment, after their release into the community.

Risk of Bias for Individual Included Studies

Controlled Trials

Table 3.1 shows ROB items and overall ratings for controlled trials. None of the controlled trials obtained an overall rating of low ROB, which required participant and researcher blinding, acceptable attrition rate, and intention-to-treat analysis. Nineteen trials were judged to have moderate ROB; the eight other trials were rated as having high ROB.

Random sequence generation. Eleven trials had unclear selection bias because they did not report their random sequence generation method; one trial reported an unsatisfactory method. Fifteen other trials reported adequate random sequence generation methods (e.g., computerized random generator).

Allocation concealment. ROB is low if the participants and investigators enrolling participants could not foresee assignment. Fourteen trials did not report an allocation concealment method. The allocation concealment method was adequate in 11 trials; in two trials, the method was inadequate.

Blinding of participants and providers. Participant blinding of substance abuse interventions can be difficult, especially if the comparator group is randomized to a waiting list or treatment as usual. Nineteen trials did not blind participants. Eight trials used identical placebos, and participants were blinded.

Blinding of outcome assessors. Three trials had unclear risk of detection bias because they did not report whether outcome assessors were blind to participant intervention conditions. Fourteen trials explicitly indicated that the outcome assessors were blind to intervention assignment.

Outcome data. Trials were judged to have attrition bias if more than 20 percent were lost to follow-up at one year or less or more than 30 percent were lost to follow-up at more than one year. Twelve trials had low risk of attrition bias, 13 had high risk, and two had unclear attrition. Only 12 trials used ITT analysis; for two trials, use of ITT was unclear.

Selective outcome reporting. No trials were judged to be high risk because of selective outcome reporting. Functional outcomes were usually secondary outcomes; the objective of most trials was to assess the effect of the intervention on illicit opioid use.

Other. The baseline demographic and substance use characteristics of comparison groups were statistically similar in the vast majority of trials (25). One trial did not report these statistics, while one trial reported significant differences at baseline.

Seven trials reported inadequate compliance with medication or differences in compliance between groups. Eleven trials did not report on compliance.

Table 3.1. Risk of Bias for Controlled Trials

Reference	Was Allocation Sequence (Randomization Method) Adequately Generated?	Was ALLOCATION Adequately Concealed (Prior to Assignment)?	Were Participants Adequately BLINDED?	Were OUTCOME ASSESSORS Adequately BLINDED?	Incomplete Outcome Data (ATTRITION BIAS) Because of Amount, Nature, or Handling of Incomplete Outcome Data	Is There Evidence of SELECTIVE OUTCOME REPORTING Bias (Yes/No)?	INTENTION-TO-TREAT Analysis? (Yes/No)	Group SIMILARITY AT BASELINE	Was There Incomplete COMPLIANCE with Interventions Across Groups?	Additional Bias: Bias Because of Problems Not Covered Elsewhere in the Table	Overall ROB
Bale et al., 1980	No	No	No	Yes	No	No	No	Unclear	Unclear	No	High
Compton et al., 2012	Unclear	No	No	No	Yes	No	No	Yes	No	No	High
Cornish et al., 1997	Unclear	Unclear	No	Unclear	Yes	No	Yes	Yes	Yes	No	Moderate
Coviello et al., 2010	Yes	Unclear	No	Yes	No	No	Yes	No	Unclear	No	Moderate
Dole et al., 1969	Yes	Unclear	No	No	No	No	No	Yes	Unclear	Yes	High
Fudala et al., 2003	Yes	Yes	Yes	Yes	No	No	No	Yes	No	No	Moderate
Gerra et al., 2007	Unclear	Unclear	No	No	Unclear	No	No	Yes	Unclear	No	High
Giacomuzzi et al., 2006	Unclear	Unclear	No	No	No	No	Unclear	Yes	No	No	High
Kinlock et al., 2009 (also reported in Gordon, 2008)	Unclear	Unclear	No	No	No	No	Yes	Yes	No	No	Moderate
Lee et al., 2016	Yes	Unclear	No	No	No	No	Yes	Yes	Unclear	No	Moderate
Ling et al., 2010	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Moderate
Lobmaier et al., 2010	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	High
Magura et al., 2009	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Moderate
Mattick et al., 2003	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Moderate

Reference	Was Allocation Sequence (Randomization Method) Adequately Generated?	Was ALLOCATION Adequately Concealed (Prior to Assignment)?	Were Participants Adequately BLINDED?	Were OUTCOME ASSESSORS Adequately BLINDED?	Incomplete Outcome Data (ATTRITION BIAS) Because of Amount, Nature, or Handling of Incomplete Outcome Data	Is There Evidence of SELECTIVE OUTCOME REPORTING Bias (Yes/No)?	INTENTION-TO-TREAT Analysis? (Yes/No)	Group SIMILARITY AT BASELINE	Was There Incomplete COMPLIANCE with Interventions Across Groups?	Additional Bias: Bias Because of Problems Not Covered Elsewhere in the Table	Overall ROB
Metrebian et al., 2015 (also reported in Byford et al., 2013)	Yes	Yes	No	Yes	No	No	Yes	Yes	Unclear	No	Moderate
Neri et al., 2005	Yes	Unclear	No	No	No	No	No	Yes	No	No	Moderate
Neumann et al., 2013	Yes	Unclear	No	Yes	Yes	No	No	Yes	Yes	No	High
Newman and Whitehill, 1979	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Yes	Unclear	No	Moderate
Rosenthal et al., 2013	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Moderate
Schwartz, 2009 (also reported in Schwartz, 2007)	Yes	Unclear	No	No	No	No	No	Yes	Unclear	No	Moderate
Sees et al., 2000	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No	Moderate
Senay et al., 1993	Unclear	Unclear	No	Unclear	Unclear	No	No	Yes	Unclear	No	Moderate
Soyka et al., 2005	Unclear	Unclear	No	No	Yes	No	No	Yes	Unclear	No	High
Soyka et al., 2008	Unclear	Unclear	No	Yes	Yes	No	Unclear	Yes	Unclear	Yes	High
Strain et al., 1993	Unclear	Yes	Yes	Unclear	Yes	No	No	Yes	Yes	No	Moderate
Strang et al., 2000	Yes	Yes	No	Yes	No	No	No	Yes	No	No	Moderate
Tiihonen et al., 2012	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Moderate

Observational Studies

Table 3.2 shows ROB items and overall ratings for observational studies. Four studies were judged as having moderate ROB, four were judged as having low ROB, and two were judged as having high ROB.

Participants. Five studies included participants who were truly representative of the average MAT patient in the community; these studies often took place in countries where all MAT patients are enrolled in a registry. Two studies included participants who were somewhat representative of the average MAT patient in the community, and two studies included a selected group of MAT users (e.g., volunteers). One study did not describe the derivation of the subject cohort. All studies either controlled for important factors such as demographic characteristics and substance abuse history in their analyses or, in the case of cohort comparisons, reported no significant differences in participant characteristics at baseline.

Outcome data. To be categorized as low ROB, observational studies were required to report less than 20 percent loss to follow-up at one year, less than 30 percent loss at one to five years, less than 40 percent loss at six to ten years, and less than 50 percent loss at 11 to 18 years. The attrition rate was inadequate in six studies. Three observational studies had 100 percent follow-up; these studies used administrative program data, legal records, or national registries and used record linkage to obtain outcome data. Five other studies used self-report of outcomes, while the other two used blind assessment of the participants.

Table 3.2. Risk of Bias for Observational Studies

Reference	Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort (e.g., Healthy Controls or Opioid-Dependent Participants Receiving a Different Medication or Not Receiving MAT)	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcome to Occur?	Adequacy of Follow-Up Cohorts	Overall ROB
Aalto et al., 2011	Truly representative of the average MAT patient in the community	Drawn from a different source	Secure record	Yes	Controls for demographics, controls for additional factors	Self-report	Yes	Dropout rate not acceptable	High
Corsenac et al., 2012	Somewhat representative of the average MAT patient in the community	Drawn from the same community as the exposed cohort	Secure record	Yes	Controls for demographics, controls for additional factors	Record link	Yes	Complete follow-up—all subjects accounted for	Low
Coviello et al., 2011	Truly representative of the average MAT patient in the community	Drawn from the same community as the exposed cohort	Secure record, structured interview	Yes	Controls for demographics, controls for additional factors	Self-report	Yes	Subjects lost to follow-up unlikely to introduce bias	Low
Crits-Christoph et al., 2015	Selected group of users (e.g., volunteers)	Drawn from the same community as the exposed cohort	Secure record	Yes	Controls for demographics	Record link	Yes	Follow-up rate not acceptable	Moderate
Farrell-MacDonald et al., 2014	Selected group of users (e.g., volunteers)	Drawn from the same community as the exposed cohort	Secure record	Yes	Controls for demographics	Record link	Yes	Complete follow-up—all subjects accounted for	Low

Reference	Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort (e.g., Healthy Controls or Opioid-Dependent Participants Receiving a Different Medication or Not Receiving MAT)	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcome to Occur?	Adequacy of Follow-Up Cohorts	Overall ROB
Giacomuzzi et al., 2005	No description of the derivation of the cohort	No description of the derivation of the nonexposed cohort	Secure record, structured interview	Yes	No differences in population characteristics	Independent blind assessment	Yes	Follow-up rate not acceptable those lost	High
Giacomuzzi et al., 2003	Somewhat representative of the average MAT patient in the community	Drawn from the same community as the exposed cohort	Secure record	Yes	Controls for additional factors	Self-report	Yes	Follow-up rate not acceptable	Moderate
Gossop et al., 1999	Truly representative of the average MAT patient in the community	Not applicable	Secure record	Yes	Controls for demographics	Self-report	Yes	Follow-up rate not acceptable	Moderate
Rapeli et al., 2009	Truly representative of the average MAT patient in the community	Drawn from a different source	Secure record	Yes	Controls for additional factors	Independent blind assessment	Yes	Follow-up rate not acceptable	Moderate
Reijneveld and Plomp, 1993	Truly representative of the average MAT patient in the community	Drawn from the same community as the exposed cohort	Secure record	Yes	No differences in population characteristics	Self-report	Yes	Subjects lost to follow-up unlikely to introduce bias	Low

Key Question 1: What Are the Effects of MAT (Using Buprenorphine, Buprenorphine Plus Naloxone, Methadone, or Naltrexone) for OUD on Functional Outcomes Compared to Wait-List, Placebo, Treatment Without Medication, Any Other Comparator, or Each Other (e.g., Buprenorphine Versus Naltrexone)?

The results are organized by the following functional effect outcome categories: cognitive, occupational, physical, behavioral/social, and neurological. Within these categories for KQ 1, we report comparisons of MAT patients to matched controls with no history of SUD separately from comparisons of persons with OUD on MAT to persons with OUD who do not receive MAT. Results from RCTs are reported first, followed by results from observational studies. Meta-analyses are documented in forest plots.

Results for comparisons between two MAT drugs such as methadone and buprenorphine are addressed in KQ 1a.

Cognitive Function

Individuals with OUD Who Were Treated with MAT Versus Controls with No History of SUD

We found two studies (Soyka et al., 2008; Rapeli et al., 2009) that reported on a battery of cognitive tests and one study (Corsenac et al., 2012) that reported on driving. The cognitive test results are documented in detail in the evidence table (Appendix D). Both studies reported on memory and attention.

Memory

Two studies measured verbal memory. Soyka et al. (2008) randomized persons with OUD to either oral methadone or sublingual buprenorphine. At eight to ten weeks, the patients completed the Verbal Learning and Memory Test (VLMT). Rapeli et al. (2009) likewise randomized persons with OUD to either oral methadone or sublingual buprenorphine; at six to nine months, patients completed a list-learning task from the Memory for Persons Data. Both studies compared patient results to those of matched controls with no history of SUD or opioid use. We converted the individual results to SMDs to facilitate the comparison across studies. Soyka et al. (2008) reported an SMD in verbal memory of 0.81 (CI 0.25, 1.36) in favor of patients on methadone while Rapeli et al. (2009) reported no difference between the groups (SMD 0.00; CI –0.74, 0.74). For patients on buprenorphine, no statistically significant differences were observed: Soyka et al. (2008) reported SMD 0.43 (CI –0.11, 0.98) and Rapeli et al. (2009) SMD –0.57 (CI –0.30, 0.16).

Rapeli also measured working memory using the Letter-Number Sequencing task from the Wechsler Memory Scale, Third Edition (WMS-III). At six to nine months, buprenorphine

patients scored significantly worse than controls (MD –2.8; CI –4.80, –0.80) as did methadone patients (MD –3.1; CI –5.08, –1.12).

Attention

The two studies previously described also measured attention. Soyka et al. (2008) reported the d2 Test of Attention at eight to ten weeks, while Rapeli reported results for the Test for Attentional Performance (TAP) at six to nine months in a separate publication from the memory results. The studies reported no statistically significant differences between patients on methadone and controls with no history of SUD or opioid use (Rapeli et al. [2009] SMD –0.38; CI –1.13, 0.37; Soyka et al. [2008] SMD –0.18; CI –0.72, 0.36). Both studies reported that buprenorphine patients scored lower than controls (Rapeli et al. [2009] SMD –0.63; CI –1.42, 0.16; Soyka et al. [2008] SMD –0.55; CI –1.10, 0.01) but the differences were not statistically significant.

Cognitive Speed

Soyka et al. (2008) measured cognitive and perceptual motor speed using the Trail Making Test of MAT treatment; lower scores indicate faster speed and better performance. At eight to ten weeks, patients on both buprenorphine (MD 5.5; CI 0.32, 10.68) and methadone (MD 5.9; CI 1.49, 10.31) scored significantly worse than controls with no history of SUD or opioid use.

Driving

One study that reported on driving ability met the inclusion criteria. Using traffic accident data from police reports and the national police database of injurious crashes, Corsenac et al. (2012) conducted a case-control study to investigate the association between the use of buprenorphine or methadone and the risk of being responsible for a road traffic crash (n = 72,685). Data on reimbursed medicines dispensed within six months before the crash were obtained by linking included drivers to the national health care insurance database using their national ID, gender, and date of birth. The authors found users of methadone or buprenorphine to be at a higher risk of injurious road traffic crashes. Analyses of odds ratios (ORs), which adjusted for age, gender, socioeconomic category, region, location, time of day, month, vehicle type, alcohol level, injury severity, concomitant levels 2 and 3 medicine exposure (for highest levels of risk), and long-term chronic diseases found use of buprenorphine or methadone to be associated with a two-fold increase in risk for injurious road traffic crashes (OR 2.02; CI 1.40, 2.91).

Individuals with OUD Who Were Treated with MAT Versus Individuals with OUD Not Treated with MAT

No studies that met our inclusion criteria compared cognitive outcomes between MAT patients and persons with OUD who were not treated with MAT medications.

Occupational Function

Individuals with OUD Who Were Treated with MAT Versus Controls with No History of SUD

No studies that met our inclusion criteria compared occupational function of MAT patients to controls with no history of SUD or opioid use.

Individuals with OUD Who Were Treated with MAT Versus Individuals with OUD Not Treated with MAT

Employment

Three RCTs that reported on occupational functioning compared patients on MAT to those enrolled in non-MAT interventions. Sees et al. (2000) compared a psychosocially enriched methadone maintenance program to a 180-day detoxification program. At 12 months, among 134 participants completing the study, they found no statistically significant difference (MD –0.01; CI –0.10, 0.08) in the Addiction Severity Index (ASI) employment score between methadone MAT and detox-only groups. At 12 months, Kinlock et al. (2009) found no significant difference in the number of days employed in the past 30 among male former prisoners randomized to either methadone MAT or passive referral upon release from a Baltimore corrections facility (n = 204). Finally, Coviello et al. (2010) reported the difference in percentage of criminal justice clients (n = 111) employed six months after release between a group on naltrexone and a group receiving standard psychological treatment without medication. They found 66 percent and 52 percent employment rates for the two groups, respectively; this difference was not statistically significant.

We also identified two observational studies that reported employment outcomes. Using the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Episode Data Set, Crits-Christoph et al. (2015) conducted a retrospective analysis of opioid misusers who were under community supervision by a state correctional agency (i.e., on parole or probation) who received outpatient substance abuse treatment (n = 873). The authors compared participants who received XR-NTX, oral naltrexone, Suboxone, or psychosocial treatment without medication. Median length of treatment for patients on XR-NTX was 97 days, compared with 63 days for those on oral naltrexone (p = 0.13). Patients on Suboxone stayed 69 days (p = 0.06 compared with XR-NTX) and those who received treatment without MAT stayed 63 days (p = 0.005). Controlling for group differences using propensity scores based on several intake variables (e.g., severity), we found the difference among the four groups in the outcome "increase in the proportion of subjects who were employed (from intake to discharge)" to not be significant. In the second observational study, Reijneveld and Plomp (1993) conducted a small cohort comparison (n = 38) of patients who left the methadone maintenance system in the Netherlands with those who stayed five years. The authors discovered no differences in terms of "time spent on job" and "paid job." However, more patients who stayed in treatment spent "sixteen hours or more with some legal aim per week." The authors concede that their study was not designed to investigate the causes behind these differences.

Physical Function

Individuals with OUD Who Were Treated with MAT Versus Controls with No History of SUD

No studies that met our inclusion criteria compared physical function of MAT patients to controls with no history of SUD or opioid use.

Individuals with OUD Who Were Treated with MAT Versus Individuals with OUD Not Treated with MAT

For the physical function domain, we identified studies reporting on fatigue, insomnia, and an indicator of general medical problems. Results are described in the next section.

Fatigue

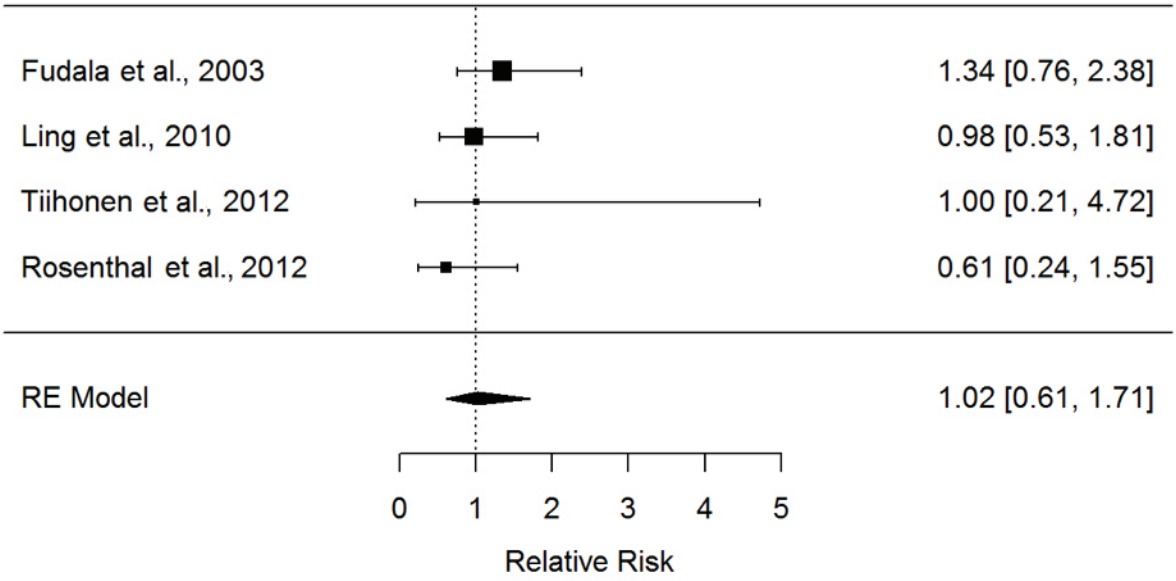
We identified one RCT that compared naltrexone to a placebo (Tiihonen et al., 2012). The randomized double-blind controlled trial of 100 drug-dependent patients observed no significant differences in fatigue between patients treated with naltrexone compared to those treated with a placebo implant (RR 1.00; CI 0.06, 15.55) at a ten-week follow-up.

A cohort study compared fatigue in 120 patients randomized with methadone or buprenorphine after six-month treatment to that of a group of untreated persons with OUD evaluated upon admission (Giacomuzzi et al., 2005). Fewer methadone patients reported fatigue than did the untreated opioid users (RR 0.78; CI 0.56, 1.09); however, the difference was not statistically significant. In the same study, buprenorphine patients were significantly less likely to report fatigue than the untreated group (RR 0.47; CI 0.29 to 0.76).

Insomnia

Four randomized controlled trials of MAT versus placebo reported the prevalence of insomnia among participants. Fudala et al. (2003), Ling et al. (2010), and Rosenthal et al. (2013) studied buprenorphine while Tiihonen et al. (2012) studied naltrexone. The studies conducted a follow-up at between one and six months (n = 645). Figure 3.2 shows the pooled results.

Figure 3.2. Insomnia: MAT (Buprenorphine, Naltrexone) Versus Placebo



NOTE: RE = random effect.

Across all available studies, there was no difference in those who reported insomnia between the MAT patients and the patients receiving a placebo (RR 1.02; CI 0.61, 1.71; 4 RCTs; I^2 18 percent). Little between-study heterogeneity was detected.

One additional study compared MAT patients with untreated persons to OUD evaluated upon admission. One hundred twenty opioid-dependent patients (Giacomuzzi et al., 2005) were randomized to either buprenorphine or methadone. At a six-month follow-up, fewer methadone and buprenorphine patients than control patients reported insomnia, but the difference was not significant (methadone: RR 0.72; CI 0.47, 1.08; buprenorphine: RR 0.72; CI 0.47, 1.08).

Overall Medical Problems

One RCT and one observational study reported the ASI medical score. One study used the European version of the index, while the other used the fifth U.S. revision. We converted results to SMDs to facilitate the comparison across studies.

Sees et al. (2000) randomized patients with OUD to either a methadone maintenance program or detoxification-only program. At 12 months, among 134 participants completing the study, they found no statistically significant difference (SMD –0.20; CI –0.54, 0.15) in the ASI medical score.

Aalto et al. (2011) conducted an observational study comparing the effectiveness of buprenorphine maintenance treatment with syringe exchange, using a matched set of patients in an SEP. Among the 60 enrolled participants, they found no statistically significant difference in mean ASI medical score at 12 months (SMD –0.57; CI –1.29, 0.15).

Behavioral/Social Function

Individuals with OUD Who Were Treated with MAT Versus Controls with No History of SUD

Aggression was the only behavioral/social function outcome reported in studies that compared MAT patients to controls with no history of SUD or opioid use.

Aggression

One study reported on aggression. Gerra et al. (2007) examined differences in aggression among patients randomized to either oral methadone or sublingual buprenorphine and a control group with no history of SUD or opioid use (total $n = 45$). Using the Point Subtraction Aggression Paradigm (PSAP) software program, the authors measured "aggressive responding," "escape responding," and "point-maintained responses" as metrics for aggression at three-month follow-up. More aggression is indicated by higher scores in the first two measures and a lower score for "point-maintained responses." Compared with controls, the methadone group scored significantly higher in aggressive responding (MD 230.79; CI 188.79, 272.79) and escape responding (MD 82.79; CI –1, 166.58) and lower in point-maintained responses (MD –2256; CI –2509.48, –200.52). The buprenorphine group also scored significantly higher in aggressive responding (MD 226.97; CI 187.54, 266.4) and lower in point-maintained responses (MD –579.66; CI –786.67, –372.65). The difference in escape responding was not statistically significant (MD 39.89; CI –64.35, 144.129).

Individuals with OUD Who Were Treated with MAT Versus Individuals with OUD Not Treated with MAT

Several studies that compared individuals with OUD who were treated to MAT and those who were not treated reported on different aspects of social or behavioral function, including family functioning, psychological function, and criminal activity. Criminal activity, as a component of antisocial behavior, was assessed in multiple studies but operationalized in a variety of different ways (e.g., the number of arrests, ASI legal score).

Family Functioning

In the study by Sees et al. (2000), which randomized 179 participants to either methadone maintenance or a "psychologically enriched" detoxification program, the ASI was used to measure family function (a lower score indicates progress). At a one-year follow-up, the difference in scores between groups was not statistically significant (MD –0.01; CI –0.04, 0.02).

Psychological Function

Two studies (including one RCT) reported on effects on the ASI psychiatric score but each used different versions, and scores were converted to SMDs.

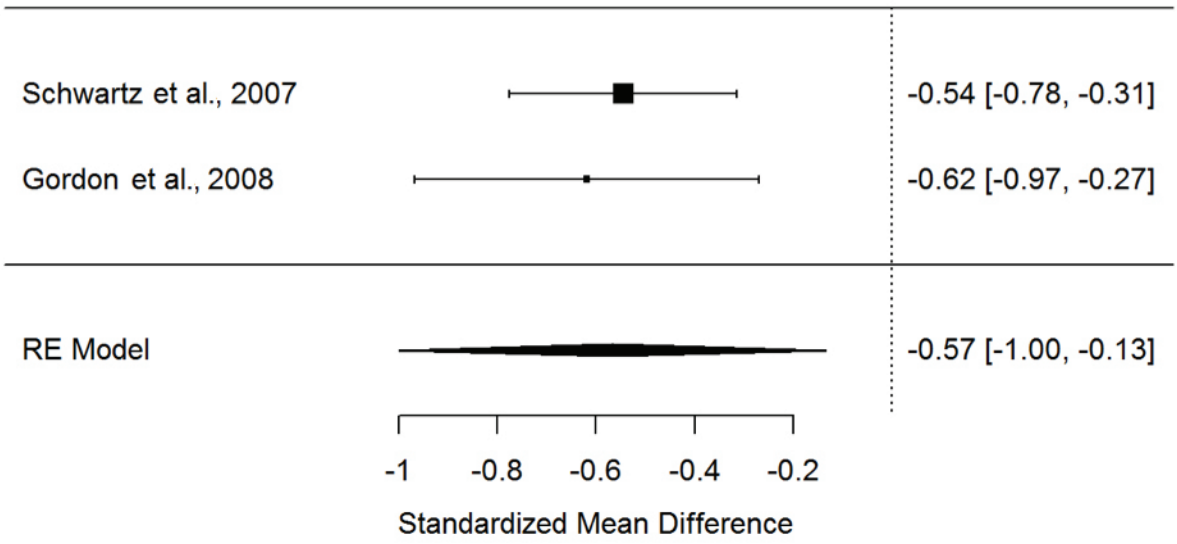
Sees et al. (2000) randomized patients with OUD to either a methadone maintenance program or detoxification-only program. The RCT reported no differences in the ASI psychiatric score between the two groups (SMD –0.20; CI –0.55, 0.14) at 12 months.

