Technical Brief
Number 28

Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings

AHRQ
Agency for Healthcare Research and Quality

Effective Health Care Program

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Prepared for:
Agency for Healthcare Research and Quality
US Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. 290-2015-00009-I

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AHRQ Publication No. 16(17)-EHC039-EF
December 2016

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00009-I). 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 decisionmakers—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.

Suggested citation:
Chou R, Korthuis PT, Weimer M, Bougatsos C, Blazina I, Zakher B, Grusing S, Devine B, McCarty D. Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings. Technical Brief No. 28. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 16(17)-EHC039-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this Technical Brief, 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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Key Informants

In designing the study questions, the EPC consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input can inform key issues related to the topic of the technical brief. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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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 $10,000 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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Medication-Assisted Treatment Models of Care for Opioid Use Disorder in Primary Care Settings

Structured Abstract

Background. The majority of medication treatment for opioid use disorder (OUD) is provided in primary care settings. Effective and innovative models of care for medication-assisted treatment (MAT) in primary care settings (including rural or other underserved settings) could facilitate implementation and enhance provision and uptake of agonist and antagonist pharmacotherapy in conjunction with psychosocial services for more effective treatment of OUDs.

Purpose. The purpose of this Technical Brief is to describe promising and innovative MAT models of care in primary care settings, describe barriers to MAT implementation, summarize the evidence available on MAT models of care in primary care settings, identify gaps in the evidence base, and guide future research.

Methods. We performed searches in electronic databases from 1995 to mid-June 2016, reviewed reference lists, searched grey literature sources, and interviewed Key Informants. We summarized representative MAT models of care in primary care settings and qualitatively summarized the evidence on MAT models of care in primary care settings and identified areas of future research needs.

Findings. We summarized 12 representative MAT models of care in primary care settings, using a framework describing the pharmacological component, the psychosocial services component, the integration/coordination component, and the educational/outreach component. Innovations in MAT models of care include the use of designated nonphysician staff to perform the key integration/coordination role; tiered care models with centralized intake and stabilization of patients with ongoing management in community settings; screening and induction performed in emergency department, inpatient, or prenatal settings with subsequent referral to community settings; community-based stakeholder engagement to develop practice standards and improve quality of care; and use of Internet-based learning networks. Most trials of MAT in primary care settings focus on comparisons of one pharmacological therapy versus another, or on the effectiveness of different intensities or types of psychosocial interventions, rather than on effectiveness of different MAT models of care *per se.* Key barriers to implementation of MAT models of care include stigma, lack of institutional support, lack of prescribing physicians, lack of expertise, and inadequate reimbursement.

Conclusions. A number of MAT models of care have been developed and implemented in primary care settings. Research is needed to clarify optimal MAT models of care and to understand effective strategies for overcoming barriers to implementation. The models of care presented in this technical brief may help inform the individualized implementation or MAT models of care in different primary care settings.

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Background

Introduction

Opioid use disorder (OUD) has been identified by the Department of Health & Human Services as a national crisis.[1] OUD involves misuse of prescription opioids or use of illicit heroin, and is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[2] as "a problematic pattern of opioid use leading to clinically significant impairment or distress." In 2014, approximately 1.9 million Americans 12 years or older were estimated to have OUD due to prescription drugs and nearly 600,000 due to heroin use.[3] OUD is associated with decreased quality of life and increased morbidity and mortality. In 2013, an estimated 16,000 individuals died as a result of prescription opioid overdose (a 2.5-fold increase from 2001) and approximately 8,000 from heroin (a 4-fold increase from 2001).[4] These trends have occurred in conjunction with markedly increased rates of opioid prescribing for chronic pain;[5-9] in fact, the majority of heroin users now report that their first opioid of misuse was a prescription opioid, not heroin.[10] Challenges in the treatment of OUD include the relapsing nature of this condition, the frequent presence of psychiatric and medical comorbidities, and the disproportionate impact on those in socioeconomically disadvantaged settings with limited access to care.[11,12] Lack of control over purity leading to high variability in dose is an additional concern with heroin as compared with prescription opioids.

As noted in 1997 by a National Institutes of Health consensus panel, OUD "is a medical disorder that can be effectively treated with significant benefits for the patient and society."[13] According to the Substance Abuse and Mental Health Services Administration (SAMHSA), medication-assisted treatment (MAT) is defined as the use of the U.S. Food and Drug Administration (FDA)-approved opioid agonist medications (e.g., methadone, buprenorphine products, including buprenorphine/naloxone combination formulations and buprenorphine mono-product formulations [including a recently approved implantable formulation]) for the maintenance treatment of OUD, and opioid antagonist medications (e.g., naltrexone products, including extended-release and oral formulations), in combination with behavioral therapies, to prevent relapse to opioid use. MAT includes screening, assessment (which includes determination of severity of OUD, including presence of physical dependence and appropriateness for MAT), and case management. It has been suggested that the term MAT is misleading because it implies that medications play an adjunctive role in treatment for OUD, and that it would be more accurate to simply refer to multimodal therapy for OUD that includes use of medications as "treatment."[14,15] In this report, we use the term MAT because it is widely used, well-understood (as defined by SAMHSA), and to help distinguish medication-based from nonmedication based (e.g., detoxification/abstinence) approaches. The term MAT is not meant to imply that medications play an ancillary role in treatment; rather, medications are central to the concept of effective multimodal treatment for OUD. Medication is to be provided in combination with comprehensive substance use disorder treatment, including but not limited to: counseling, behavioral therapies, other clinically appropriate services in order for individuals to achieve and maintain abstinence from all opioids and heroin, and, when needed, pharmacotherapy for co-occurring alcohol use disorder. MAT is to be provided in a clinically-driven, person-centered, and individualized setting."[16] MAT has been shown to be more effective than treatments that do not use medication in reducing the frequency and quantity of opioid use[17,18] and may reduce the risk of overdose, improving social functioning and decreasing criminal activity and infectious disease rates.[19] The purpose of the medication component is to block the euphoric and sedating effects of opioids, reduce the craving for opioids, and/or mitigate the

symptoms of opioid withdrawal. Psychosocial interventions address the psychosocial contributors to OUD and may help improve retention in care. Examples of psychosocial interventions include cognitive-behavioral therapy, motivational enhancement therapy, and other evidence-based psycho-social interventions in individual, group, or family counseling settings; peer-delivered recovery support services; and assessment, coordination, and management of other medical and psychiatric care needs such as provision of general primary care or treatment for other substances use disorders, HIV or hepatitis C virus (HCV) coinfection, or pregnancy.[20] In addition, comorbid psychiatric disorders are frequently present in patients with OUD and may require treatment with psychiatric medications.

Current Practices

The White House and the Department of Health & Human Services recently identified improved access to MAT as a key priority for reducing harms associated with OUD.[1,21] Following the passage of the Harrison Narcotic Act in 1914 and prior to the Drug Abuse Treatment Act (DATA) of 2000, MAT using opioid agonists could only be provided through federally-approved opioid treatment programs and the partial opioid agonist buprenorphine was not yet approved for the treatment of OUD.[22] DATA 2000 enabled physicians to obtain a waiver and prescribe for treatment of OUD schedule III-V medications approved by the FDA for this purpose; currently the only such medication is buprenorphine (also available coformulated with the opioid antagonist naloxone). An implantable formulation of buprenorphine was recently approved by the FDA. Under federal law, physicians prescribing opioid agonists for OUD must attest to the fact that they have access to ancillary counseling services. Although DATA 2000 has increased access to buprenorphine in primary care settings, research indicates that access to and use of buprenorphine remains limited.[4,23] In many rural areas, for example, no buprenorphine prescribers are available.[24] Oral naltrexone, an opioid antagonist, has long been available for treatment of OUD and extended-release naltrexone is recently available as a monthly intramuscular injection. Naltrexone is not classified as a controlled substance and can be prescribed in primary care settings by any physician, physician assistant, or nurse practitioner, but its use has been limited. Extended-release naltrexone was approved by the FDA for treatment of OUD in 2010; although oral naltrexone has long been available it is rarely used for this indication. Although extended-release naltrexone does not require a waiver to prescribe for OUD, its use currently appears low in comparison to buprenorphine, though reliable estimates on utilization are not available. Methadone for treatment of OUD is a schedule II opioid that is dispensed in licensed opioid-treatment programs (OTPs). Even in specialty substance use disorder settings, medications approved for MAT appear to be underused, with one study showing that MAT was used in only about one-third of patients.[25] Therefore, understanding the most effective and promising models of care and implementation strategies are critical for optimizing the impact of initiatives to expand access to MAT.[1]

Objective of Technical Brief

The purpose of this Technical Brief is to conduct a scoping review describing the available literature on MAT models of care and methods for effective MAT strategies, and to identify and summarize key issues and gaps in the evidence base. A Technical Brief does not synthesize data on outcomes or grade evidence. Rather, it seeks to summarize what evidence is available, provide a conceptual or organizational framework to understand key components of the intervention of interest, highlight promising new and innovative strategies, describe barriers to

implementation, and provide guidance regarding future research directions and priorities. The focus of the Technical Brief is on implementation of MAT in primary care settings, including rural or other underserved settings. Specifically, Guiding Question 1 provides an overview of MAT models of care, Guiding Question 2 describes the context in which MAT is implemented, Guiding Question 3 summarizes the current state of the evidence of MAT, and Guiding Question 4 addresses important issues and future directions for MAT. This technical brief is intended to help determine the scope of future research, such as a subsequent systematic evidence review on MAT.

