Rapid Evidence Product

Retention Strategies for Medications for Addiction Treatment in Adults With Opioid Use Disorder: A Rapid Evidence Review

Agency for Healthcare Research and Quality

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This report is based on research conducted by the Scientific Resource Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2017-00003-C). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Errata

In the original version of this report, there was an omission with respect to the search strategy. Specifically, following the reported primary search conducted on June16, 2019, that included studies published between February 12, 2009, and June 16, 2019, we conducted a “gap search” on August 20, 2019, which was not reported in the original version of the report. No additional included studies were identified from this gap search. We have updated the search strategies portion of the Methods sections of the abstract, evidence summary, and main report to reflect the gap search and updated the Results section of the main report to indicate that no new included studies were identified.

Preface

Recognized for excellence in conducting comprehensive systematic reviews, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) program is expanding its portfolio to include rapid evidence products. The program has begun to develop a range of rapid evidence products to assist end-users in making specific decisions in a limited timeframe.

In 2014, AHRQ EPCs produced a taxonomy of rapid evidence products produced by leading organizations around the world.[1-4] This taxonomy now informs the development of rapid evidence products. Based on levels of synthesis, the report classified products as evidence inventories, rapid responses, and rapid reviews. On one end of the spectrum, evidence inventories offer an assessment of the quantity and type of evidence without presenting results. On the other end, rapid reviews adapt and streamline traditional systematic review methods to provide a limited evidence synthesis. Rapid responses fall between the two; through examination of the literature but no formal evidence synthesis or conclusion, rapid responses aim to offer the end-user a solution to a targeted problem based on the best available evidence.

To shorten timelines, reviewers must make strategic choices about which processes to abridge. Common adaptations to provide rapid evidence include: narrowly focusing questions, limiting the number of databases searched and/or modifying search strategies, using a single reviewer and/or abstractor with a second to provide verification, and restricting to studies published in the English language. However, the adaptations made for expediency may limit the certainty and generalizability of the findings from the review, particularly in areas with a large literature base. Transparent reporting of the methods used, the resulting limitations of the evidence synthesis, and the strength of evidence of included studies is extremely important. While tradeoffs will likely differ for each topic, they are described so readers can adjudicate the limitations of the findings and conclusions of the review.

While rapid evidence products are often sufficient for decision making on their own, at other times they can uncover a large, complex literature base that encourages end-users to seek a full review. Rapid evidence products can provide a map of the evidence and assist decisionmakers in targeting resources to areas of highest interest and greatest potential value.

AHRQ expects that these rapid evidence products will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program.

If you have comments on this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Retention Strategies for Medications for Addiction Treatment in Adults With Opioid Use Disorder: A Rapid Evidence Review

Structured Abstract

Aims. American deaths from opioid overdose now approach 50,000 annually. While evidence shows that medications for addiction treatment (MAT) save lives, retaining patients in MAT programs is challenging. The U.S. Agency for Healthcare Research and Quality, on behalf of the U.S. Department of Health and Human Services, commissioned a rapid evidence review on the effectiveness of interventions to promote a broader understanding of the published literature on MAT retention among adults with opioid use disorder (OUD).

Methods. We searched MEDLINE and the Cochrane Library from February 12, 2009, through August 20, 2019, for systematic reviews (SRs) and randomized controlled trials (RCTs). We summarized evidence for six retention intervention types: care settings/services/logistical support, contingency management, health information technology (IT), extended-release (XR) medication-based treatment, psychosocial support, and financial support. Our primary outcome was retention, defined as continued medication engagement for at least 3 months after MAT initiation. Secondary outcomes included mortality and harms.

Findings. Key findings from 2 SRs and 39 primary studies include:

- Most studies of MAT for OUD do not focus on retention as the primary outcome, are small (e.g., one to two trials per intervention), and have design flaws.
- Care setting interventions that initiated MAT in soon-to-be-released incarcerated patients improved retention following release.
- Contingency management improved retention when combined with antagonist MAT, but not with agonist forms of MAT. Applicability, however, may be limited due to implementation challenges.
- Preliminary trials suggest that retention in MAT supported with health IT approaches may be no worse than in-person approaches.
- Early studies suggest no difference in retention with XR-buprenorphine in either injectable or implant formulations compared with daily buprenorphine. There were conflicting results with XR-naltrexone injection compared with daily buprenorphine.
- The addition of psychosocial interventions did not improve retention; however, many studies included some form of counseling in the control groups, potentially obscuring evidence of effectiveness.

Harms were infrequently reported across studies except in studies of XR formulations. Similarly, few studies reported whether participant characteristics influenced retention.

Conclusions. While patients who receive longer-term treatment with MAT have improved outcomes, fewer than half of the identified studies measured treatment retention as a primary outcome. Limited evidence suggests criminal justice prerelease MAT initiation and the use of contingency management for patients on antagonist forms of MAT may aid retention. XR

and daily buprenorphine formulations appear to be equivalent for treatment retention and comparisons of XR-naltrexone versus daily buprenorphine showed conflicting results. Integrating MAT treatment with medical and social services and the use of health IT did not change retention. Some studies were conducted outside of the United States, where policies and practices differ, focused on highly selected populations and/or conditions that are not fully representative of the spectrum of OUD, or were studied in situations that may not be easily implemented in real-world conditions. There is a critical need for studies that use standardized definitions of retention, include measures of harms as well as benefits, and reflect the full spectrum of real-life conditions.

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Evidence Summary

Main Points

- Most studies of medications for addiction treatment (MAT) for opioid-use disorder (OUD) do not focus on retention as the primary outcome, are small (e.g., one to two trials per intervention), and have design flaws.
- Care setting interventions that initiated MAT in soon-to-be-released incarcerated patients improved retention following release.
- Contingency management (CM) improved retention when combined with antagonist, but not with agonist, forms of MAT. Applicability, however, may be limited due to implementation challenges.
- Preliminary trials suggest that retention in MAT supported with health information technology (IT) approaches may be no worse than in-person approaches.
- Early studies suggest no difference in retention with XR-buprenorphine in either injectable or implant formulations compared with daily buprenorphine. There were conflicting results with XR-naltrexone injection compared with daily buprenorphine.

Background and Purpose

To help inform policy across the Department of Health and Human Services, we conducted a rapid evidence review on the effectiveness of interventions to improve MAT retention among OUD patients to inform a broader understanding of the published literature. While evidence indicates that MAT programs are effective and save lives, retention rates are low. The review focused on nonpregnant adults with OUD.

Methods

This review followed recommendations from the World Health Organization handbook[2] rapid review methodology and abridged systematic review (SR) processes. Our searches covered publication dates from February 12, 2009 to August 20, 2019. We describe our methods in detail in the full report. The protocol can be found at: [https://effectivehealthcare.ahrq.gov/topics/mat-retention-strategies-oud/rapid-protocol].

Results

Our search retrieved 1,580 unique titles and abstracts from which we reviewed 258 full-text articles and included 2 SRs and 39 unique primary studies. A partial summary of findings includes the following.

Table A. Summary of findings by intervention type

	Intervention	Comparator	Number of Studies	Number of Participants	Quality of Evidence	Summary of Retention Results
Care Settings, Services, Logistical Support	MAT for soon-to-be-released incarcerated populations	No MAT in prison	1 SR[1] + 2 additional RCTs[2, 3]	SR: n=834 (range: 32–446) 2 RCTs: n=228 (15 and 213)	SR: good; 1 fair; 1 poor	Benefit with prerelease MAT in all studies
	Psychiatric & primary care (PC) services	Specialty outpatient setting	3 RCTs[4-6]	n=631 (range: 94–316)	3 fair	Inconsistent (2 psychiatric studies, benefit in one and no difference from traditional setting in other; 1 study in PC, no difference from traditional setting)
	Emergency department (ED)/hospital setting	TAU	2 RCTs[7, 8]	n=429 (139 and 290)	2 fair	ED no worse than traditional (1 study with no difference; 1 study with benefit for hospital-initiated MAT)
	Logistical support	TAU	4 RCTs[9-12]	n=709 (range: 97–300)	1 good; 3 fair	No difference
Contingency Management	Opioid receptor antagonist MAT	Noncontingent access to a reward	3 RCTs[13-15]	n=140 (range: 35–67)	3 fair	Benefit for CM in all studies
	Opioid receptor agonist/partial agonist MAT	Noncontingent access to a reward	1 SR*[16] + 4 additional RCTs[11, 17-19]	SR: n=1616 4 RCTs: n=698 (range: 98–252)	SR: good; 1 good; 3 fair	No difference

	Intervention	Comparator	Number of Studies	Number of Participants	Quality of Evidence	Summary of Retention Results
Health IT	Telehealth	TAU	3 cohort studies[20-22]	n=3965 (range: 55–3733)	3 fair	Telehealth no worse than in-person (2 studies with no difference, 1 study with benefit for telehealth)
	Computer-based education &/or support	TAU	3 RCTs[23-25]	n=262 (range: 20–160)	2 fair; 1 poor	No difference
	Multicomponent mobile and computer-based program	TAU	1 RCT[26]	n=1426	1 fair	No difference
Extended-Release Medication-Based Treatments	Naltrexone extended-release 1-month injection	Daily naltrexone	1 RCT[27]	n=60	1 fair	Benefit for XR injection
	Buprenorphine extended-release 1-month injection	Daily SL-buprenorphine/ naloxone	1 RCT[28]	n=428	1 fair	No difference
	Buprenorphine extended-release 6-month implant	Daily SL-buprenorphine	1 RCT[29]	n=177	1 good	No difference
	Naltrexone extended-release 1-month injection	Daily SL-buprenorphine/ naloxone	2 RCTs[30, 31]	n=729 (159 and 570)	1 good; 1 fair	Inconsistent (1 study no difference, 1 study with benefit for SL-buprenorphine/ naloxone)
Psychosocial Support	Including behavioral, psychoanalytic, and counseling interventions	TAU	1 SR*[16] + 9 additional RCTs[32-40]	SR: n=3124 (range: 14–542) 9 RCTs: n=2483 (range: 49–653)	SR: good 2 good; 4 fair; 3 poor	No difference in all but one poor-quality study. Many of the studies reviewed included some form of counseling in the control groups.

CM=contingency management; IT=information technology; MAT=medications for addiction treatment; RCT=randomized controlled trial; SL=sublingual; SR=systematic review; TAU=treatment as usual; XR=extended-release

*SR applicable to two intervention types

Limitations

We were not able to address every intervention proposed to improve retention in MAT. We did not review studies of potentially promising interventions that used non-MAT comparator groups. Measures of retention varied amongst studies, making comparisons difficult.

Implications and Conclusions

According to the National Academy of Medicine, patients who receive longer-term treatment with medication for OUD have better outcomes and are less likely to die from overdose; however, fewer than half of the studies identified in this report focused on treatment retention as a primary outcome. Initiating MAT in soon-to-be-released criminal justice populations and the use of CM for people on antagonist MAT may improve retention, although there may be challenges to implementing CM interventions in real-world contexts. MAT treatment programs that include the use of health IT may be equally as effective as those delivered using traditional, exclusively in-person approaches. Studies of XR versus daily buprenorphine formulations showed similar treatment retention, and, while comparisons between XR-naltrexone injection and daily buprenorphine yielded inconclusive findings, additional comparative effectiveness trials are underway. Future research should focus on treatment retention as a primary outcome, use standardized measures of retention, report treatment harms as well as benefits, and consider the effects of participant characteristics on the effectiveness of strategies to improve retention in MAT.

Introduction

The United States is in the midst of an opioid crisis. In 2017, 2.1 million Americans 12 years and older met diagnostic criteria for opioid use disorder (OUD)[41] and 47,600 people died from an opioid-involved overdose.[42, 43] In addition to overdose deaths, OUD is associated with increased rates of comorbid conditions including HIV, hepatitis C, serious bacterial infections, mental health disorders, and other substance use disorders (SUDs).[43]

There is clear evidence, including a recent report from the National Academies of Science, Engineering, and Medicine (NASEM), that medications for addiction treatment (MAT) retention improve outcomes.[44-46] The U.S. Food and Drug Administration (FDA) has approved three medications—methadone, buprenorphine, and extended-release (XR)-naltrexone—for treatment of OUD.[47] Despite evidence that these medications successfully treat OUD, intermediate and long-term retention of patients on MAT remains challenging and highly variable, with retention at 3 months ranging from 19 percent to 94 percent.[48] Potential explanations for the wide variation in retention include—

- Barriers for access to MAT
- Stigma associated with medications
- Costs and logistical issues with obtaining and maintaining medications
- Undertreatment of comorbid psychiatric and medical conditions[49]
- Fragmented systems of care for people with OUD
- Current SUD financing and coverage policies[44]
- Coercion into treatment of people not actively seeking treatment (e.g., drug court settings)

Improving MAT retention can decrease unnecessary deaths.[50, 51] Successfully addressing the opioid crisis will require the American health system to identify, apply, and improve interventions that promote MAT retention.

The U.S. Agency for Healthcare Research and Quality (AHRQ) commissioned this rapid review on behalf of the U.S. Department of Health and Human Services (HHS) agencies to provide an overview of the published literature to assist the offices in research, practice, and policy decision making around strategies to improve MAT retention. HHS partners include the Office of the Assistant Secretary for Health, Center for Drug Evaluation and Research at FDA, the Office of the Assistant Secretary for Mental Health and Substance Use for the Substance Abuse and Mental Health Services Administration (SAMHSA), the Division of Unintentional Injury Prevention in the National Center for Injury Prevention and Control at the Centers for Disease Control and Prevention, the Office of the Assistant Secretary for Planning and Evaluation, the National Institute on Drug Abuse (NIDA) at the National Institutes of Health (NIH), and the Health Resources and Services Administration.

Objective and Guiding Questions

Our objective was to rapidly identify and summarize latest evidence on interventions to improve MAT retention among adults with OUD in order to inform policy priorities and future research directions. The following questions guided the literature search and inclusion/exclusion criteria:

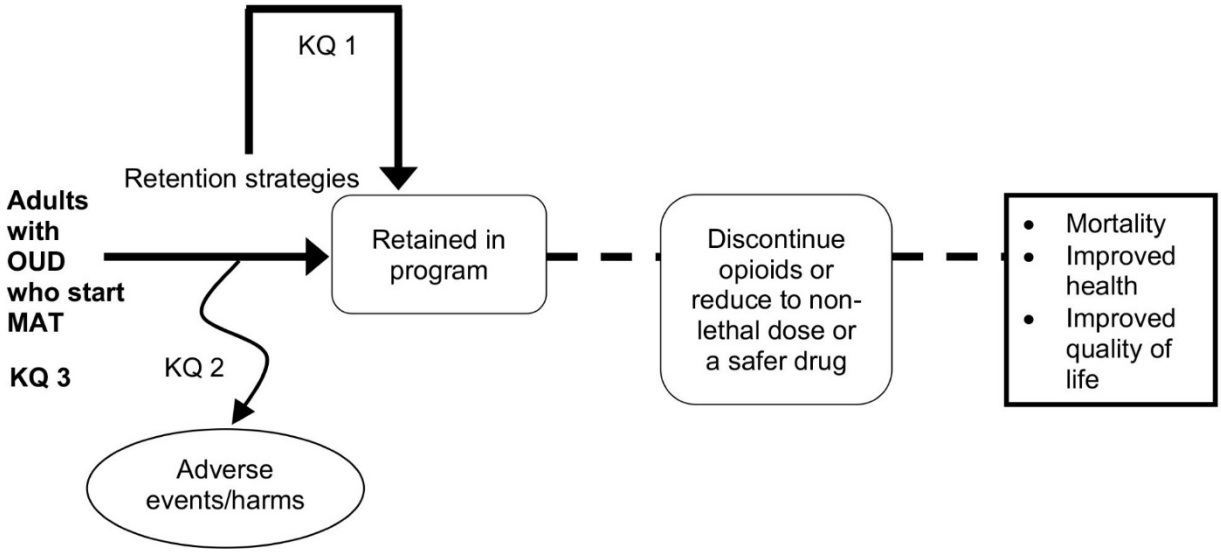
> Key Question 1: What are the effectiveness and comparative effectiveness of strategies to improve retention in MAT among nonpregnant adults with OUD?