Aalto et al. (2011) conducted an observational study comparing the effectiveness of buprenorphine maintenance treatment with an SEP. Among the 60 enrolled participants, there was no difference between groups in mean ASI psychiatric score at 12 months (SMD 0.04; CI –0.67, 0.75).

Amount of Illegal Activity

Two RCTs of methadone that measured the amount of illegal activity among participants were identified. Schwartz et al. (2007) randomized 319 subjects with OUD to either oral methadone (mean 80 mg) or wait-list; at ten months, they reported the number of days subjects engaged in illegal activity in the past 30 days. Gordon et al. (2008) randomized 141 former prisoners to oral methadone (target 60 mg daily) or a passive referral to methadone and at six months reported the number of days subjects participated in crime. Figure 3.3 shows the pooled results across the two RCTs (*n* = 460).

Figure 3.3. Illegal Activity: Methadone Versus Passive Control



Methadone patients spent significantly less time engaged in crime than did control patients (SMD –0.57; CI –1.00, –0.13; 2 RCTs; I^2 74 percent). This analysis detected substantial between-study heterogeneity. While the direction of effects was similar, point estimates varied somewhat, but given the small number of studies, we were unable to investigate sources of systematic differences between the studies.

Additional studies also reported on crime outcomes, but reported data, study designs, outcomes, or comparator did not allow a combined analysis. A double-blind RCT of 95 opioid-dependent participants studied the effects of two methadone doses (20 mg and 50 mg) compared with a placebo group (Strain et al., 1993). At a five-month follow-up, the mean number of days of illegal activity in the past 30 was not significantly different between the 20 mg methadone

group and the placebo group (MD 3.00 days; CI –2.34, 8.34). However, the mean number of days of illegal activity in the past 30 was significantly lower in the 50 mg methadone group compared with the placebo group (MD –2.50 days; CI –7.63, –2.63). The number of crimes committed was also significantly lower in the 50 mg methadone group (MD –9.23) and 20 mg methadone group (MD –4.0) compared with the placebo group.

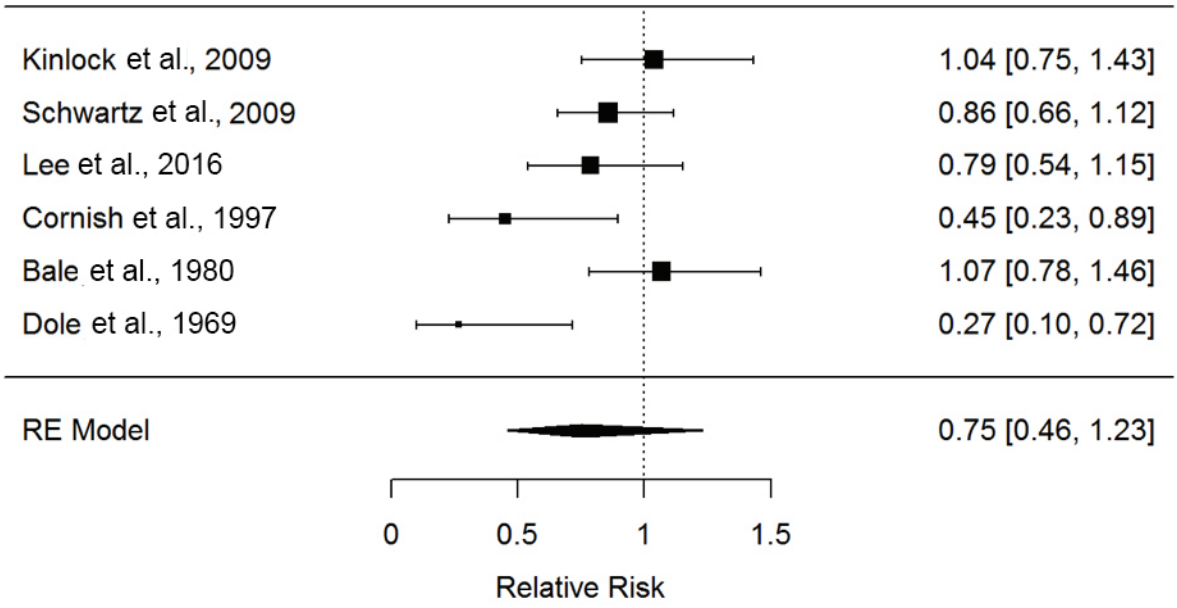
One RCT (Coviello et al., 2010) included 111 opioid-abusing criminal offenders, randomized to receive oral naltrexone with standard psychological treatment or standard psychological treatment alone (control). No significant difference was observed between the naltrexone group and control group in the average number of charges (MD –0.30) or convictions per month (MD 0.00) (SD not reported).

One additional, large cohort study (Crits-Christoph et al., 2015) also reported the number of days engaged in criminal activity. This study followed participants who received XR-NTX, oral naltrexone, Suboxone, or psychosocial treatment without medication (total n = 2,882) and found no significant differences across treatment groups in mean number of arrests 30 days after discharge. The authors suggested that their study had a short observation period and outcomes such as arrests should be studied over longer treatment durations and study periods.

Percentage of Participants Arrested, Incarcerated, or Engaging in Illegal Activity

Six RCTs of MAT versus no MAT reported the percentage of participants arrested or incarcerated. Comparators included passive referral (Kinlock et al., 2009), wait-list (Schwartz, 2009), behavioral treatment without MAT (Lee et al., 2016; Bale et al., 1980), or placebo (Dole et al., 1969; Cornish et al., 1997). Three studies reported a follow-up at six months, while the other three reported this measure at one year. Pooled results are shown in Figure 3.4 (n = 1,302).

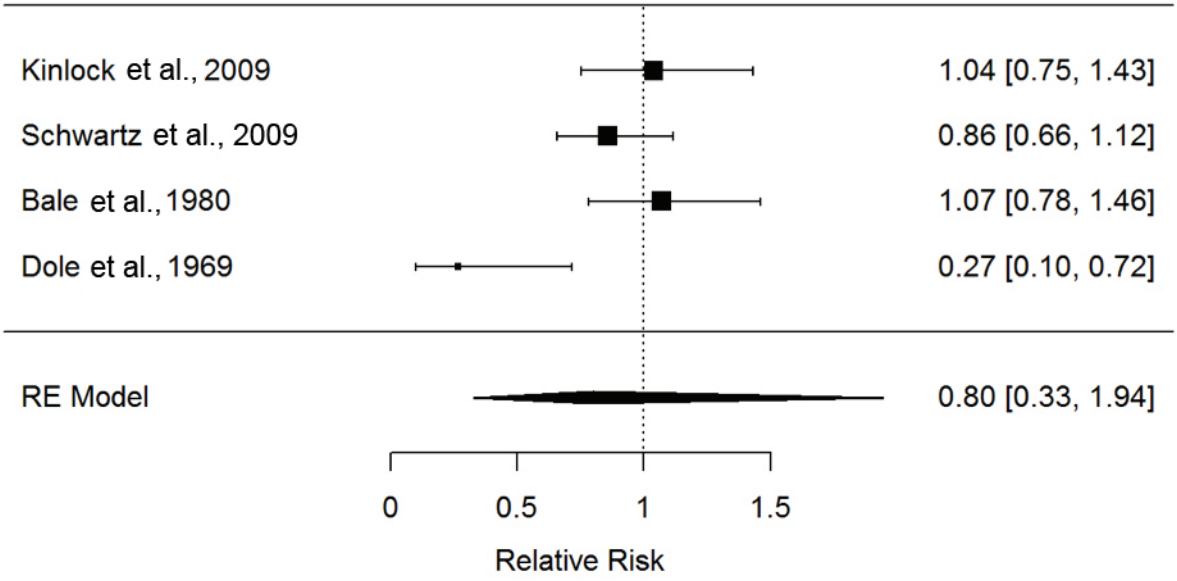
Figure 3.4. Percentage Arrested or Incarcerated: MAT Versus No MAT



The difference in arrest rates between MAT patients and those not receiving MAT was not statistically significant (RR 0.75; CI 0.46, 1.23; 6 RCTs; I^2 85 percent). Substantial heterogeneity among studies was detected; thus, we conducted a sensitivity analysis. Excluding a methadone study from 1969 that reported the largest effect (Dole et al., 1969) did not substantially reduce heterogeneity (I^2 83 percent), but excluding all studies reporting on data before 1980 did reduce heterogeneity (I^2 66 percent); however, the effect estimate also did not change substantially and still did not show a statistically significant difference between studies (RR 0.81; CI 0.50, 1.30; 4 RCTs).

Four trials included in the above meta-analysis compared patients receiving methadone to participants who did not receive MAT (Kinlock et al., 2009; Schwartz, 2009; Bale et al., 1980; Dole et al., 1969). Pooled results are shown in Figure 3.5 (n = 943).

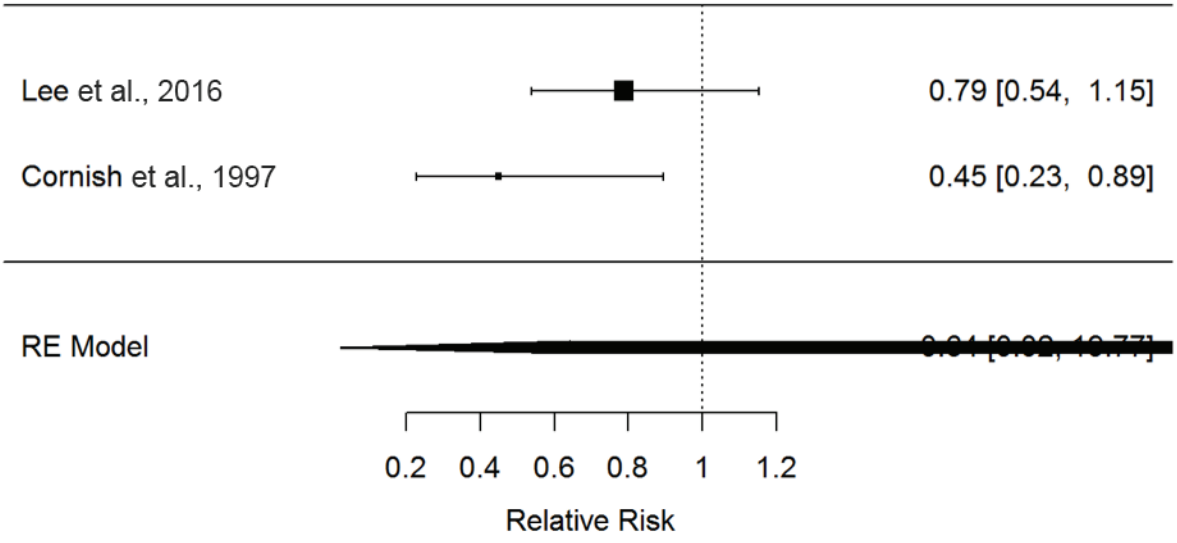
Figure 3.5. Percentage Arrested or Incarcerated: Methadone Versus No MAT



No difference was seen in the arrest rates between methadone patients and those not receiving MAT (RR 0.80; CI 0.33, 1.91; 4 RCTs; I^2 89 percent). Considerable heterogeneity among studies was detected in this analysis.

Two trials compared patients who received naltrexone to participants who did not receive MAT (Lee et al., 2016; Cornish et al., 1997). Pooled results (n = 359) are shown in Figure 3.6.

Figure 3.6. Percentage Arrested or Incarcerated: Naltrexone Versus No MAT



NOTE: CI numbers are obscured because the point estimates reported in these two studies were substantially different.

No significant difference in arrest/incarceration rates was observed between the naltrexone patients and participants not receiving MAT (RR 0.64; CI 0.02, 19.77; 2 RCTs; I^2 49 percent). Moderate between-study heterogeneity was detected, and the wide CI indicated that the point estimates reported in the two individual studies were substantially different, suggesting that the weighted average is not a good representation of the effect. (This explains why the CI numbers are obscured in the figure.) While both studies favored the MAT intervention, only one reported a statistically significant effect.

Three observational studies also reported the percentage of individuals arrested, incarcerated, or engaging in illegal activity. Based on retrospective administrative data on women offenders admitted to the Correctional Service of Canada's opioid maintenance treatment (OMT) program between 2003 and 2008 (*n* = 137), Farrell-MacDonald et al. (2014) assessed the effect of OMT on postrelease criminal reoffending and correctional readmission. Analysis by Cox proportional hazard modeling showed that patients on continued methadone maintenance therapy (MMT) had a 65-percent lower risk of returning to custody than the other two groups of terminated treatment post-release (MMT-T) and non-MMT (MMT-N) controls. Coviello et al. (2011) compared outcomes among 230 opioid-dependent patients who received active methadone maintenance or passive referral to a methadone clinic. At a six-month follow-up, the difference in the percentage of each group engaged in illegal activity in the past 30 days was not significant (RR 0.89; CI 0.45, 1.75). Reijneveld and Plomp (1993) compared outcomes of patients who left the Netherlands' methadone maintenance system to those who stayed five years (*n* = 38). Defining criminal problems as "caught at least one time by police in past half year" and "[a]t least some illegal activity/past week," they found no statistically significant differences between the two cohorts in terms of these criminal problems.

Legal Status

Two studies (Aalto et al., 2011; Sees et al., 2000) included ASI legal score as an outcome; this composite score considers self-reported frequency of illegal activity, illegal income, and feelings regarding severity of legal issues. Both studies found significant differences between MAT patients and the control group. The first study (*n* = 60) compared a matched cohort of patients enrolled in either buprenorphine maintenance treatment or an SEP and found the buprenorphine group had significantly better outcomes (i.e., lower ASI legal scores) at three, six, and 12 months (12-month MD –0.25; CI –0.39, –0.11). The second study randomized 179 participants to either methadone maintenance or a "psychologically enriched" detoxification program: At a one-year follow-up, the methadone group had a significantly lower (better) mean ASI legal score (MD 0.08; CI 0.02, 0.14).

Neurological Function

No studies reported outcomes that could be categorized as neurological (e.g., hyperreflexia, balance, coordination).

Summary

With respect to cognitive function, two studies found that MAT patients performed as well or better on verbal memory tasks as healthy controls with no history of SUD or opioid use. Two studies showed no significant difference in attention between MAT patients and matched healthy controls; however, one of these studies measured working memory and found that both buprenorphine and methadone patients scored significantly worse than controls. One of these two studies also measured cognitive speed and found that both buprenorphine and methadone patients scored significantly worse than controls with no history of SUD or opioid use.

Regarding occupational function, three RCTs and two observational studies found no significant differences between MAT patients and persons with OUD treated without medication. Our meta-analysis of four RCTs found no significant difference between subjects receiving MAT and those receiving placebo in the percentage reporting insomnia.

Regarding physical function, MAT was not associated with fatigue in one cohort study and one RCT. In one RCT, subjects completed the ASI family and psychiatric components; the authors reported no significant difference in mean score between MAT and placebo groups.

Regarding social or behavioral function (including family functioning, psychological function, and criminal activity), one small study reported aggression outcomes: Both buprenorphine and methadone users scored significantly worse than matched controls with no history of SUD or opioid use on aggressive responding. In addition, a very large observational study conducted in France found that MAT (either buprenorphine or methadone) users had twice the risk of injurious traffic accidents than nonusers. Most studies that measured crime reported that persons with OUD randomized to MAT committed fewer crimes than those randomized to placebo or passive control (e.g., wait-list). Likewise, two studies reporting the ASI legal component found MAT patients had significantly better scores than persons with OUD provided with psychosocially enhanced detox or syringe exchange. However, our meta-analyses of RCTs that reported the percentage arrested or incarcerated found no significant difference between patients randomized to MAT or no MAT.

Key Question 1a: Does the Effect Vary by Type of Medication?

This section compares effects by type of medication. Evidence stems from studies comparing patients taking methadone to patients taking buprenorphine, a study comparing Suboxone (buprenorphine and naloxone) to methadone, a study comparing buprenorphine alone with Suboxone, and a study comparing the naltrexone implant with oral methadone. Results are reported by functional outcome category, first presenting results from studies that randomly assigned participants, followed by evidence from observational studies.

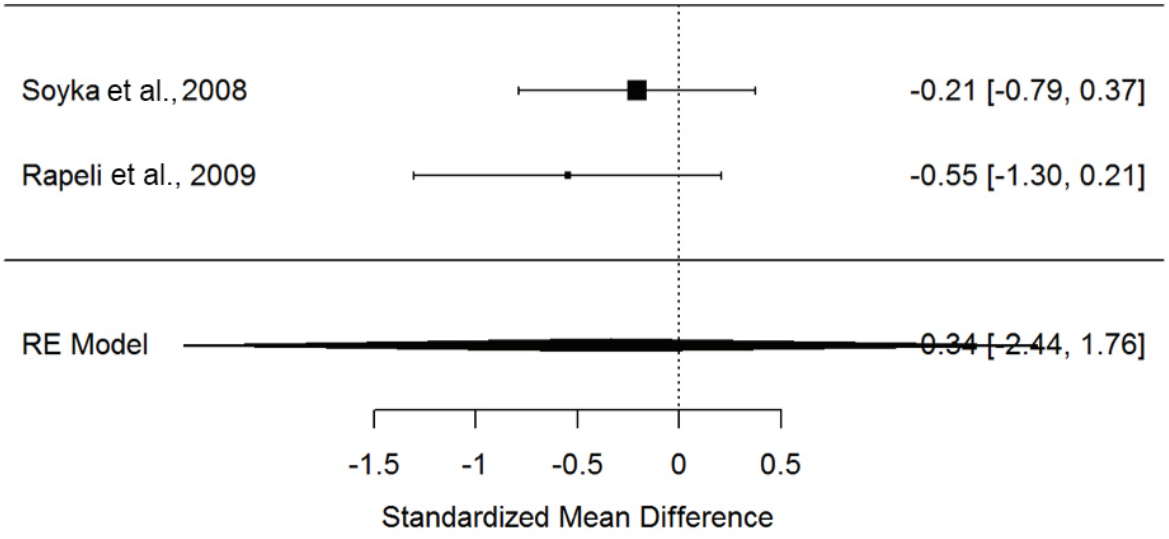
Cognitive Function

We identified three RCTs (Soyka et al., 2008; Rapeli et al., 2009, Soyka et al., 2005) that reported on a battery of cognitive tests, comparing groups taking different MATs. The cognitive test results are documented in detail in the evidence table (Appendix D). Results on memory, attention, and vision are presented in detail in the next sections.

Memory

Two head-to-head RCTs measured verbal memory. Soyka et al. (2008) randomized persons with OUD to either sublingual buprenorphine or oral methadone. At eight to ten weeks, patients completed the VLMT. Rapeli et al. (2009) likewise randomized persons with OUD to either sublingual buprenorphine or oral methadone; at six to nine months, patients completed a list learning task from the Memory for Persons Data. Figure 3.7 shows the pooled results for patients on buprenorphine compared with patients on methadone.

Figure 3.7. Verbal Memory: Buprenorphine Versus Methadone



NOTE: The numbers are somewhat obscured because the wide CI of the pooled result indicated that the effect estimates were substantially different.

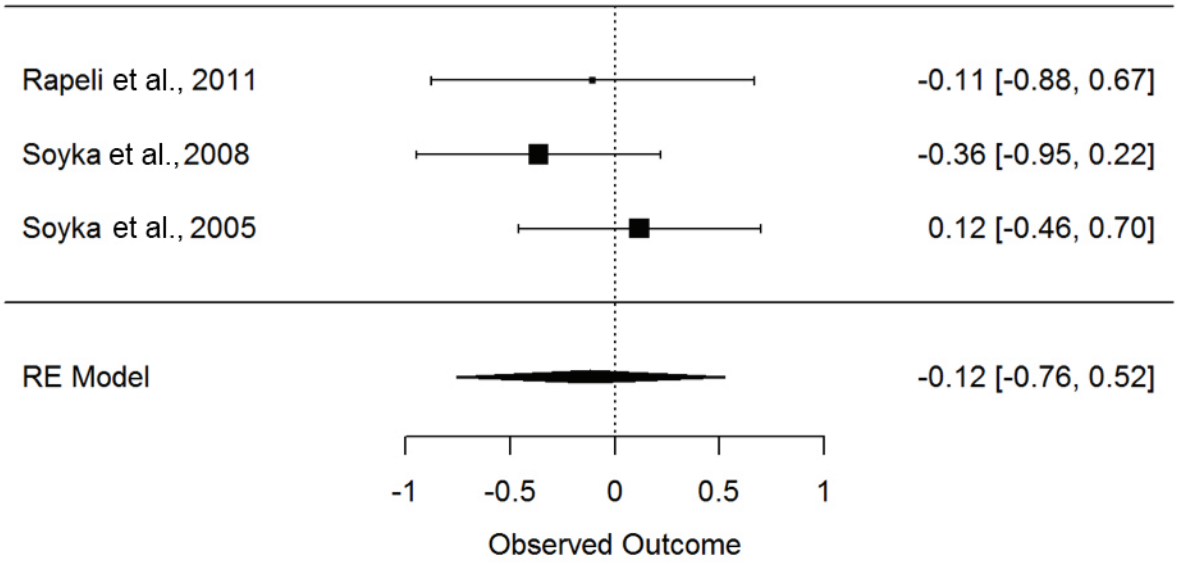
Pooled analysis (n = 87) indicates that the difference in effects on verbal memory was not statistically significantly different between the groups (SMD –0.34; CI –2.44, 1.76; 2 RCTs; I^2 9 percent). The analysis detected very little between-study heterogeneity, given that only two small studies were included. However, the wide CI of the pooled result indicated that the effect estimates were substantially different. (This is why the CI numbers are somewhat obscured in the figure.) Still, both individual studies reported the same direction of effects.

Rapeli et al. (2009) also measured working memory using the Letter-Number Sequencing task from the WMS-III. At six to nine months, the difference in mean score between the buprenorphine and methadone groups was not significant (MD 0.30; CI –1.43, 2.03). Similarly, in the Rapeli et al. study, scores on the Paced Auditory Serial Addition Task (PASAT), which also measures working memory, were not significantly different at six to nine months (MD 1.6, CI –4.94, 8.14).

Attention

The two trials just described also measured attention. Soyka et al. (2008) reported on the d2 Test of Attention at eight to ten weeks, while Rapeli et al. (2009) reported results for the TAP at six to nine months in an article published two years after publication of the memory results. One additional trial that randomized 46 patients to either buprenorphine or methadone measured effects on attention (Soyka et al., 2005). Figure 3.8 shows the pooled results for patients on buprenorphine compared with patients on methadone (n = 131).

Figure 3.8. Attention: Buprenorphine Versus Methadone



Pooled analysis indicates that the difference in attention across all available studies was not statistically significant (SMD –0.12; CI –0.79, 0.51; 3 RCTs; I^2 14 percent). The analysis detected very little heterogeneity among studies.

Vision

Patients enrolled in the RCT by Soyka et al. (2005) also completed a peripheral vision test as part of the Act and React Test System. No difference in mean reaction time (seconds) was observed between buprenorphine and methadone patients at eight to ten weeks (MD 0.00, CI –0.23, 0.23). Buprenorphine patients scored significantly better than methadone patients in visual tracking performance (MD –1.10; CI –2.20, 0.00). No statistically significant difference in visual perception was observed, as measured by correct answers on a tachistoscope test (MD –0.20; CI –2.58, 2.18).

Cognitive Speed

Soyka et al. (2005) also assessed cognitive and perceptual motor speed using the Trail Making Test at eight to ten weeks of MAT treatment. No significant differences were observed between patients on buprenorphine versus methadone (MD –0.4; CI –5.98, 5.18).

Cognitive Flexibility

Soyka et al. (2005) also reported no statically significant difference in mean Regensburger Word Fluency Test scores between the buprenorphine and methadone treatment groups (MD 0.90; CI –3.57, 5.37). This test is a commonly used measure of cognitive flexibility.

Occupational Function

No head-to-head trials comparing different medications reported occupational outcomes. One large observational study reported on employment.

Employment

As noted previously, using the SAMHSA Treatment Episode Data Set, Crits-Christoph et al. (2015) compared patients (n = 873) who received XR-NTX, oral naltrexone, Suboxone, or psychosocial treatment without medication. Controlling for group differences using propensity scores based on several intake variables (e.g., severity), the difference among the four groups in the outcome "increase in the proportion of subjects who were employed (from intake to discharge)" was not significant.

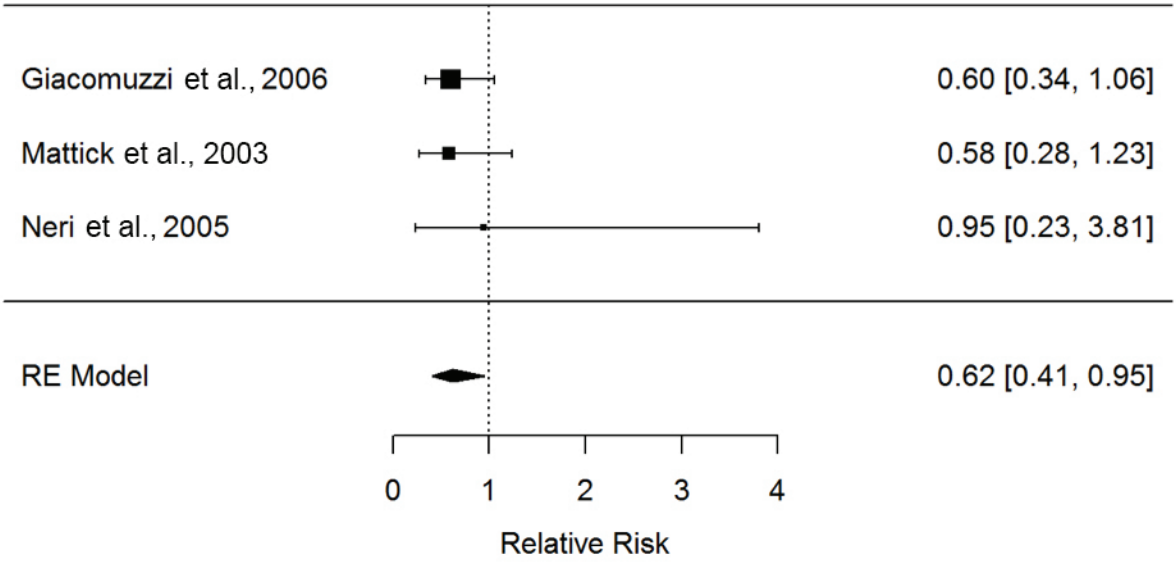
Physical Function

Within the physical function domain, we identified head-to-head studies that reported on fatigue, insomnia, pain, and nausea.