Guiding Questions

1. *Description/Overview of MAT for the Treatment of Opioid Use Disorder:*
    a. What are the different types or models of care of MAT that have been proposed or used in clinical practice?
    b. What are the potential advantages and disadvantages of these respective models of care?
2. *Context in Which MAT is Used:*
    a. In what settings is MAT currently implemented?
    b. Are there special considerations for implementing MAT in primary care, including rural or other underserved settings?
    c. What are potential barriers to implementation, including resources needed, and how do barriers vary according to the setting?
    d. What kinds of training, certification, and staffing are required for various MAT models of care?
3. *Current Evidence on MAT:*
    a. What have published and unpublished studies reported on the use of and effectiveness MAT in primary care settings, including rural or other underserved settings? The technical brief will summarize the following information:
        i. Patient population, including practice setting and country/location
        ii. Details on MAT model of care, including the types of interventions used (specifics of pharmacological and nonpharmacological treatments), provider type/staffing needs, implementation strategy/mode of delivery, frequency, and other factors
        iii. Study design/size
        iv. Comparator used in comparative studies
        v. Concurrent/prior treatments
        vi. Length of followup
        vii. Outcomes measured
        viii. Adverse events/harms/safety issues reported

4. *Important Issues and Future Directions for MAT:*
    a. What are promising new and innovative strategies in MAT models of care?
    b. Given the current state of the evidence, what are the implications for the current level of diffusion and/or further diffusion of MAT?
    c. What are the ethical, equity, and/or cost considerations that impact diffusion, decisionmaking, and/or conceptual thinking around MAT?
    d. What are important areas of uncertainty for MAT?
    e. What are possible key areas of future research on MAT, and what areas related to MAT warrant a systematic review?

Methods

The Technical Brief integrates discussions with Key Informants with searches of the published literature and grey literature to inform the Guiding Questions.

Discussions with Key Informants

We identified and interviewed 11 Key Informants (8 nonfederal and 3 federal) to represent broad and balanced perspectives relevant to MAT, with a focus on people with expertise or experience related to implementation in primary care settings, including rural or other underserved settings. The Key Informants represented the following stakeholder areas: researchers, clinicians (including primary care providers and experts in management of addiction), health policy, implementation, professional societies, patient groups, and federal representatives. Potential Key Informants were asked to disclose conflicts of interest prior to participation. The Agency for Healthcare Research and Quality (AHRQ) Task Order Officers reviewed conflicts of interests; we extended invitations to potential Key Informants who did not have conflicts of interest that precluded participation.

We organized and facilitated small group telephone discussions with the Key Informants (2 to 4 per call) to gain input on the Guiding Questions; group calls maximized efficiency and the relatively small number of Key Informants on each call allowed all representatives the chance to provide input. Members of our research team and the AHRQ Task Order Officers also attended the calls. On the calls, we interviewed Key Informants using a semi-structured approach. Key Informants were asked to respond to predetermined questions targeted to different Key Informant perspectives, share more general insights, and interact with each other (**Appendix A**). The questions were used as a guide, but we asked additional or supplemental questions based on interviewee responses. We asked which MAT models of care are in use in primary care and other related settings, including models of care which are not described in the published literature, and asked Key Informants to describe the different components of the models and which components were particularly effective or promising, the current challenges or barriers to implementation, patient preferences, and future directions, including promising new and innovative models and strategies for implementation. We also asked about specific issues to be aware of when reviewing the literature, such as outcomes to be prioritized, meaningful length of followup, study design issues, and how MAT models of care vary in terms of intensity, goals, and components of care. Because we were particularly interested the feasibility and applicability of models of care implemented in one setting or population compared with others and about identifying models of care that may be particularly suitable for specific settings, including rural and other underserved settings, we focused the questions and discussions in that area. The calls were recorded, and the key points were summarized and shared with the group for clarification and additional input. We reviewed all of the Key Informant input regarding successful and promising MAT models of care and developed a framework for categorizing the different types of components in MAT models of care, to help organize and provide a structure for future research and discussions in this area. We then integrated feedback from the Key Informants with the expertise of our project team and evidence identified from the published and unpublished literature.

Grey Literature Search

To identify grey literature, the AHRQ Evidence-based Practice Center (EPC) Scientific Resource Center sent email notification to relevant stakeholders about the opportunity to submit Scientific Information Packets via the Effective Health Care Web site.

In addition, we conducted searches of the grey literature. Specifically, we searched ClinicalTrials.gov and Health Services Research Projects in Progress (HSRProj) for ongoing research, as well as Google Scholar, NIH Reporter, and Web sites of government agencies with MAT initiatives. The grey literature searches were used to primarily inform Guiding Question 3, but if information relevant to the other Guiding Questions was identified, it is also discussed in the report.

Published Literature Search

We searched, reviewed, and summarized the available literature on MAT for OUD in primary care settings to address Guiding Question 3. An experienced research librarian created search strategies for the following databases: Ovid Medline, PsycINFO, the Cochrane Library, SocINDEX, and CINAHL. The search strategies are available in **Appendix B**. Since OUD with opioid agonists could not be treated in the primary care/nonaddiction treatment settings after the passage of the Harrison Narcotic Act in 1914 until the year 2000, with the passage of the Drug Addiction Treatment Act (DATA) 2000, and due to the focus of the report in primary care settings and the large volume of abstracts, we restricted the start date for the searches to the year 1995 and later (to mid-June 2016). The search was also used to identify contextual evidence to supplement the Key Informant input obtained for Guiding Questions 1, 2, and 4. We also reviewed the reference lists of identified publications and solicited additional references from Key Informants to supplement electronic searches. Searches will be updated while the report is undergoing peer and public review in order to capture any recently-added publications. If any new studies are identified from the update searches or arise as suggestions from the peer or public review, they will be added to the report prior to finalization.

We applied predefined screening criteria to identify the most relevant and authoritative evidence on MAT models of care in primary care settings. For Guiding Question 3, we focused on the following sources of evidence: (1) high-quality Cochrane systematic reviews of MAT; (2) randomized trials and cohort studies on the effectiveness of MAT models of care in primary care settings; (3) randomized trials evaluating the effectiveness of newer pharmacological therapies for MAT that could impact implementation or future models of care; and (4) randomized trials on the effectiveness of more intensive versus less intensive psychological interventions with MAT in primary care settings. To provide context for the other Guiding Questions, we also identified published and unpublished studies describing MAT models of care in primary care settings, including the setting for the model of care (e.g., urban vs. rural), patient characteristics (e.g., age, presence of comorbid conditions, OUD related to prescription opioids for chronic pain versus nonprescribed opioid use), and intervention characteristics (e.g., components of MAT models of care, including degree of coordination and intensity of psychosocial interventions). We also identified studies that provided contextual information on implementation strategies and barriers in primary care settings, including rural and other underserved settings. We excluded trials that focused on the dose or duration of pharmacological therapy, as the focus of this report was on MAT models of care, not on details regarding how pharmacological therapy should be provided.

All titles and abstracts identified through searches were independently reviewed for eligibility against our inclusion/exclusion criteria organized by PICOTS (population, intervention, comparator, outcome, timing, study design) (**Table 1**) by a trained member of the research team. Studies marked for possible inclusion by any reviewer underwent a full-text review. For abstracts without adequate information to determine inclusion or exclusion, we retrieved the full text and then made the determination. All results were tracked in an EndNote® database (Thomson Reuters, New York, NY). Each full-text article was independently reviewed by two trained members of the research team for inclusion or exclusion on the basis of the eligibility criteria. If the reviewers disagreed, conflicts were resolved by discussion and consensus or by consulting another member of the review team. Results of the full-text review were also tracked in the EndNote® database, including the reason for exclusion for excluded full-text publications when they did not meet the eligibility criteria.

For Guiding Question 3, we summarized information from systematic reviews and primary studies that met inclusion criteria in summary tables. For systematic reviews, we summarized information on year of publication, the purpose of the review, search dates and databases searched, the number of studies included, populations and settings in the trials, MAT intervention characteristics, the type of studies included, how quality was rated for included studies, methods of synthesis, the total number of patients included, main findings (including harms), and limitations (including whether the studies were primarily performed in an OTP or addiction specialty settings, whether the studies were conducted outside the United States, and other limitations). For randomized controlled trials, we summarized information on year of publication, comparisons evaluated, duration of followup, sample size, population characteristics, MAT model of care components, setting (including provider type and staffing if that information was provided), outcomes evaluated, and main findings.

For Guiding Question 1, we summarized data sources for the various MAT models of care, including published sources (with citations), unpublished sources (with URL information), and Key Informant input.

Table 1. Inclusion and exclusion criteria for Guiding Question 3 on the efficacy and safety of MAT for OUD

PICOTS	Include	Exclude
Populations	Patients with OUD in primary care settings, including rural or other underserved settings	MAT in inpatient settings and licensed treatment centers or specialty addiction centers; MAT provided outside the United States, Canada, Europe, and Australia/New Zealand
Interventions	MAT (including the use of pharmacological therapy for OUD with psychosocial interventions) for OUD[16]	--
Comparators	1) MAT models of care in primary care settings vs. no MAT 2) MAT model of care vs. another MAT model of care 3) MAT model of care with more intensive psychosocial interventions vs. less intensive psychosocial interventions 4) MAT model of care with newer pharmacological component vs. placebo/no medication or vs. established pharmacological component	Studies that focused on dose or duration of pharmacological component of MAT

PICOTS	Include	Exclude
Outcomes	Measures of retention in care or access Substance-use-related outcomes, including mortality, overdose, substance use Nonsubstance-use-related outcomes, including quality of life, functional status, work status, engagement in criminal activity, rates of unplanned pregnancy, acquisition or transmission of infectious conditions, and others; in pregnant women, maternal and fetal health outcomes	--
Timing	Any	--
Study Design	Cochrane systematic reviews Randomized controlled trials Cohort studies and case-control studies for comparisons #1 and #2	Nonsystematic reviews Studies without original data Non-English language Nonhuman

MAT = medication-assisted treatment; OUD = opioid use disorder; PICOTS = population, intervention, comparator, outcome, timing, study design

Note: Intervention uses the SAMHSA definition for MAT

Findings

Overview

By definition, MAT involves the use of opioid agonists or antagonists in the treatment of OUD. Two medications are currently used in the United States in office-based settings for treating OUD: buprenorphine (with or without naloxone) and naltrexone (as daily oral or extended-release formulations). Medications that have been used in primary care settings in other countries but are not available for treatment of OUD in office-based settings in the United States include methadone and sustained-release morphine; in the United States, methadone can currently only be dispensed for treatment of OUD in licensed and accredited opioid treatment programs or in rare research or demonstration settings.