Key Question 2: What are the harms of retention strategies for MAT?

Key Question 3: Does the effectiveness of the MAT retention strategy vary by participant characteristics (e.g., age, gender/sex, socioeconomic status, geographic region, polysubstance use)?

We developed an analytic framework (Figure 1) in consultation with our stakeholders to guide our approach.

Figure 1. Analytic framework for improving retention in MAT for OUD



Methods

This review followed recommendations from the World Health Organization (WHO) handbook rapid review methodology[52] and abridged systematic review (SR) processes in the following ways:

- Introduction.
- Focused on limited number of topics that were highest priority for partners.
- Searched a limited number of databases.
- One reviewer independently reviewed titles, abstracts, and papers for inclusion with 25 percent independent review by a second reviewer. Disagreements were resolved by group consensus.
- One reviewer abstracted information with second verification.
- Truncated inclusion criteria (Table 1) to include studies:
    - Published in English language
    - Published in the last 10 years

    - Populations of nonpregnant adults with OUD (excluded studies of HIV, other substance use, etc., unless focus was primarily OUD)
    - Focused on retention in MAT (rather than abstinence)
- Main focus on SRs and comparative randomized controlled trials (RCTs) with active controls.
- We were not able to perform strength-of-evidence assessment.

Table 1. Inclusion and exclusion criteria

PICOTS	Inclusion and Exclusion Criteria
Population	**Include:** Adults over 18 years enrolled in MAT program for OUD, people soon to be released from incarceration (e.g., released to the community during the study) **Exclude:** Special populations (e.g., people younger than 18 years of age, pregnant people, palliative care/end-of-life, HIV, people incarcerated for the duration of the study)
Intervention	**Include:** Medication formulation (e.g., XR), psychosocial adjuncts (e.g., counseling, CBT, peer support, 12-step programs, mindfulness therapy), CM, care settings/logistical support (e.g., MAT setting, low-threshold models), financial support (e.g., MAT medication/program reimbursement), and health IT
Comparator	**Include:** Comparator groups (e.g., TAU) must also consist of individuals with access to MAT, including usual referral and enrollment in outpatient in-person treatment programs, daily MAT formulations, XR formulations
Outcomes	**Include*** Primary: Treatment retention Secondary: Mortality Harms
Timing	**Include:** Retention in MAT was evaluated for at least 3 months.
Setting	**Include:** Only studies conducted in countries ranked as Very High Human Development by the United Nations' Development Programme's 2018 Statistical Update "Human Development Indices and Indicators." Outpatient MAT only.
Study design	**Include:** High-quality SRs, RCTs, observational studies (nonrandomized studies with control groups)
Language	**Include:** English

CBT=cognitive behavioral therapy; CM=contingency management; HIV=human immunodeficiency virus; IT=information technology; MAT=medications for addiction treatment; OUD=opioid use disorder; PICOTS=population, intervention, comparator, outcomes, timing, setting; RCT=randomized controlled trial; SR=systematic review; TAU =treatment as usual; XR=extended-release

* Systematic reviews and primary studies were included only if they report the primary or secondary outcomes of interest.

We refined the scope of this rapid review in consultation with the partners and a topic expert. The protocol was developed based on input from experts and stakeholders and was registered in the PROSPERO database (CRD42019134739)[53] and publicly posted on the AHRQ Effective Health Care Program website.[54]

While a rapid review cannot be fully exhaustive or comprehensive, we aimed to provide an overview of the literature pertaining to retention strategies for MAT to inform decision making during a national epidemic.

Search Strategies

We searched OVID MEDLINE and the Cochrane Database of Systematic Reviews from February 12, 2009, to June 16, 2019, in consultation with a medical research librarian. We conducted an additional gap search through August 20, 2019. For health information technology (IT), we also searched the Google Play and Apple stores for commercial apps. See Appendix A for search strategies and full list of databases searched.

Because of the broad scope of retention strategy interventions, we consulted with our partners, topic experts, and published and unpublished literature[16, 44, 55, 56] to develop a classification scheme to aid in synthesis. We classified MAT retention interventions in the following manner:

- Care settings, services, and logistical support
- Contingency management (CM),
- Health IT
- XR medication-based treatments
- Psychosocial support interventions
- Financial support

Study Selection

We included studies that directly compared MAT retention strategies with each other or treatment as usual (TAU) if TAU included use of and potential access to MAT. We excluded studies that tested interventions that did not use MAT or used controls that did not have access to MAT (i.e., no treatment, placebo, abstinence-only, or nonpharmacologic programs). We also excluded studies of medications that are not currently FDA approved. We defined retention as continued treatment or medication engagement for at least 3 months. In the absence of established definitions of treatment retention for MAT, we considered 3 months as the minimum clinically relevant time interval to assess retention. We were purposefully inclusive of a wide range of study definitions of retention (e.g., retention defined by self-report, medication prescribing, or visits to clinics to receive supportive treatment). In many cases, retention was not clearly defined, and we could not determine the degree to which patients were adherent to MAT, to adjunct services, or abstained from illicit substances. Participants were still considered retained in MAT if they continued to use illicit opioids or missed MAT appointments/medication dosages. We did not equate study retention with treatment retention.

When possible, we focused on SRs and on RCTs published subsequent to SRs. Systematic reviews were included if they addressed MAT retention, searched at least two databases, performed quality assessment of individual studies, and were current (within 10 years of the date of the search). If the SR identified relevant studies but did not provide a synthesis specific to retention, we used the SR to identify RCTs. In cases where there were no/few identified RCTs, we included observational studies.

Quality Appraisal

SRs were considered good quality and were included if they met four basic criteria: searched more than two databases, performed quality assessment, used predetermined inclusion/exclusion criteria, and described the search strategy used. To balance efficiency, rigor, and inclusivity, we focused on these four critical features common to quality assessment tools for SRs. For RCTs and observational studies, we conducted dual independent review of study quality using criteria developed by the U.S. Preventive Services Task Force.[57] We did not downgrade studies with

high attrition in our quality ratings, because it was related to our primary outcome. We did not exclude studies on the basis of study quality; rather, we used study quality to guide our interpretation of results and identify areas for improvement in future research.

To assess the strength of a body of evidence, we relied on published SRs when we could, which meant that assessment tools could differ across intervention sections (e.g., in sections that had SRs as well as individual studies, the SR may have used a different tool from the one we used for individual studies). Also, given the rapid nature of this review, we did not conduct quantitative analyses, which are commonly used to assess precision in formal strength of evidence assessments.

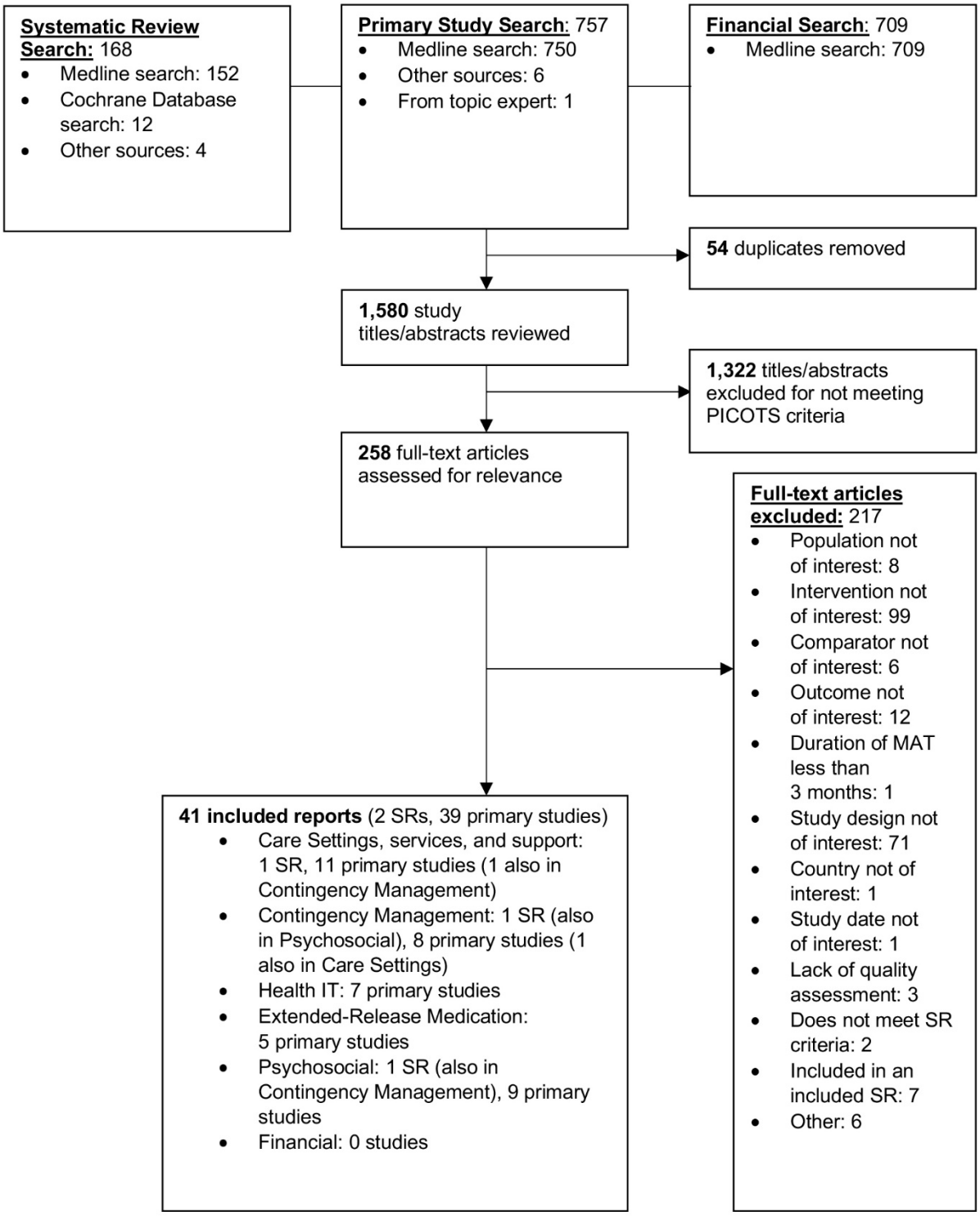
Data Collection and Synthesis

A team member abstracted details related to study design, setting, population, intervention and followup, outcomes, and harms. We reported retention outcomes for each included study, using intention-to-treat (ITT) analysis; if studies did not report ITT, we calculated this if data were available. We then assessed overall effectiveness for each intervention with a particular focus on the degree to which the literature reflects real-world clinical circumstances. Through iterative discussions with topic experts and SR experts, the study team discussed methodological weaknesses of the body of literature as well as individual studies and determined which studies provided the most reliable evidence. Qualitative synthesis placed emphasis on those studies deemed by the study team to be most reliable and of higher quality.

Results

Our search retrieved 1,580 unique titles and abstracts from which we reviewed 258 full-text articles for eligibility and included 2 SRs and 39 unique primary studies. No included studies were identified in the gap search (Figure 2). MAT retention duration ranged from 3 to 24 months. See Appendix C for quality ratings of all included studies.

Figure 2. Literature flow diagram



Care Settings, Services, and Logistical Support

We defined care settings and services as interventions that provide MAT in alternative settings or integrated models, compared with TAU conditions that offered MAT alone through specialty treatment programs. We defined logistical support as interventions that changed the process of MAT initiation and maintenance as compared with TAU, or interventions that provided MAT in conjunction with logistical supports, such as housing with health and social services assistance. We used an existing framework[58] to further categorize care setting interventions into the following:

- Interventions that initiate MAT for soon-to-be-released incarcerated populations (1 SR of 21 studies,[1] and 2 additional RCTs[2, 3])
- Integration of MAT with psychiatric or primary care services (PC) (three RCTs[4-6])
- Integration of MAT in emergency department (ED)/hospital settings (two RCTs[7, 8])

We identified one good quality SR[1] and 11 primary studies (one good quality;[9] nine fair;[3-8, 10-12] and one poor[2]) that investigated care setting/logistical support interventions.[2-7, 9-12] Most were downgraded for unblinded outcome assessment or high rates of crossover.

Key Question 1: Effectiveness and Comparative Effectiveness of MAT Retention Strategies

Table 2 provides a summary of findings across care settings/logistical support, and Appendix B Table 1 and Appendix C Table 1 provide details for included studies.

Table 2. Summary of findings for care settings / services / logistical support

Care Setting Intervention	Studies, Quality n	Results
MAT for soon-to-be-released incarcerated populations	1 SR of 21 studies[1] 2 additional studies[2, 3] (1 fair, 1 poor quality) n=228	Higher retention
Psychiatric or PC service integration	3 studies[4-6] (all fair quality) n=631	Inconsistent (2 studies, benefit in one and no difference from traditional setting in other; 1 study in PC, no difference from traditional setting)
ED / hospital setting	2 studies[7, 8] (both fair quality) n=429	ED no worse than traditional setting (1 higher retention, 1 no difference)
Logistical support	4 studies[9-12] (1 good, 3 fair quality) n=718	No difference

ED=emergency department; MAT=medications for addiction treatment; PC=primary care; SR=systematic review

Care Setting: MAT for Soon-To-Be-Released Incarcerated Populations

A good quality SR[1] of 21 studies (6 RCTs and 15 observational) and 2 additional RCTs[2, 3] examined interventions that initiate MAT in soon-to-be-released incarcerated OUD patients. The SR found that initiating MAT in this population was associated with high levels of postrelease treatment entry and retention compared with TAU controls who did not initiate MAT prior to release (retention rates 50% [range 27–75%] vs. 5% [range 0–9%]).[1] The review assessed quality

using Cochrane guidelines, with the majority of studies of fair quality (nine), followed by good and inadequate (six each). Two additional RCTs conducted in the United States (one poor[2] and one fair quality[3]) similarly reported improved retention with initiation of MAT in soon-to-be-released incarcerated populations. One was a small 6-month study (n=15) that randomized inmates to be offered the first monthly dose of XR injectable naltrexone prior to being released from prison compared with TAU and found that the intervention group had higher retention by multiple measures (mean number of injections received 2.8 (standard deviation (SD)=1.9) vs. 1.3 (SD=1.9; 22% (2/9)) received all 6 monthly injections vs. 0% (0/6); and 46% vs. 22% treatment appointments attended, p-values not reported (NR)).[2] The second study was a 2x2 factorial design (n=213) that assessed the effect of prerelease buprenorphine treatment compared with an office-based buprenorphine or traditional outpatient treatment program and found that the prerelease buprenorphine group had higher mean number of days retained in treatment at 12 months (65.9 days (standard error (SE) 12.2) vs. 21.8 (SE 7.6), p=0.005).[3] Together, these studies suggest that initiating MAT prior to release from incarceration improves retention.