Fatigue

Three RCTs (*n* = 547) comparing buprenorphine with methadone reported the percentage of subjects who experienced fatigue or somnolence during the trial (Mattick et al., 2003; Neri et al., 2005; Giacomuzzi et al., 2006). Follow-up times ranged from 13 weeks to one year. As shown in Figure 3.9, fewer buprenorphine patients than methadone patients reported fatigue across studies; the effect was statistically significant (RR 0.62; CI 0.41, 0.95; 3 RCTs; I^2 5 percent).

Figure 3.9. Fatigue: Buprenorphine Versus Methadone

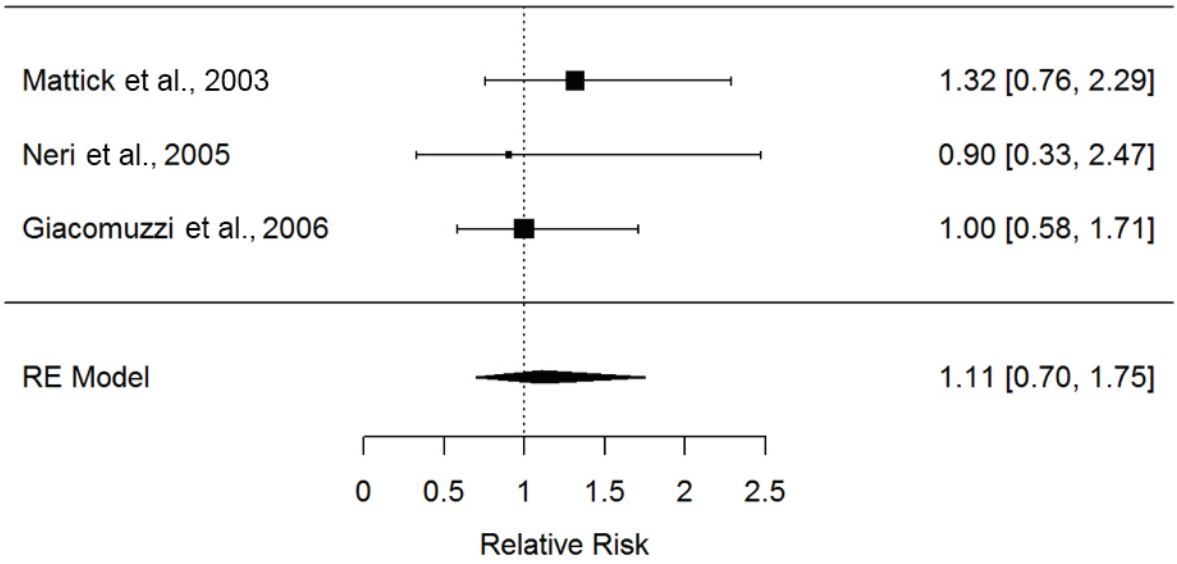


The analysis detected very little between-study heterogeneity.

Insomnia

The three RCTs mentioned immediately above also reported the number of patients experiencing insomnia (Mattick et al., 2003; Neri et al., 2005; Giacomuzzi et al., 2006).

Figure 3.10. Insomnia: Buprenorphine Versus Methadone



The difference in prevalence between the buprenorphine and methadone groups was not statistically significant (RR 1.11; CI 0.70, 1.75; 3 RCTs; I^2 6 percent). The analysis detected very little heterogeneity among the studies.

Pain

Two RCTs of buprenorphine versus methadone reported pain outcomes. Compton et al. (2012) randomized 82 patients with OUD to either sublingual buprenorphine or oral methadone. Pain response was measured at baseline (treatment entry) and at 12 to 18 weeks. Hyperalgesia was present among OUD patients at baseline and did not improve significantly over the course of treatment. No difference was seen in pain detection (measured in both volts and seconds to detection) or pain tolerance (also measured in both volts and seconds to detection) between the buprenorphine and methadone groups (details provided in the evidence table in Appendix D).

Mattick et al. (2003) also conducted an RCT that compared sublingual buprenorphine and oral methadone (*n* = 405 enrolled, 216 completed). The percentage of patients reporting pain during the trial did not differ between the groups (RR 0.95; CI 0.59, 1.53).

One RCT that compared Suboxone to methadone also reported on pain. Neumann et al. (2013) reported patient Numeric Pain Rating Scale (range 1 to 10, lower scores better) scores at six months; the difference between the groups was not statistically significant (MD –0.96; CI –3.54, 1.63).

Finally, Fudala et al. (2003) randomized patients with OUD to either Suboxone or buprenorphine alone. The difference in the percentage of patients who reported experiencing pain during the trial at four weeks was not statistically significant (RR 1.20; CI 0.71, 2.04).

Nausea

Neri et al. (2005) randomized 62 patients with OUD to sublingual buprenorphine or oral methadone. At a one-year follow-up, the percentage of patients reporting nausea during the trial did not differ between groups (RR 1.01; CI 0.31, 3.33).

Behavioral/Social Function

One head-to-head study of different medications reported on aggression, and several studies reported on crime.

Aggression

One study reported on aggression. Gerra et al. (2007) compared aggression between patients randomized to oral methadone and sublingual buprenorphine (total $n = 30$). Using the PSAP software program, the study measured "aggressive responding," "escape responding," and "point-maintained responses" as metrics for aggression at a three-month follow-up. More aggression is indicated by higher scores in the first two measures and a lower score for "point-maintained responses." The differences between the two groups in aggressive responding (MD –3.82; CI –41.76, 34.12) and escape responding (MD –42.9; CI –132.96, 47.16) were not statistically significant. The buprenorphine group scored significantly better than the methadone group in point-maintained responses (MD 1676.34; CI 1456.18, 1896.50).

Criminal Activity

An open-label RCT compared a naltrexone implant to oral methadone among 46 heroin-dependent criminal offenders. At a six-month follow-up, mean days of illegal activity per month did not differ between the naltrexone implant group and the methadone control group (MD 0.50; CI –9.98 to 10.98).

The large observational study by Crits-Christoph et al. (2015) found no difference in number of arrests in the prior 30 days, at treatment discharge, among patients who received XR-NTX, oral naltrexone, Suboxone, or psychosocial treatment without medication using the SAMHSA Treatment Episode Data Set. Group differences were adjusted using propensity scores based on several intake variables (e.g., severity). As stated earlier, the authors suggested that their study had a short observation period and outcomes such as arrests should be studied over longer periods.

Percentage of Participants Arrested or Incarcerated

A randomized controlled trial of 116 heroin-dependent inmates compared the effects of Suboxone and oral methadone in a correctional setting. Participants transferred to community MAT treatment used the same medications after release. The percentage of participants who were arrested in the three months following release was not significantly different between

participants receiving Suboxone and methadone (MD –0.02; CI –0.33, 0.29). Likewise, the difference in reincarceration rates was not significant (RR 0.80; CI 0.53, 1.20).

Neurological Function

Only one head-to-head study of different medications reported on a neurological function outcome.

Stress Tolerance

Soyka et al. (2005) randomized 62 patients to either sublingual buprenorphine or oral methadone. Patients completed the Reactive Stress Tolerance test at eight to ten weeks. The differences in mean score for phase 1 (MD 0.5; CI –2.0, 3.0), phase 2 (MD –2.4; CI –14.28, 9.48), and phase 3 (MD 2.6, CI –7.91, 13.11) were not statistically significant.

Summary

We did not find statistically robust evidence that treatment effects systematically vary by medication for any of the function domains or specific outcomes except fatigue which was reported by a smaller percentage of buprenorphine than methadone patients across three RCTs. Three RCTs that focused on cognitive function reported no statistically significant differences in memory, cognitive speed or flexibility, attention, or vision between buprenorphine and methadone, with the exception of a small study where buprenorphine patients performed better in vision tracking. Regarding aggression, one RCT reported the buprenorphine group scored significantly better than the methadone group in "point-maintained responses," but there was no difference in two other measures of aggression.

A few studies that reported on employment and neurological function using diverse measures reported no differences among medications. We identified only one RCT of naltrexone that reported functional outcomes; compared with methadone, no difference was seen in the mean number of days patients engaged in illegal activity.

Key Question 1b: Does the Effect Vary by Route of Administration?

In this section, we describe head-to-head studies that compared two or more routes of administration for the same medication. Standard of care for buprenorphine is sublingual administration, while methadone is generally administered as syrup for oral consumption. Results for comparisons of buprenorphine versus methadone are reported in the previous section (KQ 1a), which compared two or more different medication types.

We identified three RCTs (Metrebian et al., 2015; Strang et al., 2000; Rosenthal et al., 2013) reporting on effect variation by route of administration. Metrebian et al. randomized 127 patients to either injectable or oral methadone; both were administered under supervision. Strang et al.

randomized 37 patients to either injectable or oral methadone. Rosenthal et al. randomized 287 patients to buprenorphine implants, placebo implants, or Suboxone.

The RCTs reported on physical function and social function but used different outcomes and measures.

Physical Function

Physical Health

Reporting on the physical functioning component of the 36-Item Short-Form Survey (SF-36) at six months, Metrebian et al. (2015) found no statistically significant difference between injectable and oral methadone (MD 7.40; CI –4.21, 19.01). Strang et al. (2000) found no statistically significant difference in Maudsley Addiction Profile physical health scores (MD –0.80; CI –5.10, 3.50) for injectable versus oral methadone at six months.

Insomnia

Rosenthal et al. (2013) found no statistically significant difference in the percentage of participants reporting insomnia between the oral Suboxone and buprenorphine implant groups (RR 0.52; CI 0.24, 1.11) at six months.

Behavioral/Social Function

Mental Health

Regarding the mental health component of the SF-36, Metrebian et al. (2015) found no statistically significant difference between the oral and injectable methadone groups at six months (MD –2.16; CI –8.94, 4.62). Strang et al. (2000) found no statistically significant differences on the Maudsley Addiction Profile mental health score between the injectable methadone group and the oral group (MD –0.30; CI –1.01, 0.41) at six months.

SF-36 Social Functioning Component

Metrebian et al. (2015) reported no statistically significant difference between the oral versus injectable methadone groups (MD –5.20; CI –16.57, 6.17) at six months on the social functioning component of the SF-36.

Crime

Metrebian et al. (2014) found no statistically significant difference between the oral and the injectable methadone groups in the percentage of participants engaging in criminal activity in the previous month (RR 0.90; CI 0.40, 2.04) at six months. The small RCT by Strang et al. (2000) found no statistically significant difference between the two groups (MD –3.60; CI –10.02, 2.82) in the mean number of days patients reported committing shoplifting, robbery, burglary, and fraud at six months.

Summary

Overall, we did not find any indication that treatment effects systematically vary by route of administration. However, only a few studies that can answer this question have been published to date. In addition, all identified studies reported on relatively small samples and it is unclear whether studies had sufficient statistical power to detect effects in functional outcomes. Finally, the existing studies report on unique operationalizations of functional effects, and we found no measure that was used in more than one study.

Key Question 1c: Does the Effect Vary by Length of Treatment, Follow-Up Time, or Later Cessation of MAT?

We identified two observational studies (Rapeli et al., 2011; Aalto et al., 2011) and one RCT (Schwartz et al., 2009) that reported outcomes at multiple follow-up times and used these outcomes to assess variations in effect by length of treatment. In addition, one observational study (Reijneveld et al., 1993) was identified that compared patients who stayed in methadone maintenance for five years to patients who ended treatment before five years. The MDs between groups for each measure and each follow-up time are displayed in the evidence table in Appendix D, and results are summarized narratively in this section.

In addition, we conducted meta-regression analyses across studies. We added the length of follow-up to the meta-analysis model to determine if the length of follow-up systematically affected the differences between patients on MAT and patients not receiving MAT treatment. Given the small number of studies reporting on the same outcome, this indirect analysis was possible for only two outcomes (insomnia and percentage arrested or incarcerated).

Cognitive Function

One RCT reported cognitive function at multiple follow-up times. Rapeli et al. (2011) randomized persons with OUD to either oral methadone or sublingual buprenorphine. Fourteen buprenorphine and 12 methadone patients were administered a battery of cognitive tests at five to eight months and 11 to 16 months. Scores were compared with those of 14 matched healthy nondrug-using controls. Specific domains are described in the next sections.

Memory

Rapeli et al. (2011) assessed working memory using the Letter-Number Sequencing task from the WMS-III and the PASAT, while verbal memory was assessed using the Logical Memory score from the WMS-III. The authors found no significant differences between groups, time effect, or group by time interaction for the verbal memory measure.

Attention

Rapeli et al. (2011) assessed attention using two scores from the Attentional Performance Test: Go-NoGo reaction time and Go-NoGo errors. No significant time or group by time interaction effects were seen in these measures.

Occupational Function

Employment

Reijneveld et al. (1993) compared a random sample of patients enrolled in a methadone treatment program in the Netherlands for at least five years (n = 21) with a random sample of

those who ended treatment in less than five years (n = 17). Patients who were no longer on MAT were significantly less likely to report spending no time working in the past month (RR 0.54; CI 0.29, 1.00).

Physical Function

Insomnia

Our meta-regression analysis of RCTs reporting insomnia found no indication that studies with longer follow-ups reported stronger or weaker treatment effects (p = 0.20).

Overall Medical

Aalto et al. (2011) compared ASI medical component scores between patients on buprenorphine and matched controls in an SEP at three, six, and 12 months (n = 60). The reported p values for the tests of interaction between time and group were not significant (p = 0.47).

Behavioral/Social Function

Mental Health

The cohort study reported by Aalto et al. (2011) also compared ASI psychiatric component scores. The p value for the test of interaction between time (three, six, and 12 months) and group was significant ($p < 0.001$). However, results must be interpreted with caution because they appear to be primarily associated with baseline differences between groups. In addition, the SEP had a high dropout rate (from 30 patients to 11 at the one-year follow-up, compared with 30 to 25 in the buprenorphine group).

Family Function

Aalto et al. (2011) reported the ASI family/relationships component. P values for the tests of interaction between time (three, six, and 12 months) and group were significant (p = 0.05). This result appears to be associated primarily with a significant difference in improvement in the buprenorphine group compared with the control group at three months of treatment and no between-group differences at six or 12 months.

Crime

Schwartz et al. (2009) randomized 319 subjects with OUD to either methadone or wait-list. The proportion of each group who had been arrested did not differ significantly over six, 12, or 24 months (six-month RR 0.78, CI 0.48, 1.26; 12-month RR 1.03, CI 0.70, 1.50; 24-month RR 0.86, CI 0.66, 1.12).

Aalto et al. (2011) also compared ASI legal component scores between buprenorphine patients and matched controls in an SEP. *P* values for the tests of interaction between time (three, six, and 12 months) and group were not significant ($p = 0.31$).

The Reijneveld study compared patients enrolled in methadone treatment for at least five years to those who ended treatment earlier reported no difference in the percentage reporting engaging in illegal activity in the prior week (RR 0.62; CI 0.06, 6.25).

A meta-regression analysis found no association between longer follow-ups and differences between groups for the outcome percentage arrested or incarcerated ($p = 0.65$).

Summary

Of the three studies that followed MAT patients longitudinally, one found an effect of time and group on the ASI family and psychiatric components, but results are difficult to interpret. One study found that methadone patients who remained in treatment for five years had worse employment outcomes than patients who left treatment earlier. The studies had very small sample sizes and did not control for other factors possibly associated with outcomes, and no other study was identified that reported on the same characteristic of interest. A meta-regression found no indication that studies with longer follow-ups reported stronger treatment effects. In sum, we did not find robust evidence that the treatment effect systematically varies by length of treatment, follow-up time, or later cessation of MAT.

Key Question 1d: Does the Effect Vary by Treatment Modality (e.g., Methadone Clinic Versus Prescription Medication Taken at Home)?

In this section, we describe head-to-head studies comparing two or more treatment modalities that use the same medication. In the United States, methadone is traditionally dispensed under supervision at a methadone clinic, whereas buprenorphine is prescribed by a physician and can be distributed at a pharmacy. Comparisons between these two drugs are described in KQ 1a.

We identified two studies (Senay et al., 1993; Gossop et al., 1999) that compared effects of treatment modalities. Senay randomized 130 patients to take-home methadone distributed either two times per week or twice per month. Gossop compared a cohort of patients (n = 452) dispensed daily methadone either at a methadone clinic or prescribed by a general practitioner. Supervision (to be provided at retail pharmacies) was prescribed by only 14 percent of general practitioners.

Behavioral/Social Function

Addiction Severity Index Psychiatric Score

The RCT by Senay et al. (1993) reported no significant differences between groups receiving take-home methadone on different schedules at six months (SMD 0.02; CI –0.01, 0.04).

Crime

The cohort study by Gossop et al. (1999) reported on crimes (excluding drug possession and drug selling). At the six-month follow-up, the authors found a statistically significant difference favoring patients prescribed methadone from a general practitioner's office compared with patients who were dispensed the treatment at a traditional methadone clinic (MD –3.80; CI –7.06, –0.54).

The RCT by Senay et al. (1993) reported six-month ASI legal component scores and reported no difference in outcome for patients receiving take-home methadone on different schedules (MD 0.00; CI –0.02, 0.02).

Occupational Function

Senay et al. (1993) also found no difference in ASI employment scores between groups receiving take-home methadone on two different schedules (MD 0.00; CI –0.11, 0.11).

Physical Function

At six months, Senay reported no statistically significant differences in mean ASI medical scores between patient groups on the two different take-home methadone schedules (MD –0.01; CI –0.04, 0.02).

Summary

Only two studies that reported functional effects compared one treatment modality to another. One RCT reported no differences in ASI psychiatric, legal, employment, or medical scores between groups on take-home methadone distributed two times per week versus twice per month. One cohort study reported fewer nondrug-related crimes committed by patients prescribed methadone from a general practitioner's office compared with patients who were dispensed methadone at a traditional methadone clinic.

4. Discussion

This chapter begins with a summary of findings organized by KQs. KQs are organized by functional area, and within functional area, by comparison group. We then compare our findings with those of prior systematic reviews on the topic, describe the strengths and limitations of the research, and discuss the implications of our findings.

Summary of Findings

Despite an exhaustive search of more than 1,300 publications that were scrutinized as full text, only 37 studies met inclusion criteria. Because functional outcomes are most often reported as secondary outcomes in studies of substance abuse treatment, we retrieved full copies of all MAT studies of OUD patients that potentially would meet our inclusion criteria for study design and combed the results sections for relevant outcomes: 27 RCTs and ten observational studies reported in 41 publications were included in this review. No RCT was rated as low ROB, but several methodologically sound observational studies were identified. The statistical power to detect effects in functional outcomes was unclear in the majority of studies. The studies reported highly diverse functional outcome measures, with the exception of verbal memory, attention, insomnia, fatigue, and criminal activity.

Regarding function of MAT patients compared with "healthy" controls with no history of SUD or opioid use, a large observational study found that MAT users had twice the risk of injurious traffic accidents of nonusers. We identified one study that measured working memory and another that reported cognitive speed: MAT users performed significantly worse than "healthy" controls with no history of SUD or opioid use in these studies. Based on two studies, it appears that MAT users do not perform worse on verbal memory tasks than healthy controls. One study showed that patients taking buprenorphine or methadone scored higher in aggressive responding than healthy controls.

Evidence was mixed when MAT patients were compared with persons with OUD who were not on MAT. One cohort comparison found that fewer buprenorphine patients reported fatigue than did persons with OUD who did not receive MAT; other physical and behavioral/social function outcomes had mixed findings or showed no differences.

We found little statistically robust evidence that treatment effects systematically vary by medication. A comparison across RCTs found a significantly lower prevalence of fatigue in buprenorphine patients compared with methadone patients. Direct comparisons of functional effects by route of administration, length of treatment, and treatment modality were scarce and reported mixed results. A meta-regression found no indication that longer follow-up periods are associated with effect sizes for insomnia or percentage arrested.

In sum, weaknesses in the body of evidence prevent any strong conclusions about the effects of MAT on functional outcomes or differences among medication types, treatment modalities, or length of treatment. Rigorous studies of functional effects could be designed and funded to strengthen the body of literature.

Detailed findings are described in this chapter and shown in Table 4.1, along with the quality of evidence rating for each outcome. For each outcome, the table displays the number and type of studies, relative and absolute effects, quality of evidence criteria, and the GRADE category for all outcomes of interest.