We interviewed 11 Key Informants: 5 were clinicians with experience treating OUD or in administration of office-based MAT (1 internal medicine/addiction, 1 family medicine/addiction, 1 addiction psychiatry, 1 psychology, 1 registered nurse); 4 had expertise in policy and implementation (3 of these were from federal agencies, specifically the Health Resources and Services Administration/HIV and AIDS Bureau [HRSA/HAB], the SAMHSA, and the National Institute on Drug Abuse [NIDA]); 1 was from an organization representing opioid treatment programs; and 1 represented the patient perspective who also directs a MAT clinic. The interviews were conducted over four phone calls, with two to four Key Informants participating in each call. Interviews lasted from 60 to 90 minutes and consisted of 8 to 12 questions. All interviews took place in February and March 2016. A summary of data sources for Guiding Question 1 describing various MAT models of care in primary care settings is shown in **Table 2**, with sources in **Table 3**. For Guiding Question 3, abstracted data for randomized trials and systematic reviews on MAT models of care in primary care settings are shown in **Tables 4 and 5**, respectively. We abstracted data from a total of 29 publications. A figure depicting the literature flow is available in **Appendix C**, and a full list of included and excluded studies is shown in **Appendixes D and E**, respectively.

Guiding Question 1: Medication-Assisted Treatment Models of Care

A number of MAT models of care in primary care settings were described in the literature and by Key Informants. A challenge in summarizing MAT models of care is that the models of care frequently had overlapping characteristics, and varied in the degree to which they were structured and adapted to specific settings. Key Informants consistently noted four important components of MAT models of care: (1) pharmacological therapy (currently, buprenorphine (with or without coformulated naloxone) or naltrexone (oral or extended-release); (2) provider and community educational interventions; (3) coordination/integration of substance use disorder treatment and other medical/psychological needs; and (4) psychosocial services/interventions. However, they also noted variability in the degree to which each of these components is addressed. We categorized four models as primarily practice-based and eight as systems-based, though most have elements of both. We defined practice-based as a model that can be done in an individual, standalone clinic; whereas systems-based models involve components across multiple levels of the health care system to affect care throughout a network or local region.

Table 2 summarizes 12 representative models of MAT care, how they address these four key components, and into which primary category they fall. These models were selected based on

their influence on current clinical practice, innovation, or because they focus on delivery of MAT in primary care in specific populations or settings (e.g., HIV or HCV-infected people, pregnant women, or in rural settings). **Table 3** summarizes sources used to describe the model. Ten of the models were described in Key Informant interviews, six were described in the published literature (including 4 models evaluated in randomized controlled trials), and eight models were described in unpublished/grey literature sources.

In most (10 of the 12) models of care, buprenorphine/naloxone was the main (and frequently the only) pharmacological therapy offered, with relatively little emphasis on provision of naltrexone in most models. Key Informants noted that in many office-based settings there was not a high demand for naltrexone (due in part to its mechanism of action as a pure opioid antagonist) and the perception that it might not be the optimal therapy for most patients, in the context of limited empiric data regarding its use in primary care. The degree to which educational/outreach interventions were formally incorporated in MAT models of care varied. For example, some models included little or no structured education or outreach, whereas in other models there was an explicit educational/outreach component. Nonetheless, most Key Informants noted that education is important for decreasing stigma associated with MAT among both clinicians and patients, increasing the number of buprenorphine-waivered clinicians, increasing buy-in from staff involved in treatment of OUD, and increasing understanding and uptake of MAT by patients.

Educational/outreach efforts included local stakeholder meetings for training and to establish and disseminate standards of care (Southern Oregon Model), mentored buprenorphine prescribing and Internet-based provider education and support (Project Extension for Community Healthcare Outcomes [ECHO]), training aimed at getting more physicians waivered for use of buprenorphine, and education aimed at decreasing stigma and increasing use or uptake of MAT by clinicians, office staff, and patients (various models). The SAMHSA-funded Physician Clinical Support System-Buprenorphine (PCSS-Buprenorphine), a Web-based resource designed to support physicians who prescribe buprenorphine by providing training and education and linking them with a national network of trained physician mentors, was instrumental in increasing the number of buprenorphine-waivered physicians during the initial expansion of MAT into office-based settings.[26] Now supplanted by the Prescribers' Clinical Support System-Medication Assisted Treatment (PCSS-MAT),[27] PCSS represents a method for providing physician education and support services that is widely available across geographic settings and in different models of care.

Key Informants consistently noted that coordination/integration of care is critical for successful delivery of MAT in primary care settings. Coordination/integration of care was an explicit component of all of the more structured MAT models of care. In six MAT models (Hub and Spoke, Office-based Treatment Model (OBOT), Massachusetts Nurse Care Manager Model, Buprenorphine HIV Evaluation and Support (BHIVES) Collaborative Model, Project ECHO, One Stop Shop), a specific nonphysician is designated with providing care integration and coordination for treatment of OUD and coordinating primary medical care and mental health needs. The care coordinator may also serve as the main point of contact for patients, allowing for less extensive physician-patient contact. In these models, physicians primarily prescribe buprenorphine/naloxone, have less frequent face-to-face visits with the patient, and provide consultation as needed. This type of "glue" person was viewed as critical for offloading the burden of care from physicians and allowing them to manage more patients with OUD

successfully, with the provision that the glue person needs to have requisite skills and knowledge in treating OUD.

Key Informants also consistently noted that availability of psychosocial services is essential to successful MAT models of care, and that capacity to refer patients for appropriate counseling is required to meet requirements for office-based MAT as specified in DATA 2000.[28] The degree to which psychosocial services are integrated into the MAT treatment setting, the intensity of psychosocial treatments, and the intensity of psychosocial services, varied even within programs implementing the same model of care. There is disagreement regarding the types or intensity of psychosocial services required to implement successful office-based models of care in primary care settings. Some Key Informants considered models of care without integrated, comprehensive psychosocial services to be inadequate; other Key Informants noted that models of care that included brief counseling with medication treatment have been shown to be effective and that although such models might not represent the ideal, they may be easier to implement and already represent a great improvement in terms of access to care and treatment outcomes. Key Informants noted that the need for more intensive psychosocial services is likely to vary according to the setting and population treated and that models of care that do not have more intensive psychosocial services may find it difficult to manage more complex patients. In most MAT models of care, additional psychosocial services, including management of psychiatric comorbidities, group and individualized counseling, peer support, social and family support, and community support services are available on-site or nearby. In the Collaborative Opioid Prescribing (Co-OP) model, ongoing psychosocial services are provided by a partnering OTP. Although the Key Informants noted a preference for comprehensive, on-site psychosocial services, they noted that this was not always possible due to financial constraints or local availability of services. The One Stop Shop model represents a unique model in which MAT is provided in a preexisting mental health clinic with comprehensive psychosocial services and also provides primary care and other health services. Several models of care focus on identification and initiation of MAT in specific settings (e.g., emergency department, during hospitalization, or in prenatal care), with referral to ongoing treatment in community-based/primary care settings.

The following section describes the 12 representative models of care in more detail, including advantages and disadvantages of each.

Hub and Spoke Model

The system-based Hub and Spoke model was developed in Vermont.[29-32] The model consists of two levels of care, with the patient's needs determining the appropriate level. In this model, "hubs" are OTPs that serve as regional specialty treatment centers (currently numbering 6) that provide traditional treatment for OUD and also have the capacity to either directly provide or to organize comprehensive care and continuity of services in a home health model. "Spokes" are clinics in the community that provide MAT and comprehensive care for less clinically complex patients. Patients are screened to determine whether they are appropriate for initial stabilization and management in a hub or spoke. The hubs provide care for clinically complex patients, support tapering off MAT, dispense methadone if needed, and provide consultative services to the spokes. Following stabilization, patients initially managed at a hub who do not require ongoing management at the hub may have their management transferred to a spoke; conversely, patients managed in a "spoke" who require a higher level of care may be transferred to a hub. Buprenorphine/naloxone has been the primary pharmacological component in the spokes within the Hub and Spoke model. The model is financed through a Medicaid health home model waiver

state block grant. Its effect on outcomes has not been published. Vermont incentivized implementation of buprenorphine/naloxone prescribing by funding online training for physicians to obtain buprenorphine waivers and providing other technical assistance to physicians prescribing buprenorphine. The Hub and Spoke model includes some educational outreach in the community to increase the number of buprenorphine waivered physicians. Coordination and integration occurs between the hub and spoke as well as within each spoke site, and is typically carried out by a registered nurse, clinician case manager, or other "care connector" (e.g., via peer-to-peer support or behavioral health workers). Psychosocial services are embedded within spoke sites, including social workers, counseling, and community health teams.

An important advantage of the Hub and Spoke model is the availability of tiered care and the availability of regional expertise in the management of OUD. The established relationships between the hub and spokes promote ongoing coordination and integration, including efficient consultation with the hubs and transfer of care to the hub as needed. Within the spoke sites in this model of care, the use of designated nonphysician "care connectors" at the spoke sites and availability of embedded psychosocial services are important advantages over models in which the coordination/integration roles are less well defined or in which psychosocial services are not available on-site. A potential disadvantage of the Hub and Spoke model is that a hub with the appropriate expertise and resources may not be available in all settings that wish to implement a MAT model of care. Also, the spokes in the Hub and Spoke model are likely to vary in the degree of expertise and types of services provided.

Collaborative Opioid Prescribing Model

The system-based Collaborative Opioid Prescribing (Co-OP) model was developed in Baltimore.[33,34] Similar to the Hub and Spoke model, initial intake, induction with buprenorphine/naloxone, and stabilization is performed at a center (in the Co-OP model, this is an OTP). Patients are shifted to primary care clinics for ongoing MAT after stabilization on medication. Unlike the Hub and Spoke model, in the Co-OP model psychosocial services are generally provided concurrently on an ongoing basis by the OTP, rather than at the primary care site. Some outreach and education is performed by counselors involved in Co-OP to community physicians. Financing is through Medicaid and private insurance.