Care Setting: Integration of MAT With Psychiatric and Primary Care Services

Three fair-quality RCTs provide conflicting evidence on the effectiveness of integrating psychiatric or PC interventions on MAT retention.[4-6] All were small studies (n range = 94–316): two of three involved integrating psychiatric care with substance use treatment (one methadone and one buprenorphine) and were conducted in the United States, and one was a study from France that integrated methadone treatment with PC. The largest study is a U.S. study offering psychiatric services on site at a traditional methadone treatment program compared with separate nonintegrated psychiatric and substance use care. While initiation and total days of psychiatric care were improved for onsite integrated services, there was no statistically significant difference in MAT retention at 12 months (n=316, 41% vs. 41%, p=0.96).[4]

The second study integrating psychiatric care (n=94) was a fair-quality three-arm U.S. trial that offered buprenorphine treatment in psychiatric clinics, a manually matrixed psychosocial model with cognitive behavioral therapy (CBT) in private clinics, and a specialized opioid treatment program. This study reported a significant association between treatment site and retention at 20 weeks (p=0.05), with 33.3 percent retained in the psychiatric setting, 51.5 percent retained in the psychosocial model, and 21.4 percent retained in the specialized outpatient treatment (retention).[6] The one study in which treatment was integrated into PC was a noninferiority trial conducted across 10 sites in France (n=195) that compared methadone treatment integrated with PC with specialized outpatient methadone treatment programs and found no statistically significant differences at 12 months (88% retention in PC vs. 69% in urgent care, p=0.13).[5]

Care Setting: MAT in ED/Hospital Settings

We identified two RCTs of fair quality that examined retention after introducing MAT in ED or hospital settings.[7, 8] One study enrolled patients at a U.S. safety-net hospital (n=139) to initiation of buprenorphine with linkage to outpatient treatment within 7 days of discharge compared with TAU (medically supervised withdrawal and community referral to treatment). Patients in the hospital-initiated group reported a 2.4 times higher rate of buprenorphine or

methadone use over 6 months (incidence rate ratio (IRR), 2.44, 95% confidence interval [CI], 1.99 to 3.36). At 6-month followup, 12 (16.7%) patients randomized to linkage compared with two (3.0%) to TAU had continued on MAT (p=0.007).[7] The second study was a followup study conducted in the United States of a 3-arm RCT (n=290) of adults with OUD randomized to either 1) ED-initiated buprenorphine with linkage to PC within 72 hours, 2) referral to treatment (TAU), or 3) brief intervention in ED, and assessed retention at 6 and 12 months, defined by self-reported engagement in formal addiction treatment, and found no differences in retention at 6 (53% vs. 60% vs. 51%, p=0.546) or 12 months (49% vs. 49% vs. 63%, p=0.136).[8]

Logistical Support

As a whole, studies of logistical interventions enrolled patients with higher addiction severity and did not show improved MAT retention compared with a standard treatment setting. We identified one good- and three fair-quality RCTs (total n=709) that tested changes in MAT prescribing procedures, such as lessened MAT participation requirements ("low-threshold") or expedited initiation onto MAT treatment ("Script in a Day"), or the provision of housing with social/medical supports, compared with TAU.[9-12] A U.S. trial of a low-threshold, patient-centered methadone intervention (optional counseling, modified clinic rules, no discharge for administrative violations) compared with TAU found no differences in retention at 12 months (n=300, 48.6% vs. 46.3%, p=NR).[9] Similarly, another trial that involved low-threshold initiation intervention that only required once monthly counseling found no statistically significant differences in retention at 90 (n=212, 35% vs. 31%, p=not significant (NS)) and 180 days (37% vs. 29%, p=NS).[11] An innovative intervention offering immediate access to methadone from a U.K. syringe exchange followed by transfer to office-based methadone compared with TAU similarly found no differences in retention at 3 months (n=100, 51% vs. 47%, p=NR). Finally, a trial of a Housing First intervention in which participants in Canada experiencing homelessness were assigned to one of three housing with health/social services groups compared with TAU (referral to housing assistance programs and outpatient specialty treatment), assessed retention using medication possession ratio (MPR) over 2 years and found no differences between groups (n=97, MPR 0.52 vs. 0.57, p=0.60).[12] (See Appendix B Table 1.)

Key Question 2: Harms of MAT Retention Strategies

Most studies of MAT retention strategies did not evaluate possible harms. Only 4 of the 10 trials of care settings/services/logistical support reported serious harms or adverse events—of these, two did not specify in which arm the events occurred. A trial of a patient-centered methadone intervention reported 67 non–study-related hospitalizations and two non–study-related deaths, one from methadone overdose, out of 149 intervention participants. This compares with 59 hospitalizations, 4 non–study-related deaths, and 2 overdoses out of 151 TAU participants.[9] In the study of prerelease MAT with XR-naltrexone, six patients in the prerelease MAT arm reported adverse events (two serious, not specified) compared with two (none serious) in the control arm.[2]

Key Question 3: Participant Characteristics Associated With MAT Retention

The majority of studies did not examine particular population characteristics to explain variation in responses to care settings/services/logistical support. As noted above, patients with OUD in criminal justice populations may benefit from prerelease initiation of MAT. The study

of the prerelease MAT with office-based buprenorphine in a PC setting found no gender differences in retention outcomes.[3]

Contingency Management

Table 3 provides a summary of findings across CM interventions, and Appendix B Table 2 and Appendix C Table 2 provide details for included studies.

Table 3. Summary of findings for contingency management

MAT Medication Type	Studies, Quality n	Results
Opioid receptor antagonist MAT	2 RCTs, injectable naltrexone (fair quality)[13, 14] n=73 1 RCT, naltrexone (fair quality)[15] n=67	Higher retention
Opioid receptor agonist/partial agonist MAT	1 SR, 14 CM studies with methadone, buprenorphine, or LAAM[16] n=1616 3 RCTs, methadone (1 good, 2 fair quality)[11, 17, 18] n=562 1 RCT, methadone or buprenorphine (fair quality)[19] n=136	No difference

CM=contingency management; LAAM=levo-alpha acetyl methadol; MAT=medications for addiction treatment; RCT=randomized controlled trial; SR=systematic review

Contingency management interventions involve providing a reward contingent upon the achievement of specified criteria. While CM is sometimes used in conjunction with other psychosocial interventions, we analyzed it separately, similar to the approach used in a prior SR on psychosocial interventions[16].

One good-quality SR,[16] and seven RCTs (one with a followup study)[11, 13-15, 17-19] of CM interventions assessed retention outcomes among nonpregnant adults who received MAT for OUD.[59] Contingency management improved retention on antagonist MAT, but not for opioid agonist MAT (Table 3). Appendix B Table 2 provides study details. Sample sizes per study for the seven identified RCTs ranged from 35 to 252 participants and we rated one study as good quality,[18] and seven fair quality.[11, 13-15, 17, 19, 59] Most were downgraded due to lack of evidence of allocation concealment, lack of similarity of groups at baseline, and lack of blinding.

Key Question 1: Effectiveness and Comparative Effectiveness of MAT Retention Strategies

A 2011 SR of 35 studies (n=4319) that included heterogeneous CM interventions that rewarded opioid abstinence in individuals receiving agonist/partial agonist MAT (methadone, buprenorphine, or levo-alpha acetyl methadol [LAAM]) found no statistically significant difference in retention compared with agonist/partial agonist therapy (methadone, buprenorphine, or LAAM) alone (14 trials, n=1616, risk ratio (RR) 1.02[0.96,1.08]).[16] The evidence included in the SR was assessed with Grading of Recommendations Assessment, Development and Evaluation (GRADE) as being high strength of evidence.

Four of the seven additional trials (of fair to good quality) that we identified also used agonist/partial agonist MAT (methadone or buprenorphine) and confirmed findings of the

SR.[11, 17-19] The remainder, three fair-quality studies, reported improved retention in MAT.[13-15] These three studies were conducted at the same site, but with separate populations. They used antagonist therapy (naltrexone), had similar criteria for accessing the reward (participants were required to take naltrexone that was provided free of charge and in close proximity to access to the reward), and provided a similar type of reward (access to a therapeutic workplace where participants earned vouchers to exchange for preferred goods and services). The studies differed in the type of naltrexone formulation administered (two using monthly XR-naltrexone and one using daily naltrexone). Regardless of formulation, retention outcomes were greater in contingency participants compared with participants who were permitted access to the workplace without contingency: injectable, XR-naltrexone (two studies, n=35, 66% vs. 35% received all scheduled injections, p=0.026[13]; n=38, 74% vs. 26% received all scheduled injections, p=0.004);[14] and daily naltrexone (n=67, 54% vs. 16% retention at end of study, p<0.01).[15] In an additional followup study, the group differences in retention were no longer observed 6 months after the intervention ended (n=67, p=0.66).[59]

Key Question 2: Harms of MAT Retention Strategies

The SR[16] sought data on adverse events but did not report any, and only one of the eight RCTs reported harms. The 1 RCT that reported harms used daily naltrexone and reported adverse events in 8 out of 67 participants, 6 of whom were in the contingency group.[15] The adverse events included one lethal opioid overdose in a contingency group participant that occurred a month after study conclusion. Other adverse events included sexual dysfunction, abdominal problems, headache, sleep problems, opioid withdrawal, nausea, chills, rapid heart rate, and shakiness.

Key Question 3: Participant Characteristics Associated With MAT Retention

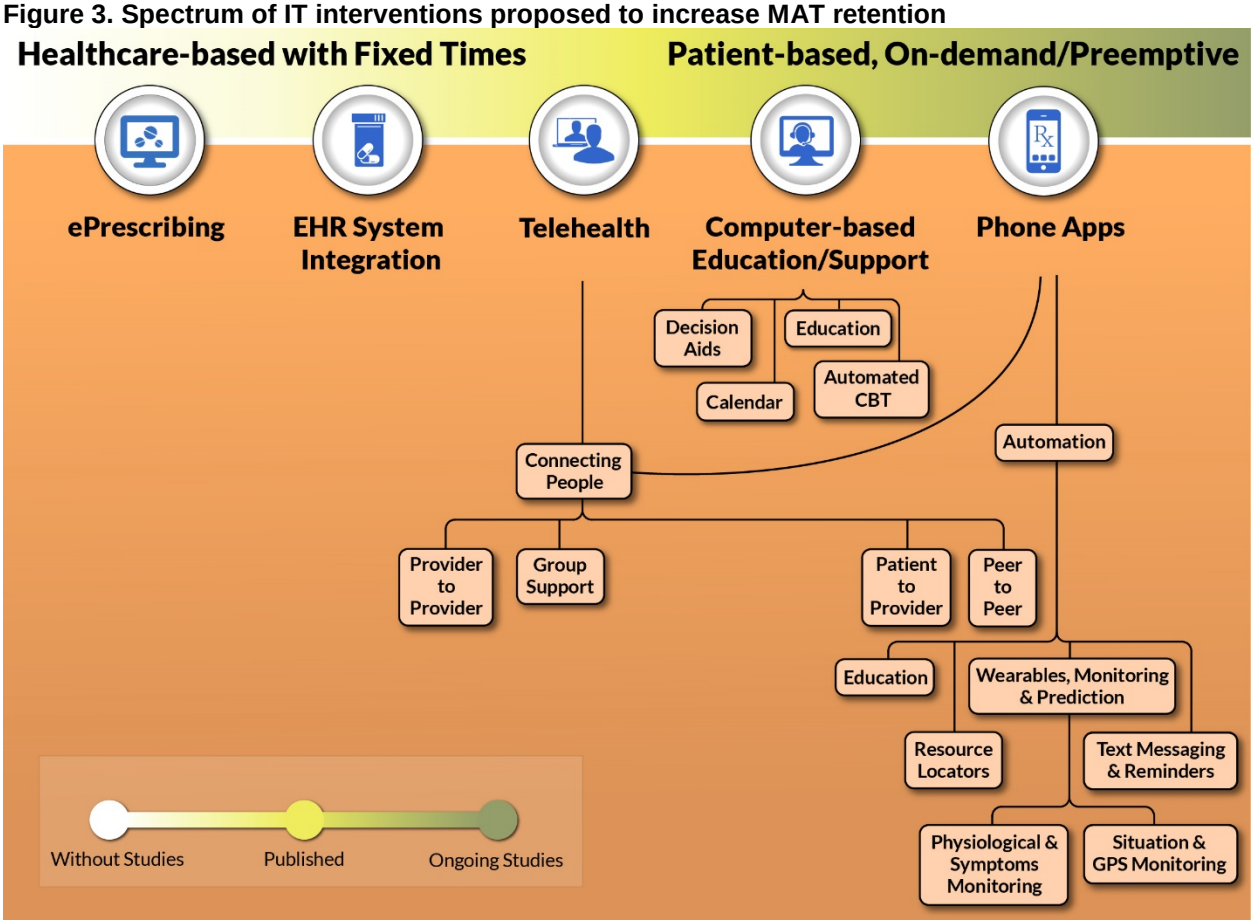
The identified studies did not assess differential effectiveness of CM on retention by defined participant characteristics (e.g., gender/sex, socioeconomic status, etc.).

Health Information Technology

We adopted the Office of the National Coordinator for Health IT Playbook definition and categorization of health IT that defines the scope of IT to include electronic medical record interventions such as prescription drug monitoring, phone apps, e-prescribing, telehealth/teleconsult, and computerized decision aids.[56] Figure 3 presents an overarching framework, adapted from the Health IT Playbook, for the ways in which health IT interventions are proposed to increase retention in MAT.

Seven unique completed studies (three fair-quality RCTs, one poor-quality RCT, and three fair-quality cohort studies),[20-26, 60] met the inclusion criteria for health IT interventions, including an active control involving in-person MAT as a comparator, and MAT retention as an outcome. Table 4 provides a summary of findings across health IT interventions and Appendix B Table 3 provides details for included studies.

Figure 3. Spectrum of IT interventions proposed to increase MAT retention



Apps=applications; CBT=cognitive behavioral therapy; EHR=electronic health record; GPS=global positioning system
This figure adapted from the Office of the National Coordinator for Health IT Playbook definition and categorization of health IT.[56]

Table 4. Summary of findings for health IT

Intervention	Studies, Quality n	Results
Telehealth	0 RCTs; 3 fair-quality cohort studies[20-22] n=3965	Telehealth no worse than in-person (higher retention in largest study and no difference in two smaller)
Computer-based education and/or support	2 fair-[23, 24] and 1 poor-quality RCT[25] n=262	No difference
Multicomponent mobile and computer-based program	1 fair-quality RCT[26] n=1426	No difference
Phone apps	None	6 commercially available apps identified

IT= information technology; RCT= randomized controlled trial

Key Question 1: Effectiveness and Comparative Effectiveness of MAT Retention Strategies

Four RCTs (three fair quality[24-26] and one poor[23]) and three fair-quality retrospective cohort studies[20-22] assessed IT interventions for MAT retention. No RCT found IT intervention to be less effective than in-person approaches.