Table 4.1. Summary of Findings

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
Key Question 1. Effects of MAT on functional outcomes												
MAT versus healthy nondrug-using controls												
Cognitive function: verbal memory—methadone versus healthy nondrug-using controls	2 cohorts	High	Inconsistent	Direct	Imprecise	N/A	1.6 (1.6) 16.3 (3.1)	3.1 (2) 14.2 (3.1)	1 favored methadone, SMD 0.81 (0.25, 1.36); 1 no statistically significant difference, SMD 0.00 (–0.74, 0.74).	N/A	N/A	Very low
Cognitive function: verbal memory—buprenorphine versus healthy nondrug-using controls	2 cohorts	High	Consistent	Direct	Imprecise	N/A	1.6 (1.6) 16.3 (3.1)	2.6 (2.7) 14.1 (3.3)	No statistically significant difference, SMD 0.43 (–0.11, 0.98), SMD –0.57 (–0.30, 0.16)	N/A	N/A	Low
Cognitive function: attention—methadone versus healthy nondrug-using controls	2 cohorts	High	Consistent	Direct	Imprecise	N/A	0.2 (0.4) 481.6 (67.4)	0.5 (1.0) 468.4 (74.7)	No statistically significant difference, SMD –0.38 (–1.13, 0.37), SMD –0.18 (–0.72, 0.36)	N/A	N/A	Low
Cognitive function: attention—buprenorphine versus healthy nondrug-using controls	2 cohorts	High	Consistent	Direct	Imprecise	N/A	0.2 (0.4) 481.6 (67.4)	0.6 (0.8) 439.2 (83.4)	No statistically significant difference, SMD –0.63 (–1.42, 0.16); SMD –0.55 (–1.10, 0.01)	N/A	N/A	Low
Cognitive function: working memory—methadone versus healthy non-drug-using controls	1 cohort	High	Not replicated	Direct	Imprecise	N/A	11.6 (2.9)	8.6 (2.1)	Favors controls, SMD	N/A	N/A	Very low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
									–1.14 (–1.94, –0.34)			
Cognitive function: working memory—buprenorphine versus healthy nondrug-using controls	1 cohort	High	Not replicated	Direct	Imprecise	N/A	11.6 (2.9)	9.2 (2.3)	Favors controls, SMD –0.89 (–1.64, –0.14)	N/A	N/A	Very low
Cognitive function: cognitive speed—methadone versus healthy nondrug-using controls	1 cohort	High	Not replicated	Direct	Imprecise	N/A	24.3 (6.9)	30.2 (8.6)	Favors controls, SMD 0.74 (0.16, 1.33)	N/A	N/A	Very low
Cognitive function: cognitive speed—buprenorphine versus healthy nondrug-using controls	1 cohort	High	Not replicated	Direct	Imprecise	N/A	24.3 (6.9)	29.8 (10.5)	Favors controls, SMD 0.61 (0.02, 1.21)	N/A	N/A	Very low
Cognitive function: driving accidents—methadone and buprenorphine versus nondrug users	1 case control	Low	Not replicated	Direct	Precise	N/A	196 total	72,489 total	MAT users more likely in accidents, OR 2.02 (1.40, 2.91)	Not calcul-able	Not calcul-able	Low
Behavioral/social function: aggression—methadone versus healthy nondrug-using controls	1 cohort	High	Not replicated	Direct	Precise	N/A	112.36 (60.57)	343.15 (56.74)	Methadone higher in aggressive responses, SMD 3.83 (2.62, 5.03)	N/A	N/A	Very low
Behavioral/social function: aggression—buprenorphine versus healthy nondrug-using controls	1 cohort	High	Not replicated	Direct	Precise	N/A	112.36 (60.57)	339.33 (48.99)	Buprenorphine higher in aggressive responses, SMD 4.01 (2.77, 5.25)	N/A	N/A	Very low
MAT versus no MAT												
Physical function: fatigue—methadone versus untreated opioid users	1 cohort	High	Not replicated	Direct	Imprecise	N/A	76.8/120	20/40	No statistically significant difference, RR 0.78 (0.56, 1.09)	640	N/A	Very low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
Physical function: fatigue—buprenorphine versus untreated opioid users	1 cohort	High	Not replicated	Direct	Imprecise	N/A	76.8/120	12/40	Favors buprenorphine, RR 0.47 (0.29, 0.76)	640	–339.2 (–454.4, –153.6)	Very low
Physical function: insomnia—MAT (buprenorphine or naltrexone) versus placebo	4 RCTs	Low	Consistent	Direct	Imprecise	Not calculable	39.24/ 266	57.05/375	No statistically significant difference, RR 1.02 (0.61, 1.71)	146.5	N/A	Moder-ate
Physical function: insomnia—methadone versus untreated opioid users	1 cohort	High	Not replicated	Direct	Imprecise	N/A	67.2/120	16/40	No statistically significant difference, RR 0.72 (0.47 to 1.08)	560	N/A	Very low
Physical function: ASI medical score—methadone versus psychosocial + detox	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	0.20 (0.31)	014 (0.292)	No statistically significant difference, SMD –0.20 (–0.54, 0.15)	N/A	N/A	Very low
Physical function: ASI medical score—buprenorphine versus syringe exchange	1 cohort	High	Not replicated	Direct	Imprecise	N/A	0.47 (0.28)	0.29 (0.32)	No statistically significant difference SMD –0.57 (–1.29, 0.15)	N/A	N/A	Very low
Behavioral/social function: ASI psych function—methadone versus psychosocial + detox	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	0.15 (0.189)	0.11 (0.205)	No statistically significant difference, SMD –0.20 (–0.55, 0.14)	N/A	N/A	Very low
Behavioral/social function: ASI psych function—buprenorphine versus syringe exchange	1 cohort	High	Not replicated	Direct	Imprecise	N/A	0.33 (0.22)	0.34 (0.27)	No statistically significant difference, SMD 0.04 (–0.67, 0.75)	N/A	N/A	Very low
Behavioral/social function: ASI family function—methadone versus psychosocial + detox	1 RCT	Low	Not replicated	Direct	Precise	N/A	0.15 (0.113)	0.14 (0.086)	No statistically significant difference, SMD –0.01 (–0.04, 0.02)	N/A	N/A	Very low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
Behavioral/social function: crime—days of illegal activity, methadone versus wait-list or passive referral	2 RCTs	Low	Consistent results, but substantial heterogeneity	Direct	Precise		7.3 (9.64) 56.5 (45)	2.1 (9.45) 28.5 (45)	RCTs favored methadone, SMD –0.57 (–1.00, –0.13)	N/A	N/A	Low
Behavioral/social function: crime—mean number of charges, month, naltrexone versus treatment as usual	1 RCT	Low	Not replicated	Direct	Not reported	N/A	0.5 (not reported [NR])	0.2 (NR)	No statistically significant difference, MD 0.00 (SD not reported)	N/A	N/A	Very low
Behavioral/social function: crime—percentage arrested or convicted, MAT (methadone, naltrexone) versus no MAT	6 RCTs	Moderate	Inconsistent	Direct	Imprecise	Not calculable	225.05/ 521	190.49/527	No statistically significant difference, RR 0.75 (0.46, 1.23)	500	N/A	Low
Behavioral/social function: crime—percentage arrested or convicted, methadone versus no MAT	4 RCTs	Moderate	Consistent	Direct	Imprecise	Not calculable	170.58/ 349	146.61/340	No statistically significant difference, RR 0.80 (0.33, 1.94)	500	N/A	Low
Behavioral/social function: crime—percentage arrested or convicted, naltrexone versus no MAT	2 RCTs	Low	Consistent	Direct	Imprecise	Not calculable	54.57/ 172	35.04/187	No statistically significant difference, RR 0.64 (0.02, 19.77)	425	N/A	Low
Behavioral/social function: crime—mean number of arrests 30 days after discharge, XR-NTX, oral naltrexone, or Suboxone versus psychosocial treatment alone	1 cohort	Low	Not replicated	Direct	Not reported	N/A	38/677	6.56/196	No statistically significant difference, RRs not reported	56	N/A	Very low
Behavioral/social function: ASI legal—methadone versus psychosocial + detox	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	0.05 (0.13)	0.13 (0.193)	Favors methadone, SMD 0.50 (0.15, 0.85)	N/A	N/A	Very low
Behavioral/social function: ASI legal—buprenorphine versus syringe exchange	1 cohort	Low	Not replicated	Direct	Imprecise	N/A	0.38 (0.21)	0.13 (0.19)	Favors buprenorphine, SMD –1.25 (–2.01, –0.48)	N/A	N/A	Very low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
Occupational function: employment, percentage employed, naltrexone versus treatment as usual	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	16.64/32	20.46/31	No statistically significant difference, RR 1.21 (0.80 to 1.84)	520	N/A	Very low
Occupational function: employment, ASI score—methadone versus psychosocial + detox	1 RCT	Low	Not replicated	Direct	Precise	N/A	0.77 (0.262)	076 (0.251)	No statistically significant difference, SMD –0.04 (–0.38, 0.3)	N/A	N/A	Very low
Occupational function: employment, number of days working in past 30, methadone versus passive referral	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	12 (10.3)	8.5 (10.5)	No statistically significant difference (–7.01, 0.01)	N/A	N/A	Very low
Occupational function: employment—five years of methadone versus < five years	1 cohort	High	Not replicated	Direct	Unclear	N/A	6.97/17	15.96/21	No statistically significant difference	760	N/A	Very low
Occupational function: employment—XR-NTX, oral naltrexone, or Suboxone versus psychosocial treatment alone	1 cohort	High	Not replicated	Direct	Unclear	N/A	153/677	37.32/196	No statistically significant difference	226	N/A	Very low
Key Question 1a. Do the effects differ by drug?												
Buprenorphine versus methadone												
Cognitive function: verbal memory	2 RCTs	High	Consistent	Direct	Imprecise	Not calculable	3.1 (2.0) 14.9 (0.2)	2.6 (2.7) 14.6 (0.7)	No statistically significant difference, SMD –0.34 (–2.44, 1.76)	N/A	N/A	Low
Cognitive function: attention	3 RCTs	High	Consistent	Direct	Imprecise	Not calculable	466.5 (72.1) 468.4 (74.7) 0.5 (1.0)	474.2 (54.3) 439.2 (83.4) 0.6 (0.8)	No statistically significant difference, SMD –0.12 (–0.76, 0.52)	N/A	N/A	Low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
Cognitive function: vision, reaction time	1 RCT	High	Not replicated	Direct	Imprecise	N/A	1.2 (0.4)	1.2 (0.4)	No statistically significant difference, SMD 0 (–0.58, 0.58)	N/A	N/A	Very low
Cognitive function: vision, tracking performance	1 RCT	High	Not replicated	Direct	Imprecise	N/A	4.8 (2.4)	3.7 (1.3)	No statistically significant difference, SMD –0.55 (–1.14, 0.04)	N/A	N/A	Very low
Cognitive function: visual perception	1 RCT	High	Not replicated	Direct	Imprecise	N/A	30.7 (4)	30.5 (4.2)	No statistically significant difference, SMD –0.05 (–0.63, 0.53)	N/A	N/A	Very low
Physical function: insomnia	3 RCTs	Low	Consistent	Direct	Imprecise	Not calculable	43.2/271	45.96/255	No statistically significant difference, RR 1.11 (0.70, 1.75)	241	N/A	Low
Physical function: fatigue	3 RCTs	Low	Consistent	Direct	Precise	Not calculable	42.18/ 271	24.6/255	Favors buprenorphine RR 0.62 (0.41, 0.95)	138	–52.44 (–81.42, –6.9)	Moderate
Physical function: pain	2 RCTs	High	Consistent	Direct	Imprecise	Not calculable	30.3/202	26.88/192	No statistically significant difference Detection (seconds) SMD –0.2 (–1.16, 0.76); (volts) SMD –0.06 (–1.02, 0.9) Tolerance (seconds) SMD 0.42 (–0.55, 1.39); (volts)	N/A	N/A	Low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect- Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
									SMD 0.26 (–0.7, 1.22)			
Physical function: nausea	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	5/29	4/23	No statistically significant difference, RR 1.01 (0.31, 3.33)	172	N/A	Very low
Behavioral/social: aggression	1 RCT	High	Not replicated	Direct	Imprecise	N/A	343.15 (56.73)	339.33 (48.99)	No statistically significant difference, SMD –0.07 (–0.79, 0.65)	N/A	N/A	Very low
Neurological: stress tolerance	1 RCT	High	Not replicated	Direct	Imprecise	N/A	2.8 (3.6)	3.3 (4.9)	No statistically significant difference Phase 1 SMD 0.12 (–0.46, 0.69) Phase 2 SMD –0.11 (–0.69, 0.46) Phase 3 SMD 0.14 (–0.44, 0.72)	N/A	N/A	Very low
Suboxone versus buprenorphine												
Physical function: pain	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	24/107	19/103	No statistically significant difference, RR 1.22 (0.71, 2.08)	184	N/A	Very low
Suboxone versus methadone												
Physical function: pain	1 RCT	High	Not replicated	Direct	Imprecise	N/A	6.1 (0.87)	5.2 (0.99)	No statistically significant difference, SMD –0.28 (–1.05, 0.50)	N/A	N/A	Very low
Behavioral/social: crime	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	0.71 (0.77)	0.69 (0.95)	No statistically significant	N/A	N/A	Very low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
									difference, SMD –0.02 (–0.39, 0.34)			
Naltrexone versus methadone												
Behavioral/social: crime	1 RCT	High	Not replicated	Direct	Imprecise	N/A	14.4 (13.11)	14.9 (12.34)	No statistically significant difference, SMD 0.04 (–0.78, 0.86)	N/A	N/A	Very low
XR-NTX, oral naltrexone, Suboxone, versus psychosocial treatment												
Behavioral/social: employment	1 observa-tional study	Low	Not replicated	Direct	Not reported	N/A	153/677	37.32/196	No statistically significant difference	226	N/A	Very low
Behavioral/social: crime	1 observa-tional study	Low	Not replicated	Direct	Not reported	N/A	379.12/ 677	65.6/196	No statistically significant difference	56	N/A	Very low
Key Question 1b. **Do the effects vary by route of administration?**												
Methadone: injectable versus oral												
Physical function: SF-36 physical score	2 RCTs	Low	Consistent	Direct	Imprecise	Not calculable	75.9 (28.7) 14.2 (6.5)	83.3 (23.2) 13.4 (6)	No statistically significant difference, SMD 0.28 (–0.16, 0.73) SMD –0.13 (–0.81, 0.56)	N/A	N/A	Low
Behavioral/social: SF-36 mental health score	2 RCTs	Low	Consistent	Direct	Imprecise	Not calculable	38 (17.25) 1.6 (1.3)	35.84 (12.81) 1.3 (0.6)	No statistically significant difference SMD –0.14 (–0.58, 0.3) SMD –0.30 (–0.99, 0.39)	N/A	N/A	Low
Behavioral/social: SF-36 social score	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	70.1 (25.4)	64.9 (26.1)	No statistically significant difference,	N/A	N/A	Very low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
									SMD –0.2 (–0.64, 0.24)			
Behavioral/social: crime	2 RCTs	Low	Consistent	Direct	Imprecise	Not calculable	9/38 5.8 (10.8)	9/42 2.2 (7.3)	No statistically significant difference, SMD –0.39 (–1.08, 0.3)	237	N/A	Low
Suboxone: implant versus sublingual												
Physical function: insomnia	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	9./114	17.62/119	No statistically significant difference, RR 0.52 (0.24, 1.11)	130	N/A	Very low
Key Question 1c. Do the effects vary by length of treatment, follow-up time, or later cessation of MAT?												
Length of treatment												
Cognitive function: memory, methadone versus buprenorphine versus healthy matched controls	1 RCT	High	Not replicated	Direct	N/A	N/A	N/A	N/A	No significant effect	N/A	N/A	Very low
Cognitive function: attention, methadone versus buprenorphine versus healthy matched controls	1 RCT	High	Not replicated	Direct	N/A	N/A	N/A	N/A	No significant effect	N/A	N/A	Very low
Physical: medical ASI score, buprenorphine versus syringe exchange	1 cohort	High	Not replicated	Direct	N/A	N/A	N/A	N/A	No significant effect $p = 0.47$	N/A	N/A	Very low
Behavioral/social function: ASI psychiatric score, buprenorphine versus syringe exchange	1 cohort	High	Not replicated	Direct	N/A	N/A	N/A	N/A	Time by group interaction ($p < 0.001$), see text	N/A	N/A	Very low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
Behavioral/social function: ASI family function score, buprenorphine versus syringe exchange	1 cohort	High	Not replicated	Direct	N/A	N/A	N/A	N/A	Time by group interaction (p = 0.05), see text	N/A	N/A	Very low
Behavioral/social function: ASI legal score, buprenorphine versus syringe exchange	1 cohort	High	Not replicated	Direct	N/A	N/A	N/A	N/A	No significant effect, p = 0.31	N/A	N/A	Very low
Behavioral/social function: percentage arrested, methadone versus wait-list	1 RCT	Moderate	Not replicated	Direct	N/A	N/A	N/A	N/A	No significant effect	N/A	N/A	Very low
Physical function: insomnia, meta-regression	4 RCTs	Low	Consistent	Indirect	Imprecise	Not calculable	N/A	N/A	No systematic effect, p = 0.20	N/A	N/A	Low
Behavioral/social: percentage arrested, meta-regression	6 RCTs	Moderate	Inconsistent	Indirect	Imprecise	Not calculable	N/A	N/A	No systematic effect, p = 0.65	N/A	N/A	Very low
Cessation of MAT												
Occupational: percentage employed	1 cohort	High	Not replicated	Direct	Imprecise	N/A	15.96/21	6.97/17	Favors ceased MAT, RR 0.54 (0.29, 1.00)	760	–349.6, (–539.6, 0)	Very low
Behavioral/social: percentage arrested	1 cohort	High	Not replicated	Direct	Imprecise	N/A	2.1/21	1.02/17	No significant difference, RR 0.62 (0.06, 6.25)	100	N/A	Very low
Key Question 1d. **Do the effects vary by treatment modality (e.g., methadone clinic versus prescription medication taken at home)?**												
Twice per month versus take-home methadone: 2 or 3 times per week												
Physical function: ASI medical	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	0.025 (0.069)	0.015 (0.052)	No statistically significant difference, SMD –0.17 (–0.57, 0.23)	N/A	N/A	Very low
Behavioral/social: ASI psychological	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	0.021 (0.065)	0.036 (0.086)	No statistically significant difference, SMD 0.19 (–0.21, 0.58)	N/A	N/A	Very low

Outcome	Number of Studies, Design	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Absolute Risk, Control: Score (SD) or n/N	Absolute Risk, Intervention Group: Score (SD) or n/N	Relative Effect-Direction/ Magnitude (95% CI)	Control Risk (per 1,000)	Absolute Effect (95% CI)	GRADE
Behavioral/social: ASI legal	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	0.013 (0.057)	0.014 (0.049)	No statistically significant difference, SMD 0.02 (–0.38, 0.42)	N/A	N/A	Very low
Occupational: ASI employment	1 RCT	Low	Not replicated	Direct	Imprecise	N/A	0.072 (0.273)	0.069 (0.275)	No statistically significant difference, SMD –0.01 (–0.41, 0.39)	N/A	N/A	Very low
Methadone: methadone clinic versus general practitioner's (GP's) office												
Behavioral/social: number of nondrug crimes	1 cohort	Low	Not replicated	Direct	Imprecise	N/A	2.4 (8)	6.2 (22.4)	Favors GP office, MD 3.8 (0.54, 7.06)	N/A	N/A	Very low

NOTE: ASI = Addiction Severity Index; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial, RR = relative risk; SD = standard deviation; SMD = standardized mean difference. For dichotomous variables, n = number of persons experiencing an event (e.g., arrest), while N = sample size.

Key Question 1: Effect of MAT on Functional Outcomes

Of the five functional outcome categories, we identified at least one study in four of the categories: cognitive, physical, behavioral/social, and occupational. Outcomes reported in more than one study were verbal memory, attention, insomnia, fatigue, and criminal activity. Several functional outcomes were reported in only one study; if this was the case, we rated the quality of evidence as very low unless the study was of extremely high quality and reported precise results.

MAT Patients Versus "Healthy" Controls

Two studies randomized patients to either methadone or buprenorphine and compared their performance on a battery of cognitive tests to that of healthy controls with no history of SUD or opioid use. One of these studies found a significant difference in verbal memory favoring methadone patients compared with controls but no difference for buprenorphine. The other found no difference when healthy controls were compared with users of either medication. Quality of evidence is very low for methadone versus controls for verbal memory; we downgraded by an additional level because only one of the studies reported statistically significant results. No differences in attention were observed between the methadone or buprenorphine groups and controls. One of these studies also measured working memory and found that both buprenorphine and methadone patients scored significantly worse than controls. The other study measured cognitive speed and found that both MAT groups scored significantly worse than controls. Quality of evidence for both working memory and cognitive speed was rated very low due to high risk of study bias and lack of replication. Regarding driving, a very large observational study with low ROB found that MAT users (buprenorphine or methadone) had twice the risk of traffic accidents as nonusers, controlling for other important factors. Still, lack of RCT data led us to rate the quality of evidence for this outcome as low.

Regarding behavioral/social function, one small study reported aggression outcomes; patients randomized to buprenorphine or methadone scored significantly worse than controls with no history of OUD on aggressive responding. Quality of evidence is very low.

MAT Patients Versus Persons with OUD Not on MAT

No studies of MAT versus no MAT reported cognitive or behavioral function.

Regarding physical function, our meta-analysis of four RCTs found no significant difference in the percentage reporting insomnia between participants receiving MAT (buprenorphine, naltrexone) and those receiving placebo. Quality of evidence for insomnia was moderate because the RCTs had low ROB and results were consistent but imprecise. In one cohort study, a significantly lower percentage of buprenorphine patients reported fatigue than did persons with OUD who did not receive MAT, while the rate of fatigue did not differ between methadone patients and controls. Quality of evidence for the outcome of fatigue for methadone treatment is very low given the lack of RCT evidence, lack of replication, and high ROB. One RCT of

methadone versus a non-MAT intervention reported no difference in ASI medical scores; quality of evidence was very low because of imprecision and lack of replication. A cohort study that compared buprenorphine to syringe exchange also reported no difference in this score.

Regarding behavioral/social function, one RCT found no significant differences in mean family or psychiatric score between MAT and placebo groups; quality of evidence was rated very low for these outcomes due to lack of replication. Two RCTs with low ROB that measured crime reported that patients on methadone spent fewer days engaged in criminal activity than those randomized to placebo or passive control (e.g., wait-list); results were precise, but quality of evidence was low due to heterogeneity. Likewise, two studies that reported legal outcomes found MAT patients had significantly better scores than subjects provided with psychosocially enhanced detox or syringe exchange; quality of evidence was very low for methadone and buprenorphine because only one study reported this outcome for each drug. In contrast, our meta-analyses of RCTs that reported the percentage arrested or incarcerated found no significant difference between patients randomized to MAT or no MAT; quality of evidence for percentage arrested was low for methadone and naltrexone due to heterogeneity and imprecision.

Three RCTs and two observational studies reported no significant differences in employment outcomes between MAT patients and persons with OUD treated without MAT.

In sum, we identified several RCTs, and this robust study design has the potential to allow strong conclusions to be drawn. However, no RCT was rated as having low ROB, usually because of lack of participant blinding, high attrition, or a combination of both. Given the difficulties in blinding head-to-head studies of medications that are clearly different in appearance (methadone is usually administered as a syrup, while buprenorphine is sublingual) and the nature of SUD, these challenges were anticipated. Some studies compared MAT patients to matched controls with no history of SUD, whereas other studies compared MAT patients to persons with OUD who received a placebo or a non-MAT intervention or were assigned to a passive control condition. Several of the studies that compared MAT patients to persons with OUD who did not receive MAT reported significant positive effects of MAT on functional outcomes. However, in several studies, MAT patients performed significantly worse than matched controls with no history of SUD. Because of the limited number and quality of the studies, the quality of evidence supporting significant differences is low or very low.

Key Question 1a: Effects by Type of Medication

Sixteen studies compared different MAT medication types. Ten compared buprenorphine, a relatively new drug, to methadone, which was first implemented widely in the 1970s. Other studies compared buprenorphine to Suboxone, Suboxone to methadone, and methadone to naltrexone. Only cognitive function (memory, attention), physical function (insomnia, fatigue, pain), and behavioral (crime) outcomes were reported in more than one study.

We found little statistically robust evidence that treatment effects systematically vary by medication. Three RCTs that focused on cognitive function compared buprenorphine to

methadone; no statistically significant differences in memory, cognitive speed and flexibility, attention, or vision were reported, with the exception of a small study in which buprenorphine patients performed better in vision tracking than those on methadone. Quality of evidence for memory and attention was low due to high ROB and imprecision. Quality of evidence for cognitive speed, cognitive flexibility, and vision was very low due to high ROB, imprecision, and lack of replication.

Regarding physical function, a meta-analysis of three RCTs showed a significantly lower prevalence of fatigue in buprenorphine patients than in methadone patients. In absolute terms, 52 fewer buprenorphine patients than methadone patients per 1,000 reported fatigue; quality of evidence for fatigue was moderate, as the trials had low ROB, and results were consistent and precise. Our meta-analysis of three RCTs that reported insomnia found no statistical difference between the buprenorphine and methadone groups; the insomnia analysis included the same trials, but quality of evidence was low because the results were imprecise. Two RCTs that reported pain found no significant difference between buprenorphine and methadone groups: Quality of evidence was low due to high ROB and imprecision.

The only RCT of Suboxone versus methadone that reported functional outcomes found no significant difference in pain-rating scores at six months. The only RCT of methadone versus naltrexone that reported functional outcomes found no significant difference in the mean number of days patients engaged in illegal activity. Finally, a large observational study of a nationally representative sample found no difference in the outcomes "increase in the proportion of subjects who were employed (from intake to discharge)" and "number of arrests in the past 30 days (at treatment discharge)," among patients who received XR-NTX, oral naltrexone, Suboxone, or psychosocial treatment without medication. Group differences were adjusted using propensity scores based on several intake variables (e.g., severity). Despite the low ROB of this observational study, quality of evidence was very low due to lack of replication and lack of RCT data.

Key Question 1b: Effects by Route of Administration

Despite the considerable literature available on MAT, we identified only three RCTs that directly compared routes of administration and reported on functional outcomes. Specifically, the identified studies reported on physical and social function, but they used different outcomes and measures. None reported significant differences on these outcomes. Quality of evidence was very low for no difference in risk of insomnia between oral Suboxone and Suboxone implant; evidence was downgraded due to lack of replication. Quality of evidence is low for no difference between the effects of oral and injected methadone on mental health or physical health due to imprecision and small sample size. Quality of evidence was very low for no difference in effect between oral and injected methadone on social function because of lack of replication, imprecision, and small sample size. One large observational study on a nationally representative sample reported no differences in percentage employed or arrested during treatment among

patients receiving Suboxone, oral naltrexone, injection naltrexone, or non-MAT treatment; quality of evidence was very low due to lack of replication and lack of RCT data.

Key Question 1c: Effect by Length of Treatment, Follow-Up, and Later Cessation

Among three studies that followed MAT patients longitudinally, effect of time by group was significant in only one cohort study for two outcomes: ASI family component and psychiatric component. That study had high ROB because of an unacceptable drop-out rate. We judged the quality of evidence for an effect of treatment length by group on family and psychiatric function to be very low, as the only identified study has a high ROB, is not an RCT, and has not been replicated independently. Likewise, we rated the quality of evidence as very low for an effect of length of treatment by group on memory, attention, and legal issues because of ROB and lack of replication; each outcome was reported in one study that reported multiple follow-ups.

Our meta-regression analyses found no indication that RCTs with longer follow-ups reported larger (or smaller) differences between groups for the outcomes insomnia or percentage arrested. Quality of evidence for insomnia is low because although the four included RCTs had low ROB, the small number of studies has low statistical power to detect differences. Similarly, the quality of evidence for percentage arrested was very low given the small number of studies and overall moderate ROB.

We identified only one study (Reijneveld and Plomp, 1993) that contributed to the question of how and when functional outcome effects change after cessation of MAT. This small cohort study compared MAT patients who remained in MAT treatment at five years to patients who left treatment prior to five years. Current MAT patients were significantly more likely to be out of work than were former patients. The percentage arrested in the past 30 days was not significantly different. Quality of evidence for these outcomes was very low because of small sample size (n = 38), imprecision, lack of replication, and lack of RCT data.

Key Question 1d: Effects by Treatment Modality

Only two studies were identified that compared treatment modalities. One RCT, with low ROB, reported no differences in ASI psychiatric, legal, employment, or medical scores between groups on take-home methadone distributed two times per week versus twice per month. However, given the unclear statistical power to detect differences in these functional outcomes and the lack of replication of the results, the quality of evidence was judged to be very low. One cohort study with low ROB reported a lower rate of nondrug-related crimes by patients prescribed methadone from a general practitioner's office compared with patients dispensed methadone at a traditional methadone clinic. Quality of evidence was rated very low due to lack of replication and lack of RCT evidence.

Prior Systematic Reviews

We identified four recent systematic reviews relevant to this project; all focused on cognitive function. All used less-restrictive inclusion criteria than our review: The majority of the included individual studies used cross-sectional designs with no follow-up. The results reported in these publications echo our findings that MAT patients may perform worse than controls without a history of SUD or opioid use, although quality of evidence in our review was rated low or very low. Prior reviews reported mixed results regarding comparison of MAT patients with former opioid users.

Baldacchino et al. (2017) conducted several meta-analyses to synthesize data from 23 studies. Outcomes of interest included cognitive flexibility, attention and information processing, short-term memory, long-term memory, and impulsivity. Two studies were longitudinal in design, and 21 were cross-sectional, observational studies. Of these, 21 studies compared chronic methadone patients to "healthy participant populations," and seven studies compared chronic methadone patients to abstinent former opioid users. The author conducted meta-analyses on impulsivity, cognitive flexibility, short-term memory, long-term memory, and attention; methadone patients scored significantly worse than controls for all outcomes. Standardized effect sizes were large, ranging from 0.41 to 0.89. When current methadone patients were compared with abstinent former opioid users, nonsignificant differences in effect size were observed for impulsivity, cognitive flexibility, and attention. For short- and long-term memory, better performance was found among former opioid users than among chronic methadone patients. In sum, this review suggests that some neuropsychological functional domains may be negatively affected by chronic methadone use. However, it is unclear if the observed differences were due to methadone use or long-term use of opioids in general.

Strand et al. (2013) examined the effects of methadone and buprenorphine maintenance on driving ability, including 54 experimental studies with a control group and five epidemiological studies with risk analysis. The authors included the following populations: persons with OUD receiving MAT with methadone or buprenorphine, persons with OUD not receiving MAT, and controls without a significant history of drug use. Meta-analysis was not conducted. The epidemiological studies had mixed findings: The largest analyzed a national database using case-control and case-crossover analyses. The case-control analysis revealed a higher risk of causing a motor vehicle accident among patients who received methadone and/or buprenorphine the day of the accident (OR 2.9; CI 1.51, 3.16). However, the case-crossover analysis did not find a significant relationship between methadone and/or buprenorphine exposure and a motor vehicle accident (OR 1.26; CI 0.93, 1.70). Among the experimental studies, patients who received methadone showed signs of impairment compared with controls in 127 of 407 tests across 28 studies, and patients receiving buprenorphine showed signs of impairment compared with controls in 22 of 83 tests across seven studies. Across the eight studies that directly compared methadone to buprenorphine, patients taking buprenorphine showed significantly less

impairment than those taking methadone in 13 of 76 tests. This review concluded that buprenorphine and methadone can impair driving abilities in healthy controls and may impair some functions in maintenance patients. Our systematic review found only one study that assessed the ability to drive an automobile. This observational study of injurious traffic accidents in France found statistically significant results; controlling for many important factors, patients taking methadone or buprenorphine were twice as likely to be involved in injurious accidents as individuals not on MAT.