Like the Hub and Spoke model, an advantage of the Co-OP model is that initial evaluation and management occurs in a specialty center; in addition, the specialty center continues to provide psychosocial services following the handoff to the primary care site. Therefore, this model takes advantage of the expertise and resources available at the OTP on an ongoing basis. A potential disadvantage of the Co-OP model is that because ongoing psychosocial services are provided by the OTP, it may require relatively close proximity between the primary care sites and the OTP, which may not be available in all settings that wish to implement a MAT model of care. Also, because the OTP in the Co-OP model provides ongoing services, this could limit the number of patients that could be managed compared with the Hub and Spoke model, in which ongoing care for most patients is more dispersed and provided more independently within the spoke centers.

Office-Based Opioid Treatment

An early model for Office-Based Opioid Treatment (OBOT), a practice-based model, has been widely disseminated throughout the United States. In OBOT, physicians who complete 8 hours of training and receive a DEA waiver number may prescribe buprenorphine/naloxone in

the context of primary care While many providers offer OBOT without staff assistance, some practices designate a clinic staff member, or "glue person" (often a nurse or social worker) who works in collaboration with a primary care clinician to coordinate services.[35-37] The glue person is instrumental for coordinating and integrating care, including primary care and mental health. Psychosocial services include regular brief counseling provided by the physician and glue person or other staff; other psychosocial services vary but can include integrated cognitive behavioral therapy or motivational enhancement therapy. Psychosocial services may be located on-site or off-site. Early OBOT trials provided education and training of new buprenorphine prescribers, which led to the development of the PCSS-Buprenorphine (now PCSS-MAT) model nationally, including mentoring by more experienced prescribers. OBOT is financed through provider reimbursement of billable visits. Medicare and many state Medicaid programs cover buprenorphine, though prior authorization is frequently required.

A key advantage of the OBOT model is its use of a glue person to coordinate ongoing care. This provides an efficient way for the prescribing physician to manage more patients. The model also takes advantage of a training and mentoring resource available via the Web. Although regular brief counseling is a core aspect of this model, a potential disadvantage is that the availability of additional psychosocial services is highly variable, which could make management more difficult for more complex patients. In addition, coordination and ongoing relationships with OTPs appear relatively informal or undefined in this model.

Massachusetts Nurse Care Manager Model

This system-based model was developed in Massachusetts, where Medicaid reimburses Federally Qualified Health Center nurses for OUD care management.[38-40] This model is similar to the OBOT model in that a key aspect is the use of a nonphysician to coordinate and manage much of the care. Unlike the OBOT model, the Massachusetts model specifically uses nurse care managers who team with primary care physicians to provide MAT (primarily buprenorphine/naloxone, with integration of extended-release naltrexone over the last 2 years). The nurse care manager performs initial screening, intake, and education, often with assistance from a medical assistant. The nurse care manager also provides ongoing management of OUD and other medical issues, including drop-in or same day visits, management of acute issues, coordination of prior authorization requests, communication with pharmacists, and perioperative care coordination. The diagnosis of OUD and appropriateness of MAT are confirmed by the prescribing physician, who comanages the patient with the nurse care manager. One Key Informant described an adaptation of this model at a community-based health care system in Massachusetts in which a "care partner" (usually a master's level individual who is not a nurse care manager) performs this role. This model uses a training program to get more primary care physicians involved in prescribing buprenorphine and education is provided on best MAT practices; the nurse care manager receives training in MAT and addiction. Psychological services are integrated on-site or nearby, though the specific services that are available vary from site to site. Patients who require a higher level of care can be expedited into treatment in an OTP. The model is financed through direct Medicaid reimbursement to FQHCs for nurse care manager time as a billable service, in addition to usual Medicaid coverage for pharmacotherapy and physician visits.

A key advantage of this model is that it uses a nonphysician to offload some of the burden from prescribing physicians, which in turn enables the prescribing physicians to manage more patients. This model also emphasizes training and education to engage more primary care

physicians in prescribing buprenorphine. Another advantage of this model is that it may be more sustainable financially, because Medicaid reimburses federally qualified health center (FQHC) nurses in Massachusetts for OUD care management and the state supports additional coordination services using Block Grant resources. However, this reimbursement mechanism is not available in all states. A disadvantage is that the availability of psychosocial services and whether they are present on-site vary. In addition, the model is highly dependent on the availability of a skilled person who can assume the nurse care manager or analogous role effectively.

Buprenorphine HIV Evaluation and Support Collaborative Model

The practice-based Buprenorphine HIV Evaluation and Support (BHIVES) Collaborative model uses the OBOT framework to provide a chronic care model for providing buprenorphine in HIV primary care settings.[41-51] Like the OBOT Model, a clinic coordinator glue person (typically a counselor or social worker) is essential for coordinating care, working in conjunction with the primary care provider. HIV care can be provided by the primary care provider or by another on-site provider in coordination with the primary care provider. BHIVES sites generally have on-site psychological services, including individual counseling, though the types of services vary. HIV clinics coordinate with affiliated OTPs for patients switching to or from methadone. A HRSA[52] monograph promotes adoption of BHIVES in United States HIV clinics and BHIVES is considered the standard of care for engaging HIV-infected patients with OUD in treatment.[53,54] Buprenorphine and HIV care are typically covered by patient insurance. Ryan White Care Act funding supplements medication coverage, care coordination and counseling services in some states.

An advantage of the BHIVES model is that it is specifically designed to address MAT, HIV care, and primary care within a single setting. It also has the same advantages as other models that use a glue person for chronic care management and coordination. A potential disadvantage is that the availability of on-site psychological services and the types of available services vary and are not well specified. In addition, it requires clinicians with expertise and knowledge in both MAT as well as HIV care, which may not be available in all settings. PCSS now includes physician mentors with expertise in HIV care, an educational model that could potentially be expanded for other chronic comorbid conditions.

Project Extension for Community Healthcare Outcomes

Project Extension for Community Healthcare Outcomes (ECHO), a system-based model of care first developed in New Mexico, links primary care clinics in rural areas with a university health system utilizing an Internet-based audiovisual network for mentoring and education[55-57] regarding an array of medical conditions. The University of New Mexico developed a module for supporting rural primary care providers in MAT management. It emphasizes nurse practitioner- or physician assistant-based screening with referral to a collaborating physician prior to initiation of MAT and for ongoing treatment, typically with buprenorphine/naloxone. Counseling and behavioral therapies are offered from all ECHO team members. Complex patients can be referred for further assessment and/or evaluation at an OTP. There is also an emphasis on recruitment of physicians for buprenorphine waiver training and provision of continuing medical education in OUD. It is financed through various federal grants and Medicaid.

An important advantage of the ECHO model is that it enhances the ability of rural primary care clinics to provide MAT though its Internet-based mentoring and educational network. The ECHO model may be considered a rural adaptation of the Hub and Spoke or Co-OP models, in that it engages the expertise of a "hub" center to assist in provision of MAT. A potential disadvantage of the ECHO model over traditional tiered care models is that due to the geographic distance between the primary care sites and the hub, initial intake and assessment does not occur at the centralized hub, due to the dispersed and rural settings in which care is provided. Rather, all care, including initial intake and assessment, occur at the primary care sites. The limited availability of on-site or face-to-face expertise in MAT could pose challenges for the management of complicated or high-risk patients. The ECHO model may have had some impact in New Mexico placing among the top states in buprenorphine-waivered physicians per capita; New Mexico has also had more rapid growth in the number of waivered physicians practicing in rural areas than in other areas of the United States since its initiation in 2005.[55] In addition, the ECHO model focuses on utilizing mid-level care providers for performing initial screening, which may be critical for expanding access to MAT in many rural settings. There is also a strong emphasis on provision of psychosocial services in the ECHO model. The ECHO model is a tele-education/tele-consulting approach considered distinct from telemedicine, as there is no direct doctor-patient relationship between off-site experts and patients, who are de-identified. A potential advantage of this approach is that it only requires basic, widely-available teleconferencing technology and does not require the high startup costs required for Health Insurance Portability and Accountability Act (HIPAA)-compliant telemedicine expansion or the sustainable funding necessary to purchase and maintain telemedicine technology and services. A potential disadvantage is the lack of direct contact between off-site experts and patients, which could make it more difficult to manage complicated patients and obtain reimbursement for providing consultative expertise.

Medicaid Health Home Model for Those With Opioid Use Disorder

The Medicaid Health Home Model is a flexible, system-based model through Centers for Medicare and Medicaid Services that allows states that apply for a Medicaid waiver to integrate MAT and behavioral health therapies with primary care for patients with OUD.[58,59] Provider and community education is emphasized to increase uptake (by clinicians and patients) and to decrease stigma. A core aspect of this model is that core psychosocial services are required (i.e., comprehensive care management, care coordination, health promotion, comprehensive transitional care/followup, individual and family support, and referral to community and social support services). Some telehealth services are also offered, though their availability and use vary. Implementation of Medicaid Health Home Models differs from state to state with differences in how the models are structured and overlap with other models of care (e.g., Hub and Spoke) described in this section. In several states (e.g., Rhode Island and Maryland), implementation of the Medicaid Health Home Model has been in OTPs or psychiatric clinics, rather than in primary care clinic settings,[59] although as described above, the Hub and Spoke model involves a tiered model of care that includes community-based "spokes." Buprenorphine/naloxone has been the primary pharmacological component of treatment, with integration of injectable naltrexone over the last 2 years. States determine the structure of health care delivery, for example with Hub and Spoke models in Vermont, and approach to payment, which may include per member per month payments (Maryland) and weekly bundled payments (Rhode Island) that fund care coordinators in addition to other billable health care services.

An advantage of the Medicaid Health Home Model is that it requires care coordination and a set of core psychosocial services. In addition, provider and community education are emphasized as key aspects of this model. The flexibility of this model is an advantage in enabling service delivery and provision to vary according to the needs and resources of the particular setting. At the same time, the flexibility of the model may be viewed as a disadvantage in that some aspects (e.g., who provides coordination/integration, who performs initial screening and assessment) are not standardized or well-defined.