The largest RCT (five times the size of the others combined) of fair quality (n=1426) is an industry-sponsored study where patients new to buprenorphine treatment were randomized to receive in-person buprenorphine MAT (TAU) or buprenorphine MAT plus a Here-To-Help (HTH) IT intervention consisting of calls from care coaches and access to online educational materials, treatment calendars, and self-reported information from previous participants.[26, 60] At 12 months, ITT analysis indicated no significant difference between groups (55.0% HTH vs. 56.1% TAU, p-value=NR). Planned post-hoc analysis revealed that people who completed a greater number of intervention calls with coaches had a greater probability of retention in MAT (adjusted logistic regression Exp (β)=1.01, p<0.001) and 64 percent of participants in the HTH program who completed at least three HTH sessions remained in buprenorphine MAT compared with 56 percent in TAU (p<0.025).[26]

Health IT is relatively new to healthcare and not part of the provision of MAT in the United States, so it is not known, if offered, the degree to which people would use it. While OUD treatment differs widely from the United States, a large retrospective Canadian study (n=3733) suggests that up to half of patients might choose health IT as part of their treatment if offered, without worsened retention.[20]

Key Question 2: Harms of MAT Retention Strategies

As a whole, harms were not well reported across health IT studies, with the majority not mentioning whether they assessed potential harms. One RCT reported that 12 adverse events occurred in a study of 82 participants (15% overall; 17% in intervention group and 12% in TAU), but no details were provided about the nature of the events.[23]

A small feasibility study that did not report on retention and therefore was not included in our review provides helpful detail on some challenges and harms that may be unique to IT.[61] These issues included difficulties with computers or internet problems, lack of study staff training in technical support with patient connectivity, difficulties with compatibility with organizational security systems, patient privacy, and loss of clinical care time due to IT issues.

Key Question 3: Participant Characteristics Associated With MAT Retention

There is inconclusive information to determine which patients are most likely to benefit from IT and which types of IT might be most appropriate for specific patients (e.g., patient-provider communication, treatment, and/or counseling, educational support, reminders, monitoring). The large retrospective cohort study from Ontario, Canada, found a significant association between sex, clinic region (northern vs. southern), age, and peak methadone dose but not for clinic rurality.[20] Patients who chose treatment delivery via predominantly telemedicine (greater than 75% of appointments) came from both urban (77%) and rural (23%) populations. Findings from a secondary analysis of an RCT that replaced the second half-hour of every in-person counseling session with an IT Therapeutic Educational System found that including a Therapeutic Educational System as part of care was better for patients who were employed, highly anxious, ambivalent about opioid abstinence, and had crack cocaine use in the past 30 days.[62]

Commercially Available Mobile Apps

Six apps were identified via the Google Play and Apple store (Opioid Addiction Recovery Support, Pear Re-SETO, Thrivee, A-CHESS, COR-12, FlexDek: MATList). There were no published studies about these apps with regard to OUD treatment. All apps have some educational component. Five of six apps contain some feature that allow patients to connect with peers, either through interaction in forums, virtual group therapy, or direct contact, and allow users to track their progress through treatment. At least two apps (A-CHESS and FlexDek MAT) provide patients with resources to identify local Narcotics Anonymous meetings, either through direct Global Positioning System (GPS) locating or by acting as a repository for schedules. We only identified evidence for the A-CHESS app, which was initially developed for alcohol use disorder, but an ongoing RCT is evaluating A-CHESS for OUD.

Extended-Release Medication-Based Treatment for OUD

Extended-release is a long-acting form of MAT delivered as either injectable or implant-based formulations. The only three XR formulations currently approved by the U.S. FDA for the treatment of OUD are a 1-month buprenorphine injection, a 6-month buprenorphine implant, and a 1-month naltrexone injection.

We identified a total of five fair-to-good–quality RCTs[27-31] comparing XR formulations (naltrexone injection, buprenorphine injection, and buprenorphine implant) head-to-head against daily MAT formulations (naltrexone, buprenorphine/naloxone, and buprenorphine). Most were downgraded for unblinded treatment or outcome assessment.

Table 5a provides a summary of treatment retention findings for XR and daily formulations for the same drug, while Table 5b summarizes retention findings for XR and daily formulations for drugs across different agonist/antagonist categories and formulations (see Appendix B Table 4 and Appendix C Table 4 for details).

Table 5a. Summary for extended-release versus daily MAT formulations within the same agonist/antagonist drug categories

Comparison	Studies	Results for Extended-Release	Study Setting
Naltrexone Extended-Release 1-Month Injection vs. Daily Naltrexone	1 study[27], fair quality n=60	Higher retention (57.1% vs. 28.1%, hazard ratio=2.18, 95% CI=1.07, 4.43, at 6 months of treatment)	Inpatient followed by outpatient specialty treatment center medicine setting
Buprenorphine Extended-Release 1-Month Injection vs. Daily SL-Buprenorphine/Naloxone	1 study[28], fair quality n=428	Similar retention (56.8% vs. 58.1%, p-value NR, at 24 weeks)	Outpatient specialty treatment center
Buprenorphine Extended-Release 6-Month Implant vs. Daily SL-Buprenorphine	1 study[29], good quality n=177	Similar retention (93.1% vs. 93.3%, p-value NR, at 6 months)	Outpatient specialty treatment center

CI=confidence interval; MAT=medications for addiction treatment; NR=not reported; SL=sublingual

Table 5b. Summary for extended-release versus daily MAT formulations across different agonist/antagonist categories

Comparison	Studies	Results for Extended-Release	Study Setting
Naltrexone Extended-Release 1-month Injection vs. Daily SL-Buprenorphine/Naloxone	2 studies[30, 31], 1 fair, 1 good quality n=729 (570, 159)	Inconclusive (n=570, 33.9% vs. 40.0%, p-value NR, at 24 weeks) (n=159, mean (SD) time 69.3 (25.9) vs. 63.7 (29.9) days, p-value NR, at 3-months)	Inpatient followed by outpatient specialty treatment center medicine setting (larger study); Outpatient specialty treatment center (small study)

MAT=medications for addiction treatment; NR=not reported; SL=sublingual

Key Question 1: Effectiveness and Comparative Effectiveness of MAT Retention Strategies

One fair-quality study (n=60)[27] compared XR-naltrexone monthly injection with daily naltrexone. Retention was defined as documented clinical contact at 6 months and favored the XR-naltrexone group (57.1% vs. 28.1%, hazard ratio (HR)=2.18, 95% CI=1.07, 4.43).

Two studies compared XR and daily buprenorphine formulations, though neither assessed retention as a primary outcome.[28, 29] One was a good-quality multisite trial (n=177) that randomized participants who were stable on a low dose of daily buprenorphine prior to enrollment to a buprenorphine 6-month implant versus daily sublingual (SL)-buprenorphine and found no difference in rates of treatment retention at 6 months (93.1% vs. 94.3%, p-value NR).[29] The other was a larger fair-quality trial (n=428) of a weekly, followed by monthly, buprenorphine injection compared with daily SL-buprenorphine/naloxone that enrolled treatment-seeking participants and found no difference in retention at 24 weeks (56.8% vs. 58.1%, p-value NR).[28]

Two studies comparing XR-naltrexone injection versus daily SL-buprenorphine/naloxone had inconsistent results.[30, 31] One was a good-quality study conducted in Norway (n=159) that recruited patients from outpatient and inpatient settings.[31] Treatment retention was defined as mean days until dropout from the study medication and did not differ between the two groups (mean (SD) days 69.3 (25.9) XR-naltrexone vs. 63.7 (29.9) days SL-buprenorphine/naloxone, p-value NR) The other was a fair-quality U.S. study that recruited 570 patients from community outpatient treatment programs.[30] Retention was defined as percentage of patients receiving MAT at 3 months and was lower with XR-naltrexone compared with SL-buprenorphine/naloxone using ITT analysis (33.9% vs. 40.0%, p-value NR).

Our synthesis identified study design issues that may have impacted the retention results, particularly for XR-naltrexone formulations. The study that found that XR-naltrexone injection improved retention compared with SL-buprenorphine/naloxone randomized only those participants who successfully completed medically supervised opioid withdrawal. In contrast, the other study that found lower retention with XR-naltrexone randomized patients prior to their completion of supervised withdrawal and had high rates of treatment induction failure (72% vs. 94%, p<.0001) in the XR-naltrexone compared with the SL-buprenorphine/naloxone group; this could explain the lower retention rates reported. Restrictive study inclusion criteria that exclude participants with alcohol dependence or polysubstance use[28, 31] are also likely to affect generalizability of the results.

Key Question 2: Harms of MAT Retention Strategies

Studies of XR formulations reported a variety of adverse events, ranging from serious fatal and nonfatal adverse events to adverse events presumed secondary to treatment medication. All studies reported nonserious adverse events at XR-naltrexone and XR-buprenorphine injection sites.

Sullivan et al. 2019 (n=60) reported one severe adverse drug-related event when one of 28 participants developed hives after receiving XR-naltrexone injection and was removed from the study.[27] Lee et al. 2018 (n=570) reported a total of 28 overdose events among 23 participants.[30] While these overdose events were not categorized as drug related, 18 (64%) of the 28 events were among participants randomized to XR-naltrexone, and included eight participants who had failed treatment induction and never received an injection. Five overdose events were fatal and included two participants in the XR-naltrexone arm and three in the SL-buprenorphine/naloxone arm.

Key Question 3: Participant Characteristics Associated With MAT Retention

There is limited information to determine which patients are most likely to benefit from XR formulations. None of the studies we reviewed noted differences in participant characteristics that predicted retention for XR formulations.

Psychosocial Support

We used a prior review[16] to define psychosocial support interventions, which include psychiatric care, psychotherapy, counseling, and social work services that provide psychological support ranging from structured psychotherapies such as CBT and supportive expressive therapy to behavioral interventions. We analyzed CM interventions separately above.

One good-quality SR[16] and nine additional RCTs[32-40] (sample size range=49–653) examining psychosocial supports for MAT met inclusion criteria; an additional two studies included IT interventions and are reviewed in that section.[24, 26] We rated two studies as good quality[39, 40]; four as fair[35-38], and three as poor.[32-34]

Most were downgraded due to unblinded outcome assessment. Table 6 provides a summary of findings and Appendix B Table 5 provides study details. Quality ratings for individual studies are reported in Appendix C Table 5.

Table 6. Summary of findings for psychosocial interventions

Psychosocial Intervention	Studies, Quality n	Results
Psychosocial interventions: • behavioral (e.g., CBT) • psychoanalytic (e.g., short-term interpersonal therapy) • counseling (e.g., intensive outpatient counseling) • other (e.g., 12-step facilitation therapy)	1 SR of 27 studies, n=3124[16] (SR rated evidence as high quality using GRADE) 9 RCTs, n=2483 (3 poor,[32-34] 4 fair,[35-38] 2 good quality[39, 40])	No difference in retention between psychosocial intervention and control groups (SR and RCTs) in all but one poor quality study Many of the studies reviewed included some form of counseling in the control groups, which may explain the lack of demonstrated effectiveness.

CBT=cognitive behavioral therapy; GRADE=Grading of Recommendations Assessment, Development and Evaluation; RCT=randomized controlled trial; SR=systematic review

Key Question 1: Effectiveness and Comparative Effectiveness of MAT Retention Strategies

An SR with meta-analysis found that adding structured psychosocial interventions to MAT did not improve retention compared with standard MAT (27 studies, n=3124, RR 1.03, 95% CI 0.98 to 1.07).[16] The SR assessed the strength of the body of evidence with GRADE and rated it as high quality. Of the nine additional RCTs, eight reported no statistically significant effect of psychosocial interventions.[33-40] However, many of the studies reviewed included some form of counseling in the control groups, which may explain the lack of effect. One poor-quality study reported significantly higher buprenorphine MAT retention in the intervention group, which included a Community Reinforcement Approach (CRA) component that makes use of an individual's social networks to encourage adherence to the program compared with CM alone (n=170, 80% CRA vs. 64% CM-alone; odds ratio (OR) 2.3, 95%CI 1.15-4.60).[32]

Key Question 2: Harms of MAT Retention Strategies

The one study in which there was a statistically significant benefit of psychosocial intervention did not report any significant harms.[32] Another study (n=300) reported significant potential harm from psychosocial intervention.[34] In this study, when controlling for number of days in treatment, more exposure to counseling was significantly associated with increased frequency of heroin use, cocaine use, and criminal activity (all $p<0.01$). The authors suspected that this association was due to confounding by indication as clinicians tended to insist on participation in additional services for patients who were not progressing. This same study also reported higher self-reported burden on participants and found the intervention group reported increased burden compared with the control ($p<0.05$). Looking across studies, we found differences in time commitment between intervention and control conditions in six studies that may have affected intervention fidelity, attrition rates, and retention outcomes due to increased treatment burden.[32, 34, 37-40]

Another study (n=542) of pharmacist-delivered motivational interviewing versus normal practice for methadone patients found that self-reported physical health was statistically poorer for the intervention group; they theorized these results were due to increased awareness of health due to increased conversations between participant and pharmacist in the treatment group.[33] Other studies reported adverse events and non–overdose-related deaths that the study authors judged to be unrelated to the interventions studied.[35, 38]

Key Question 3: Participant Characteristics Associated With MAT Retention

Few included studies provided information about which patients, if any, are most likely to benefit from psychosocial interventions. A study (n=125) of XR-naltrexone coupled with a Behavioral Naltrexone Therapy (BNT) intervention compared with XR-naltrexone coupled with Compliance Enhancement reported a significant interaction ($p=0.03$) between condition and severity of OUD.[36] For low-severity patients (less than six bags of heroin per day), retention was highest in the BNT group (60% at 6 months). BNT adapted elements of CRA in encouraging positive social reinforcement.

Financial Support

We defined financial support as individual and system-level interventions to lower financial barriers to MAT, ranging from financial subsidies to assist enrollment in MAT programs to

expanding MAT coverage by Medicaid and private health plans. We did not identify any SRs or RCTs of financial interventions to improve retention in MAT; expanded searches of observational studies also did not yield relevant studies.

Discussion

Although MAT improves short- and long-term outcomes for people with OUD and reduces mortality, various reports estimate that fewer than half are retained in MAT treatment at followup.[48] Overall, we found few studies evaluating interventions to improve retention in MAT and many did not assess retention longer than 3 months. Studies also varied in experimental design, measures of retention, and intervention types, making across-study comparisons difficult. The majority of the studies were downgraded in quality due to a lack of blinding of outcome assessors and high study attrition rates.

Care Settings/Services/Logistical Support

Our findings suggest that interventions that introduce MAT to soon-to-be-released incarcerated patients are an effective way to improve retention in this high-risk population. Given the high proportion of OUD in criminal justice populations and the exponential increase in overdose risk within the first few weeks of reentry into the community,[63, 64] interventions in this setting have potential to be high impact.

We also found that interventions integrating MAT into hospital and emergency settings prior to discharge were no worse for retention at 3 months than when MAT is delivered in traditional settings, though only two studies were included in our review suggesting additional studies may change conclusions.

Providing healthcare and social services alongside MAT makes intuitive sense to improve convenience and provide patient-centered care, and improve retention, particularly in areas where there are few specialty treatment programs. However, studies supporting MAT delivery in nontraditional settings were small, heterogeneous, or were conducted in non-U.S. settings that have different treatment regulations, so applicability to the United States is uncertain.[65] Multiple well-designed studies are underway, including the Helping to End Addiction Long-term℠ (HEAL) Initiative that will test a variety of interventions in multiple settings across the States. Study measures will include assessment of retention at 6 months to provide much-needed evidence in this area.[66]

Contingency Management

Our review found that CM interventions may improve retention for patients taking antagonist MAT, but not agonist MAT. A prior SR similarly did not identify benefit of these interventions with agonist and partial agonist MAT (methadone and buprenorphine).[16] Our review included studies that used antagonist (naltrexone) MAT.

The type of MAT may be important in CM intervention effectiveness. Introduction of an outside reward may be of limited value in agonist and partial-agonist MAT, in which the medication provides some self-reinforcing effects (i.e., relief from withdrawal symptoms), compared with antagonist MAT, in which the medication does not provide any desired drug effects that may promote continued MAT use.[68] This could partially explain the positive effects on retention in all studies with a CM intervention for naltrexone treatment, and the noneffect on retention in studies that employed methadone or buprenorphine MAT.