Wang, Wouldes, and Russell (2013) synthesized the results from 35 studies, including 22 cross-sectional, five longitudinal, and eight RCTs on the effects of methadone maintenance on cognitive function compared with controls without a history of SUD. Meta-analysis was not conducted. Cognitive impairments among methadone patients included decreased performance on memory (eight studies), attention (two studies), psychomotor speed (four studies), decisionmaking (two studies), emotional interpretation (two studies), and verbal function (two studies) when compared with controls. However, the authors noted that two studies observed no significant differences, three studies observed small differences, and two studies found improved reaction times among methadone patients.

Finally, Biernacki et al. (2016) synthesized results from 22 studies that compared current or former opioid users to controls who did not have a significant history of drug abuse and were not currently using illicit drugs. This review categorized MAT patients as current opioid users and did not differentiate them from current users of illicit drugs. The design of included studies was not reported. Fifteen studies measured decisionmaking among current opioid users; in a meta-analysis, performance on decisionmaking measures was significantly worse in current users than in controls with no history of SUD. Among current opioid users, no significant association was found between the duration of opioid use and the size of the effect on decisionmaking based on results from 11 studies. Performance on decisionmaking measures was significantly worse among former opioid users when compared with controls with no history of SUD but not significantly different when compared between former and current users.

In sum, these recent reviews indicate that MAT patients perform worse in cognitive function than healthy controls with no history of SUD or opioid use. However, it is unclear if the observed differences are due to MAT or long-term use of opioids in general. Although controls are usually matched to patients on demographic and other characteristics, they clearly differ in substance abuse history and may differ in unreported psychological, psychiatric, and family history characteristics that might contribute to poor function.

Strengths and Limitations

This review has several strengths: an *a priori* research design, duplicate study selection and data abstraction of study information, a comprehensive search of electronic databases, ROB assessments, and use of comprehensive quality of evidence assessments to formulate review

conclusions. To not miss relevant studies, we screened 1,327 full text articles for functional outcomes.

However, our review has several limitations. First, very few studies of MAT reported functional outcomes; 37 MAT studies that met our study design criteria reported cognitive, physical, occupational behavioral/social, or neurological outcomes; while 307 studies of MAT were excluded for no functional outcomes. This lack of relevant data was not entirely unexpected, as studies of interventions for SUD tend to focus on reduction or cessation of substance use, treatment retention, and harm reduction. Functional outcomes were secondary outcomes in most included studies. Functional measures were primary outcomes in only six controlled trials; it is unclear if the other trials, which were statistically powered to detect differences in illicit use of opioids or treatment retention, had adequate power to detect differences in function.

The small number of studies reporting specific functional outcome measures limited our ability to conduct meta-analyses across medication types, comparators, settings, and routes of administration. Only six studies of naltrexone reported functional outcomes; most evidence is based on trials of methadone, buprenorphine, or buprenorphine plus naloxone (marketed as Suboxone). Furthermore, the included controlled trials had moderate to high ROB, primarily because of lack of participant blinding, high attrition rates, and failure to report the method of randomization and allocation. We did not contact individual study authors: Results and quality ratings reported in the review are based on published data. Finally, although we calculated the I-squared statistic to assess heterogeneity among studies included in our meta-analyses, some undetected heterogeneity may exist. The I-squared statistic is dependent on statistical power, which is primarily influenced by the number of studies and secondarily by the size of the studies; our meta-analyses included a small number of studies, and study sample size was often small compared with typical studies of medications and health care interventions.

Implications for Future Research and Practice

Making clinical and policy recommendations is beyond the scope of the systematic review; the goal of this report was to summarize, synthesize, and assess the quality of the existing evidence. Weaknesses in the body of evidence prevent any strong conclusions about the effects of MAT on functional outcomes or differences among medication types, treatment modalities, or length of treatment. Some studies that compared MAT patients to persons with OUD who did not receive MAT reported significant beneficial effects. However, this finding does not imply that performance meets the standards required for military deployment.

One RCT reported that the mean number of days of illegal activity in the past 30 days was not significantly different between the 20 mg methadone group and the placebo group but was significantly lower in the 50 mg methadone group. The number of crimes committed was significantly lower in both methadone groups compared with the placebo group, with the 50 mg

group reporting significantly fewer crimes than the 20 mg group (MD –9.23 versus –4.0). These results suggest a possible dose-response relationship that could be explored through future research, as dosage issues were beyond the scope of this project.

Importantly, in several studies, MAT patients performed significantly worse than matched controls with no history of SUD or OUD on measures of aggression, working memory, and cognitive speed. Unfortunately, no studies were conducted on active-duty service members or reported performance on specific occupational tasks. No studies reported the current or former occupations of participants, and applicability of the outcome measures to successful military deployment was not discussed in any study.

The original GRADE system (Atkins et al., 2004), developed to support clinical practice guidelines, recommended four factors to be considered when making a recommendation: (1) the trade-offs, taking into account the estimated size of the effect for the main outcomes, the confidence limits around those estimates, and the relative value placed on each outcome; (2) the quality of the evidence; (3) translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects, such as availability of necessary expertise; and (4) uncertainty about baseline risk for the population of interest (to accurately balance benefits and harms). We rated the quality of evidence according to GRADE criteria; quality is low or very low for all outcomes. If data on the ability of MAT patients to perform typical activities of deployed service members in diverse occupations are needed, rigorous studies of applicable tasks could be designed and funded. RCTs are the highest standard of evidence; however, trials of this nature would be difficult to conduct. The time needed to obtain results that reflect real-world MAT programs might be prohibitive, given DoD's decisionmaking time line. It is possible that secondary analyses of existing administrative or health databases could be conducted quickly; however, we are aware of no sources of MAT data that collect information on detailed task performance. If decisions on deployment must be made without conducting further studies, expert opinion, political will, feasibility, troop morale, and other factors should be considered.

Appendix A. Food and Drug Administration Warnings Table

FDA Warnings	Buprenorphine[a]	Buprenorphine with Naloxone (Suboxone)[a]	Methadone[b]	Naltrexone[c]
Respiratory	Respiratory depression	Respiratory depression	Respiratory depression	—
Cardiac	—	—	Arrhythmias, cardiac conduction effects, including QT interval prolongation and torsades de pointes	—
Hepatic	Cytolysis hepatitis and hepatitis with jaundice	Cytolysis hepatitis and hepatitis with jaundice	—	Hepatocellular injury in excessive doses
Central nervous system (CNS)	CNS depression	CNS depression	Interactions with CNS depressants Interactions with alcohol and drugs of abuse	—
Others	Allergic reactions Dependence Opiate withdrawal effects	Allergic reactions Dependence Opiate withdrawal effects	Interactions with alcohol and drugs of abuse Head injury and increased intracranial pressure Acute abdominal conditions Hypotensive effect Dependence	Eosinophilic pneumonia Injection-site reactions

[a] "Patient Information Leaflet, Patient Information: Suboxone, Subutex," undated.
[b] Roxane Laboratories, undated.
[c] "Vivitrol," undated.

Appendix B. Search Methodology

DATABASE SEARCHED AND TIME PERIOD COVERED
PubMed: January 1, 1970–January 16, 2017

LANGUAGE
English

SEARCH STRATEGY
((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*)) OR "Opioid-Related Disorders"[Mesh]
AND
"medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone
AND
(humans[MESH] OR ((inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb]) NOT (mice[ti] OR mouse[ti] OR rats[ti] OR rat[ti] OR dogs[ti])))

DATABASE SEARCHED AND TIME PERIOD COVERED
PubMed: January 1, 1970–December 31, 2000

LANGUAGE
English

SEARCH STRATEGY
"Opioid-Related Disorders"[Mesh] OR narcotic* OR opiate* OR opioid* OR heroin OR morphine
AND
misuse or abus* or addict* OR habit* OR withdraw*
AND
random* OR randomized controlled trial[pt] OR randomized controlled trials OR rct* OR blind* OR double-blind* OR single-blind*

==========

DATABASE SEARCHED AND TIME PERIOD COVERED
PsycINFO: January 1, 1970–January 31, 2017

LANGUAGE
English

SEARCH STRATEGY
TI ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR SU ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR AB ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone)
AND

TI ((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*)) OR SU ((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*)) OR AB ((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*))
AND
TI (randomi* OR "systematic review") OR SU (randomi* OR "systematic review") OR AB (randomi* OR "systematic review")

==========

DATABASE SEARCHED AND TIME PERIOD COVERED
PsycINFO: January 1, 1970–January 16, 2017

LANGUAGE
English

SEARCH STRATEGY
[TI ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR SU ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR AB ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR DE "Narcotic Antagonists" OR DE "Nalorphine" OR DE "Naloxone" OR DE "Naltrexone"
AND
DE "Opiates" OR DE "Codeine" OR DE "Heroin" OR DE "Morphine"
AND
DE "Drug Addiction" OR DE "Addiction" OR DE "Drug Dependency" OR DE "Heroin Addiction" OR DE "Drug Abuse" OR DE "Drug Overdoses" OR DE "Drug Withdrawal" OR DE "Intravenous Drug Usage" OR DE "Substance Use Disorder"

OR

TI ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR SU ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR AB ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR DE "Narcotic Antagonists" OR DE "Nalorphine" OR DE "Naloxone" OR DE "Naltrexone"
AND
TI (narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*) OR SU ((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*) OR AB ((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*))

AND

TI (control* OR case-control*) OR SU (control* OR case-control*) OR AB (control* OR case-control*)
OR
TI (random* OR rct*) OR SU (random* OR rct*) OR AB (random* OR rct*)

AND
Narrow by Population: - human

==========

DATABASE SEARCHED AND TIME PERIOD COVERED
CINAHL: January 1, 1970–December 31, 2016

LANGUAGE
English

SEARCH STRATEGY
TI ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR AB ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone) OR SU ("medication assisted treatment" OR "medication-assisted treatment" OR buprenorphine OR methadone OR naltrexone)
AND
TI ((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*)) OR AB ((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*) OR SU ((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse or abus* or addict* OR habit* OR withdraw*))
AND
TI (randomi* OR "systematic review") OR SU (randomi* OR "systematic review") OR AB (randomi* OR "systematic review")
OR
TI (control* OR case-control) OR AB (control* OR case-control) OR SU (control* OR case-control)

==========

DATABASE SEARCHED AND TIME PERIOD COVERED
Cochrane Database of Systematic Reviews, Other Reviews, CENTRAL: January 1, 2000–October 31, 2016

SEARCH STRATEGY
(narcotic* or opiate* or opioid* or heroin or morphine) and (misuse or abus* or addict* or habit* or withdraw*):ti,ab,kw (Word variations have been searched) OR MeSH descriptor: [Opioid-Related Disorders] explode all trees
AND
"medication assisted treatment" or "medication-assisted treatment" or buprenorphine or methadone or naltrexone:ti,ab,kw (Word variations have been searched)

==========

DATABASE SEARCHED AND TIME PERIOD COVERED
Cochrane CENTRAL: January 1, 1970–December 31, 2000

SEARCH STRATEGY:
(narcotic* or opiate* or opioid* or heroin or morphine) and (misuse or abus* or addict* or habit* or withdraw*):ti,ab,kw (Word variations have been searched) OR MeSH descriptor: [Opioid-Related Disorders] explode all trees
AND

“medication assisted treatment” or “medication-assisted treatment” or buprenorphine or methadone or naltrexone:ti,ab,kw (Word variations have been searched)

==========

DATABASE SEARCHED AND TIME PERIOD COVERED
EMBASE: From inception–February 1, 2017

LANGUAGE
English

SEARCH STRATEGY
‘narcotic dependence’/exp OR ((narcotic* OR opiate* OR opioid* OR heroin OR morphine) AND (misuse OR abus* OR addict* OR habit* OR withdraw* OR depend*))
AND
‘medication assisted treatment’ OR ‘medication-assisted treatment’ OR buprenorphine OR methadone OR naltrexone
AND
random* OR rct* OR blind* OR ‘double blind*’ OR ‘single blind*’ OR systematic OR ‘meta analy*’ OR ‘double blind procedure’/de OR ‘randomized controlled trial’/de OR ‘randomized controlled trial (topic)’/de OR ‘systematic review’/de

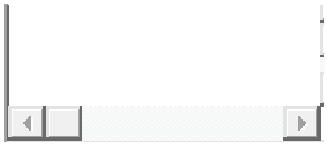
Appendix C. Risk of Bias Instruments

QUALITY ASSESSMENT: CONTROLLED TRIALS

Was the allocation sequence (randomization method) adequately generated?
There is a LOW RISK OF BIAS if the investigators describe a random component in the sequence generation process such as: referring to a random number table,
using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots.
There is a HIGH RISK OF BIAS if the investigators describe a non-random component in the sequence generation process, such as: sequence generated by odd
or even date of birth, date (or day) of admission, hospital or clinic record number; or allocation by judgement of the clinician, preference of the participant,
results of a laboratory test or a series of tests, or availability of the intervention.
If the trial was not randomized, please check “high risk”
IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

Low risk

High risk notes



Was ALLOCATION adequately concealed (prior to assignment)?

There is a LOW RISK OF BIAS if the participants and investigators enrolling participants could not foresee assignment because one of the following,
or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance;
or sequentially numbered, opaque, sealed envelopes.
There is a HIGH RISK OF BIAS if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias,
such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);
alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures.
IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

Clear Respon

High risk notes

Were participants adequately BLINDED?

There is a LOW RISK OF BIAS if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding,
but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

- Low risk
- High risk
- Unclear

Clear Response

High risk notes

Were OUTCOME ASSESSORS adequately BLINDED?
There is LOW RISK OF BIAS if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken.
Please make sure you assess the blinding of whoever measured the FUNCTIONAL OUTCOME, rather than outcomes such as drug use.

- Low risk
- High risk
- Unclear

Clear Response

High risk notes

Incomplete outcome data (ATTRITION BIAS) due to amount, nature or handling of incomplete outcome data

There is a LOW RISK OF BIAS if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome;
missing outcome data were balanced in numbers, with similar reasons for missing data across groups
(****The percentage of withdrawals and drop-outs should not exceed 20% for
short-term follow-up [<=1 year] and 30% for long-term follow-up [>1 year]****).
IF HIGH RISK OF BIAS, EXPLAIN IN NOTES. Again, please assess for FUNCTIONAL outcome, rather than other outcomes.
Participants may provide urine for drug testing, but not show up for functional tests or provide data on functional outcomes at follow-up.

- Low risk
- High risk

Unclear

Clear Response

High risk notes

Is there evidence of SELECTIVE OUTCOME REPORTING bias (Yes/No)?

Are all outcomes in the Methods section (all pre-specified outcomes) reported, were all components of composite outcomes reported?
DESCRIBE ISSUES IN NOTES.

Yes

No

Unclear

Clear Response

Notes

INTENTION-TO-TREAT analysis? (Yes/No)

Intention to treat (ITT) analysis means all patients who were enrolled and randomly allocated to treatment are included in the analysis and are analyzed in the groups
to which they were randomized. Everyone who is randomized in the trial is considered to be part of the trial regardless of whether he or she completes the trial.
YES if they state ITT and methods used were actually ITT, or **all** participants were analyzed in the group to which they were allocated by randomization (no cross-over).
IF NO ITT, EXPLAIN IN NOTES.

Yes

No

Unclear

Clear Response

Notes

Group SIMILARITY AT BASELINE

There is LOW RISK OF BIAS if groups are similar at baseline for demographic and other factors ("Table 1").
Also LOW risk of bias if any baseline differences were adjusted for in all relevant analyses.
IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- ○ Low risk
- ○ High risk
- ○ Unclear

Clear Response

Notes

Was there incomplete COMPLIANCE with interventions across groups?
There is LOW RISK OF BIAS if compliance with the interventions was acceptable (>=80% across intervention duration), based on the reported actual compliance during or at the end of the intervention.
There is HIGH RISK OF BIAS if compliance was low (<80%) during or at the end of the intervention.
There is UNCLEAR RISK OF BIAS if these data were not reported.

- ○ Low risk
- ○ High risk
- ○ Unclear

Clear Response

Notes

Additional Bias: Bias due to problems not covered elsewhere in the table

- ○ Yes
- ○ No

Clear Response

Notes

QUALITY ASSESSMENT: OBSERVATIONAL STUDIES

Selection

1) Representativeness of the exposed cohort

- ☐ Truly representative of the average MAT patient in the community
- ☐ Somewhat representative of the average MAT patient in the community
- ☐ Selected group of users, e.g. nurses, volunteers
- ☐ No description of the derivation of the cohort

2) Selection of the non-exposed cohort (e.g. "healthy controls" or opioid dependent participants receiving a different medication or not receiving MAT)

- ☐ Drawn from the same community as the exposed cohort
- ☐ Drawn from a different source
- ☐ No description of the derivation of the non-exposed cohort
- ☐ Not applicable

3) Ascertainment of exposure

- ☐ Secure record (e.g. medical records, participation in a specific treatment program)
- ☐ Structured interview
- ☐ Written self-report
- ☐ No description

4) Demonstration that outcome of interest was not present at start of study (if relevant, which will almost never be the case) or author's statement
that a valid outcome measure was chosen (e.g. a validated instrument measuring depression, anxiety, insomnia, etc).

- ☐ Yes
- ☐ No

Comparability

1) Comparability of cohorts on the basis of the design or analysis
If the authors describe factors for which they adjusted or noted that cohorts were matched on important factors and listed the factors, count that as a "yes"

- ☐ Study controls for demographic information, if drug users not in treatment -- controls for severity of drug use
- ☐ Study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor)

Outcome

1) Assessment of outcome

- ☐ Independent blind assessment

☐ Record linkage

☐ Self-report

☐ No description

2) Was follow-up long enough for outcome to occur (e.g. if the authors say they chose a particular follow-up time, definitely select “yes”; otherwise use your own judgment).

☐ Yes (select an adequate follow-up period for outcome of interest)

☐ No

3) Adequacy of follow-up cohorts

☐ Complete follow-up -- all subjects accounted for

☐ Subjects lost to follow up unlikely to introduce bias - small number lost - >80% retention for ≤ 1 year followup; >30% loss for 1-5 years followup; >40% loss for 6-10 years followup; >50% loss for 11-18 years followup; or description provided of those lost

☐ Follow-up rate not acceptable (according to levels described above) and no description of those lost

☐ No statement

Appendix D. Evidence Table

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Aalto et al., 2011 Location: Europe Study design: case-control	Number enrolled: 60 Number completed: 54 Mean age: buprenorphine: 26.7 (4.9), SEP: 26.5 (4.6) Percentage female: 20 Race/ethnicity: NR Years of opioid use: buprenorphine: 3.6 (1.7) SEP: 4.2 (1.8) Inclusion criteria: The inclusion criteria for the buprenorphine program were opioid dependence under the International Classification of Diseases–10 criteria and previous participation in at least one detoxification treatment. Another 30 opioid-dependent patients, who reported mainly using buprenorphine and who participated in the SEP, were recruited for the study in Helsinki between October 2005 and May 2006. Exclusion criteria: NR	Intervention: buprenorphine Setting: other substance abuse treatment Route of administration: oral Duration (months): 23 Non-MAT comparator: 1. SEP	Physical : ASI medical score, 12 months, buprenorphine (outpatient versus control—matched controls in an SEP, MD: –0.18, 95% CI: (–0.39, 0.03) Behavioral/social : ASI legal score, 12 months, buprenorphine—outpatient versus control—matched controls in an SEP, MD: –0.25, 95% CI: (–0.39, –0.11) ASI psychiatric score, 12 months, buprenorphine—outpatient versus control—matched controls in an SEP, MD: 0.01, 95% CI: (–0.16, 0.18)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Bale et al., 1980 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 585 Number completed: 545 Mean age: >25 years = 63% Percentage female: 0 Race/ethnicity: White: 39%, Black: 41%, Hispanic: 12% Years of opioid use: NR Inclusion criteria: Subject must have been using narcotics daily just prior to admission. He or she must not have been recently discharged from a longer-term treatment program at the hospital (because the nature of the discharge could preclude his readmission to a longer-term program). Exclusion criteria: Major psychiatric problems. Some patients were later found to be ineligible for VA treatment because of an "undesirable" military discharge or because they had falsified their names or records to gain entry to the detoxification ward. These patients were excluded from the study at the point when such information was discovered. Finally, patients who had felony charges pending were excluded.	Intervention: methadone Setting: methadone clinic Route of administration: oral Duration (months): NR Non-MAT comparator: 1. The family is a residential therapeutic community with 20 to 35 residents, including five to seven heroin addicts. The program is strongly committed to abstinence from all psychoactive substances and uses group confrontation and support (often called "attack" or "Synanon style" therapy). 2. Quadrants, a therapeutic community with 20 to 30 residents. All of the program residents have been addicted to heroin. Is less committed to complete abstinence, and some prescribed medications (but not methadone) are used. Uses limited group confrontation in combination with other therapeutic techniques. 3. Satori, a therapeutic community with 15 to 20 residents, all have been addicted to heroin. Psychoactive medications, including methadone, are occasionally prescribed. Emphasis on historical material and reconstruction therapy, attack style of confrontation is not employed.	Behavioral/social : Arrests during year (proportion of group), 1 year, all subjects (combined) in residential program versus outpatient MMT program, RR: 0.94, 95% CI: (0.68, 1.28) Percentage participants reincarcerated, 1 year, all subjects (combined) in residential program versus outpatient MMT program, RR: 1.24, 95% CI: (0.52, 2.95)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Compton et al., 2012 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 103 Number completed: 51 Mean age: control: 30.14 (11), buprenorphine: 33.41 (9) methadone: 34.55 (12) Percentage female: 35.9 Race/ethnicity: White: 79.6%, Black: 5.8%, Asian: 1.9%, other: 12.6% Years of opioid use: NR Inclusion criteria: At least 18 years of age; in good physical health; agreeable to and capable of signing an informed consent; no existing conditions that would affect sensitivity to cold (e.g., Raynaud's disease, urticaria); no neuropathology that would affect pain responses (e.g., peripheral neuropathy, neuropathic pain); and no cardiovascular conditions that could put participants at risk for blood pressure increases. Noncontrol group participants were seeking opioid maintenance therapy for the treatment of a DSM-IV diagnosed heroin dependence disorder. Exclusion criteria: A known sensitivity to buprenorphine or methadone; dependence on alcohol, benzodiazepines, or other drugs of abuse (except nicotine); any acute medical condition that would make participation medically hazardous; acute psychosis, severe depression, or in need of acute inpatient treatment/suicidal; taken levo-alpha-acetylmethadol, methadone or naltrexone within 30 days of enrolling in the study; discontinued participation in an opiate-substitution (i.e., methadone, levo-alpha-acetylmethadol) treatment program within 30 days of enrolling in the study; or any pending legal action that could prohibit sustained participation. For the control group, a current or past history of substance abuse, current use of analgesic medication, or being a nursing or pregnant female excluded participation.	Intervention: methadone Setting: other substance abuse treatment Route of administration: NR Duration (months): 4.5 Intervention 2: buprenorphine Setting: other substance abuse treatment Route of administration: NR Duration (months): 4.5 Non-MAT Comparator: 1. drug-free controls	Physical : Pain detection—volts, 18 weeks, buprenorphine versus methadone, MD: –0.94, 95% CI: (–5.16, 3.28) Pain tolerance—volts, 18 weeks, buprenorphine versus methadone, MD: 3.61, 95% CI: (–2.13, 9.35) Pain detection—volts, 18 weeks, buprenorphine versus control, MD: 2.09, 95% CI: (–4.7, 8.88) Pain tolerance—volts, 18 weeks, buprenorphine versus control, MD: –9.17, 95% CI: (–19.42, 1.08) Pain detection—volts, 18 weeks, buprenorphine versus methadone, MD: –0.84, 95% CI: (–12.1, 10.42) Pain tolerance—volts, 18 weeks, buprenorphine versus methadone, MD: 4.04, 95% CI: (–9.44, 17.52) Pain detection time (seconds), 18 weeks, buprenorphine versus control, MD: –3.63, 95% CI: (–6.79, –0.47) Pain tolerance—time (seconds), 18 weeks, buprenorphine versus control, MD: –25.35, 95% CI: (–38.87, –11.83) Pain detection time (seconds), 18 weeks, methadone versus control, MD: –2.69, 95% CI: (–7.32, 1.94) Pain tolerance—time (seconds), 18 weeks, methadone versus control, MD: –28.96, 95% CI: (–42.83, –15.09) Pain detection time (seconds), 18 weeks, methadone versus control, MD: 2.93, 95% CI: (–8.05, 13.91) Pain tolerance—time (seconds), 18 weeks, methadone versus control, MD: –13.21, 95% CI: (–27.82, 1.4)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Cornish et al., 1997 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 51 Number completed: 24 Mean age: 39 Percentage female: 10 Race/ethnicity: White: 24%, Black: 62%, Hispanic: 14% Years of opioid use: NR Inclusion criteria: Federal probationers or parolees with a history of opioid addiction Exclusion criteria: NR	Intervention: naltrexone Setting: an office within the probation department Route of administration: oral Duration(months): 6 Non-MAT comparator: 1. Subjects were required to attend three orientation and counseling sessions per week during the first 2 weeks of the study. These sessions were conducted by the research technician and focused on obtaining drug use and treatment histories, acquired immune deficiency syndrome (AIDS) education and risk reduction, and orientation to the research protocol. In addition, the subjects saw their parole/probation officer (PO) and provided a monitored urine specimen and breathalyzer reading twice weekly. From week 3 through week 24, control subjects saw their PO twice weekly and one of the two visits was randomly selected for the subject to provide a monitored urine specimen and breathalyzer reading.	Behavioral/social: Percentage participants reincarcerated, 6 months, naltrexone versus placebo, RR: 0.46, 95% CI: (0.23, 0.94)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Corsenac et al., 2012 Location: Europe Study design: case control	Number enrolled: 72,685 Number completed: 72,685 Mean age: NR Percentage female: 31.5 Race/ethnicity: NR Years of opioid use: not applicable Inclusion criteria: Drivers were included through their national ID, gender, and date of birth, as extracted from police reports. An application, based on optical character recognition, was developed to automatically extract from the image files the date of the crash, an individual's national ID, gender, and date of birth. Data on reimbursed medicines dispensed within six months before the crash were obtained by linking included drivers to the national health care insurance database using their national ID, gender, and date of birth. Exclusion criteria: not applicable	Intervention: methadone, buprenorphine Setting: not applicable, study of traffic accident data Route of administration: not applicable Duration (months): not applicable Non-MAT comparator: 1. General population. Collected from police reports and databases through ID extraction.	Cognitive: Responsible for traffic accidents, buprenorphine, or methadone versus nondrug user, 3 years, OR: 2.02, 95% CI: (1.40, 2.91)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Coviello et al., 2010 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 111 Number completed: 34 Mean age: 33.5 Percentage female: 18 Race/ethnicity: White: 47%, Black: 26%, Hispanic: 27% Years of opioid use: Heroin: 7.7 Inclusion criteria: Subjects were eligible for participation if they: (1) signed an informed consent form agreeing to randomization to one of the two treatment groups; (2) were between the ages of 18 and 55; (3) had a diagnosis of opioid dependence based on DSM-IV criteria and a structured psychiatric interview; (4) were in good general health as determined by a complete physical examination and laboratory tests; (5) had been assigned to probation/parole for a minimum of 6 months; and (6) had a negative result for urinary opioids and reported being at least 3 days opioid-free prior to randomization. Exclusion criteria: Subjects were excluded if they had: (1) current severe alcohol dependence that required medical supervision for alcohol withdrawal symptoms; (2) current psychosis, dementia, mental retardation, or history of schizophrenia; (3) clinically significant abnormalities in hematology, chemistry, or urinalysis; (4) clinically significant cardiovascular, neurological, hepatic, renal, pulmonary, metabolic, endocrine, or gastrointestinal disorders; (5) a diagnosis of chronic pain disorder; or (6) taken an opioid antagonist within the prior six months. Female subjects who were pregnant or lactating, or women of childbearing potential who were not using birth control were also excluded.	Intervention: naltrexone Setting: university research offices Route of administration: oral Duration (months): 6 Non-MAT comparator: 1. TAU (treatment as usual): psychological treatment. Participants in the TAU group received 6 months of psychosocial treatment at one of several community-based treatment programs or at the university provided by the research study. The university-based psychosocial treatment consisted of 3 hours of group therapy, 1 hour of individual therapy, and 1 hour of case management for 6 weeks of intensive outpatient treatment followed by 20 weeks of outpatient treatment consisting of 1 hour of individual and 1 hour of case management per week. The psychosocial therapy provided by the community-based programs was similar in content, but typically included additional hours of group therapy.	Occupational: Percentage of participants employed, 6 months, naltrexone versus standard psychosocial TAU, RR: 1.27, 95% CI: (0.84, 1.93) Behavioral/social : Average number of charges (prior versus follow-up), 6 months, oral naltrexone plus standard psychosocial treatment versus standard psychosocial TAU, MD: –0.3, 95%, CI: not calculable Average number of convictions (prior versus follow-up), 6 months, oral naltrexone plus standard psychosocial treatment versus standard psychosocial TAU, MD: 0, 95%, CI: not calculable