Southern Oregon Model

The Southern Oregon Model is an example of a local and informal system-based model for delivery of MAT in a rural primary care network.[60] It focuses almost exclusively on buprenorphine/naloxone. A notable characteristic of the Southern Oregon Model is that it has used regular meetings of stakeholders (including regional Medicaid-accountable care organizations) for education, training, and development of practice standards around the prescription of opioids for chronic pain and addiction treatment. Coordination or integration of care is variable and often limited, though an on-site clinical social worker is available. A leader of this model is also medical director of a local federal oversight OTP clinic, providing a source of referral and consultation to providers in the region. However, access to OTPs for complex patients is not formally integrated. The model is financed through direct support from Accountable Care Organizations and usual fee for service billing.

An advantage of this model is that it is a grass-root, community-based effort, which may promote buy-in from clinicians and those in the community. This could serve as a model for implementation of MAT in rural settings where there may be increased stigma associated with MAT and resistance to its use. However, a number of key components of this model are not yet well-defined, and a Key Informant noted that psychosocial services and coordination/integration of care is often limited. The Key Informant also noted that the relationship with the local OTP is suboptimal and at times office-based MAT is viewed as a competitor rather than a partner by the OTP.

Emergency Department Initiation of Office-Based Opioid Treatment

This system-based model focuses on the emergency department (ED) identification of OUD, with buprenorphine/naloxone induction initiated in the ED.[61] Patients are connected to ongoing OBOT, then transferred to ongoing, office-based maintenance treatment or detoxification. Brief "medical management" counseling is performed by physicians; other psychosocial services vary. Medications, ED visits, and OBOT are funded through patient Medicaid and other insurance plans.

An advantage of this model is that it identifies patients who might benefit from MAT and may not have access to primary care, or only sporadic access. Initiation of buprenorphine/naloxone in the ED also appears to increase retention in care rates versus a simple referral. A potential disadvantage of this model is added congestion in the ED as a means to access treatment. In the randomized trial that evaluated this model, ongoing management in primary care settings was provided through the OBOT model, which may not be the model available in all settings. However, the ED initiation model could be used to "feed" into various office-based models of care, depending on what is available in the community.

Inpatient Initiation of Medication-Assisted Treatment

This system-based model involves the identification of OUD in the hospital, with initiation of MAT (methadone, buprenorphine/naloxone, or naltrexone) during the hospitalization by a multidisciplinary addiction consult service.[62] Patients are connected with primary care or specialty addictions care (patients initiated on methadone must be followed in an OTP), where treatment continues following hospital discharge. In some programs, when relevant, there is a buprenorphine "bridge" clinic for stabilization prior to transitioning to primary care. Ongoing psychosocial services are provided at primary care sites. A variation of this model involves identification of OUD in the hospital and brief counseling, with facilitated referral to a community-based clinic for induction of MAT and ongoing care following hospital discharge.[63] Another variation uses a program nurse to identify inpatients with OUD, a bridge clinic for initiation of methadone following discharge with provision of psychosocial services (case management, group health education, counseling), and transition to another OTP for long-term management; such a program could be adapted for office-based prescribing of buprenorphine/naloxone.[64] This model requires hospital support for initial development of inpatient consult services.

Like the model involving ED initiation, an important advantage of inpatient screening and initiation is that it identifies patients with complex morbidity and high risk of mortality who otherwise may have had limited or no access to MAT. Likewise, inpatient initiation appears to enhance retention in care rates versus simple referral for outpatient initiation of MAT after hospitalization. Like the ED initiation model, this model of care focuses on the inpatient aspect, but could be linked to one of the office-based models of care described above for ongoing management. Patients initiated on methadone would not be eligible for referral to office-based care.

Integrated Prenatal Care and Medication-Assisted Treatment

This practice-based model involves the provision of prenatal care to pregnant women who are treated with buprenorphine in primary care. Women receive prenatal and postpartum care, with care continued in an office-based setting after birth. Psychosocial services are provided on-site as well as through affiliated OTPs.

Like the models of ED and inpatient MAT initiation, this model can identify women with limited or no access to care who come into contact with the medical system for prenatal care and might benefit from MAT. In addition, women may be more amenable to MAT in the prenatal setting due to concerns about the fetus and the desire to integrate care in one location. An additional advantage of this model is that it provides ongoing care in the postpartum period, providing additional continuity. Outcome studies conducted in OTP settings suggest that there is a reduction in Neonatal Abstinence Syndrome when pregnant women with OUD are maintained with buprenorphine rather than methadone.[65,66] This model is typically financed through existing Medicaid and other insurance reimbursement. A potential disadvantage is the need to transition at some point to a setting that can provide ongoing, long-term care, unless the office-based setting is equipped to do so. In one model (Southern Oregon), ongoing care is provided through transition to a primary care clinic that can provide MAT.

One Stop Shop Model

The One Stop Shop model was developed in response to an outbreak of HIV infection in rural Indiana due to sharing of infected syringes.[67] Based in an existing mental health clinic, it provides integrated care including management of HIV/HCV infection, MAT, mental health, and primary care needs, as well as other services including syringe exchange.[68] This practice-based model focuses on use of extended-release naltrexone as the pharmacological component. Peer navigators and social workers provide coordination with primary care providers. Because it is based in an existing mental health clinic, this model provides comprehensive on-site psychological services, including a visiting psychiatrist who is available on a weekly basis for consultation. Financing is from a combination of existing Medicaid and federal funding.

An advantage of this model is that it makes use of an existing mental health clinic to provide comprehensive integrated care, including extensive psychosocial services under a single roof. However, Key Informants noted that this model represents a unique response to the HIV outbreak and may not be reproducible in other settings due to the resources and unique clinical setting (i.e., an existing mental health clinic prepared to provide MAT) required. In addition, this model was implemented recently, with more data needed to understand how successfully it can be implemented.

Table 2. Overview of MAT models of care for OUD in primary care (including rural or other underserved settings)

Model	Summary	Components				
		Pharmacologic	**Education/Outreach**	**Coordination/Integration of Care**	**Psychosocial**	**Other**
Practice-based models						
OBOT	Buprenorphine prescribed by primary care providers who complete DATA2000 waiver training	Primarily buprenorphine–naloxone	Not a major component; Provider Clinical Support Service for MAT (PCSS-MAT) available to mentor primary care providers	A non-physician clinic staff member sometimes used to coordinate MAT prescribing and integration with primary and mental health care.	Physician or other onsite or off-site counseling at least monthly; Other psychosocial services vary, including integrated cognitive behavioral therapy and motivational enhancement therapy; some psychosocial services off-site.	–
Buprenorphine HIV Evaluation and Support Collaborative model	OBOT adaptation for providing buprenorphine–naloxone in an HIV primary care clinic setting	Buprenorphine–naloxone	Patient and provider educational material available online	Treatment for OUD and primary care, including HIV care integrated in the same setting. A non-physician clinic staff coordinates care and collaborates with HIV primary care provider.	On-site psychological services vary, including individual and group counseling.	Coordination with OTP for patients switching to or from methadone
One-stop shop model	Integrated model based in mental health clinic to provide "one-stop," comprehensive management of HIV/HCV infection and MAT	Primarily naltrexone	Provider education in MAT, HIV, and hepatitis C management	Treatment for OUD, mental health, and primary care (including HIV/HCV care) provided in the same setting. Peer navigators and social workers provide coordination with primary care providers.	Centered in a mental health clinic that provides comprehensive psychological services; psychiatrist once weekly.	Syringe exchange and other services also available; Model developed to respond to specific outbreak of HIV and Hepatitis C in rural area.
Integrated prenatal care and MAT	Model providing prenatal care to pregnant women who are treated with buprenorphine	Buprenorphine	Not a major component, though PCSS-MAT service available.	Primary care clinic provides MAT, as well as prenatal and postpartum care; care continued in office-based setting for 1 y after delivery. In some programs, women can work with doulas.	Services provided on-site or via partnering OTP.	–

Model	Summary	Components				
		Pharmacologic	**Education/Outreach**	**Coordination/Integration of Care**	**Psychosocial**	**Other**
System-based models						
Hub-and-spoke model (Vermont)	Centralized intake and initial management (buprenorphine induction) at "hub"; patients are then connected to "spokes" in the community for ongoing management	Primarily buprenorphine–naloxone	Outreach to prescribers in the community to increase the number of buprenorphine-waivered physicians	Coordination/integration between hub and spoke as well as within each primary care site spoke. Registered nurse clinician case manager and/or care connector (peer or behavioral health specialist) for coordination/integration of care at spokes.	Embedded in spoke sites, including social workers, counseling, and community health teams.	Hubs provide consultative services and are available to manage clinically complex patients; support tapering of MAT; or prescribe methadone, if needed
Medicaid health home model	A flexible model that provides MAT in combination with behavioral health therapies and integrated with primary care	Primarily buprenorphine–naloxone	Provider and community education emphasized to increase uptake and decrease stigma	Required component, but mechanism of coordination varies.	6 core psychosocial services are required: comprehensive care management, care coordination, health promotion, comprehensive transitional care/follow-up, individual and family support, and referral to community and social support services.	Some telehealth services offered
Project ECHO (New Mexico)	Model of care for linking primary care clinics in rural areas with a university health system, emphasizing NP or PA screening and MAT (physician prescribing) combined with counseling and behavioral therapies	Primarily buprenorphine–naloxone	Mentored buprenorphine prescribing for providers, including an Internet-based, audiovisual network for provider education. Free buprenorphine training provided several times yearly. ECHO staff provide patient education 1-to-1 or in group setting.	NP/PA performs initial evaluation and screening to educate patient and refer to collaborating physician for treatment. NP/PA performs monitoring treatment and follow-up appointments, including laboratory tests, urine testing, monitoring, patient education and support, and other coordination (e.g., vaccinations).	Counseling and behavioral therapies offered from all ECHO team members, including CHWs; however, CHWs and NPs provide education/support; psychosocial support, including 12-step programs; crisis counseling; referrals; and relapse-prevention plans.	Refer any patients with high or moderate risk scores for opioid use to NP for further assessment and/or referral to OTP