Additionally, features of the CM intervention used in the studies that demonstrated an effect on retention may have contributed to the effectiveness of the intervention, including the type of response required to meet the contingency and the salience of the reward.[69] In the studies that reported improved retention, the behavior rewarded was adherence to prescribed MAT medication dosages, whereas, in the studies without effects, the behavior that was rewarded was primarily drug use abstinence. Further, the reward, access to a workplace where participants could gain work skills and earn vouchers to exchange for goods and services, was provided in close proximity to the location of the reward and free of charge, which may have limited some of the barriers to meeting the contingency criteria. Future studies might optimize effectiveness of CM interventions by maximizing the value of the reward to the participant (i.e., individualizing rewards) and optimizing the response required by the participant to meet the contingency (i.e., minimizing MAT costs and transportation effort).

Despite the demonstrated benefit of access to a workplace contingent upon taking naltrexone, these studies were small and were all conducted at one study site (in Baltimore, Maryland), raising concern for applicability to other settings. Further, such interventions may be difficult to implement in real-world settings due to cost, concerns that they may interfere with intrinsic motivation, and durability of effect.[67]

Health IT

We found very few published studies of IT interventions and no published evaluations of commercially available apps to improve MAT retention. Overall, studies reported no worse retention rates with IT approaches than with in-person approaches. Recognizing that there are few addiction specialists and counselors and that most are concentrated in urban areas, IT is promising for those with access to computers/internet, but questions remain on how to implement these programs at scale. The NIH NIDA Clinical Trials Network (CTN) study "Rural Expansion of Medication Treatment for Opioid Use Disorder" (CTN-102 Rural MOUD) plans to conduct an RCT evaluating the comparative effectiveness between office-based opioid treatment (OBOT) alone and OBOT plus telemedicine in highly impacted rural areas. The primary outcome is number of patient-days of buprenorphine treatment retention in the year following intervention implementation.[70]

Ongoing research is beginning to examine wearables and GPS monitoring capabilities to provide patients with increasing self-management and predictive analytics that can anticipate problems and offer real-time strategies and resources to avoid return to use. The AHRQ-funded project "Increasing Access to Medication-Assisted Treatment of Opioid Abuse in Rural Primary Care Practices" (https://integrationacademy.ahrq.gov/about/opioids-substance-use/primary-care-medication-assisted-treatment-grantees) leverages smartphone apps, virtual training, telementoring, and consultations through Project Extensions for Community Healthcare Outcomes (Project ECHO) to support rural PC practices in five States in delivering MAT. The project started in 2016 and should have helpful data in the next few years.

It is concerning that commercially available apps do not have published evaluations. Because IT interventions have undergone few trials and many of those are pilots, future research should focus on studies with long-term outcomes (beyond 3 months), with sample sizes adequate to demonstrate true equivalence, and with blinded outcome assessors. Such studies should consider potential harms as well as benefits and process issues (e.g., connectivity or software compatibility) for patients, clinicians, and clinical settings.

Extended-Release Medication-Based Treatment for OUD

XR formulations are conceptually attractive to increase MAT retention because they do not require daily administration. One of the two XR medications available in the United States, XR-naltrexone, is a mu opioid receptor antagonist that provides long-lasting blockade of opioid receptors. The other, XR-buprenorphine, is an opioid receptor partial agonist that reduces withdrawal symptoms without decreased opioid tolerance. Unlike naltrexone, buprenorphine does not require a period of complete abstinence from opioids to initiate treatment and is used to manage acute opioid withdrawal and as long-term treatment of OUD.

Similar to a prior review,[55] we found inconsistent results for treatment retention with XR-naltrexone injection vs. daily MAT formulations. Our review also included recent studies that compared XR and daily buprenorphine that showed no statistically significant differences in retention between the two formulations.[30, 31]

The lack of studies comparing XR formulations head-to-head highlights the need for future comparative effectiveness trials that may change conclusions. We also identified study design issues related to patient selection, timing of randomization relative to completion of supervised withdrawal, and medically supervised withdrawal procedures that affected the study findings' applicability and generalizability. Additional studies of XR-buprenorphine in real-world settings could be useful to address limitations of XR-naltrexone and other antagonist therapies that require a period of complete abstinence from opioids for treatment initiation. Future studies should also use treatment-based controls.

Few studies in our review examined how participant characteristics affected retention, though there was evidence that those with lower opioid use severity or comorbid alcohol use were more likely to complete medically supervised opioid withdrawal and thus may benefit more from XR-naltrexone formulations.[30] XR formulations could be particularly effective in some patient populations such as those at high risk of unforeseen treatment disruptions (such as homelessness or incarceration), those at risk for medication diversion and misuse, populations at risk for access disruptions or who live in remote areas, and those concerned about the stigma or inconvenience of daily maintenance therapy. Several ongoing trials may add to this evidence. For example, the NIH NIDA CTN "Retention-Duration-Discontinuation" trial (CTN-100 RDD Study) is currently in progress.[71] This multisite, multi-arm trial enrolls 1,800 participants with OUD across 20 large outpatient OUD treatment clinics nationwide, provides the participants with a choice of buprenorphine or XR-naltrexone, and follows participants for 2 years, with MAT retention at 6 months as the primary retention outcome.[72] It will assess the optimal duration and discontinuation of MAT. The results of these trials should help demonstrate whether long-acting formulations can improve retention outcomes.

Psychosocial Support

Our review of psychosocial support interventions (not including CM) largely aligns with the prior SR that found no effect on retention.[16] The lack of observed differences between the experimental and control groups may be explained by the inclusion of psychosocial support in the control groups. Of note, eight of nine studies reviewed had control groups that received elements of psychosocial support through counseling,[32, 34-36] 12-step programs,[40] self-help groups,[37, 39] or CM,[38] and one study did not sufficiently describe their control.[33] Further, researchers could employ attention control groups (e.g., controls that receive an intervention that

mimics the amount of time and attention received by the treatment group but is not thought to exert effect) to reduce bias that may arise from participant awareness of assignment.

Financial Support

We did not find studies of financial interventions to improve MAT retention that met our inclusion criteria, suggesting an area for future study. We identified, however, studies of financial interventions that measured other outcomes that may give suggestions for future studies. A mixed-methods study involving stakeholder and focus group interviews examining the impact of out-of-pocket pharmacy costs on medication adherence identified out-of-pocket pharmacy costs for MAT as a barrier for continued treatment retention;[73] another observational study evaluating the impact of Medicaid expansion of MAT coverage found reductions in opioid use–related healthcare utilization, but did not measure retention.[74] Similarly, a cohort time-series analysis of a dose-based prior authorization policy for buprenorphine by Massachusetts Medicaid found that the policy implementation led to increased treatment dropout and significant increases in relapse rates among those prescribed higher doses of buprenorphine.[75]

Future Directions

Our review provides opportunities to inform future research. First, there is a need for a standardized definition of MAT retention. While evidence suggests that retention in MAT may be key in improving OUD outcomes,[44] MAT retention was the primary outcome in fewer than half of the studies we reviewed. Definitions of retention varied widely, from number of days until dropout from study medication[4-6, 25, 27, 30, 31, 36, 38, 76] to proportion of participants remaining in treatment at 12 months;[8, 9, 22] there was variability in how investigators assessed retention outcomes, and studies often were not clear in how retention was defined, making comparisons difficult.

Ideally, a standardized definition of retention might have specified parameters around 1) duration of participation in MAT, 2) degree of participation (e.g., if discontinuous, to what degree of discontinuity is acceptable), 3) and measurement of retention (e.g., urine screen for presence of MAT medication, patient self-report).

Second, future research would benefit from study designs that improve applicability and generalizability. Future trials should enroll diverse groups of participants that are representative of the heterogeneous population of OUD patients and be conducted in a variety of practice settings to more closely resemble “real-world” conditions. Additionally, future studies should consider patient preferences for either agonist, partial agonist, or antagonist forms of MAT and design trials to allow for patient preference in assigning treatment. Some studies we reviewed were conducted outside of the United States, where policies and practices differ, limiting generalizability.

In addition to improving generalizability, future studies would benefit from improved internal validity. While blinding of investigators and providers delivering MAT is generally not practical for most interventions, other methodological approaches such as blinding outcome assessors are almost always possible and should be performed. Large-scale ongoing implementation studies, such as the CTN-100 RDD study[70] that allows for patient preference and compares multiple retention strategies across a diverse array of real-world treatment settings, hold promise to inform clinical practice and public health policy.

Limitations of the Review

Our review has several limitations. We were not able to review every intervention proposed to improve retention in MAT. Instead, we focused the scope of our review based on stakeholder input. We did not include non-RCT study designs, with few exceptions, and excluded RCTs that used placebo or non-MAT comparator groups, which required excluding studies of some interventions. We used a rapid review methodology, which involved searching limited databases, not conducting formal meta-analyses, and including findings from existing published SRs. Consistent with the rapid review standard practice, we used existing SRs to define the categories of interventions to include into our review. We did not conduct a formal assessment of strength-of-evidence assessment (e.g., publication bias assessment, differing tools for quality assessment), as we relied on the existing strength-of-evidence assessments provided within the included SRs.

The interventions we reviewed were broad and diverse, which limited comparisons across studies. Further, we included only those studies that measured retention for at least 3 months. A 3-month requirement was recommended by content experts as the minimum clinically relevant study duration to assess retention. Longer studies are needed to ascertain the sustained effects of various interventions on treatment retention; however. few studies identified in our search continued beyond 3 months. Finally, our review focused predominantly on the outcome of treatment retention. When considering healthcare or policy decisions, it would be important to consider other relevant outcomes, such as mortality and morbidity outcomes, access to treatment, as well as quality of life and other patient-centered outcomes.

Conclusions

In our review of the current evidence, we found few studies that assessed MAT retention as a primary outcome, and less evidence on harms of interventions and patient characteristics associated with differential effectiveness of the interventions. We found that retention in MAT may be improved through several avenues, including use of integrated care settings with criminal justice populations, and use of CM interventions for patients on antagonist MAT. Preliminary studies suggest that alternative means of care delivery (health IT) and integration of medical, psychiatric, and social services with MAT may not worsen retention outcomes. While the few comparative effectiveness studies to date show no difference in retention between XR formulations and SL daily formulations, this evidence is evolving. There are several areas for which future research is needed, given the paucity of controlled studies, including the use of IT interventions, telehealth-delivered MAT, and interventions to reduce the financial barriers to care. Overall, there is a critical need for better quality studies and explicit attention to harms as well as benefits. Because retention is associated with improved outcomes, future OUD research should develop standard measures for retention to be used in reporting results.

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
BNT	Behavioral Naltrexone Therapy
CBT	cognitive behavioral therapy
CI	confidence interval
CM	contingency management
CRA	Community Reinforcement Approach
CTN	Clinical Trials Network
ECHO	Extensions for Community Healthcare Outcomes
ED	emergency department
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
GPS	Global Positioning System
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HEAL	Helping to End Addiction Long-term
HHS	Department of Health and Human Services
HR	hazard ratio
HTH	Here To Help
IRR	incidence rate ratio
IT	information technology
ITT	intention-to-treat
LAAM	levo-alpha acetyl methadol
MAT	medication(s) for addiction treatment
NASEM	National Academies of Sciences, Engineering, and Medicine
MOUD	medication treatment for opioid use disorder
MPR	medication possession ratio
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NR	not reported
NS	not significant
OBOT	office-based opioid treatment
OR	odds ratio
OUD	opioid use disorder
PC	primary care
PICOTS	population, intervention, comparator, outcomes, timing, setting
RCT	randomized controlled trial
RR	risk ratio
SAMHSA	Substance Abuse and Mental Health Services Administration

SD	standard deviationSE standard error
SL	sublingual
SR	systematic review
SUD	substance use disorder
TAU	treatment as usual
TOO	Task Order Officer
WHO	World Health Organization
XR	extended-release

Appendix A. Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2009 to June 16, 2019

#	Searches	Results
1	Opioid-Related Disorders/ or Heroin Dependence/ or Morphine Dependence/ or Opium Dependence/ or Substance-Related Disorders/	112848
2	((carfentanyl or codeine or fentanyl or heroin or hydrocodone or hydromorphone or morphine or opioid or opiate* or opium or oxycodone or substance) adj3 (abuse* or addict* or depend* or disorder* or misuse* or user or users)).ti,ab,kf.	55392
3	or/1-2	132763
4	Opiate Substitution Treatment/ or Buprenorphine/ or Buprenorphine, Naloxone Drug Combination/ or Methadone/ or Naloxone/ or Naltrexone/ or (dt or th or rh or tu).fs.	4399399
5	("alpha-2 agonist*" or "opioid agonist" or "opioid antagonist" or buprenorphine or LAAM or "Levomethadyl acetate" or "medication assisted" or methadone or naloxone or naltrexone or ((opiate* or opioid*) adj5 (maintenance or pharmacotherap* or pharmaco-therap* or substitution or therap* or treat*))).ti,ab,kf.	52155
6	(Belbuca or Buprenex or Butrans or Diskets or Dolophine or Evzio or Lofexidine or Methadose or Narcan or Revia or Suboxone or BUP-XR or CAM2038 or INDV-6200 or Probuphine or RBP-6000 or Sublocade or Vivitrol or depot or "extended release" or implant or long-acting or "slow release" or "sustained release" or XR-NTR).ti,ab,kf.	150777
7	or/4-6	4512344
8	"Treatment Adherence and Compliance"/ or "Patient Acceptance of Health Care"/ or Patient Compliance/ or Medication Adherence/ or No-show Patients/ or Patient Dropouts/ or Recurrence/ or Social Support/ or Treatment Refusal/	367217

#	Searches	Results
9	(attend* or attrition or abstain* or abstinen* or adhere* or non-adhere* or nonadhere* or continu* or discontinu* or dropout* or drop-out* or engag* or longer or "loss to followup" or "lost to followup" or month or months or no-show or recovery or reengag* or re-engag* or relaps* or retain* or retention or shorter or terminat* or year or years or detection or wearable or wearables).ti,ab,kf.	5973579
10	or/8-9	6135642
11	exp telemedicine/ or exp "online systems"/ or exp internet/ or "cell phones"/ or smartphone/ or "text messaging"/ or exp "mobile applications"/	119185
12	(tele* or mobile* or mhealth* or m-health* or ehealth* or e-health* or digital* or online* or Internet* or web or web-based or technology* or app or apps or application* or applet* or SMS or text or text-messag* or cellphone* or cell-phone* or phone* or smartphone* or iphone* or ipad* or android* or email* or virtual* or game or gaming or social media or social network* or Facebook* or "Google Play" or Itunes or Skype* or Twitter* or Snapchat* or Instagram*).ti,ab,kf.	1623971
13	("Addiction CHESS" or "A-CHESS" or "COR-12" or FlexDekor or "Opioid addiction recovery support app" or OARS or "Pear reSET-O").ti,ab,kf.	1355
14	or/11-13	1656439
15	3 and 7 and 10 and 14	1913
18	limit 15 to yr="2009 -Current"	1164

EBM Reviews (Ovid) - Cochrane Database of Systematic Reviews 2009 to June 16, 2019

Date searched: June 16, 2019

Searched by: Robin Paynter, MLIS

#	Searches	Results
1	((carfentanyl or codeine or fentanyl or heroin or hydrocodone or hydromorphone or morphine or opioid or opiate* or opium or oxycodone) adj3 (abuse* or addict* or depend* or disorder* or misuse* or user or users)).ti,ab,kf.	40
2	("alpha-2 agonist*" or "opioid agonist" or "opioid antagonist" or buprenorphine or LAAM or "Levomethadyl acetate" or "medication assisted" or methadone or naloxone or naltrexone or ((opiate* or opioid*) adj5 (maintenance or pharmacotherap* or pharmaco-therap* or substitution or therap* or treat*))).ti,ab,kf.	104
3	(Belbuca or Buprenex or Butrans or Diskets or Dolophine or Evzio or Lofexidine or Methadose or Narcan or Revia or Suboxone or BUP-XR or CAM2038 or INDV-6200 or Probuphine or RBP-6000 or Sublocade or Vivitrol or depot or "extended release" or implant or long-acting or "slow release" or "sustained release" or XR-NTR).ti,ab,kf.	182
4	(((attend* or attrition or client* or clinic* or community* or group or office* or outpatient* or out-patient* or participant* or patient* or "primary care" or prison* or telemedicine or tele-medicine or telerehab* or tele-rehab*) adj15 (abstain* or abstinen* or adhere* or non-adhere* or nonadhere* or continu* or discontinu* or dropout* or drop-out* or engag* or longer or loss or lost or month or months or no-show or recovery or reengag* or re-engag* or relaps* or retain* or retention or shorter or terminat* or (treatment adj2 outcome*) or year or years)) or (access* or homeless* or housing or "social services" or "social support*" or (social adj2 (work or worker or workers)) or transportation)).ti,ab,kf.	2485
5	or/2-3	278
6	1 and 4 and 5	12

NIH RePORTer

Additionally, because both health IT is rapidly expanding and opioids have been a focus of research funding, we also searched NIH RePORTer using advanced search using the terms: medication-assisted treatment” and mobile or telehealth, “Medication-assisted treatment” and opioid and retention, Medication-assisted treatment and opioids and smart phone, "medication-assisted therapy" and opioid and mhealth, “MAT" and opioid and mhealth, “MAT" and opioid and smart phone, and we searched NIH RePORTer Matchmaker using the following terms: opioid, medication-assisted treatment, MAT, medications for addiction treatment, Medication-assisted therapy, opioid, opioids, opioid use disorder, retention, retention, retention, smart phone, smartphone, app, telehealth, Mhealth, mhealth, mobile, IT, retention, retention on June 12,2019.