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Coviello et al., 2011 Location: United States or Canada Study design: cohort comparison	Number enrolled: 490 Number completed: 230 Mean age: 44.2 Percentage female: 18 Race/ethnicity: White: 45%, Black: 51%, Hispanic: 4%, Asian: NR, other: NR Years of opioid use: heroin: 17.7, other opioids: 3.0 Inclusion criteria: All patients discharged from three methadone treatment programs in a 3-year period, regardless of whether they completed "successfully." Exclusion criteria: NR	Intervention: methadone Setting: methadone clinic Route of administration: oral Duration (months): 3 Non-MAT comparator: 1. No methadone maintenance treatment in past 3 months.	Behavioral/social : Mean number of days of illegal activity in the past 30 days, 3 months, methadone—outreach case management (OCM) (treatment) versus methadone—passive referral (no treatment)—control, MD: –3.4, 95% CI: (–6.01, –0.79) Mean number of days of illegal activity in the past 30 days, 9 months, methadone—OCM (treatment) versus methadone—passive referral (no treatment)—control, RR: 0.94, 95% CI: (0.48, 1.83)
Reference: Crits-Christoph et al., 2015 Location: United States or Canada Study design: cohort comparison	Number enrolled: 2,882 Number completed: 2,882 Mean age: 34.7 (10.5) Percentage female: 25.2 Race/ethnicity: White: 57.1%, Black: 39.7%, Other: 3.2% Years of opioid use: NR Inclusion criteria: The analysis included men and women ages 18 and older, who reported opioid use as their primary, secondary, or tertiary substance use problem at admission and had intake data. The study group was limited to individuals who were under community supervision by the state correctional agency (i.e., on parole or probation). All patients were treated in outpatient centers that received funding from the Missouri Division of Behavioral Health during fiscal year 2013 (July 1, 2012–June 30, 2013) in a six-county area plus the city of St. Louis. Exclusion criteria: NR	Intervention: naltrexone Setting: NR Route of administration: implant Duration (months): 3 Intervention 2: naltrexone Setting: NR Route of administration: oral Duration (months): 2 Intervention 3: Suboxone Setting: NR Route of administration: NR Duration (months): 2.5 Non-MAT comparator: 1. Psychosocial only. Adjusted median durations of episode of care were: psychosocial only, 85 days	Behavioral/social: percentage arrested in past 30 days, extended-release naltrexone, oral naltrexone, Suboxone, versus psychosocial only; no difference among groups when controlling for baseline variables and propensity scores Occupational: percentage employed at discharge; extended-release naltrexone, oral naltrexone, Suboxone, versus psychosocial only; no difference among groups when controlling for baseline variables and propensity scores

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Dole et al., 1969 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 32 Number completed: NR Mean age: 30.0 (5.1) Percentage female: NR Race/ethnicity: White: 46.8%, Black: 31.2%, Asian: 21.9% Years of opioid use: 12.7 Inclusion criteria: Opioid dependence for 5 or more years, 5 or more previous convictions, not already committed to the custody of addiction services agency Exclusion criteria: NR	Intervention: methadone Setting: prison, then methadone clinic Route of administration: oral Duration (months): NR Non-MAT comparator: 1. Untreated controls	Behavioral/social: Percentage of participants convicted of crimes committed after release, 1 year, methadone versus placebo, RR: 0.27, 95% CI: (0.10, 0.71)
Reference: Farrell-MacDonald et al., 2014 Location: United States or Canada Study design: cohort comparison	Number enrolled: 137 Number completed: 137 Mean age: continued MMT: 33.0 (7.2); MMT-T: 34.5 (8.0); no MMT 31.3 (7.4) Percentage female: 100 Race/ethnicity: NR Years of opioid use: NR Inclusion criteria: Data for this retrospective study were drawn from administrative data on a sample of women federal offenders who were initiated on MMT (the only available OMT option during the study period) while incarcerated in a Correctional Service of Canada (CSC) facility between January 1, 2003, and December 31, 2008, and who were released into the community Exclusion criteria: NR	Intervention: methadone Setting: prison, then community Route of administration: oral Duration (months): NR Non-MAT comparator: 1. A comparison group of offenders admitted to CSC and community-released during the study period, who were assessed at correctional intake as having a moderate to severe substance abuse problem with opioid use confirmed as their primary problem drug, but who did not participate in MMT while incarcerated	Behavioral/social: Percentage participants reincarcerated, 27 weeks, continuing methadone versus no MAT, hazard ration (HR): 0.35, 95% CI: (0.13, 0.90) Percentage participants reincarcerated, 27 weeks, terminated methadone versus no MAT, HR: 1.20, 95% CI: (0.72, 2.02)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Fudala et al., 2003 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 326 Number completed: 243 Mean age: Suboxone: 38.1 (8.3), buprenorphine: 36.6 (8.9), placebo: 38.0 (9.3) Percentage female: 35.3 Race/ethnicity: White: 61%, Black: 28.5%, Hispanic: 7.1%, Asian: 2.2%, other: 1.2 (Native American)% Mean years of opioid use: 7 Inclusion criteria: Men and women who met the diagnostic criteria for opiate dependence according to the DSM-IV, who were seeking opiate-substitution pharmacotherapy, who were between the ages of 18 and 59 years, and who were able to give informed consent and comply with study procedures were eligible to participate. Exclusion criteria: Women who were pregnant or nursing were excluded. Other criteria for exclusion included any medical condition that made study participation medically hazardous; aspartate or alanine aminotransferase levels greater than three times the upper limit of normal; a current, primary, Axis I psychiatric diagnosis (according to the DSM-IV) other than opiate, caffeine, or nicotine dependence; and use of methadone, levomethadyl acetate, or naltrexone within the 14 days before enrollment.	Intervention: Suboxone Setting: doctor's office Route of administration: oral Duration (months): 1 Intervention 2: buprenorphine Setting: doctor's office Route of administration: oral Duration (months): 1 Non-MAT comparator: 1. Placebo: All the tablets were identical in appearance and taste. All the subjects received counseling regarding human immunodeficiency virus (HIV) infection and up to 1 hour of individualized counseling per week. Emergency counseling (e.g., after a relapse) and referrals (e.g., to community legal aid programs) could be provided, but no other counseling or services (e.g., regarding family or employment issues) were offered.	Physical : Number (percentage) of patients who reported experiencing pain during the trial, 4 weeks, Suboxone versus buprenorphine, RR: 1.22, 95% CI: (0.71, 2.08) Number (percentage) of patients who reported experiencing pain during the trial, 4 weeks, Suboxone versus placebo, RR: 1.2, 95% CI: (0.71, 2.03) Number (percentage) of patients who reported experiencing pain during the trial, 4 weeks, buprenorphine versus placebo, RR: 0.98, 95% CI: (0.56, 1.73) Percentage of participants reporting insomnia, 4 weeks, Suboxone versus buprenorphine, RR: 0.65, 95% CI: (0.36, 1.19) Percentage of participants reporting insomnia, 4 weeks, Suboxone versus placebo, RR: 0.88, 95% CI: (0.46, 1.67) Percentage of participants reporting insomnia, 4 weeks, buprenorphine versus placebo, RR: 1.35, 95% CI: (0.76, 2.38)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Gerra et al., 2007 Location: Europe Study design: randomized controlled trial	Number enrolled: 45 Number completed: NR Mean age: heroin users: 25 (5.3); healthy controls: 24.4 (3.6) Percentage female: 0 Race/ethnicity: NR Years of opioid use: 9.2 (3.9) Inclusion criteria: Heroin-dependent patients were randomly assigned to buprenorphine or methadone treatment after they contacted the outpatient center seeking treatment. All the subjects were available for methadone or buprenorphine treatment, without any preference for a specific substitution treatment. Fifteen healthy male volunteers, who were recruited from hospital staff, university students, and workers, were matched to the patients for age. Exclusion criteria: Exclusion criteria included severe chronic liver or renal diseases or other chronic physical disorders, recent weight loss or obesity, endocrinopathies, immunopathies and, in particular, HIV disease. The subjects treated with other prescribed drugs in association with psychosocial therapy were not included in the study.	Intervention: buprenorphine Setting: other (outpatient center) Route of administration: oral Duration (months): 3 Intervention 2: methadone Setting: other (outpatient center) Route of administration: oral Duration (months): 3 Non-MAT comparator: 1. Fifteen healthy male volunteers, who were recruited from hospital staff, university students, and workers, and who were matched to the patients for age (20–33 years: mean ± S.D. = 24.4 ± 3.6 years), served as controls. Subjects were confirmed to be healthy based on physical examination and routine biochemical tests.	Behaviorals/social : Aggressive responding—point subtraction aggression paradigm (PSAP) software program, 3 months, buprenorphine versus healthy controls (CONT), MD: 226.97, 95% CI: (187.54, 266.4) Aggressive responding—PSAP software program, 3 months, buprenorphine versus methadone, MD: –3.82, 95% CI: (–41.76, 34.12) Aggressive responding—PSAP software program, 3 months, methadone versus healthy controls, MD: 230.79, 95% CI: (188.79, 272.79) Escape responding—PSAP software program, 3 months, buprenorphine versus healthy controls, MD: 39.89, 95% CI: (–64.35, 144.13) Escape responding—PSAP software program, 3 months, buprenorphine versus methadone, MD: –42.9, 95% CI: (–132.96, 47.16) Escape responding—PSAP software program, 3 months, methadone versus healthy controls, MD: 82.79, 95% CI: (–1, 166.58) Point-maintained responses—PSAP software program, 3 months, buprenorphine versus healthy controls, MD: –579.66, 95% CI: (–786.67, –372.65) Point-maintained responses—PSAP software program, 3 months, buprenorphine versus methadone, MD: 1676.34, 95% CI: (1456.18, 1896.5) Point-maintained responses—PSAP software program, 3 months, methadone versus healthy controls, MD: –2256, 95% CI: (–2509.48, –2002.52)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Giacomuzzi et al., 2003 Location: Europe Study design: cohort comparison	Number enrolled: 67 Number completed: 53 Mean age: methadone: 26.2, buprenorphine: 30.2 Percentage female: 34 Race/ethnicity: NR Years of opioid use: methadone: 7.9, buprenorphine: 9.2 Inclusion criteria: The only requirements for inclusion in the methadone or buprenorphine program were a confirmed diagnosis of opioid dependence (DSM-IV 304.0) and informed consent. Exclusion criteria: Forced discharge criteria were limited only to drug trafficking in the clinical center and aggressive behavior.	Intervention: methadone Setting: university hospital Route of administration: oral Duration (months): 6 Intervention 2: buprenorphine Setting: university hospital Route of administration: oral Duration (months): 6 Non-MAT comparator: none	Occupational/employment: Job: Satisfaction scores of the Lancashire Quality of Life Profile, 6 months, methadone—oral (treatment) versus buprenorphine—sublingual (control), MD: 0.3, 95% CI: (–0.70, 1.30) Physical: Satisfaction scores of the Lancashire Quality of Life Profile, 6 months, methadone—oral (treatment) versus buprenorphine—sublingual (control), MD: 0.0, 95% CI: (–0.81, 0.81) Fatigue or tiredness: percentage of participants methadone—oral (treatment) versus buprenorphine—sublingual (control), RR: 0.53, 95% CI: (0.28, 1.02) Fatigue or tiredness: percentage of participants—6 months, methadone—oral (treatment) versus buprenorphine—sublingual (control), risk difference (RD): –0.26, 95% CI: (–0.52, –0.00) Insomnia: Percentage of participants—6 months, methadone—oral (treatment) versus buprenorphine—sublingual (control), RR: 0.83, 95% CI: (0.47, 1.46) Insomnia: percentage of participants—6 months, methadone—oral (treatment) versus buprenorphine—sublingual (control), RD: –0.09, 95% CI: (–0.36, 0.18) Neurological Aggression: percentage of participants—6 months, methadone—oral (treatment) versus buprenorphine—sublingual (control), RR: 0.54, 95% CI: (0.24, 1.19) Aggression: percentage of participants—6 months, methadone—oral (treatment) versus buprenorphine—sublingual (control), RD: –0.20, 95% CI: (–0.45, 0.05)
Reference: Giacomuzzi et al., 2005 Location: Europe Study design: randomized controlled trial	Number enrolled: 53 Number completed: 35 Mean Age: methadone: 29.9 (5.5); buprenorphine 33.4 (7.6) Percentage female: 40 Race/ethnicity: NR Years of opioid use: 11.3 Inclusion criteria: The only requirement for inclusion in the follow-up was participation in the first study period including a confirmed diagnosis of opioid dependence (DSM-IV 304.0) and informed consent. Exclusion criteria: NR	Intervention: buprenorphine Setting: NR Route of administration: oral Duration (months): 36 Intervention2: methadone Setting: NR Route of administration: NR Duration (months): 36 Non-MAT comparator: none	Physical: Fatigue: percentage participants, 3 years, methadone (treatment versus buprenorphine (control), RR: 0.41, 95% CI: (0.17, 0.99) Insomnia: percentage participants, 3 years, methadone (treatment versus buprenorphine (control), RR: 0.77, 95% CI: (0.31, 1.87) Fatigue: percentage participants, 3 years, methadone (treatment versus buprenorphine (control), RD: –0.44, 95% CI: (–0.79, –0.09) Insomnia: percentage participants, 3 years, methadone (treatment versus buprenorphine (control), RD: –0.11. 95% CI: (–0.50, 0.27) Neurological: Aggressiveness: percentage participants, 3 years, methadone (treatment versus buprenorphine (control), RR: 0.46, 95% CI: (0.10, 2.08) Aggressiveness: percentage participants, 3 years, methadone (treatment versus buprenorphine (control), RD: –0.18. 95% CI: (–0.51, 0.15)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Giacomuzzi et al., 2006 Location: Europe Study design: randomized controlled trial	Number enrolled: 240 Number completed: NR Mean age: methadone: 27.3 (6.4), buprenorphine: 26.3 (7.5), morphine: 27.8 (4.8), control at admission: 25.3 (7.1) Percentage female: 40.4 Race/ethnicity: NR Years of opioid use: 8.1 years (SD 5.6) Inclusion criteria: Current diagnosis of opioid dependence based on DSM-IV at admission or participation in a methadone, sublingual buprenorphine, or slow-release oral morphine maintenance program for 6 months; aged 17 years or older; live within commuting distance of the hospital; and mentally competent to give informed consent. Exclusion criteria: Having an acute medical condition, currently using antipsychotic medication, or in another clinical trial. Forced discharge criteria were limited to drug trafficking in the clinical center or aggressive behavior.	Intervention: methadone Setting: university psychiatry department Route of administration: oral Duration (months): 6 Intervention2: buprenorphine Setting: university psychiatry department Route of administration: oral Duration (months): 6 Non-MAT comparator: 120 opioid users seeking a maintenance treatment program served as a comparison.	Physical : Number of participants reporting fatigue or tiredness, 6 months, buprenorphine versus treatment seekers (control), RR: 0.47, 95% CI: (0.29, 0.77) Number of participants reporting fatigue or tiredness, 6 months, buprenorphine versus methadone, RR: 0.6, 95% CI: (0.34, 1.06) Number of participants reporting fatigue or tiredness, 6 months, methadone versus treatment seekers (control), RR: 0.78, 95% CI: (0.56, 1.09) Percentage of participants reporting inability to sleep, 6 months, buprenorphine versus treatment seekers (control), RR: 0.75, 95% CI: (0.52, 1.07) Percentage of participants reporting inability to sleep, 6 months, buprenorphine versus methadone, RR: 1.31, 95% CI: (0.77, 2.21) Percentage of participants reporting inability to sleep, 6 months, methadone versus treatment seekers (control), RR: 0.57, 95% CI: (0.37, 0.88) Percentage of participants reporting insomnia, 6 months, buprenorphine versus treatment seekers (control), RR: 0.71, 95% CI: (0.47, 1.08) Percentage of participants reporting insomnia, 6 months, buprenorphine versus methadone, RR: 1, 95% CI: (0.58, 1.71) Percentage of participants reporting insomnia, 6 months, methadone versus treatment seekers (control), RR: 0.71, 95% CI: (0.47, 1.08)
Reference: Gossop et al., 1999 Location: Europe Study design: cohort comparison	Number enrolled: 452 Number completed: 452 Mean age: 29 Percentage female: 26.5 Race/ethnicity: NR Years of opioid use: 8.8 Inclusion criteria: Criteria for agency participation were location (agencies were chosen throughout England), and capacity to recruit a sufficient number of cases within the time available. All consecutive patients treated at an agency during the time period were included. Exclusion criteria: NR	Intervention: methadone Setting: methadone clinic Route of administration: oral Duration (months): NR Intervention 2: methadone Setting: doctor's office Route of administration: oral Duration (months): NR Non-MAT comparator: none	Crime: crime (non–drug related) Mean score, 6 months, methadone from specialist drug clinic (treatment) versus methadone from GP (control), MD: –3.8, 95% CI: (–7.06, –0.54)

Reference: Kinlock et al., 2009 (also Gordon et al., 2008) Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 211 Number completed: 204 Mean age: 40.3 (7.1) Percentage female: 0 Race/ethnicity: White: 24.0%, Black: 69.6%, Hispanic: NR, Asian: NR, other: 6.4% Years of opioid use: NR Inclusion criteria: Eligibility criteria were (1) 3 to 6 months before anticipated release from prison; (2) meeting DSM-IV criteria for heroin dependence at time of incarceration and being physiologically dependent during the year prior to incarceration; (3) suitability for methadone maintenance as determined by medical evaluation; (4) willingness to enroll in a prison-based methadone maintenance treatment program; and, (5) residing in Baltimore following release. Individuals who did not meet the heroin-dependence criterion were eligible if they were enrolled in an opioid treatment program in the year before incarceration. Exclusion criteria: Any of the following conditions: (1) renal failure; (2) liver failure; (3) pending/unadjudicated charges, which could have resulted in transfer to another correctional facility and/or additional prison time; and (4) a pending parole hearing.	Intervention: methadone Setting: prison, then community Route of administration: oral Duration (months): 12 Non-MAT comparator: 1. Counseling only—counseling in prison, with passive referral to treatment upon release. All participants received an individual intake by the study counselor and were subsequently scheduled to receive, within treatment condition, 12 weekly sessions of group-based education and discussion on relapse and overdose prevention, cocaine and alcohol abuse, and other reentry issues. Immediately prior to release, all participants were scheduled to meet with the study's counselor to discuss plans for release, including housing, employment concerns, and treatment options. 2. Counseling and transfer—counseling in prison, with immediate access to methadone maintenance treatment upon release from prison, but no maintenance treatment in prison. All participants received an individual intake by the study counselor and were subsequently scheduled to receive, within treatment condition, 12 weekly sessions of group-based education and discussion on relapse and overdose prevention, cocaine and alcohol abuse, and other reentry issues. Immediately prior to release, all participants were scheduled to meet with the study's counselor to discuss plans for release, including housing, employment concerns, and treatment options.	Occupational : Number of days employed during past 30 (12-month post-release), 12 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release, MD: –1.8, 95% CI: (–5.35, 1.75) Number of days employed during past 30 (12-month post-release), 12 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling only—counseling in prison, with passive referral to treatment upon release, MD: –3.5, 95% CI: (–7.01, 0.01) Number of days employed during past 30 (12-month post-release), 12 months, counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release versus counseling only—counseling in prison, with passive referral to treatment upon release, MD: –1.7, 95% CI: (–5.3, 1.9) Behavioral/social : Arrested (yes/no) during 12-month follow-up period, 12 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release, RR: 0.9, 95% CI: (0.67, 1.2) Arrested (yes/no) during 12-month follow-up period, 12 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling only—counseling in prison, with passive referral to treatment upon release, RR: 1.04, 95% CI: (0.75, 1.44) Arrested (yes/no) during 12-month follow-up period, 12 months, counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release versus counseling only—counseling in prison, with passive referral to treatment upon release, RR: 1.16, 95% CI: (0.85, 1.59) Frequency (number of days) committing crimes in past year, 12 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release, MD: 16.6, 95% CI: (–17.52, 50.72) Frequency (number of days) committing crimes in past year, 12 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling only—counseling in prison, with passive referral to treatment upon release, MD: –24.9, 95% CI: (–65.43, 15.63) Frequency (number of days) committing crimes in past year, 12 months, Counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release versus counseling only—counseling in prison, with passive referral to treatment upon release, MD: –41.5, 95%