Model	Summary	Components				
		Pharmacologic	**Education/Outreach**	**Coordination/Integration of Care**	**Psychosocial**	**Other**
Collaborative opioid prescribing model (Maryland)	Links OTPs with office-based buprenorphine providers; initial intake, induction, and stabilization performed at OTP then shifted to primary care clinic	Buprenorphine–naloxone	Outreach performed by counselors to community physicians	Initial assessment, psychosocial treatment, and expert consultation initiated in drug treatment program and patients transitioned to primary care in a federally qualified health center after stabilization.	Provided concurrently via OTP, including ongoing counseling and monitoring	In Baltimore, Maryland, supports to facilitate access to health coverage through Medicaid and to coordinate care through HealthCare Access Maryland
Massachusetts nurse care manager model	A primary care–based model that teams nurse care managers with primary care physicians; nurse care managers generally perform initial screening, intake, education, observed/supports induction, follow-up, maintenance, stabilization, and medical management with the physician and team	Primarily buprenorphine–naloxone, with recent addition of extended-release naltrexone	A training program exists to get more physicians (especially residents) and faculty on board. The Department of Public Health trains staff on best practices. Nurse care managers receive 8 h of training in MAT, shadowing in model MAT site, site visits, e-mail and telephone support, case review, quarterly training, and an addiction listserv.	Nurse care managers (registered nurses or family NPs) manage 100 to 125 patients alongside primary care clinicians, with assistance from a medical assistant. Alternatively, care partners (usually persons with a master's degree) assist the primary care staff with screening, brief intervention, and referral to treatment.	Psychological services are integrated on-site or nearby	Patients who require a higher level of care can be expedited into an OTP, assistance with transfers of care, and day-support programs
ED initiation of OBOT	Model involving ED identification of OUD; buprenorphine–naloxone induction initiated in the ED; coordination with OBOT, nurse with expertise in buprenorphine working in collaboration with primary care clinician	Buprenorphine–naloxone	Not a major component	OUD identified in ED and patients started on buprenorphine therapy and connected to ongoing OBOT provided by physicians and nurses for 10 wk, then transferred to office-based ongoing maintenance treatment or detoxification.	"Medical management" counseling visits with physician and nurse	–

Model	Summary	Components				
		Pharmacologic	**Education/Outreach**	**Coordination/Integration of Care**	**Psychosocial**	**Other**
Inpatient initiation of MAT	Model involving identification of OUD in the hospital and connecting patients to office-based MAT and primary care	Buprenorphine–naloxone and naltrexone	Not a major component	MAT started by multidisciplinary addiction consult service during medical hospitalization and connected with primary care. Treatment continued in primary care; some programs have buprenorphine "bridge" clinic before transition to primary care.	Provided at primary care site	–
Southern Oregon model	A local and informal model for delivery of MAT in a rural primary care network	Almost exclusively buprenorphine–naloxone	A group of local stakeholders from many perspectives who prescribes opioids (Oregon Pain Guidance) meets regularly to develop guidance and provide education.	Relatively limited support for coordination/integration of care.	On-site licensed clinical social worker with experience in treating patients for pain and addiction, not necessarily in MAT.	Access to OTPs for complex patients not formally integrated.

CHW = community health worker; ECHO = Extension for Community Healthcare Outcomes; ED = emergency department; HCV = hepatitis C virus; MAT = medication-assisted treatment; NP = nurse practitioner; OBOT = office-based opioid treatment; OTP = opioid treatment program; OUD = opioid use disorder; PA = physician assistant

* Includes rural or other underserved settings

Table 3. Sources for MAT models of care

Model	Published Literature	Grey Literature	Key Informant Interview
Buprenorphine HIV (BHIVES) Integrated Care Model	Altice, 2011[41] Chaudhry, 2011[69] Cheever, 2011[70] Egan, 2011[71] Fiellin, 2011[43] Finkelstein, 2011[72] Friedland, 2011[73] Korthuis, 2011[44] Korthuis, 2011[45] Lucas, 2010[46]* Lum, 2011[74] Schackman, 2011[75] Sullivan, 2006[48]* Sullivan, 2011[76] Vergara-Rodriguez, 2011[77] Weiss, 2011[50] Weiss, 2011[51]	https://www.careacttarget.org/library/beehive-buprenorphine-program-tools[49] http://www.slideshare.net/SarahCookRaymond/buprenorphine-therapy-in-the-hiv-pruma[47]	✓
Collaborative Opioid Prescribing (Co-OP) Model	Stoller, 2015[34]	http://www.atforum.com/pdf/CoOPtalkforONDCP_SAMHSAAug2015Stoller.pdf[33]	✓
Emergency Department (ED) Initiation of OBOT Model	D'Onofrio, 2015[61]*	--	✓
Hub and Spoke Model (Vermont)	--	https://www.pcpcc.org/initiative/vermont-hub-and-spokes-health-homes;[30] http://www.healthvermont.gov/adap/documents/HUBSPOKEBriefingDocV122112.pdf[31] http://www.leg.state.vt.us/reports/2014ExternalReports/299315.pdf[29] http://www.achp.org/wp-content/uploads/Vermont-Health-Homes-for-Opiate-Addiction-September-2013.pdf[32]	✓
Inpatient Initiation of MAT	Liebschutz, 2014[62]*	--	--
Integrated Prenatal Care and MAT (Expert suggestion)	--	--	--
Massachusetts Nurse Case Manager Model	Alford , 2007[39] Alford , 2011[38] LaBelle, 2016[40]	http://www.mass.gov/eohhs/gov/departments/dph/stop-addiction/get-help-types-of-treatment.html[78]	✓
Medicaid Health Home Model For Those With Opioid Use Disorder	-	https://www.medicaid.gov/Federal-Policy-Guidance/Downloads/CIB-07-11-2014.pdf[58] https://www.medicaid.gov/state-resource-center/medicaid-state-technical-assistance/health-homes-technical-assistance/downloads/hh-irc-health-homes-opiod-dependency.pdf[59]	✓

Model	Published Literature	Grey Literature	Key Informant Interview
Office-based Opioid Treatment (OBOT)	Fiellin, 2002[37]* Fiellin, 2006[36]* Fiellin, 2008[35]	--	✓
One Stop Shop Model	--	http://www.lifespringhealthsystems.org /[68]	✓
Project Extension for Community Healthcare Outcomes (ECHO) (New Mexico)	Komaromy, 2016[55]	http://echo.unm.edu/wp-content/uploads/2014/10/Opioid-Abuse-and-Addiction-Management-Protocol.pdf[56] http://www.aafp.org/news/chapter-of-the-month/20140930nmafp-chapspot.html[57]	✓
Southern Oregon Model	--	www.oregonpainguidance.org[60]	✓

MAT = medication-assisted treatment

*****Randomized controlled trial evaluating the model of care

Guiding Question 2: Settings in Which Medication-Assisted Treatment Is Implemented

MAT is currently implemented in a variety of primary care settings. As described above, models of care are implemented in general primary care settings as well as in settings in which primary care is integrated with management of other conditions (e.g., HIV, pregnancy, mental health). Certain models use the ED and inpatient settings to identify patients with OUD who could benefit from induction and referral to office-based treatment. Most studies on MAT in primary care settings have been conducted in centers that are either university-affiliated or hospital-based. Because of the need to expand access to the medically underserved and to support access to MAT in office-based settings for Medicaid beneficiaries[58] and in FQHCs,[79] aspects of MAT models of care developed in university-affiliated or hospital-based settings may be transferable to community-based settings (e.g., use of a glue person for care coordination and initial management, association with a centralized center of excellence, focus on integration and coordination of care, and provision of psychosocial services).

DATA 2000 and the approval of buprenorphine in 2002 increased the availability of MAT by permitting waivered physicians to prescribe buprenorphine for treatment of OUD. A 2006 report from SAMHSA on the effects of the DATA Waiver Program found that about 56 percent of waivered physicians were from a nonaddiction specialty[80] (the proportion that were primary care providers was not reported). However, not all waivered physicians actually prescribed buprenorphine. Among waivered physicians, approximately two-thirds reported prescribing buprenorphine. As of 2016, 21,781 physicians in the United States were certified to provide buprenorphine treatment for up to 30 patients and 10,459 were certified to provide buprenorphine treatment for up to 100 patients (total 32,240).[81]

There is geographic variability in the United States in access to and utilization of MAT. One study found that buprenorphine use was highest in the Northeast (Vermont, Maine, and Massachusetts) and lowest in South Dakota, Iowa, and Kansas.[82] Many geographic areas in the United States continue to experience shortages in access to MAT in primary care settings, especially for patients living in rural areas. A survey found that only 3 percent of primary care physicians in rural American had received a Drug Enforcement Administration (DEA) DATA waiver to prescribe buprenorphine for OUD. Although the proportion of the United States population residing in rural counties has declined substantially, about half of United States counties have no buprenorphine-waivered physicians, and it is estimated that more than 30 million people live in counties (predominantly in nonmetropolitan areas) without access to buprenorphine treatment.[24,83,84] One study estimated that the number of physicians with buprenorphine waivers (per 10,000 population) is about 7 to 9 times higher in urban compared with rural settings.[85] Another study found that states that opted to expand Medicaid following the passage of the Affordable Care Act and establish a state-based health insurance exchange experienced greater growth in the supply of buprenorphine-waivered physicians than states that did not take these actions.[86] In another study, states with increased Medicaid funding, more opioid overdose deaths, and specific state guidance for office-based buprenorphine use were associated with more buprenorphine-waivered physicians.[84] We did not identify published estimates regarding utilization of naltrexone for OUD. Key Informants indicated that oral naltrexone is rarely used in primary care settings for OUD, given evidence suggesting ineffectiveness and low compliance. Although Key Informants noted that extended-release naltrexone is an appropriate treatment for OUD (approved for this indication by the FDA in 2010), they noted that utilization of extended-release naltrexone is highly variable.