Google Play Store

A search of the Google Play store on May 18, 2019 searched the key terms “Opioid Use Disorder” “Medication Assisted Treatment” “Methadone” “Buprenorphine” and/or “Suboxone” to identify potential mobile applications (apps) aimed at increasing retention in MAT. To be included, the Google Play store app description needed to mention retention, be specific to OUD and MAT, and include some sort of interactive program (not be strictly informational). Descriptions of apps in the Google Play store were analyzed to determine key features of apps.

Appendix B. Data Tables

Table 1. Published literature on care settings, services, and logistical support

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Pre-release MAT settings	**Hedrich, 2012,[1]** **SR**	27 articles	Methadone, buprenorphine and methadone, buprenorphine-naloxone, levo-alpha acetyl methadol (LAAM)	6 months after release Retention: % participants remaining in MAT	Intervention: MAT in prison vs Control: No MAT in prison	KQ1: More than 50% [range 27-75%] retained in intervention group vs fewer than 5% [range 0-9%] retained in control group KQ2: Not reported KQ3: Not reported	Good
	Friedmann, 2018[2] **RCT** **USA**	15 Pre-release v Post-release n=9 vs 5 Mean Age= 38.9 vs 33.6 Gender: 7% female Race/Ethnicity: 17% non-White Years education: 11.6 vs 11.0 Employed: 14.1 vs 33.3 ASI drug risk: 1.9 vs 1.0	Naltrexone (XR and injection)	6 months Retention: 1. Injections received 2. Percentage who received all 6 monthly injections 3. Treatment appointments attended	Pre-release intervention: Participants received 1 XR-naltrexone injection 1-2 weeks prior to release from prison plus up to 5 monthly injections in community vs Post-release: No pre-release injection. Up to 6 post-release injections in community	KQ1: Mean (SD) number of injections received (p-values not reported): 2.8(1.9) pre-release vs 1.3(1.9) post-release Received all 6 injections: 2/9 (22%) in pre-release group vs 0/6 (0%) in post-release group Treatment appointments attended: 46% pre-release group vs 22% post-release group KQ2: Not reported KQ3: Not reported	Poor

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Pre-release MAT settings	**Gordon, 2017[3]** **2 x 2 factorial design RCT** **USA**	213 Mean Age: 39.08(8.8) years Gender: 29.9% female Race/Ethnicity: 70.1% African American; 25.6% White Prior drug treatment: 81.9% Prior buprenorphine treatment: 15.2% # heroin use days prior to incarceration: 24.45(10.1)	Buprenorphine	12 months Retention: Days in treatment program post-release up to 12 months	2 (Pre-release Treatment Condition: Buprenorphine Treatment Vs. Counseling Only) x 2 (Post-Release Service Setting: OTP vs. CHC) Buprenorphine began either (1) in prison and continue care in an OTP or in (2) an outpatient substance abuse program within a CHC; or to begin buprenorphine after release from prison (3) in an OTP or (4) in the CHC Post-release: titrated dose to 8 mg/day, then 16 mg 3x/week.	KQ1: Mean (SE) number of days retained in treatment: 65.9(12.2) pre-release vs 21.8(7.6) post-release (p=0.005) KQ2: Not reported KQ3: No differences in retention outcomes by gender	Fair

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Integrated MAT into Primary Care	**Brooner, 2013[4]** **RCT** **USA**	316 A vs B: n= 160 vs 156 Mean Age: 40.2(0.71) vs 39.4(0.68) Gender: 62.5% vs 62.2% female Race/Ethnicity: 42.5% vs 40.4% minority race Education: 11.14 vs 10.88 Employed: 12.5% vs 16.7% Cocaine: 31.9% vs 26.3%	Methadone	12 months Retention: 1. % participants remaining in substance abuse treatment at 12 months 2. Treatment days over 12 months	On-site and integrated substance abuse and psychiatric care with methadone vs. Off-site and non-integrated substance abuse and psychiatric care. Traditional specialty methadone outpatient treatment program	KQ1: Completed 12-month substance abuse treatment: 41.3% on-site vs 41.0% off-site (p=0.96) Mean (SE) treatment days: 226.0 (10.8) on-site vs 228.7(10.7) off-site (p=0.89) KQ2: Not reported KQ3: Not reported	Fair
	Carrieri, 2014[5] **RCT** **France**	195 Primary care (PC) vs Specialized care (SC): n=147 vs 48 Mean Age: 32[27-38] vs 30[27-39] Gender: 14% vs 21% female	Methadone	12 months Retention: % participants retained in methadone treatment	Integration of methadone into primary care (PC) vs. Methadone received in specialty clinic setting (SC)	KQ1: Retention: 33/48 (69%) in SC vs 129/147 (88%) in PC were still in treatment. pLog rank=0.13 (per protocol analysis) KQ2: Not reported KQ3: Not reported	Fair

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Integrated MAT into Primary Care	**Miotto, 2012[6]** **RCT** **USA**	94 Opioid-treatment program (OTP) vs psychiatrist's private practice (PCS) vs manualized matrix model (MMM): Mean Age: 34.51(10.47) vs 36.46(9.76) vs 35.24(9.88) Gender: 32.14% vs 48.48% vs 42.42% female Race/Ethnicity: 42.86% vs 57.58% vs 69.70% White Unemployed: 17.86% vs 21.21% vs 27.27%	Buprenorphine	12 months Retention: 1. Weeks retained: Number of weeks between induction and the last day the participant was assessed during treatment period 2. % of group who were present at week 20	PCS: physician provided supportive and educational counseling about drug abuse and recovery; vs Behaviorally oriented psychosocial treatment (MMM) using matrix recovery-relapse prevention model vs Usual care: Outpatient OTP	KQ1: Mean number of weeks retained: 18.52(21.77) PCS vs 24.85(22.09) MMM vs 13.96(14.96) OTP (p=0.11) Present at week 20: 33.3% PCS vs 51.52% MMM vs 21.43% OTP (p=0.05) KQ2: Not reported KQ3: Not reported	Fair

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
MAT in ED/Hospital Settings	**Liebschutz, 2014[7]** **RCT** **USA**	139 Mean Age: 40.5(11.8) Gender: 18.8% female Race/Ethnicity: 43.2% Non-Hispanic White Mean Rate of Opioid Use: 20.8(9.7) days Prior OAT 57(41.0)	Buprenorphine	6 month outcomes from enrollment assessed Retention: 1. Engagement in outpatient buprenorphine treatment at 6 months 2. Opioid agonist treatment (OAT) days - self-reported in the 30 days before 3-, 6-month interviews using standard 30-day timeline follow-back	Linkage group: received 12 mg buprenorphine/naloxone on day 2 and 16 mg on day 3 and remainder of hospitalization. Linked to hospital associated primary care buprenorphine OAT with initial intake within 7 days of discharge vs Treatment as usual (TAU)	KQ1: Engaged in OAT at 6 months: 12(16.7%) linkage group vs 2(3%) TAU group (p=0.007) Self-report days of OAT use per 30 follow-up days: 16.4 linkage group vs 6.4 TAU group, P<.01. KQ2: Not reported KQ3: Not reported	Fair

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
MAT in ED/Hospital Settings	**D'Onofrio, 2017[8]** **RCT** **USA**	290 Mean Age: 31.5 Gender: 24.1% female Race/Ethnicity: 75.5% White Married: 11.0% Unemployed: 22.4% Unstable Housing: 8.3% Primary Opioid Heroin: 75.9%	Buprenorphine	6 months and 12 months Retention: self-reported formal engagement in addiction treatment using Treatment Services Review instrument	ED initiated buprenorphine with linkage to outpatient primary care vs Referral (TAU) vs Brief Intervention of 10-15 minute manual-driven audio taped Brief Negotiation Interview conducted by study RA	KQ1: 6-month retention: 49/92 (53%) 95% CI 43–64 vs B. 42/70 (60%) 95% CI 48–72 vs C. 39/76 (51%) 95% CI 40– 63, p=0.546 12 months retention: A. 42/86 (49%) 95% CI 38–60 vs B. 36/73 (49%) 95% CI 38–61 vs. C 49/78 (63%) 95% CI 52–74, p = 0.136 KQ2: Not reported KQ3: Not reported	Fair

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Logistical Support	**Schwartz, 2017[9]** **RCT** **USA**	300 Mean Age: 42.7(10.1) Gender: 41% female Race/Ethnicity: 42% African American; 41% White	Methadone	12 months Retention: 1. Treatment retention in original OTP at 12 months 2. Enrollment at any MAT program at 12 months *Treatment retention in original OTP was measured from program records and in any other OTP or buprenorphine treatment from self-report	Patient-centered methadone treatment (PCM): Encouraged but not required to attend individual/group counseling. Counselors served solely as therapists. Modified clinic rules. No administrative discharge. vs Treatment as usual (TAU)	KQ1: Retention at 12 months: 48.6% PCM group vs 46.3% TAU group, OR=0.91(0.58,1.44) Risk diff 0.02(-0.09,0.14) p=0.69 % enrolled in any OTP or buprenorphine treatment at 12 months: 78.9% PCM group vs 76.7% TAU group, OR= 0.88(0.48,1.62), p=0.68 KQ2: 4 non-study related deaths in TAU. 2 overdoses in TAU. PCM had 2 non-study related deaths, 1 from methadone overdose; 59 non-study related hospitalizations in TAU and 67 in PCM. KQ3: Not reported	Good

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Logistical Support	**Beattie, 2016[10]** **RCT** **UK**	100 Gender: 16% female Race/Ethnicity: 93.4% White; 6.1% Caribbean/Asian/ Other Had GP: 69% Prior Treatment SUD: 90% Current Mental Health Care: 12% Homeless: 26%	Methadone	3 months Retention: Percentage of patients on opioid substitution treatment (OST) at 3-months after randomization	Treatment intervention at a syringe exchange program (SEP) Intervention group: Script in a day" Offers immediate access to OST through referral to local specialist primary care center. Peer support volunteer accompanied participant to office, initiated on 30-40 mL methadone, and script for 6 days for 21 days, then transfer to GP practice vs Treatment as usual (TAU)	KQ1: In OST at 3-months: 51% intervention group vs 47% TAU group (OR 1.17 95% CI 0.54-2.57) KQ2: Not reported KQ3: Not reported	Fair

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Logistical Support	**Kidorf, 2018[11]** **3 arm RCT** **USA**	212 Standard care intervention (SCI) vs Voucher reinforcement intervention (VRI) vs Low threshold intervention (LTI): Mean Age: 40.3(10.9) vs 40.3(10.0) vs 38.8(9.4) Gender: 54% vs 47% vs 65% male Race/Ethnicity: 34 vs 43 vs 36% White Education: 11.2(2.1) vs 11.5 (2.3) vs 11.3 (2.0) Employed: 6% vs 13% vs 6% HIV+: 3% vs 6% vs 9%	Methadone	6 months Retention: % retained at 90 days and 180 days	Treatment intervention at a syringe exchange program (SEP) Voucher reinforcement intervention (VRI): SCI supplemented with contingency management - contingent on adherence to daily schedules of dosing and counseling. One time per week based on adherence the prior week. Initial value $12, maximum $174, $30 bonus for 3 weeks of adherence, earnings were exchanged for goods/services from local community vs Low threshold intervention (LTI): Participants excluded from adaptive treatment. Only required to attend 1 counseling session/month. vs Standard care intervention (SCI): Routine program, evidenced-based adaptive treatment model	KQ1: 90 day retention: 34% VRI vs 35% LTI vs 31% SCI (p=0.28) 180 day retention: 34% VRI vs 37% LTI vs 29% SCI (p=0.36) KQ2: Not reported KQ3: Not reported	Fair

Topic	Author, Year, Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Logistical Support	**Parpouchi, 2018[12]** **RCT** **Canada**	97 Mean Age: 39.1(8.9) Gender: 36.5% female Race/Ethnicity: 56.7% White; 20.6% Indigenous; 22.7% Other Unemployed:94.8%	Methadone	Retention: Medication possession ratio (MPR): Proportion of days during an observation period for which a person has been dispensed medication between randomization and end of study period (March 31, 2013) or date of death.	Housing first (HF) model: 3 interventions:1) market rental apartments with associated assertive community treatment (ACT) teams; 2) market rental + intensive case management; 3) dedicated building with integrated health and social service providers on-site. vs Treatment as usual (TAU) referral to housing	KQ1: Mean MPR: 0.52 HF group vs 0.57 TAU group (p=0.559) KQ2: Not reported KQ3: Not reported	Fair

MAT= medications for addiction treatment; SR= systematic review; RCT= randomized controlled trial; n=number of participants; LAAM= levo-alpha acetyl methadol; KQ= key question; XR= extended-release; NTX= naltrexone; SD= standard deviation; OTP= opioid treatment program; CHC= community health center; SE= standard error; PC= primary care; SC= specialized care; PCS= psychiatrist's private practice; MMM= manualized matrix model; OAT= opioid agonist treatment; TAU= treatment as usual; ED= emergency department; PCM= patient-centered methadone treatment; OST= opioid substitution treatment; SEP= syringe exchange program; SCI= standard care intervention; VRI= voucher reinforcement intervention; LTI= low threshold intervention; MPR= medication possession ratio; HF= housing first; ACT= assertive community treatment