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
			CI: (–80.35, –2.65) Number of days in last 6 months committed crime, 6 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release, MD: –7.1, 95% CI: (–22.12, 7.92)
(Continued) Reference: Kinlock et al., 2009 (also Gordon et al., 2008)			Number of days in last 6 months committed crime, 6 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling only—counseling in prison, with passive referral to treatment upon release, MD: –28, 95% CI: (–43.32, –12.68) Number of days in last 6 months committed crime, 6 months, counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release versus counseling only—counseling in prison, with passive referral to treatment upon release, MD: –20.9, 95% CI: (–36.32, –5.48) Number of days incarcerated in last 6 months, 6 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release, MD: –1.9, 95% CI: (–16.92, 13.12) Number of days incarcerated in last 6 months, 6 months, counseling + methadone—methadone maintenance and counseling in prison, continued in community versus counseling only—counseling in prison, with passive referral to treatment upon release, MD: 0, 95% CI: (–15.32, 15.32) Number of days incarcerated in last 6 months, 6 months, counseling + transfer—counseling in prison, with transfer to methadone maintenance upon release versus counseling only—counseling in prison, with passive referral to treatment upon release, MD: 1.9, 95% CI: (–13.52, 17.32)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Lee et al., 2016 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 308 Number completed: 245 Mean age: Sample mean 44 years; intervention 44.4 (9.2); control 43.2 (9.4) Percentage female: 15 Race/ethnicity: White: intervention 20.4%; control 19.4%, Black: intervention 53.3%; control 47.7%, Hispanic: intervention 24.3%; control 29.0% Years of opioid use: NR Inclusion criteria: Eligibility criteria were current (within the previous 12 months) or lifetime (any previous) opioid dependence (as defined by DSM-IV); a stated goal of opiate-free treatment rather than opioid agonist or partial-agonist maintenance therapy; an opioid-free status as confirmed by negative urine toxicological screening for all opioids before randomization; residence in the community and receipt of an adjudicated sentence that included supervision (e.g., parole, probation, outpatient drug-court programs, or other court-mandated treatment) or, in the previous 12 months, release from jail or prison, a plea-bargain arrangement, or any community supervision as above; general good health as determined by history and physical examination; an age of 18 to 60 years; and the ability to provide written informed consent. Exclusion criteria: Exclusion criteria were other drug or alcohol dependence requiring a level of care that would interfere with trial participation; pregnancy or a plan to conceive during the 24-week treatment phase, lactation, or an inability to use adequate contraceptive methods; an untreated psychiatric disorder or medical condition that might make participation hazardous, including liver-enzyme levels more than three times the upper limit of the normal range and a body mass index of more than 40; allergy to naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or other components of the diluent; a current diagnosis of chronic pain for which opioids were prescribed; or a drug overdose in the previous 3 years requiring inpatient hospitalization.	Intervention: naltrexone Setting: doctor's office Route of administration: injection Duration (months): 6 Non-MAT comparator: 1. Participants in the usual-treatment group received similar counseling that was focused on adverse events, the prevention of relapse and overdose, and support for community treatment involvement from the same trial personnel.	Behavioral/social: Mean number of days incarcerated in the last 78 weeks, 78 weeks, XR-NTX versus counseling + referral to community treatment, MD: –6.16, 95% CI: (–36.65, 24.33) Percentage participants reincarcerated, 78 weeks, XR-NTX versus counseling + referral to community treatment, RR: 0.79, 95% CI: (0.54, 1.16)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Ling et al., 2010 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 163 Number completed: 88 Mean age: buprenorphine: 35.8 (11.0), placebo: 39.3 (11.7) Percentage female: 31.3 Race/ethnicity: White: 74.8%, Black: 12.3%, Hispanic: 14.7%, other: 12.9% Years of opioid use: NR Inclusion criteria: Men or nonpregnant women, aged 18 to 65 years, were required to meet DSM-IV diagnosis of current opioid dependence. Exclusion criteria: Exclusion criteria were AIDS, met DSM-IV criteria for current dependence on psychoactive substances other than opioids or nicotine, currently using nonprescribed benzodiazepines, had received medication treatment for opioid dependence within the previous 90 days, or had a current diagnosis of chronic pain that required opioid treatment. Patients were also excluded if they had any of the following: aspartate aminotransferase levels at least three times higher than the upper limit of normal, alanine aminotransferase levels at least three times the upper limit of normal, total bilirubin levels of at least 1.5 times the upper limit of normal, or creatinine levels at least 1.5 times the upper limit of normal.	Intervention: buprenorphine Setting: VA Route of administration: implant Duration(months): 6 Non-MAT comparator: 1. At the end of the induction phase, patients were randomized (stratified by sex and site) at a 2:1 ratio to double blind treatment with four placebo implants. The 2:1 ratio was used to reduce patient exposure to placebo implants.	Physical: Percentage of participants reporting insomnia, 6 months, buprenorphine versus placebo implant, RR: 0.98, 95% CI: (0.53, 1.81)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Lobmaier et al., 2010 Location: Europe Study design: randomized controlled trial	Number enrolled: 46 Number completed: unclear Mean age: 35.1 (7.0) Percentage female: 6.5 Race/ethnicity: NR Years of opioid use: NR Inclusion criteria: Inclusion criteria were pre-incarceration heroin dependence and at least 2 months, sentence time remaining. Exclusion criteria: Individuals were excluded if they presented with untreated major depression or psychosis, severe hepatic impairment, or if they were already in agonist maintenance treatment or pregnant.	Intervention: naltrexone Setting: prison, then community Route of administration: implant Duration (months): 6 Intervention 2: methadone Setting: prison, then community Route of administration: oral Duration (months): 6 Non-MAT comparator: none	Behavioral/social: Mean days per month illegal activity, 6 months, naltrexone (implant) versus methadone, MD: 0.5, 95% CI: (–9.98, 10.98)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Magura et al., 2009 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 116 Number completed: 91 Mean age: buprenorphine: 38.4 (7.9) methadone: 40.7 (9.1) Percentage female: 0 Race/ethnicity: White: NR, Black: 25%, Hispanic: 63.8%, Asian: NR, other: NR Years of opioid use: NR Inclusion criteria: Inmates who were eligible for the Key Extended Entry Program (KEEP), 18–65 years of age, sentenced to at least 10 days but less than 90 days of jail time (this was more restrictive than KEEP, to allow time for postrelease follow-up), expected to reside in New York City after release Exclusion criteria: Receiving methadone treatment in the community at remand to Rikers (such inmates are offered continuity of methadone maintenance by KEEP at the doses they received in the community), took nonprescribed "street" methadone within the previous 3 days, currently receiving more than 20 mg per day of prescribed methadone, current psychotic symptoms (e.g., schizophrenia, schizoaffective disorder) requiring referral for psychiatric intervention or currently treated with antipsychotic medication, HIV infection with T-lymphocytes less than 200 mm of blood, and/or presence of a serious opportunistic infection requiring treatment, receiving the HIV medication atazanavir, unable to complete an English-language interview	Intervention: Suboxone Setting: prison, then community Route of administration: oral Duration (months): 3 Intervention 2: methadone Setting: prison, then community Route of administration: oral Duration (months): 3 Non-MAT comparator: none	Behavioral/social: Percentage of participants arrested after release, 3 months, buprenorphine/naloxone versus methadone, MD: –0.02, 95% CI: (–0.33, 0.29) Percentage of participants reincarcerated, 3 months, buprenorphine/naloxone versus methadone, RR: 0.8, 95% CI: (0.53, 1.2)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Mattick et al., 2003 Location: Australia, New Zealand Study design: randomized controlled trial	Number enrolled: 405 Number completed: 216 Mean age: 30 (8) Percentage female: 31 Race/ethnicity: other: English-speaking background: methadone 79%, buprenorphine: 79%; non-English-speaking background: methadone: 16% buprenorphine: 16%; indigenous: methadone: 5%, buprenorphine: 6% Years of opioid use: methadone: 7.6 (6.7), buprenorphine: 7.7 (7.0) Inclusion criteria: Patients were eligible for the study if they had a current diagnosis of opioid dependence using the criteria in the fourth edition of the DSM-IV); were aged 18 years or older; lived within commuting distance of the clinic; appeared mentally competent to give informed consent; and signed informed consent. Exclusion criteria: Patients were excluded from the study if they were pregnant or nursing, or were deemed likely to become pregnant in the study period; suffering an acute medical condition that could make participation in the study medically hazardous (e.g., active tuberculosis, unstable cardiovascular, or serious acute liver disease); currently using anticonvulsant medication, disulfiram, or antipsychotic medication; in opioid replacement treatment (methadone was the only available medication at the time of the study) in the preceding 30 days (and this status was verified from state department of health records); unable to attend the clinic daily for the study period; in a study of buprenorphine previously, or were currently in another clinical trial.	Intervention: buprenorphine Setting: methadone clinic Route of administration: oral Duration (months): 3.25 Intervention 2: methadone Setting: methadone clinic Route of administration: oral Duration (months): 3.25 Non-MAT comparator: None	Physical : Percentage reporting somnolence, 13 weeks, buprenorphine versus methadone, RR: 0.56, 95% CI: (0.26, 1.18) Number (percentage) of patients who reported experiencing pain during the trial, 13 weeks, buprenorphine versus methadone, RR: 0.93, 95% CI: (0.58, 1.51) Percentage of participants reporting insomnia, 13 weeks, buprenorphine versus methadone, RR: 1.3, 95% CI: (0.75, 2.26)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Metrebian, 2015 (also Gordon et al., 2008) Location: Europe Study design: randomized controlled trial	Number enrolled: 127 Number completed: NR Mean age: 37.2 (6.5) Percentage female: 27 Race/ethnicity: White: 96 Years of opioid use: 16.6 Inclusion criteria: Specific eligibility criteria were based on national guidance on injectable opiate treatment. The sample was thus locally residing, treatment-resistant, chronic, opiate-dependent patients receiving oral substitution treatment (methadone or buprenorphine treatment) for at least 6 months preceding recruitment to the trial and who, despite this, were still injecting street heroin on most days. Exclusion criteria: NR	Intervention: methadone Setting: methadone clinic Route of administration: injection Duration (months): 6 Intervention 2: methadone Setting: methadone clinic Route of administration: oral Duration (months): 6 Non-MAT comparator: 1. Supervised injectable heroin. This intervention is not used as MAT in the United States.	Physical : SF-36 physical function, 6 months, supervised injectable methadone versus optimized oral methadone, MD: 7.4, 95% CI: (–4.21, 19.01) Behavioral/social: SF-36—mental health, 6 months, supervised injectable methadone versus optimized oral methadone, MD: –2.16, 95% CI: (–8.94, 4.62) SF-36 social functioning, 6 months, supervised injectable methadone versus optimized oral methadone, MD: –5.2, 95% CI: (–16.57, 6.17) Criminal behavior in previous month—percentage of participants, 6 months, supervised injectable methadone versus optimized oral methadone, RR: 0.9, 95% CI: (0.4, 2.04) Percentage of participants committing crimes over follow-up period, 26 weeks, injectable methadone (supervised) versus oral methadone (optimized), RR: 1.05, 95% CI: (0.64, 1.72)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Neri et al., 2005 Location: Europe Study design: randomized controlled trial	Number enrolled: 62 Number completed: 57 Mean age: methadone: 27 (6), buprenorphine: 24 (5) Percentage female: 11.3 Race/ethnicity: NR Years of opioid use: methadone: 2, buprenorphine: 2 Inclusion criteria: Diagnosis according to the DSM-IV criteria Exclusion criteria: Subjects with severe psychiatric illness (dementia, psychosis, and cognitive impairment) who were unable to answer the questions were not enrolled in the investigation, as were individuals presenting with codependence of alcohol, amphetamines, cannabinoids, and benzodiazepines; however, sporadic use (less than a month with negative urine screen) was not considered an exclusion criterion. Subjects who missed medication for 3 consecutive days (for methadone) and once (for buprenorphine) were removed from the study.	Intervention: methadone Setting: other substance abuse treatment Route of administration: oral Duration (months): 12 Intervention 2: buprenorphine Setting: other substance abuse treatment Route of administration: oral Duration (months): 12 Non-MAT comparator: none	Physical: Number of participants reporting fatigue, 12 months, buprenorphine versus methadone, RR: 0.95, 95% CI: (0.23, 3.81) Number of participants reporting nausea, 12 months, buprenorphine versus methadone, RR: 1.01, 95% CI: (0.31, 3.33) Number of participants reporting sleepiness, 12 months, buprenorphine versus methadone, RR: 1.26, 95% CI: (0.28, 5.67) Percentage of participants reporting insomnia, 12 months, buprenorphine versus methadone, RR: 0.9, 95% CI: (0.33, 2.47)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Neumann et al., 2013 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 54 Number completed: 26 Mean age: 38.3 (9.7) Percentage female: 46.3 Race/ethnicity: White: 85.2% Years of opioid use: NR Inclusion criteria: Men and women ages 18 years or older with well-documented chronic nonmalignant pain related to the spine or a large joint (e.g., hip, knee, shoulder) and an addiction to prescription opioids. Exclusion criteria: Individuals were excluded from the study if (1) they were homeless or placed on parole; (2) were unable to give consent (e.g., because of neurological disorders, including dementia or cognitive dysfunction, psychosis) or lacked consent from the attending physician; (3) had a co-occurring psychiatric disorder (e.g., schizophrenia); (4) had an electrocardiogram showing prolonged QT and/or previous cardiac/pulmonary issues; (5) were taking a medication that is contraindicated with methadone or buprenorphine; (6) had a prior history of methadone or buprenorphine maintenance treatment; or (7) were pregnant.	Intervention: Suboxone Setting: doctor's office Route of administration: oral Duration (months): 6 Intervention 2: methadone Setting: doctor's office Route of administration: oral Duration (months): 6 Non-MAT comparator: none	Physical: Numerical rating scale pain score, 6 months, buprenorphine/naloxone versus methadone, MD: –0.96, 95% CI: (–3.54, 1.63)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Newman and Whitehill, 1979 Location: Asia Study design: randomized controlled trial	Number enrolled: 100 Number completed: 100 Mean age: 38 Percentage female: NR Race/ethnicity: NR Years of opioid use: methadone: 15; control: 12 Inclusion criteria: (1) Male, age 22–58 years, (2) documented history of heroin addiction for at least 4 years and at least one previous course of treatment, (3) evidence of current addiction to heroin as determined by 3 consecutive positive urine tests for morphine, (4) voluntary application for admission (referrals by the criminal justice system were excluded), (5) a resident with proven fixed address in Kowloon in a district near the treatment clinic, (6) absence of past or present major psychiatric or medical illness (for example, tuberculosis, peptic ulcer, psychosis). Exclusion criteria: NR	Intervention: methadone Setting: methadone clinic Route of administration: oral Duration (months): NR Non-MAT comparator: 1. Control group was weaned from methadone by a dose reduction of 1 mg/day, weaning (detoxification) being completed after 60 days. Thereafter, controls were maintained on a placebo solution that was indistinguishable by taste from the methadone solution.	Behavioral/social: Conviction rate per 100 man-months of study, 3 years, methadone versus placebo, incidence rate ratio: 0.45, 95% CI: not calculable

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Rapeli et al., 2009 (also Rapeli et al., 2011) Location: Europe Study design: case control	Number enrolled: 43 Number completed: unclear Mean age: methadone: 29.2 (6.8), buprenorphine: 27.7 (6.8), control: 28.7 (9.6) Percentage female: 44.2 Race/ethnicity: NR Years of opioid use: methadone: 15.0 (5.1), buprenorphine: 13.4 (5.2) Inclusion criteria: All participants included in the study were between 18 and 50 years old and native Finnish speakers. For opioid substitution patients, additional inclusion criteria were opioid dependence diagnosis, benzodiazepine dependence or abuse diagnosis, start of opioid substitute therapy during the last 2 months, and treatment using methadone, buprenorphine, or buprenorphine/naloxone. Exclusion criteria: Participants showing signs of current intoxication, ongoing binge on any substance of abuse, or any extra psychoactive drug dose within 24 hours were excluded. Participants with uncontrolled polysubstance abuse, acute alcohol abuse, or acute axis I psychiatric morbidity other than substance abuse related were excluded. Also excluded were participants with severe brain injury, chronic neurological disease, history of other than substance induced psychoses, epileptic seizures, HIV infection, pregnancy, or primary cognitive deficit. For these purposes, psychiatric interviews by clinical psychiatrist were conducted for all participants, and diagnostic criteria from the DSM-IV were applied.	Intervention: methadone Setting: other substance abuse treatment Route of administration: oral Duration (months): 6–9 Intervention 2: buprenorphine, Suboxone Setting: other substance abuse treatment Route of administration: oral Duration (months): 6–9 Non-MAT comparator: 1. Healthy nondrug-using adults recruited from adult education centers and by word of mouth	Cognitive : Go-NoGo errors: TAP, 12–17 months (T3), buprenorphine versus healthy controls, MD: 0.4, 95% CI: (–0.1, 0.9) Go-NoGo errors: TAP, 12–17 months (T3), buprenorphine versus methadone, MD: 0.1, 95% CI: (–0.59, 0.79) Go-NoGo errors: TAP, 12–17 months (T3), methadone versus healthy controls, MD: 0.3, 95% CI: (–0.26, 0.86) Go-NoGo errors: TAP, 6–9 months (T2), buprenorphine versus healthy controls, MD: 0, 95% CI: (–0.58, 0.58) Go-NoGo errors: TAP, 6–9 months (T2), buprenorphine versus methadone, MD: –0.5, 95% CI: (–1.12, 0.12) Go-NoGo errors: TAP, 6–9 months (T2), methadone versus healthy controls, MD: 0.5, 95% CI: (–0.13, 1.13) Go-NoGo reaction time (milliseconds [ms]): TAP, 12–17 months (T3), buprenorphine versus healthy controls, MD: 31, 95% CI: (–3.61, 65.61) Go-NoGo reaction time (ms): TAP, 12–17 months (T3), buprenorphine versus methadone, MD: –36, 95% CI: (–77, 5) Go-NoGo reaction time (ms): TAP, 12–17 months (T3), methadone versus healthy controls, MD: 67, 95% CI: (25.83, 108.17) Go-NoGo reaction time (ms): TAP, 6–9 months (T2), buprenorphine versus healthy controls, MD: 37, 95% CI: (–7.58, 81.58) Go-NoGo reaction time (ms): TAP, 6–9 months (T2), buprenorphine versus methadone, MD: -68, 95% CI: (–127.44, –8.56) Go-NoGo reaction time (ms): TAP, 6–9 months (T2), methadone versus healthy controls, MD: 105, 95% CI: (38.74, 171.26) Letter-number sequencing from the WMS-III, 12–17 months (T3), buprenorphine versus healthy controls, MD: –0.6, 95% CI: (–2.69, 1.49) Letter-number sequencing from the WMS-III, 12–17 months (T3), buprenorphine versus methadone, MD: 1.8, 95% CI: (0.03, 3.57) Letter-number sequencing from the WMS-III, 12–17 months (T3), methadone versus healthy controls, MD: –2.4, 95% CI: (–4.5, –0.3) Letter-number sequencing from the WMS-III, 6–9 months (T2), buprenorphine versus healthy controls, MD: –2.8, 95% CI: (–4.8, –0.8) Letter-number sequencing from the WMS-III, 6–9 months (T2), buprenorphine versus methadone, MD: 0.3, 95% CI: (–1.43, 2.03)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
(Continued) Reference: Rapeli et al., 2009 (also Rapeli et al., 2011)			Letter-number sequencing from the WMS-III, 6–9 months (T2), methadone versus healthy controls, MD: –3.1, 95% CI: (–5.08, –1.12) Letter-number sequencing from the WMS-III, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus healthy controls, MD: –2.4, 95% CI: (–4.27, –0.53) Letter-number sequencing from the WMS-III, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus methadone, MD: 0.6, 95% CI: (–1.03, 2.23) Letter-number sequencing from the WMS-III, 6–9 months, methadone versus healthy controls, MD: –3, 95% CI: (–4.86, –1.14) PASAT, 12–17 months (T3), buprenorphine versus healthy controls, MD: –14, 95% CI: (–21.17, –6.83) PASAT, 12–17 months (T3), buprenorphine versus methadone, MD: 0.9, 95% CI: (–7.18, 8.98) PASAT, 12–17 months (T3), methadone versus healthy controls, MD: –14.9, 95% CI: (–22.15, –7.65) PASAT, 6–9 months (T2), buprenorphine versus healthy controls, MD: –10.8, 95% CI: (–16.89, –4.71) PASAT, 6–9 months (T2), buprenorphine versus methadone, MD: 1.6, 95% CI: (–4.94, 8.14) PASAT, 6–9 months (T2), methadone versus healthy controls, MD: –12.4, 95% CI: (–19.49, –5.31) PASAT from the FORAMEN Rehab software package, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus healthy controls, MD: –11.9, 95% CI: (–18.02, –5.78) PASAT from the FORAMEN Rehab software package, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus methadone, MD: 2.5, 95% CI: (–3.82, 8.82) PASAT from the FORAMEN Rehab software package, 6–9 months, methadone versus healthy controls, MD: –14.4, 95% CI: (–20.82, –7.98) Phasic alertness/reaction time with warning signal (ms): TAP, 12–17 months (T3), buprenorphine versus healthy controls, MD: 4, 95% CI: (–11.76, 19.76) Phasic alertness/reaction time with warning signal (ms): TAP, 12–17 months (T3), buprenorphine versus methadone, MD: –25, 95% CI: (–50.91, 0.91) Phasic alertness/reaction time with warning signal (ms): TAP, 12–17 months (T3), methadone versus healthy controls, MD: 29, 95% CI: (2.76, 55.24) Phasic alertness/reaction time with warning signal (ms): TAP, 6–9 months (T2), buprenorphine versus healthy controls, MD: 5, 95% CI: (–11.19, 21.19) Phasic alertness/reaction time with warning signal (ms): TAP, 6–9 months (T2), buprenorphine versus methadone, MD: –26, 95% CI: (–44.88, –7.12)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
(Continued) Rapeli et al., 2009 (also Rapeli et al., 2011)			Phasic alertness/reaction time with warning signal (ms): TAP, 6–9 months (T2), methadone versus healthy controls, MD: 31, 95% CI: (12.67, 49.33) Tonic alertness/simple reaction time (ms): TAP, 12–17 months (T3), buprenorphine versus healthy controls, MD: 1, 95% CI: (–18.28, 20.28) Tonic alertness/simple reaction time (ms): TAP, 12–17 months (T3), buprenorphine versus methadone, MD: –25, 95% CI: (–48.57, –1.43) Tonic alertness/simple reaction time (ms): TAP, 12–17 months (T3), methadone versus healthy controls, MD: 26, 95% CI: (3.04, 48.96) Tonic alertness/simple reaction time (ms): TAP, 6–9 months (T2), buprenorphine versus healthy controls, MD: 3, 95% CI: (–11.99, 17.99) Tonic alertness/simple reaction time (ms): TAP, 6–9 months (T2), buprenorphine versus methadone, MD: –27, 95% CI: (–41.99, –12.01) Tonic alertness/simple reaction time (ms): (TAP, 6–9 months (T2), methadone versus healthy controls, MD: 30, 95% CI: (14.44, 45.56) List learning—Memory for Persons Data, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus healthy controls, MD: –0.3, 95% CI: (–0.67, 0.07) List learning—Memory for Persons Data, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus methadone, MD: –0.3, 95% CI: (–0.67, 0.07) List learning—Memory for Persons Data, 6-9 months, methadone versus healthy controls, MD: 0, 95% CI: (–0.15, 0.15) Logical memory, delayed—Logical Memory from the WMS-III, 12–17 months (T3), buprenorphine versus healthy controls, MD: –3.5, 95% CI: (–6.49, –0.51) Logical memory, delayed—Logical Memory from the WMS-III, 12–17 months (T3), buprenorphine versus methadone, MD: 0.6, 95% CI: (–2.78, 3.98) Logical memory, delayed—Logical Memory from the WMS-III, 12–17 months (T3), methadone versus healthy controls, MD: –4.1, 95% CI: (–7.2, –1) Logical memory, delayed—Logical Memory from the WMS-III, 6–9 months (T2), buprenorphine versus healthy controls, MD: –3.6, 95% CI: (–6.39, –0.81) Logical memory, delayed—Logical Memory from the WMS-III, 6–9 months (T2), buprenorphine versus methadone, MD: –1.7, 95% CI: (–4.78, 1.38) Logical memory, delayed—Logical Memory from the WMS-III, 6–9 months (T2), methadone versus healthy controls, MD: –1.9, 95% CI: (–4.55, 0.75)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
(Continued) Rapeli et al., 2009 (also Rapeli et al., 2011)			Logical memory, immediate—Logical Memory from the WMS-III, 12–17 months (T3), buprenorphine versus healthy controls, MD: –2.4, 95% CI: (–5.17, 0.37) Logical memory, immediate—Logical Memory from the WMS-III, 12–17 months (T3), buprenorphine versus methadone, MD: 1.2, 95% CI: (–2.03, 4.43) Logical memory, immediate—Logical Memory from the WMS-III, 12–17 months (T3), methadone versus healthy controls, MD: –3.6, 95% CI: (–6.32, –0.88) Logical memory, immediate—Logical Memory from the WMS-III, 6–9 months (T2), buprenorphine versus healthy controls, MD: –2.5, 95% CI: (–4.93, –0.07) Logical memory, immediate—Logical Memory from the WMS-III, 6–9 months (T2), buprenorphine versus methadone, MD: –1, 95% CI: (–3.61, 1.61) Logical memory, immediate—Logical Memory from the WMS-III, 6–9 months (T2), methadone versus healthy controls, MD: –1.5, 95% CI: (–4.06, 1.06) Raw score for Memory Complaint Questionnaire (MCQ)—Finnish version, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus healthy controls, MD: 4.1, 95% CI: (0.63, 7.57) Raw score for MCQ—Finnish version, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus methadone, MD: –1.1, 95% CI: (–4.91, 2.71) Raw score for MCQ—Finnish version, 6–9 months, methadone versus healthy controls, MD: 5.2, 95% CI: (3.3, 7.1) Story recall task—Logical Memory from the WMS III: immediate free recall, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus healthy controls, MD: –2.2, 95% CI: (–4.49, 0.09) Story recall task—Logic Memory from the WMS III: immediate free recall, 6–9 months, buprenorphine (buprenorphine/naloxone or buprenorphine only) versus methadone, MD: –0.1, 95% CI: (–2.47, 2.27) Story recall task—Logic Memory from the WMS III: immediate free recall, 6–9 months, methadone versus healthy controls, MD: –2.1, 95% CI: (–4.4, 0.2)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reijneveld and Plomp, 1993 Location: Europe Study design: cohort comparison	Number enrolled: 38 Number completed: 38 Mean age: current clients: 31.0 (1.5) and former clients 30.1 (1.2) Percentage female: 36.8 Race/ethnicity: NR Years of opioid use: current clients 14.6 and former clients 11.9 Inclusion criteria: Born in the Netherlands or a (former) Dutch colony (Surinam or the Dutch Antilles), registered inhabitants of the city of Amsterdam, and registered in the central methadone registry for the first time 5 years ago. Exclusion criteria: Clients who had left care were only included if they had received methadone in at least two instances 50 days apart to exclude clients only passing through the methadone maintenance system.	Intervention: methadone Setting: doctor's office Route of administration: oral Duration (months): varies Non-MAT comparator: 1. Individuals who enrolled in methadone maintenance but dropped out	Behavioral/social: Percentage of crime that reports some illegal activity in past week, patients continuing on methadone for 5 years versus dropouts (RD –0.04; CI –0.20, 0.13) Occupational: Percentage of employment reporting no time spent on job, past month, patients continuing on methadone for 5 years versus dropouts, RD –0.35; CI (–0.65, –0.05)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Rosenthal et al., 2013 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 287 Number completed: 163 Mean age: 35.7 Percentage female: 39 Race/ethnicity: White: 83.3%, Black: 13.0% Years of opioid use: NR Inclusion criteria: Men and nonpregnant women (aged 18–65 years) met the DSM-IV diagnosis of current opioid dependence as determined by the Mini International Neuropsychiatric Interview Exclusion criteria: Individuals were excluded if they had AIDS, a clinically low platelet count, substance dependence on other than opioids or nicotine, received methadone or buprenorphine for opioid dependence within 90 days, current diagnosis of chronic pain requiring opioid analgesics or currently using nonprescribed benzodiazepines. Subjects were also excluded with aspartate aminotransferase levels three times the upper limit of normal; alanine aminotransferase levels three times the upper limit of normal; total bilirubin one and a half times the upper limit of normal; and/or creatinine one and a half times the upper limit of normal.	Intervention: buprenorphine Setting: home Route of administration: implant Duration (months): 6 Intervention 2: Suboxone Setting: other substance abuse treatment Route of administration: oral Duration (months): 6 Non-MAT comparator: 1. Placebo implants. Manual-guided individual drug counseling sessions (10) were provided by experienced counselors twice weekly during weeks 1–12, and then weekly for the subsequent 12 weeks.	Physical: Percentage of participants, reporting insomnia, 6 months, buprenorphine—implant versus placebo implants (control), RR: 0.59, 95% CI: (0.23, 1.49) Percentage of participants reporting insomnia, 6 months, buprenorphine—implant versus buprenorphine/naloxone—sublingual, RR: 0.53, 95% CI: (0.25, 1.14) Percentage of participants reporting insomnia, 6 months, buprenorphine/naloxone—sublingual versus placebo implants (control), RR: 1.1, 95% CI: (0.49, 2.47)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Schwartz et al., 2009 (also Schwartz et al., 2007) Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 319 Number completed: 134 Mean age: 41.4 (6.0) Percentage female: 41 Race/ethnicity: White: 6.6%, Black: 93.4%, Hispanic: NR, Asian: NR, other: NR Years of opioid use: NR Inclusion criteria: NR Exclusion criteria: NR	Intervention: methadone Setting: clinic, unclear Route of administration: NR Duration (months): 10 Non-MAT comparator: 1. Waiting list	Behavioral/social : Days of illegal activities/last 30 days, 10 months, methadone—interim maintenance versus methadone—waiting list, MD: –5.2, 95% CI: (–7.37, –3.03) Days of illegal activities/last 30 days, 4 months, methadone—interim maintenance versus methadone—waiting list, MD: –5.2, 95% CI: (–7.14, –3.26) Percentage of participants arrested, 12 months, methadone—interim maintenance versus methadone—waiting list (control), MD: –0.06, 95% CI: (–0.34, 0.22) Percentage of participants arrested, 24 months, methadone—interim maintenance versus methadone—waiting list (control), MD: –0.15, 95% CI: (–0.6, 0.3) Percentage of participants arrested, 6 months, methadone—interim maintenance versus methadone—waiting list (control), MD : –0.14, 95% CI: (–0.35, 0.07) Percentage of participants with no arrest charge (0), 12 months, methadone—interim maintenance versus methadone—waiting list (control), RR : 0.99, 95% CI: (0.86, 1.14) Percentage of participants with no arrest charge (0), 24 months, methadone—interim maintenance versus methadone—waiting list (control), RR: 1.12, 95% CI: (0.92, 1.36) Percentage of participants with no arrest charge (0), 6 months, methadone—interim maintenance versus methadone—waiting list (control), RR: 1.06, 95% CI: (0.95, 1.18) Percentage of participants with nonsevere arrest charges (1–4), 12 months, methadone—interim maintenance versus methadone—waiting list (control), RR: 0.99, 95% CI: (0.65, 1.49) Percentage of participants with nonsevere arrest charges (1–4), 24 months, methadone—interim maintenance versus methadone—waiting list (control), RR: 0.84, 95% CI: (0.63, 1.12) Percentage of participants with non-severe arrest charges (1–4), 6 months, methadone—interim maintenance versus methadone—waiting list (control), RR: 0.65, 95% CI: (0.39, 1.1) Percentage of participants with severe arrest charges (5–7), 12 months, methadone—interim maintenance versus methadone—waiting list (control), RR: 1.4, 95% CI: (0.37, 5.34) Percentage of participants with severe arrest charges (5–7), 24 months, methadone—interim maintenance versus methadone—waiting list (control), RR: 0.98, 95% CI: (0.37, 2.62) Percentage of participants with severe arrest charges (5–7), 6 months, methadone—interim maintenance versus methadone—waiting list (control), RR: 3.75, 95% CI: (0.44, 32.25)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Sees et al., 2000 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 179 Number completed: 134 Mean age: methadone detox 39.4 (7.91); methadone maintenance 39.4 (8.57) Percentage female: 41.3 Race/ethnicity: White: 51.4%, Black: 30.2%, Hispanic: 12.8%, other: 5.6% Years of opioid use: methadone detox 15.7 (9.26); MMT 16.6 (9.42) Inclusion criteria: DSM-III-R criteria for a diagnosis of opioid dependence and had an initial urine screening test positive for opioid other than methadone and negative for methadone. Women of childbearing age were required to be practicing birth control. Exclusion criteria: Medical or psychiatric conditions that contraindicated methadone treatment, enrolled in a substance abuse treatment program, had been in a methadone treatment program within the previous week or were in a follow-up phase of a previous methadone detoxification research protocol, could not be expected to remain in the study for 12 months, did not have signs of opioid withdrawal on three occasions, younger than 18 years old, or pregnant or breastfeeding.	Intervention: methadone detox only Setting: VA Route of administration: oral Duration (months): 14 Intervention 2: methadone Setting: VA Route of administration: oral Duration (months): 14 Non-MAT comparator: none	Physical : ASI medical score, 12 months, psychosocially enriched 180-day methadone-assisted detoxification versus methadone, MD: –0.06, 95% CI: (–0.16, 0.04) Occupational : ASI employment score, 12 months, psychosocially enriched 180-day methadone-assisted detoxification versus methadone, MD: –0.01, 95% CI: (–0.1, 0.08) Behavioral/social : ASI family function score, 12 months, psychosocially enriched 180-day methadone-assisted detoxification versus methadone, MD: –0.01, 95% CI: (–0.04, 0.02) ASI legal score, 12 months, psychosocially enriched 180-day methadone-assisted detoxification versus methadone, MD: 0.08, 95% CI: (0.02, 0.14) ASI psychiatric score, 12 months, psychosocially enriched 180-day methadone-assisted detoxification versus methadone, MD: –0.04, 95% CI: (–0.11, 0.03)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Reference: Senay et al., 1993 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 130 Number completed: 130 Mean age: 41.4 Percentage female: 33 Race/ethnicity: White: 70.8%, Black: 17.7%, Hispanic: 11.5% Years of opioid use: NR Inclusion criteria: Ages 21–60, in methadone treatment for past 1 year and no plans to attend detoxification in the next year, not on parole or probation at the time of entrance to the study, for the most recent 6-month period—all urines clean, employed or engaged in appropriate activity, no arrests, and compliance with treatment as evidenced by fulfilling all assignments in the treatment plan. Exclusion criteria: NR	Intervention: methadone Setting: home Route of administration: oral Duration (months): 6 Intervention 2: methadone Setting: methadone clinic Route of administration: oral Duration (months): 6 Non-MAT comparator: none	Physical : ASI medical score, 6 months, twice a month methadone take-home schedule versus control (twice or three times a week take-home schedule), MD: –0.01, 95% CI: (–0.04, 0.02) Occupational : ASI employment score, 6 months, twice a month methadone take-home schedule versus control (twice or three times a week take-home schedule), MD: 0, 95% CI: (–0.11, 0.11) Behavioral/social : ASI legal score, 6 months, twice a month methadone take-home schedule versus control (twice or three times a week take-home schedule), MD: 0, 95% CI: (–0.02, 0.02) ASI psychiatric score, 6 months, twice a month methadone take-home schedule versus control (twice or three times a week take-home schedule), MD: 0.02, 95% CI: (–0.01, 0.04)
Reference: Soyka et al., 2005 Location: Europe Study design: randomized controlled trial	Number enrolled: 62 Number completed: 46 Mean age: buprenorphine, 34.2; methadone: 32 Percentage female: 41.3 Race/ethnicity: NR Years of opioid use: buprenorphine: 11.5, methadone: 11 Inclusion criteria: All patients met the International Statistical Classification of Diseases, 10th revision, and DSM-IV criteria for opioid dependence. All patients were free of withdrawal symptoms when tested, had a driver's license (valid or withdrawn), or were experienced drivers. Exclusion criteria: Patients were excluded if they had a disabling physical disorder or organic brain disorder.	Intervention: buprenorphine Setting: unclear Route of administration, other: NR Duration (months): 2–2.5 (entire study) Intervention 2: methadone Setting: unclear Route of administration: NR Duration (months): follow up at 2–2.5 months (entire study 6 months) Non-MAT comparator: none	Cognitive : Attention test (Q1), correct answers, 8–10 weeks, buprenorphine versus methadone, MD: 7.7, 95% CI: (–29, 44.4) Decision and reaction test (DR2)—false decisions, 8–10 weeks, buprenorphine versus methadone, MD: 1.37, 95% CI: (–2.76, 0.02) DR2—time of decision, 8–10 weeks, buprenorphine versus methadone, MD: 13.88, 95% CI: (–34.45, 62.21) Peripheral vision test (PVT)—reaction time, total seconds, 8–10 weeks, buprenorphine versus methadone, MD: 0, 95% CI: (–0.23, 0.23) PVT—tracking performance (mean deviation), 8–10 weeks, buprenorphine versus methadone, MD: –1.1, 95% CI: (–2.2, 0) Visual perception, tachistoscope test (TT15), correct answers, 8–10 weeks, buprenorphine versus methadone, MD: –0.2, 95% CI: (–2.58, 2.18) Neurological : Reactive stress tolerance test (RST3), phase 1, omissions, 8–10 weeks, buprenorphine versus methadone, MD: 0.5, 95% CI: (–2, 3) RST3, phase 2, omissions, 8–10 weeks, buprenorphine versus methadone, MD: –2.4, 95% CI: (–14.28, 9.48) RST3, phase 3, omissions, 8–10 weeks, buprenorphine versus methadone, MD: 2.6, 95% CI: (–7.91, 13.11)