Facilitators and Barriers for Implementing Medication-Assisted Treatment in Primary Care

Our Key Informants and literature review identified a number of important considerations for implementing MAT in primary care. Insufficient institutional support is frequently cited as a barrier to implementation.[87,88] Institutional support may include sponsored training, resources and staffing for coordination and integration of care, and provision of nonphysician staff with expertise in OUD in order to implement a team-based approach, utilizing the skills appropriate to each profession, as well as offloading some of the burden from prescribing physicians. Primary care physicians also report important knowledge gaps in the area of addiction. These gaps reduce the likelihood that they will prescribe MAT unless they have ready access to addiction expertise (e.g., for complex patients). Addiction expertise could be accessed through telehealth initiatives (e.g., Project ECHO), mentored prescribing (e.g., PCSS-MAT), coordination with local OTPs or experts in addiction (e.g., Hub and Spoke model or Co-OP model), or other methods. Barriers to telehealth include substantial start-up costs to be HIPAA-compliant, the need for ongoing resources for staffing and maintenance, and variable reimbursement. Implementing MAT also requires the integration of enhanced psychosocial services that may not be readily available in all primary care settings. Because provision of MAT involves multiple practitioners with varying types of expertise, improvement in communication and exchange of health information could greatly facilitate implementation.

Another consideration is whether there are enough patients and sufficient reimbursement to justify the resources and time required to implement MAT in primary care settings. Key Informants noted that there needs to be a minimum number of waivered physicians available to provide cross-coverage to avoid burn-out among prescribing physicians. In rural settings, Key Informants observed that travel time can be a significant barrier, with some patients facing a 2-hour commute to clinic; this can result in high travel costs and jeopardize the ability of patients to maintain employment.[89]

Key Informants and the literature describe other barriers to implementation of MAT in primary care settings.[87,88,90] A key barrier is the relative lack of physicians with an FDA waiver to prescribe buprenorphine for treatment of OUD. In December 2013, the average state had only eight waivered physicians per 100,000 residents.[91] Increasing the limit on the number of patients that a physician can prescribe buprenorphine for OUD (currently 30 or 100) could be more effective at increasing buprenorphine use and access than increasing the number of addiction treatment facilities or increasing the number of waivered physicians.[91] One study found that the greatest impact on the amount of buprenorphine prescribed was the number of waivered physicians able to treat up to 100 patients with buprenorphine.[85] Although some Key Informants felt that the current patient limits could be a barrier to implementation, most primary care clinicians are not close to the prescribing limit and there are concerns that increasing the limits could result in suboptimal care. Most (70% to 95%) physicians prescribing buprenorphine never turned away any patient because of patient prescribing limits.[92] As noted above, there seems to be an unwillingness on the part of some physicians to prescribe, even though they have a waiver.[90] The same survey found that about two-thirds of physicians with a buprenorphine waiver elected to not be included on the public Centers for Substance Abuse Treatment Locator List in 2008; among these, about two-thirds reported no prescribing of buprenorphine in the last 90 days. Among physicians on the Locator List, 86 percent reported prescribing in the last 90 days. A related barrier is that DATA 2000 only permits "qualifying physicians" to prescribe schedule III, IV, or V medications for treatment of OUD. The inability of physician assistants

and nurse practitioners to prescribe buprenorphine is especially important in rural areas and low income clinics, where these providers often outnumber physicians. One Key Informant noted that in Oregon, such providers can prescribe any amount of schedule II opioid for pain, but cannot prescribe buprenorphine for OUD. Pharmacists also play an important role in providing MAT and could assist with dispensing, monitoring for adherence and diversion, and patient education.

Key Informants consistently noted that stigma towards MAT remains an important barrier to implementation. Surveys of physicians[90] describe stigma as pervasive and present among physicians, clinic staff, patients, law enforcement, policymakers, insurers, and the community. Key Informants noted that some patients do not even want to be in the same waiting room as patients who are receiving MAT. This could result in significant barriers due to the need to create separate clinic areas. In some states and other settings, abstinence is still viewed as a "better" treatment than MAT, despite evidence to the contrary. The perception persists that using an opioid agonist is replacing one addicting drug with another and promotes a preference for detoxification and abstinence rather than agonist or antagonist therapy. In rural settings in particular, Key Informants noted that MAT is often discouraged due to these beliefs. The Key Informants noted a general lack of training and understanding[90] regarding MAT even among physicians, and emphasized the need for education of physicians as well as the community regarding the evidence on effectiveness of MAT in order to increase the number of buprenorphine waivered physicians, increase uptake of MAT by patients, and increase buy-in among the community.

Other barriers to prescribing buprenorphine for OUD frequently cited in a survey of family physicians in Vermont and New Hampshire includes inadequately trained staff, insufficient time, inadequate office space, and cumbersome regulations.[91] Several Key Informants noted that a fear of potential Drug Enforcement Agency site visits,[93] as per DATA 2000, was a deterrent to obtaining a buprenorphine waiver.

Key Informants also noted barriers to use of extended-release naltrexone in primary care settings. These include unfamiliarity with its use (this medication was approved by the FDA for treatment of OUD in 2010), perception of low patient demand (due in part to its mechanism of action as a pure opioid antagonist), the need to taper patients off opioids prior to starting naltrexone, high cost, and potential for overdose in patients who relapse, since they are no longer opioid-tolerant.

Reimbursement remains an important barrier.[87] For example, although nurse care managers in the Massachusetts model are reimbursed for their services, people serving similar functions in other models are not necessarily reimbursed in the same way. Several Key Informants noted that lack of reimbursement is a barrier to use of extended-release naltrexone. In the Project ECHO model, off-site experts provide consultative expertise to primary care providers. There is no doctor-patient relationship, and therefore these services are not reimbursable. Key Informants also noted variability in policies related to reimbursement of provision of telemedicine services in which there is an established, direct doctor-patient relationship. Without adequate reimbursement, implementation of MAT models of care in many primary care settings is unsustainable financially. Key Informants also noted onerous prior authorization requirements as a barrier to prescribing buprenorphine, as well as arbitrary limits on the treatment duration and doses. A survey of 45 states found that in 2013, only 11 percent of states had Medicaid policies that excluded coverage for methadone and buprenorphine, whereas nearly three-quarters (71%) had policies to cover both buprenorphine and methadone in Medicaid enrollees.[94] However, there

was also an increase in adoption of policies that could hinder access to buprenorphine or methadone, such as prior authorization requirements.

Training, Certification, and Staffing Needs

DATA 2000 allows physicians to provide MAT using buprenorphine outside of licensed OTPs if they complete 8 hours of training and submit an application to receive a waiver. Physicians who obtain a waiver may be subject to periodic DEA audits of patient records (a potential barrier to obtaining a waiver). DATA 2000 further specifies that brief counseling be offered in conjunction with buprenorphine; this can be provided by the physician or nonphysician staff. Models that integrate treatment of OUD with management of other chronic conditions require expertise in management of those conditions; this can be provided by the same physician that is managing the OUD or by other clinicians (not necessarily a physician).

Additional staffing and training requirements vary depending on the model of care. Several models use a designated staff person to support the prescribing physician and serve as a main point of clinical contact. In the Massachusetts model, an RN case manager performs screening, supports the prescribing physician, and coordinates care and in Project ECHO, nurse practitioners and physician assistants assume similar roles. There are no formal certifications or trainings required to fulfill these roles, though DATA 2000 buprenorphine waiver trainings are open to and attended by nonphysicians. The success of such models is likely to depend to a large degree on the knowledge and skill that such people have in the area of addiction. Additional staffing largely depends on the types of psychosocial services that are offered and may include psychologists, social workers, peer counselors or mentors, psychiatrists, addiction specialists, and others.

Guiding Question 3: Current Evidence on Medication-Assisted Treatment

Medication-Assisted Treatment Models of Care

We identified six trials on the effectiveness of MAT models of care in primary care/office-based settings[36,37,46,48,61,62] (**Table 4**). Two trials compared buprenorphine/naloxone with more intensive versus less intensive counseling in the OBOT (Yale) model.[36,37] One trial compared buprenorphine/naloxone with more intensive versus less intensive counseling among HIV-infected patients in the BHIVES model[48] and another trial of HIV-infected patients compared clinic-based buprenorphine/naloxone in the BHIVES model versus case management and referral to an OTP.[46] One trial compared the Emergency Department Initiation of OBOT model with buprenorphine/naloxone versus referral for treatment (with or without a brief intervention)[61] and one trial compared the Inpatient Initiation of MAT model with buprenorphine/naloxone versus linkage to care.[62] No trial compared the effectiveness of one MAT primary care model versus another.

Detailed tables of included trials for Guiding Question 3 are available in **Appendix F**.

Psychosocial Interventions

A number of trials have evaluated the comparative effectiveness of different psychosocial interventions given as a component of MAT. However, relatively few trials on psychosocial interventions have been conducted in office-based settings. A Cochrane review included 35 trials

on the effectiveness of psychological therapies plus any agonist maintenance treatment as a component of MAT for OUD (**Table 5**).[95] Thirty-one trials were conducted in the United States. In six trials the pharmacological component was buprenorphine/naloxone; the remainder evaluated methadone (no study evaluated naltrexone). Of the trials, only one was conducted in a primary care/community-based setting.[36] It compared standard medical management with brief (20 minutes/session) medically-focused counseling versus extended medical management with more in-depth counseling (45 minutes/session) in patients prescribed buprenorphine/naloxone and found no clear differences in effectiveness. We identified nine additional trials that evaluated the effectiveness of more intensive psychosocial interventions or compared one psychosocial intervention versus another in office-based settings (**Table 4**). The comparisons evaluated were internet-based community reinforcement approach plus contingency management versus contingency management alone,[96] cognitive behavioral therapy versus standard counseling,[97,98] network therapy versus standard medication management,[99] cognitive behavioral therapy plus directly observed, thrice-weekly buprenorphine versus physician management with weekly buprenorphine, brief versus extended counseling,[100-102] guided drug counseling plus standard medical management versus medical management alone,[37] and brief physician management versus brief physician management plus nurse-administered drug counseling and adherence management.[48] The evaluation of different comparisons makes it difficult to assess overall findings of the trials, but in most studies there were no clear differences in outcomes between different psychosocial interventions.