Table 2. Published literature on contingency management

Author, Year Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Intervention	Results	Quality Rating
Amato, 2011[13] **SR**	4319	Methadone Buprenorphine Levo-alpha acetyl methadol (LAAM)	Timing variable (6 - 48 weeks) Retention: # participants in treatment at the end of the study	Any psychosocial / behavioral + any agonist maintenance treatment vs Standard agonist treatment	KQ1: Results do not show benefit for retention in treatment (26 studies, 2582 participants) KQ2: Not reported KQ3: Not reported	Good
DeFulio, 2012[14] **RCT** **USA**	38 Contingency group: Gender: 58% female Race/Ethnicity: 84% African American Unemployed over past 3 years: 74% Control group: Gender: 26% female Race/Ethnicity: 95% White Unemployed over past 3 years: 58%	Naltrexone injections	6 months Retention: % of participants who completed entire course of naltrexone injections	CM: Access to therapeutic workplace contingent upon acceptance of naltrexone injection vs Prescription: Access to therapeutic workplace noncontingent upon acceptance of naltrexone injection	KQ1: 74% CM group vs 25% prescription group, $\chi 2\ (1) = 8.53$, $p = .004$ KQ2: Not reported KQ3: Not reported	Fair

Author, Year Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Intervention	Results	Quality Rating
Dunn, 2013[15] **RCT** **&** **Dunn, 2015**[16] **RCT** **USA**	67 Mean Age: 45 Gender: 39% female Race/Ethnicity: 86% African American	Oral naltrexone	Retention: 1. % of participants who completed course of medication. 26 weeks. 2. % of participants who had naltrexone-positive urine screens at 100% of 30-day check-points. 3. Self-reported drug treatment in 30 days before 12 month assessment[16]	CM: Access to therapeutic workplace contingent upon supervised ingestion of medication vs Prescription: Access to therapeutic workplace noncontingent upon medication ingestion.	KQ1: Completed course of medication: 54% CM group vs 16% prescription group ($p<0.01$) Naltrexone-positive urine screens at 100% of 30-day check-points: 43% CM group vs 3% prescription group ($p<0.01$) Drug treatment at 12 months: 17% CM group vs 23% prescription group ($p=0.45$) KQ2: 1/67 deaths in contingency, 1 month after study KQ3: Not reported	Fair

Author, Year Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Intervention	Results	Quality Rating
Epstein, 2009[17] **RCT** **USA**	252 Gender: 52% female Race/Ethnicity: 66% African American Unemployed: 18%	Methadone	20 weeks Retention: % of participants retained in study through study completion	CM: Vouchers for goods and services provided for submitting opioid-negative urine samples vs Non-CM: Vouchers awarded independent of urine screen results on a schedule yoked to the performance of another participant	KQ1: No group differences in retention Log-rank $\chi 2 = 2.51$, df=2, p=0.29 KQ2: Not reported KQ3: Not reported	Good
Everly, 2011[18] **RCT** **USA**	35 Mean Age: 42.5% Contingency group: Gender: 42.5% female Control group: Gender: 53% female	Naltrexone injections	26 weeks Retention: % of participants who accepted all scheduled naltrexone injections	CM: Access to therapeutic workplace contingent upon acceptance of naltrexone injections vs Prescription: Access to therapeutic workplace not contingent upon acceptance of naltrexone injections	KQ1: Received all injections: 66% CM group vs 35% prescription group $\chi 2$ (1) = 4.94, p=0.026; HR = 0.32; 95% CI = 0.117 - 0.874 KQ2: Not reported KQ3: Not reported	Fair

Author, Year Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Intervention	Results	Quality Rating
Holtyn, 2014[19] **RCT** **USA**	98 Work reinforcement group: Gender: 33% female Race/Ethnicity: 63% African American Abstinence, methadone, and work reinforcement: Gender: 45% female Race/Ethnicity: 73% African American	Methadone	26 weeks Retention: % of participants enrolled in MAT at 30-day assessments	CM: Access to therapeutic workplace contingent upon verified enrollment in outside MAT program Non-CM: Access to workplace independent of MAT enrollment status	KQ1: 30-day retention: 81% CM group vs 82% non-CM group OR (95% CI) 1.40 (0.40-4.83), p=0.60 KQ2: Not reported KQ3: Not reported	Fair

Kidorf, 2018[11] **RCT** **USA**	212 (Standard care intervention) vs (Voucher reinforcement intervention) vs (Low threshold intervention): Mean Age: 40.3(10.9) vs 40.3(10.0) vs 38.8(9.4) Gender: 54% vs 47% vs 65% male Race/Ethnicity: 34 vs 43 vs 36% White Education: 11.2(2.1) vs 11.5 (2.3) vs 11.3 (2.0) Employed: 6% vs 13% vs 6% HIV+: 3% vs 6% vs 9%	Methadone	6-months Retention: % retained at 90 days and 180 days	Treatment intervention at a syringe exchange program (SEP) Voucher reinforcement intervention (VRI): SCI supplemented with contingency management - contingent on adherence to daily schedules of dosing and counseling. One time per week based on adherence the prior week. Initial value $12, maximum $174, $30 bonus for 3 weeks of adherence, earnings were exchanged for goods/services from local community vs Low threshold intervention (LTI): Participants excluded from adaptive treatment. Only required to attend 1 counseling session/month. vs Standard care intervention (SCI): Routine program, evidenced-based adaptive treatment model	KQ1: 90 day retention: 34% VRI vs 35% LTI vs 31% SCI (p=0.28) 180 day retention: 34% VRI vs 37% LTI vs 29% SCI (p=0.36) KQ2: Not reported KQ3: Not reported	Fair

Author, Year Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Intervention	Results	Quality Rating
Specka, 2013[20] **RCT** **Germany**	136 Gender: 67% male Unemployed: 72%	Methadone Buprenorphine	26 weeks Retention: % of participants who completed the study	CM: Received escalating number of take-home dosages of medication contingent upon increasing number of opioid-free urine samples vs Treatment as usual (TAU): Received 4 days of medication dosages for 12 consecutive opioid-free weekly urine screens	KQ1: 62.5% CM group vs 64.1% TAU group (p=0.85) KQ2: Not reported KQ3: Not reported	Fair

MAT= medications for addiction treatment; SR= systematic review; RCT= randomized controlled trial; LAAM= levo-alpha acetyl methadol; KQ= key question; CM= contingency management; SEP= syringe exchange program; SCI= standard care intervention; VRI= voucher reinforcement intervention; LTI= low threshold intervention; TAU= treatment as usual

Table 3. Published literature on health IT for MAT

Author, Year Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Marsch, 2014[21] **RCT** **USA**	160 Mean Age: 40.7 Gender: 25% female Race/Ethnicity: 27.4% Hispanic Married: 9.4% Unemployed: 46.8%	Methadone	12 months Retention: % retained in treatment over duration of treatment	Computer-based education & support Intervention: 50%/50% in-person/Therapeutic Education System (TES) vs Treatment as usual (TAU): MAT + clinic resources (In-person counseling & group therapy)	KQ1: Retention: 31/80 (39%) intervention group vs 31/80 (39%) TAU group p=0.56, OR CI (0.5-1.2) KQ2: Not reported KQ3: Not reported	Fair
Moore, 2018[22] **RCT** **USA**	82 Treatment arm (n=40): Mean Age: 43.6 Gender: 60% male Race/Ethnicity: 65% White Married: 60% Unemployed: 63%	Methadone	3-months Retention: % of days of medication adherence	Computer-based education & support Intervention: Automated, computer-based, cognitive behavioral therapy (CBT) interactive voice response (IVR) system vs TAU: Methadone + clinic resources (In-person counseling & group therapy)	KQ1: 94% p=0.60 (retention only reported for entire study population, not individual groups) KQ2: 12 Adverse Events not described (7 of 40 [17%] Intervention, 5 Control of 42 [12%]); 1 Control removed from study due to medical issues KQ3: Not reported Greater IVR use, more days abstinent. IVR group requested continued access to IVR post study. Qualitative interviews patients reported just knowing resource was available was beneficial.	Poor

Author, Year Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Ruetsch, 2012[23] **RCT** **USA**	1426 Participant characteristics not reported	Buprenorphine	12 months Retention: Medication taken at the prescribed dose on at least 80% of days (22/28 days) based on participant self-report of the previous 28 days	Computer-based education & support Intervention: Here to Help: online educational materials, treatment calendar, peer stories, telephone coaching + MAT vs TAU: MAT + clinic resources (In-person counseling & group therapy)	KQ1: 55% intervention group vs 56.1% TAU group (p= not reported) KQ2: Not reported KQ3: Not reported	Fair
Shi, 2019[24] **RCT** **USA**	20 Mean Age: 18+ Gender: Predominantly male Race/Ethnicity: Predominantly White Education: Most completed high school Employment: "About half"	Buprenorphine	3-months Retention: Mean number of days in 12-week protocol	Computer-based education & support Intervention: Web-based CBT vs TAU: MAT + clinic resources (In-person counseling & group therapy)	KQ1: Mean days in 12-week protocol: 83 days intervention group vs 69 days TAU group (p=0.19) KQ2: Not reported KQ3: Not reported	Fair

Author, Year Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Eibl, 2017[25] **Retrospective cohort** **Entire Province of Canada**	3733	Methadone, Buprenorphine	12-months Retention: At least 1- year consecutive MAT	Telehealth Patients stratified by primary treatment modality: >75% telehealth vs. 25-75% mixed vs. <25% in-person	KQ1: 50%; aOR 1.27 (1.14-1.41) 47% aOR 1.27 (1.08-1.47) 39% (reference) KQ2: Not reported KQ3: Receiving care in Northern clinics was positively associated with retention. Significant associations were also detected for sex, clinic region, age, and peak methadone dose, but not for clinic rurality.	Fair
Weintraub, 2018[26] **Retrospective chart review** **USA**	177 Mean Age: 35.1 Gender: 89% male Race/Ethnicity: 82% White Insurance: 96% Medicaid Self-reported abstinence at initial evaluation: 72%	Buprenorphine	3-months Retention: % retained in treatment	Telehealth Telehealth (to patient), teleconsult (to provider) not specified; connection of academic medical center to rural treatment center Patients were detoxified prior to study	KQ1: 57.4% KQ2: Not reported KQ3: Not reported	Fair

Author, Year Study Design Country	Number of Participants Participant Characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Zheng, 2017[27] **Retrospective chart review** **USA**	55* Mean Age: 37.2 and 34.4 Race/Ethnicity: mostly White Unemployed: mostly unemployed *study n= 100, 55 followed for 12 months	Buprenorphine	12 months Retention: % of patients in program at 12 months	Telehealth Intervention: Telehealth psychiatry vs In-person psychiatry	KQ1: 41.7% 35.5% p = 0.55 KQ2: Not reported KQ3: Not reported	Fair

IT= informational technology; MAT= medications for addiction treatment; RCT= randomized controlled trial; TES= Therapeutic Education System; TAU= treatment as usual; KQ= key question; CBT= cognitive behavioral therapy; IVR= interactive voice response

Table 4. Published literature on extended-release medication based treatments

Author, Year Study Design Country Funder	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Tanum, 2017[28] **RCT** **Norway**	159 Mean Age: 35.1 Gender: 72.3% male Race/Ethnicity: 89.2% White IV drug users: 85.5% Only participants who successfully completed medically supervised withdrawal were randomized into the study	XR NTX monthly injection Daily SL buprenorphine/ naloxone	3 months Retention: number of days until dropout from study medication and by the number of patients completing the study at week 12.	XR NTX monthly injection vs Daily SL buprenorphine/ naloxone	KQ1: Retention, mean (SD) time: 69.3 (25.9) XR NTX vs 63.7 (29.9) days daily buprenorphine / naloxone. At 12 weeks 66% participants had attended all scheduled follow-up and taken their medications as prescribed. KQ2: Serious adverse events not different between the two groups (8.5% vs 4.2%, p=0.33). 10 participants (4 in the XR NTX group and 6 in the buprenorphine/ naloxone group) exited the study due to adverse events: KQ3: Not reported	Good

Author, Year Study Design Country Funder	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Lee, 2018[29] **RCT** **USA**	570 Age: 18+ Gender: 70.5% male Race/Ethnicity: 74% White Heroin Users: 81% Prescription Opioid Users: 15.5% Participants were randomized into the study either prior to or following successful completion of medically supervised withdrawal	XR NTX monthly injection Daily SL buprenorphine/ naloxone	6 months Retention: % study participants who completed 6 months of the study	XR NTX monthly injection vs Daily SL buprenorphine/ naloxone	KQ1: Retention at 6 months: 96/283 (33.9%) XR NTX vs 115/287 (40%) daily buprenorphine/ naloxone (p value not reported) KQ2: serious adverse events not different between groups (14% and 11%). 28 overdose events, 18 (64%) in the XR NTX group, including 8 among induction failures and 10 among those who received at least a single XR NTX injection. 5 overdoses were fatal, including 2 in the XR NTX group and 3 in the daily buprenorphine/naloxone group. KQ3: Not reported	Fair

Author, Year Study Design Country Funder	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Sullivan, 2019[30] **RCT** **USA** **NIDA**	60 Mean Age: 39.5 Gender: 83.3% male Race/Ethnicity: 63.3% White Heroin Users: 26.7% Prescription Opioid Users: 85.0% Participants were randomized after successfully completing medically supervised opioid withdrawal	XR NTX monthly injection Daily naltrexone	6 months Retention: % study participants who completed 6 months of the study.	XR NTX monthly injection vs Daily naltrexone	KQ1: Retention at 6 months: 57.1% XR NTX vs 28.1% daily naltrexone (HR=2.18, 95% CI=1.07, 4.43) KQ2: 9 serious adverse events, including 5 in the XR NTX and 3 in the daily naltrexone group. 5 participants were from the study which included 1 participant who developed hives after an XR NTX injection. KQ3: Not reported	Fair
Rosenthal, 2016[34] **RCT** **USA** **Braeburn Pharmaceuticals**	177 Age: 18+ Gender: 59.1% male Race/Ethnicity: 94.9% White, Heroin Users: 21.0% Prescription Opioid Users: 74.4%	XR Buprenorphine 6-month implant Daily SL buprenorphine	6 months Retention: % study participants who completed 6 months of the study.	Clinically stable on daily buprenorphine for 6 months before enrollment: XR Buprenorphine 6-month implant vs Daily SL buprenorphine	KQ1: Retention: 81/87 (93.1%) implant vs 84/90 (94.3%) daily buprenorphine (p-value not reported) KQ2: 5 serious adverse events reported, 3 in the daily buprenorphine and 2 in the buprenorphine implant group. 1 participant in the buprenorphine implant exited the study. KQ3: Not reported	Good

Author, Year Study Design Country Funder	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Lofwall, 2018[35] **RCT** **USA** **Braeburn Pharmaceuticals** **University of Kentucky**	428 Age: 18+ Gender: 61.4% male Race/Ethnicity: 74.2% White Heroin Users: 70.8% Prescription Opioid Users: 29.2%	XR Buprenorphine monthly injection Daily SL buprenorphine /naloxone	24 weeks Retention: % participants retained on the study medication regimen at 24 weeks of treatment	XR Buprenorphine injections (weekly during weeks 1 – 11, monthly during weeks 12 – 24) + daily SL placebo vs Placebo injections (weekly during weeks 1 – 11, monthly during weeks 12 – 24) + daily SL buprenorphine/ naloxone	KQ1: Retention: 56.8% XR buprenorphine vs 58.1% daily buprenorphine/naloxone (p-value not reported) KQ2: 18 participants reported at least 1 serious non-fatal adverse event; which lead to study disenrollment among 3.3% buprenorphine injection and 1.4% daily buprenorphine participants. only 1 serious adverse event was related to the buprenorphine injection. 5 daily buprenorphine/ naloxone participants reported nonfatal overdoses. KQ3: Not reported	Fair