Reference: Soyka et al., 2008 Location: Europe Study design: randomized controlled trial	Number enrolled: 59 Number completed: 46 Mean age: NR Percentage female: NR Race/ethnicity: NR Years of opioid use: NR Inclusion criteria: (a) No confirmed subjective memory complaints or history of organic brain syndrome or seizures, (b) no measurable cognitive and memory impairment, (c) IQ of 85 or greater, and (d) neither neurological nor psychiatric diagnosis or history apart from the opioid dependence in the patient group. A group of healthy normal controls, matched for age, sex, and education level, was recruited, to detect possible impairments of cognitive ability in the patient group. Exclusion criteria: NR	Intervention: methadone Setting: outpatient clinic Route of administration: oral Duration (months): 6 Intervention 2: buprenorphine Setting: other, outpatient clinic Route of administration: oral Duration(months): 6 Non-MAT comparator: 1. A group of healthy normal controls, matched for age, sex, and education level, was recruited, to detect possible impairments of cognitive ability in the patient group.	Cognitive: Regensburg Word Fluency Test (RWT)—lexical, 8–10 weeks (t2), buprenorphine versus healthy controls, MD: –7.2, 95% CI: (–11.09, –3.31) RWT—lexical, 8–10 weeks (t2), buprenorphine versus methadone, MD: 0.9, 95% CI: (–3.57, 5.37) RWT—lexical, 8–10 weeks (t2), methadone versus healthy controls, MD: –8.1, 95% CI: (–13.13, –3.07) RWT—phonemic, 8–10 weeks (t2), buprenorphine versus healthy controls, MD: –3.1, 95% CI: (–6.66, 0.46) RWT—phonemic, 8–10 weeks (t2), buprenorphine versus methadone, MD: –0.1, 95% CI: (–3.21, 3.01) RWT—phonemic, 8–10 weeks (t2), methadone versus healthy controls, MD: –3, 95% CI: (–6.12, 0.12) RWT—shifting (lexical), 8–10 weeks (t2), buprenorphine versus healthy controls, MD: –3.4, 95% CI: (–6.19, –0.61) RWT—shifting (lexical), 8–10 weeks (t2), buprenorphine versus methadone, MD: –1.1, 95% CI: (–4.45, 2.25) RWT—shifting (lexical), 8–10 weeks (t2), methadone versus healthy controls, MD: –2.3, 95% CI: (–5.27, 0.67) RWT—shifting (phonemic), 8–10 weeks (t2), buprenorphine versus healthy controls, MD: –2.8, 95% CI: (–5.65, 0.05) RWT—shifting (phonemic), 8–10 weeks (t2), buprenorphine versus methadone, MD: –2.2, 95% CI: (–5.44, 1.04) RWT—shifting (phonemic), 8–10 weeks (t2), methadone versus healthy controls, MD: –0.6, 95% CI: (–3.57, 2.37) Trail-Making Test A (TMT-A), 8–10 weeks (t2), buprenorphine versus healthy controls, MD: 5.5, 95% CI: (0.32, 10.68) TMT-A, 8–10 weeks (t2), buprenorphine versus methadone, MD: –0.4, 95% CI: (–5.98, 5.18) TMT-A, 8–10 weeks (t2), methadone versus healthy controls, MD: 5.9, 95% CI: (1.49, 10.31) TMT-B, 8–10 weeks (t2), buprenorphine versus healthy controls, MD: 26, 95% CI: (–43.35, 95.35) TMT-B, 8–10 weeks (t2), buprenorphine versus methadone, MD: 4.4, 95% CI: (–78.87, 87.67) TMT-B, 8–10 weeks (t2), methadone versus healthy controls, MD: 21.6, 95% CI: (–59.33, 102.53) VLMT—verbal digit span, 8–10 weeks (t2), buprenorphine versus healthy controls, MD: –0.2, 95% CI: (–2.34, 1.94) VLMT—verbal digit span, 8-10 weeks (t2), buprenorphine versus methadone, MD: 0.6, 95% CI: (–1.77, 2.97) VLMT—verbal digit span, 8–10 weeks (t2), methadone versus healthy controls, MD: –0.8, 95% CI: (–2.88, 1.28) VLMT–verbal learning, 8–10 weeks (t2), buprenorphine versus healthy controls, MD: –12.5, 95% CI: (–17.21, –7.79) VLMT—verbal learning, 8–10 weeks (t2), buprenorphine versus methadone, MD: –1.2, 95% CI: (–6.66, 4.26)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
(Continued) Soyka et al., 2008			VLMT—verbal learning, 8–10 weeks (t2), methadone versus healthy controls, MD: –11.3, 95% CI: (–16.04, –6.56) VLMT—verbal memory, 8–10 weeks (t2), buprenorphine versus healthy controls, MD: 1, 95% CI: (–0.3, 2.3) VLMT—verbal memory, 8–10 weeks (t2), buprenorphine versus methadone, MD: –0.5, 95% CI: (–1.88, 0.88) VLMT—verbal memory, 8–10 weeks (t2), methadone versus healthy controls, MD: 1.5, 95% CI: (0.48, 2.52) d2-Test of Attention, 8–10 weeks (t2), buprenorphine versus healthy controls, MD : –11.5, 95% CI: (–29.45, 6.45) d2-Test of Attention, 8–10 weeks (t2), buprenorphine versus healthy controls, MD: –42.4, 95% CI: (–86.46, 1.66) d2-Test of Attention, 8–10 weeks (t2), buprenorphine versus methadone, MD: –13.4, 95% CI: (–32.26, 5.46) d2-Test of Attention, 8–10 weeks (t2), buprenorphine versus methadone, MD: –29.2, 95% CI: (–75.11, 16.71) d2-Test of Attention, 8–10 weeks (t2), methadone versus healthy controls, MD: 1.9, 95% CI: (–17.81, 21.61) d2-Test of Attention, 8–10 weeks (t2), methadone versus healthy controls, MD: –13.2, 95% CI: (–53.45, 27.05)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Strain et al., 1993 Location: United States or Canada Study design: randomized controlled trial	Number enrolled: 95 Number completed: 95 Mean age: 34.7 (5.2) Percentage female: 32 Race/ethnicity: Black: 52% Years of opioid use: 7.4 Inclusion criteria: Ages between 18 and 50 years old, history of intravenous opioid dependence (including 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), no chronic medical illnesses, absence of major mental illness, a negative pregnancy test for females, and at least 3 months since the patient's last treatment at the clinic. Exclusion criteria: NR	Intervention: methadone Setting: methadone clinic Route of administration: oral Duration (months): 9 Intervention 2: methadone Setting: methadone clinic Route of administration: oral Duration (months): 9 Non-MAT comparator: 1. Patients assigned to the 0 mg (placebo) condition received a 35-day methadone detoxification starting at 25 mg in the first week, and decreasing by 5 mg each week. Patients were assigned an individual counselor who set treatment goals and developed an individualized treatment plan. Patients received weekly group therapy focusing upon relapse prevention. On-site medical services were provided by a full-time internist and a part-time nurse practitioner.	Behavioral/social : Mean number of days' illegal activity in the past 30 days, 20 weeks, 20 mg methadone versus placebo, MD: 3, 95% CI: (–2.34, 8.34) Mean number of days' illegal activity in the past 30 days, 20 weeks, 50 mg methadone versus 20 mg methadone, MD: –5.5, 95% CI: (–9.6, –1.4) Mean number of days' illegal activity in the past 30 days, 20 weeks, 50 mg methadone versus placebo, MD: –2.5, 95% CI: (–7.63, 2.63) Number of crimes committed, 20 weeks, 20 mg methadone versus placebo, MD: –4, 95% CI: (not calculable) Number of crimes committed, 20 weeks, 50 mg methadone versus 20 mg methadone, MD: –5.23, 95% CI: (not calculable) Number of crimes committed, 20 weeks, 50 mg methadone versus placebo, MD: –9.23, 95% CI: (not calculable)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Strang et al., 2000 Location: Europe Study design: randomized controlled trial	Number enrolled: 37 Number completed: 33 Mean age: IV MMT, 31.9; oral MMT, 32.1 Percentage female: IV MMT, 9.5; oral MMT, 6.3 Race/ethnicity: other, nonwhite, IV MMT, 9.5%; oral MMT: 12.5% Years of opioid use: NR Inclusion criteria: Aged at least 23 years; illicit injecting for at least the last 3 years; at least one previous episode of opiate substitution treatment; adequate venous access on arms. Exclusion criteria: Current serious medical or psychiatric comorbidity or pregnant.	Intervention: methadone Setting: methadone clinic Route of administration: injection Duration (months): 6 Intervention 2: methadone Setting: methadone clinic Route of administration: oral Duration (months): 6 Non-MAT comparator: none	Physical : Maudsley Addiction Profile (MAP): 10-item physical health symptom scale from the MAP measuring general health, cardiorespiratory, gastrointestinal, musculoskeletal, and neurological symptoms, 6 months; injectable methadone versus oral methadone, MD: –0.8, 95% CI: (–5.1, 3.5) Behavioral/social : Number of days the individual reported committing shoplifting, robbery, burglary, and fraud (time period not reported), 6 months, injectable methadone versus oral methadone, MD: –3.6, 95% CI: (–10.02, 2.82)

Study Details	Participants	Intervention Treatment	Functional Outcomes Results
Tiihonen et al., 2012 Location: Europe Study design: randomized controlled trial	Number enrolled: 100 Number completed: 40 Mean age: placebo: 29.3 (4.38), naltrexone: 28.0 (4.10) Percentage female: NR Race/ethnicity: NR Years of opioid use: placebo: 8.7 (2.83), naltrexone: 8.2 (3.75) Inclusion criteria: Primary DSM-IV diagnosis of concurrent amphetamine and opioid dependence, present for at least 1 year; age between 18 and 50 years; education level of high school graduate or above; negative urine toxicology and alcohol breath tests; no current use of psychotropic medications; at least one relative willing to participate in the treatment (e.g., to monitor the administration of medications, assist in follow-up, and provide outcome data); a stable address in St. Petersburg or in the nearest districts of Leningrad Region; a home telephone number at which the patient could be reached; willingness and ability to give informed consent and otherwise participate; and, for women of childbearing age, a negative pregnancy test and use of adequate contraception. Exclusion criteria: Clinically significant cognitive impairment, schizophrenia, a paranoid disorder, bipolar disorder, or a seizure disorder; advanced neurological, cardiovascular, renal, or hepatic disease; active tuberculosis; a current febrile illness; an AIDS-defining illness; a significant laboratory abnormality, such as severe anemia, unstable diabetes, or liver function test results greater than three times normal values; pregnancy; pending legal charges with potential impending incarceration; concurrent participation in another treatment study; and concurrent treatment in another substance abuse program.	Intervention: naltrexone Setting: other substance abuse treatment Route of administration: implant Duration (months): 2.5 Non-MAT comparator: 1. Placebo implant identical in appearance	Physical : Number of participants reporting fatigue, 10 weeks, naltrexone (sustained release implant) versus placebo, RR: 1, 95% CI: (0.06, 15.55) Percentage of participants reporting insomnia, 10 weeks, naltrexone (sustained release implant) versus placebo, RR: 1, 95% CI: (0.21, 4.72) Neurological : Percentage of participants reporting nervousness, irritability, 10 weeks, naltrexone (sustained release implant) versus placebo, RR: 1, 95% CI: (0.15, 6.82) Number of participants reporting nervousness, 10 weeks, naltrexone (sustained release implant) versus placebo, RR: 0, 95% CI: (not calculable)

Appendix E. Excluded Publications

Publications That Do Not Meet Inclusion Criteria (with Reasons for Exclusion)

Abbott, P. J., B. Moore, H. Delaney, and S. Weller, "Retrospective Analyses of Additional Services for Methadone Maintenance Patients," *Journal of Substance Abuse Treatment*, Vol. 17, No. 1–2, July–September 1999, pp. 129–137. Reason for exclusion: Only measures effects of a co-intervention.

Abbott, P. J., S. B. Weller, H. D. Delaney, and B. A. Moore, "Community Reinforcement Approach in the Treatment of Opiate Addicts," *American Journal of Drug and Alcohol Abuse*, Vol. 24, No. 1, February 1998, pp. 17–30. Reason for exclusion: Only measures effects of a co-intervention.

Abidizadegan, Afsaneh, Alireza Moradi, and Robert Famam, "The Executive Functions in Methadone Maintenance Patients," *Advances in Cognitive Science*, Vol. 10, No. 3, Fall 2008, 2008, pp. 75–82. Reason for exclusion: Wrong study design.

Abrahms, J. L., "A Cognitive-Behavioural Versus Nondirective Group Treatment Program for Opioid Addicted Persons: An Adjunct to Methadone Maintenance," *The International Journal of the Addictions*, Vol. 14, No. 4, 1979. Reason for exclusion: Only measures effects of a co-intervention.

"Abuse-Deterrent Opioid Formulations," *Medical Letter on Drugs and Therapeudics*, Vol. 57, No. 1476, August 31, 2015, pp. 119–121. Reason for exclusion: Wrong study design.

Accurso, A. J., and D. A. Rastegar, "The Effect of a Payer-Mandated Decrease in Buprenorphine Dose on Aberrant Drug Tests and Treatment Retention Among Patients with Opioid Dependence," *Journal of Substance Abuse Treatment*, Vol. 61, February 2016, pp. 74–79. Reason for exclusion: No functional outcomes.

Achmad, Y. M., A. N. Istiqomah, S. Iskandar, R. Wisaksana, R. van Crevel, and T. Hidayat, "Integration of Methadone Maintenance Treatment and HIV Care for Injecting Drug Users: A Cohort Study in Bandung, Indonesia," *Acta Medica Indonesiana*, Vol. 41, Supplement 1, July 2009, pp. 23–27. Reason for exclusion: No functional outcomes.

Acosta, Michelle C., Lisa A. Marsch, Haiyi Xie, Honoria Guarino, and Yesenia Aponte-Melendez, "A Web-Based Behavior Therapy Program Influences the Association Between Cognitive Functioning and Retention and Abstinence in Clients Receiving Methadone Maintenance Treatment," *Journal of Dual Diagnosis*, Vol. 8, No. 4, November 2012, pp. 283–293. Reason for exclusion: Only measures effects of a co-intervention.

"Addiction," *DATA: The Brown University Digest of Addiction Theory and Application,* Vol. 27, No. 1, 2008, p. 2p. Reason for exclusion: Not MAT using methadone, buprenorphine, Suboxone, and naltrexone.

"Addiction Research Roundup," *DATA: The Brown University Digest of Addiction Theory and Application*, Vol. 27, No. 10, 2008, p. 2p. Reason for exclusion: Wrong study design.

"Addiction: Research Roundup," *DATA: The Brown University Digest of Addiction Theory and Application*, Vol. 29, No. 8, 2010, p. 2p. Reason for exclusion: Wrong study design.

Adi, Y., A. Juarez-Garcia, D. Wang, S. Jowett, E. Frew, E. Day, S. Bayliss, T. Roberts, and A. Burls, "Oral Naltrexone as a Treatment for Relapse Prevention in Formerly Opioid-Dependent Drug Users: A Systematic Review and Economic Evaluation," *Health Technology Assessment*, Vol. 11, No. 6, February 2007, pp. iii–iv, 1–85. Reason for exclusion: No functional outcomes.

Ahmadi, J., "A Controlled Trial of Buprenorphine Treatment for Opium Dependence: The First Experience from Iran," *Drug and Alcohol Dependence*, Vol. 66, No. 2, April 1, 2002, pp. 111–114. Reason for exclusion: No functional outcomes.

Ahmadi, Jamshid, "A Randomized, Clinical Trial of Buprenorphine Maintenance Treatment for Iranian Patients with Opioid Dependency," *Addictive Disorders and Their Treatment*, Vol. 1, No. 1, 2002, pp. 25–27. Reason for exclusion: Not English.

Ahmadi, J., "Methadone Versus Buprenorphine Maintenance for the Treatment of Heroin-Dependent Outpatients," *Journal of Substance Abuse Treatment*, Vol. 24, No. 3, April 2003, pp. 217–220. Reason for exclusion: No functional outcomes.

Ahmadi, J., and K. Ahmadi, "Controlled Trial of Maintenance Treatment of Intravenous Buprenorphine Dependence," *Irish Journal of Medical Science*, Vol. 172, No. 4, October–December 2003, pp. 171–173. Reason for exclusion: No functional outcomes.

Ahmadi, J., K. Ahmadi, and J. Ohaeri, "Controlled, Randomized Trial in Maintenance Treatment of Intravenous Buprenorphine Dependence with Naltrexone, Methadone or Buprenorphine: A Novel Study," *European Journal of Clinical Investigation*, Vol. 33, No. 9, September 2003, pp. 824–829. Reason for exclusion: No functional outcomes.

Ahmadi, J., and M. Ahmadi, "Twelve-Month Maintenance Treatment of Heroin-Dependent Outpatients with Buprenorphine," *Journal of Substance Use*, Vol. 8, No. 1, March 2003, pp. 39–41. Reason for exclusion: No functional outcomes.

Ahmadi, J., M. Babaee-Beigi, M. Alishahi, I. Maany, and T. Hidari, "Twelve-Month Maintenance Treatment of Opium-Dependent Patients," *Journal of Substance Abuse Treatment*, Vol. 26, No. 1, January 2004, pp. 363–366. Reason for exclusion: No functional outcomes.

Ahmadi, J., and N. Bahrami, "Buprenorphine Treatment of Opium-Dependent Outpatients Seeking Treatment in Iran," *Journal of Substance Abuse Treatment*, Vol. 23, No. 4, December 2002, pp. 415–417. Reason for exclusion: No functional outcomes.

Ahmadi, Jamshid, Hassan Farrashbandi, Masoud Moosavinasab, Mohammadali Babaee, Ali Firoozabadi, Mohammadsadegh Mohagheghzadeh, Joel Porter, Saxby Pridmore, and Gholamreza Dehbozorgi, "Treatment of Heroin Dependence," *German Journal of Psychiatry,* Vol. 7, No. 2, 2004, pp. 1–5. Reason for exclusion: No functional outcomes.

Ahmadi, J., I. Maany, and M. Ahmadi, "Treatment of Intravenous Buprenorphine Dependence: A Randomized Open Clinical Trial," *German Journal of Psychiatry*, Vol. 6, No. 1, 2003, pp. 23–29. Reason for exclusion: No functional outcomes.

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