MAT= medications for addiction treatment; RCT= randomized controlled trial; IV= intravenous; XR= extended-release; NTX= naltrexone; SL= sublingual; KQ= key question; CI= confidence interval; KCL= King's College London; SLaM= South London and Maudsley; NHS= National Health Service

Table 5. Published literature on psychosocial support interventions

Author, Year Study Design Country	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Amato, 2011[13] **SR**	4319 Age: 18+, average 35, range: 27-45 years Gender: 73% male Non-pregnant Naïve/stable in treatment: varies at individual study level	Methadone Buprenorphine Levo-alpha acetyl methadol (LAAM)	Timing variable (6 - 48 weeks) Retention: # participants in treatment at the end of the study	Any psychosocial / behavioral + any agonist maintenance treatment vs Standard agonist treatment	KQ1: Results do not show benefit for retention in treatment (26 studies, 2582 participants) KQ2: Not reported KQ3: Not reported	Quality of included studies for outcome of retention assessed as 'high' using GRADE
Christensen, 2014[36] **RCT** **USA**	170 Mean Age: 20-63 Non-pregnant Not incarcerated Naïve/stable in treatment: naïve, but unclear of if any patients had previous MAT	Buprenorphine induction Buprenorphine-naloxone tablet maintenance	3-months Retention: % participants completed all 3-months	Web-based community reinforcement approach (CRA) + contingency management (CM) + minimal therapist counseling + MAT vs CM + minimal therapist counseling + MAT	KQ1: Retention: 80% CRA+CM vs 64% CM+ counselling OR =2.30 (1.15, 4.60) KQ2: Not reported KQ3: when stratified by prior treatment the hazard of dropping out for CM-alone participants was 6.57 times ($\chi2(1) = 9.01$, p=0.003) that for CRA+ participants. For treatment-naïve participants, the hazard for CM-alone participants was 1.15 times ($\chi2(1) = 0.13$, p=0.718) that for CRA+ participants	Poor

Author, Year Study Design Country	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Fiellin, 2013[37] **RCT** **USA**	141 Mean Age: 33 Gender: <70% male Race/Ethnicity: <80% White Prescription drug use: 36% Prior detox attempt: 49%	Buprenorphine Naloxone	6 months Retention: % participants completed all 6 months	Physician management + cognitive behavioral therapy (CBT) vs Physician management alone	KQ1: Retention: 39% CBT vs 45% physician management alone (p=0.43) KQ2: Not reported KQ3: Not reported	Good
Jaffray, 2014[38] **RCT** **Scotland**	542 Mean Age: 32 Gender: 64% male Unemployed: 91% Naïve/stable in treatment: "initiated in the last 24 months" - stable	Methadone	6 months in study; baseline mean 9 months in methadone Retention: % participants still receiving treatment at 6 months	Motivational interviewing + resource pack (with area-specific information on available services for pharmacists) + normal practice methadone treatment vs Normal practice methadone treatment	KQ1: Retention: 88% intervention vs 81% usual care (Adjusted p=0.34) OR = 1.76 (0.55, 5.64) KQ2: Physical and psychological health of the intervention group significantly deteriorated between baseline and follow-up, whilst the control group remained relatively unchanged KQ3: Not reported	Poor

Author, Year Study Design Country	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Marsden, 2019[39] **RCT** **UK**	273 Age: 18+ All participants were treatment resistant (i.e., had used illicit or non-prescribed opioids or cocaine on one or more days in the past 28 days at study screening, which was verified by positive urine drug screen)	Buprenorphine Methadone	18 weeks Retention: # days from randomization to the endpoint or exit	Personalized psychosocial intervention + treatment as usual vs Treatment as usual (TAU)	KQ1: No between-group difference in retention in either unadjusted or adjusted analyses. KQ2: The number of adverse events was similar between groups, and no severe adverse events in either group were judged to be treatment related. KQ3: Not reported	Fair
Mitchell, 2013[40] **RCT** **USA**	300 Age: 18+ Race/Ethnicity: African American population Newly admitted to buprenorphine treatment at one of the participating treatment programs	Buprenorphine	6 months Retention: % participants in buprenorphine treatment at 6 months	Intensive outpatient (IOP) vs Standard outpatient (OP)	KQ1: Retention: 56.6% IOP vs 58.7% OP KQ2: Controlling for # of days in treatment, greater counseling exposure was associated with significantly less improvement for three outcomes: days of heroin use, days of cocaine use, and days of criminal activity (however authors suggest the association is not causal) KQ3: Not reported	Poor

Author, Year Study Design Country	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Schwartz, 2012[41] **RCT** **USA**	230 Mean Age: 43.2 Gender: 70% male Race/Ethnicity: 77.4% African American Married: 13.5% Employed During 30 Days Prior to Baseline: 32.6% Non-pregnant Opioid dependent for 1 year+	Methadone	12 months Retention: % participants retained in original MTP	Interim methadone (IM; supervised methadone with emergency counseling only for the first 4 months of treatment) vs Restored methadone (RM; routine counseling with smaller case loads vs Standard methadone (SM; with routine counseling)	KQ1: Retention: 60.6% IM vs 37% RM vs 54.8% SM $\chi 2(2) = 4.8$ ($p>0.05$) KQ2: Not reported KQ3: Not reported	Fair
Stein, 2015[42] **RCT** **USA**	49 Mean Age: 41 Gender: 65.3% male Race/Ethnicity: 85.7% Non-Latino White Reported they had ever received prescribed buprenorphine: 28.6%	Buprenorphine-naloxone induction Buprenorphine maintenance	3-months Retention: % participants retained in treatment	DT (distress tolerance) intervention + buprenorphine-naloxone induction then 3-months buprenorphine maintenance vs HE (health education) control + buprenorphine-naloxone induction then 3-months buprenorphine maintenance	KQ1: Retention: 75% DT vs 76% control Between group mean difference (95% CI) −1.0 (−25.1; 23.1) KQ2: Not reported KQ3: Not reported	Good

Author, Year Study Design Country	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Sullivan, 2015 **RCT** **USA**	125 Mean Age: 38 Gender: 21% female Race/Ethnicity: 43% White Heavy use (>6 bags heroin/day): 34%	XR Naltrexone Oral Naltrexone	6 months Retention: % of participants retained in treatment	Behavioral Naltrexone Therapy (BNT) + standard (oral and injectable naltrexone) treatment vs Compliance Enhancement (CE) + standard (oral and injectable naltrexone) treatment vs Behavioral Naltrexone Therapy (BNT) + placebo injection and oral naltrexone vs Compliance Enhancement (CE) + placebo injection and oral naltrexone	KQ1: Retention: 47.8% BNT + standard Naltrexone vs 16.7% CE +standard naltrexone vs 23.8% BNT + placebo vs 14.3% CE+placebo KQ2: Not reported KQ3: For low-severity opioid users, retention was highest (60% at 6 months) in Behavioral Naltrexone Therapy with a single administration of injection naltrexone (XR-naltrexone) post-detoxification. For high-severity opioid users, BNT-XR-naltrexone + oral naltrexone did not perform as well.	Fair

Author, Year Study Design Country	Number of participants Participant characteristics	MAT Medications	Timing & Outcome	Interventions	Results	Quality Rating
Weiss, 2011[44] **RCT** **UK**	653 Mean Age: 32.9 Gender: 38% female Race/Ethnicity: 91.5% White Unmarried: 49.2% Employment: 63.8% FTE Met DSM IV criteria for current opioid dependence on prescription opioids	Buprenorphine-naloxone	Phase 1: 4 weeks (2 week stabilization, 2 week taper) Retention: # of SMM (standard medical management) visits Phase 2: 16 weeks (12 week treatment, 4 week taper)	SMM + ODC (opioid drug counseling) vs SMM alone	KQ1: Mean (SD) visits Phase 1: 4.4 (1.5) ODC vs 4.5 (1.5) SMM alone (z=1.24, p=0.39) Phase 2: 14.1 (4.4) ODC vs 13.9 (4.0) SMM alone (z=0.86, p=0.21) KQ2: Psychiatric symptoms were the most common serious adverse events (7 of 36), particularly depression leading to hospitalization (n=5); all of these occurred soon after completion of the Phase 1 (n=2) or Phase 2 (n=3) taper. KQ3: A history of ever using heroin was associated with lower Phase 2 success rates while taking buprenorphine-naloxone Chronic pain at baseline was not related to outcomes either in Phase 1 or during Phase 2 while taking buprenorphine-naloxone	Fair

MAT= medications for addiction treatment; SR= systematic review; LAAM= levo-alpha acetyl methadol; KQ= key question; GRADE= Grading of Recommendations Assessment, Development and Evaluation; RCT= randomized controlled trial; CRA= community reinforcement approach; CM= contingency management; CBT= cognitive behavioral therapy; TAU= treatment as usual; IOP= Intensive outpatient; OP= standard outpatient; MTP= methadone treatment program; IM= interim methadone; RM= restored methadone; SM= standard methadone; DT= distress tolerance; HE= health education; XR= extended-release; BNT= Behavioral Naltrexone Therapy; CE= compliance enhancement; SMM= standard medical management; ODC= opioid drug counseling; SD= standard deviation

Appendix C. Quality Rating Tables

Table 1. Quality ratings for care settings, services, logistical support

Topic	Author, Year	Randomization	Allocation Concealment	Groups Similar at Baseline	Blinded Outcome Assessors	Blinded Care Provider	Blinded Patient	Intention-To-Treat (ITT) Analysis	Acceptable Levels of Overall Attrition	Avoidance of Selective Outcomes Reporting	Final Quality Rating
Pre-Release MAT Models	Friedmann, 2018[2]	Unclear	Unclear	Yes	No	No	No	Yes	Yes	No	Poor
	Gordon, 2017[3]	Yes	Yes	Yes	Unclear	No	No	Yes	Yes	Yes	Fair
MAT Integrated into Primary Care	Brooner, 2013[4]	Yes	Unclear	Yes	Unclear	No	No	Yes	Unclear	Yes	Fair
	Carrieri, 2014[5]	Yes	Unclear	Yes	Unclear	No	No	Yes	Yes	Yes	Fair
	Miotto, 2012[6]	Yes	Yes	No	No	No	No	Yes	Unclear	Yes	Fair
MAT in ED/ Hospital Settings	Liebschutz, 2014[7]	Yes	Unclear	Yes	No	No	No	Yes	Yes	Yes	Fair
	D'Onofrio[8]	Yes	Yes	Yes	Unclear	No	No	No	Yes	Yes	Fair
MAT in Community Settings/ Social Services	Schwartz, 2017[9]	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Good
	Beattie, 2016[10]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Fair
	Kidorf, 2018[11]	Yes	Unclear	Unclear	Unclear	No	No	Yes	Yes	No	Fair
	Parpouchi, 2018[12]	Yes	Unclear	Yes	Unclear	No	No	No	Unclear	Yes	Fair

Table 2. Quality ratings for contingency management

Author, Year	Randomization	Allocation Concealment	Groups Similar at Baseline	Blinded Outcome Assessors	Blinded Care Provider	Blinded Patient	Intention-To-Treat (ITT) Analysis	Acceptable Levels of Overall Attrition	Avoidance of Selective Outcomes Reporting	Final Quality Rating
DeFulio, 2012[14]	Yes	Unclear	Yes	Unclear	No	No	Yes	Yes	Yes	Fair
Dunn, 2013[15]	Yes	Unclear	Yes	Unclear	No	No	Yes	Yes	Yes	Fair
Dunn, 2015[16]	Yes	Unclear	No	Unclear	No	No	Yes	Yes	Yes	Fair
Epstein, 2009[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Everly, 2011[18]	Yes	Unclear	Yes	Unclear	Unclear	No	Yes	Yes	Yes	Fair
Holtyn, 2014[19]	Yes	No	Unclear	Unclear	No	No	Yes	Yes	No	Fair
Kidorf, 2018 [11]	Yes	Unclear	Unclear	Unclear	No	No	Yes	Yes	No	Fair
Specka, 2013[20]	Unclear	Unclear	Unclear	No	No	No	Yes	Yes	Yes	Fair

Table 3a. Quality ratings for health IT RCTs

Author, Year	Randomization	Allocation Concealment	Groups Similar at Baseline	Blinded Outcome Assessors	Blinded Care Provider	Blinded Patient	Intention-To-Treat (ITT) Analysis	Acceptable Levels of Overall Attrition	Avoidance of Selective Outcomes Reporting	Final Quality Rating
Marsch, 2014[21]	Yes	No	Yes	Yes	No	No	Yes	Yes	Unclear	Fair
Moore, 2019[22]	Unclear	No	Unclear	No	No	No	Yes	Yes	Unclear	Poor
Reutsch, 2012[23]	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Fair
Shi, 2019[24]	Yes	Unclear	Yes	Unclear	No	No	Yes	Yes	Yes	Fair

Table 3b. Quality ratings for health IT cohort studies

Author, Year	Randomization	Allocation Concealment	Groups Similar at Baseline	Blinded Outcome Assessors	Blinded Care Provider	Blinded Patient	Intention-To-Treat (ITT) Analysis	Acceptable Levels of Overall Attrition	Avoidance of Selective Outcomes Reporting	Final Quality Rating
Eibl, 2017[25]	N/A	Yes	Yes	No	No	No	No	Unclear	Yes	Fair
Weintraub, 2018[26]	N/A	Yes	Yes	No	No	No	No	Unclear	Yes	Fair
Zheng, 2017[27]	N/A	Yes	Yes	No	No	No	Yes	Unclear	Yes	Fair

Table 4. Quality ratings for extended-release medication based treatments

Author, Year	Randomization	Allocation Concealment	Groups Similar at Baseline	Blinded Outcome Assessors	Blinded Care Provider	Blinded Patient	Intention-To-Treat (ITT) Analysis	Acceptable Levels of Overall Attrition	Avoidance of Selective Outcomes Reporting	Final Quality Rating
Tanum, 2017[28]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Good
Lee, 2018[29]	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair
Sullivan, 2019[30]	Yes	Unclear	Yes	No	No	No	Yes	Yes	Yes	Fair
Rosenthal, 2016[34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Lofwall, 2018[35]	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair

Table 5. Quality ratings for psychosocial

Author, Year	Randomization	Allocation Concealment	Groups Similar at Baseline	Blinded Outcome Assessors	Blinded Care Provider	Blinded Patient	Intention-To-Treat (ITT) Analysis	Acceptable Levels of Overall Attrition	Avoidance of Selective Outcomes Reporting	Final Quality Rating
Christensen, 2014[36]	No	No	No	No	No	No	Unclear	No	Yes	Poor
Fiellin, 2013[37]	Yes	Yes	Yes	Unclear	No	No	Yes	Yes	Yes	Good
Jaffray, 2014[38]	Unclear	Unclear	Yes	Unclear	No	Yes	Yes	No	Yes	Poor
Marsden, 2019[39]	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Fair
Mitchell, 2013[40]	Yes	Yes	No	Unclear	No	No	Yes	No	Unclear	Poor
Schwartz, 2012[41]	Yes	Unclear	Yes	Unclear	No	No	Yes	No	Yes	Fair
Stein, 2015[42]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Good
Sullivan, 2015	Unclear	Yes	Yes	Unclear	No	Yes	Unclear	No	Yes	Fair
Weiss, 2011[44]	Unclear	Unclear	Yes	No	No	No	Yes	Yes	Yes	Fair

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