Detailed tables of included systematic reviews for Guiding Question 3 are available in **Appendix G**.

Pharmacological Therapies

A number of trials evaluated the pharmacological component of MAT. In all trials, psychosocial interventions were also provided, though the psychological component was often not well-described. Relatively few trials were conducted in office-based settings. Some trials evaluated methadone and sustained-release morphine, which are not approved by the FDA for this indication. We included those medications in this section as they could inform future MAT strategies if they become available in the United States.

Buprenorphine

A Cochrane systematic review on buprenorphine as a component of MAT included 31 trials (**Table 5**).[17] The trials in the review focused on the effectiveness of buprenorphine (typically formulated with naloxone) versus placebo or versus another medication, rather than the effectiveness of MAT models of care per se. In addition, the studies had characteristics that might impact applicability to MAT in United States primary care settings. Of the 31 trials, 15 were conducted in North America, and only two trials were clearly conducted in community-based settings. One trial[103] compared buprenorphine/naloxone versus buprenorphine versus placebo in a United States setting and the other trial[104] compared buprenorphine versus methadone in an Australian setting (**Table 4**). We identified trials of a newer implantable formulation of buprenorphine, but they were conducted in addiction settings and did not meet inclusion criteria for this report.[105,106]

Naltrexone

For oral naltrexone as a component of MAT, a Cochrane review included 13 RCTs (**Table 5**).[107] Of these, four were conducted in the United States; all focused primarily on patients who had been recently incarcerated, with none clearly conducted in primary care settings. For extended-release naltrexone, another Cochrane review[108] (**Table 5**) included only one trial on effectiveness, which was conducted in an inpatient setting.[109] Although searches for the Cochrane review appear outdated (conducted in 2007), we identified no recent studies of extended-release naltrexone conducted in primary care settings.[109-115]

Methadone

A Cochrane review of methadone as a component of MAT included 11 trials, but none were clearly conducted in primary care or community-based settings (**Table 5**).[18] We identified four trials not included in the Cochrane review that compared methadone maintenance in an office-based setting versus a methadone clinic setting (**Table 4**). Two studies were conducted in France[116,117] and two studies in the United States.[118,119] The trials generally found that methadone maintenance in office-based settings was associated with similar outcomes as methadone maintenance in addiction treatment settings.

Sustained-Release Morphine

A Cochrane review included three trials of sustained-release morphine as part of MAT (not approved by the FDA for this use), but none of the trials were conducted in primary care/office-based settings.[120]

Special Populations

One Cochrane review evaluated the effectiveness of MAT in pregnant women, but evidence on effectiveness of FDA-approved office-based treatments for MAT was extremely limited (**Table 5**).[121] In addition, although three trials (sample sizes 18, 30, and 175) evaluated buprenorphine versus methadone maintenance treatment, none were conducted in primary care or community-based settings. One trial evaluated buprenorphine/naloxone in community settings for treatment of OUD in young people (15 to 21 years of age), but did not meet inclusion criteria because it compared treatment for 12 weeks versus a 2-week taper.[122] A Cochrane review evaluated effectiveness of oral agonist treatment for OUD in injecting drug users on risk behaviors and rates of HIV,[123] but did not focus on medications approved for use in office-based settings and only included two trials in which patients were managed in primary care settings (**Table 5**).[124,125] A trial of HIV-infected patients with OUD found no difference between office-based treatment with buprenorphine/naloxone versus referral to an OTP in HIV RNA levels and CD4 counts.[46] Trials of MAT in office-based settings primarily enrolled patients with OUD due to heroin; we identified no systematic review or randomized trial on effectiveness of MAT in primary care settings, specifically patients with OUD related to prescription opioids. Another Cochrane review of MAT for OUD related to prescribed opioids included six trials that found that methadone or buprenorphine appeared equally effective for outcomes related to opioid use and treatment retention (**Table 5**).[126] Five of the trials were conducted in the United States, but none of the studies were conducted in primary care settings.

Table 4. Trials for Guiding Question 3

Model name Author, year	Comparators	Followup	N	Country	Population Characteristics	Findings
MAT Models of Care						
D'Onofrio, 2015[61]	Screening and referral to treatment (referral) vs. screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention) vs. screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week followup (buprenorphine)	30 days	329	USA	76.3% male mean age 31 years 34.3% use alcohol to intoxication	Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk. These findings require replication in other centers before widespread adoption.
Fiellin, 2002[37]	Buprenorphine/naloxone and medication management (thrice-weekly sessions with a nurse and a monthly meeting with a physician) vs. buprenorphine and medication management plus drug counseling (not described)	13 weeks	14	USA	71% male mean age 36 years 79% with history/current alcohol dependence	Overall, patients had fewer positive urine opioid tests and experience high treatment retention through the maintenance phase; fewer patients in medication management group vs. medication management plus counseling group achieved greater than or equal to 1 week of negative urine opioid tests, although this difference was not statistically significant; A greater proportion of the medication management plus counseling group had negative urine opioid tests compared with the medication management alone group, although this difference was not statistically significant.
Fiellin, 2006[36]	Standard medical management (20 minutes with a nurse) and once-weekly medication dispensing (buprenorphine/naloxone) vs. standard medical management and thrice-weekly medication dispensing vs. enhanced (45 minutes with a nurse) medical management and thrice-weekly medication dispensing All groups met monthly with a physician	24 weeks	166	USA	78% male mean age 36 years	The efficacy of brief weekly counseling and once-weekly medication dispensing did not differ significantly from that of extended weekly counseling and thrice-weekly dispensing.
Liebschutz, 2014[62]	Detoxification plus referral vs. induction plus contact from long-term opioid agonist treatment staff that facilitated linkage to hospital-associated primary care buprenorphine/naloxone treatment	6 months	139	USA	71.2% male mean age 41 years	Compared with an inpatient detoxification protocol, initiation of and linkage to buprenorphine treatment is an effective means for engaging medically hospitalized patients who are not seeking addiction treatment and reduces illicit opioid use 6 months after hospitalization. However, maintaining engagement in treatment remains a challenge.
Lucas, 2010[46]	Clinic-based, nurse-administered treatment with buprenorphine/naloxone vs. case management and referral to an intensive opioid treatment program (referred treatment)	12 months	93	USA	72% male median age 45-46 years 73% positive for hepatitis C antibody 10% AIDS-defining opportunistic condition in previous 3 month	Participation in opioid agonist therapy was significantly higher in clinic-based buprenorphine than for referred treatment. Positive test results for opioids and cocaine were significantly less frequent in clinic-based buprenorphine than in referred treatment, and study participants receiving clinic-based buprenorphine attended significantly more HIV primary care visits than those receiving referred treatment. Use of antiretroviral therapy and changes in HIV RNA levels and CD4 cell counts did not differ between the 2 groups.

Model name Author, year	Comparators	Followup	N	Country	Population Characteristics	Findings
Sullivan, 2006[48]	Buprenorphine/naloxone and physician management (brief, biweekly) vs. buprenorphine/naloxone and physician management plus once-weekly drug counseling and adherence management	12 weeks	16	USA	94% male mean age 47 years 29% reported one or more days of alcohol use in past 30 days 100% HIV positive 81% HCV positive	There was no difference in treatment retention or illicit drug use by counseling group; Overall, the proportion of opioid-positive weekly urine screens decreased substantially over trial; CD4 counts remained stable; viral load declined significantly; demonstrated feasibility of integrating buprenorphine into HIV clinical care for treatment of opioid dependence
Psychosocial Interventions						
Christensen, 2014[96]	Buprenorphine/naloxone and individual counseling plus contingency management (based on urine results linked to points for gift cards or money) vs. buprenorphine and individual counseling and contingency management plus internet-based community reinforcement approach Both groups had individual counseling every 2 weeks	12 weeks	170	USA	54% male 13% with concurrent alcohol dependence	Compared with those receiving contingency management-alone, community reinforcement approach recipients had more total days of abstinence and were less likely to drop out of treatment; prior treatment for opioid dependence moderated the additional improvement of community reinforcement approach for longest continuous days of abstinence
Fiellin, 2002[37] (also a model of care)	Buprenorphine/naloxone and medication management (thrice-weekly sessions with a nurse and a monthly meeting with a physician) vs. buprenorphine and medication management plus drug counseling (not described)	13 weeks	14	USA	71% male mean age 36 years 79% with history/current alcohol dependence	Overall, patients reduced opioid-positive urine toxicology tests and good retention through maintenance; less patients in medication management group vs. medication management plus counseling group achieved greater than or equal to one week of opioid-free urine screens, though this difference was not statistically significant; A greater proportion of the medication management plus counseling group had opioid-free urine screens compared with the medication management alone group, though this difference was not statistically significant
Fiellin, 2006[36] (also a model of care)	Standard medical management (20 minutes with a nurse) and once-weekly medication dispensing (buprenorphine/naloxone) vs. standard medical management and thrice-weekly medication dispensing vs. enhanced (45 minutes with a nurse) medical management and thrice-weekly medication dispensing All groups met monthly with a physician	24 weeks	166	USA	78% male mean age 36 years	The efficacy of brief weekly counseling and once-weekly medication dispensing did not differ significantly from that of extended weekly counseling and thrice-weekly dispensing
Fiellin, 2013[97]	Physician management (15-20 minutes weekly for the first 2 weeks, every 2 weeks for the next 4 weeks, and then monthly) with buprenorphine/naloxone or physician management with buprenorphine/naloxone plus CBT (up to 12 50-minute weekly sessions during the first 12 weeks of treatment)	24 weeks	141	USA	74% male mean age 34 years	The effectiveness of physician management did not differ significantly from that of physician management plus cognitive behavioral therapy.
Galanter, 2004[99]	Buprenorphine/naloxone plus medication management (2 individual sessions per week) vs. buprenorphine plus network therapy (1 individual and 1 group counseling session per week)	18 weeks	66	USA	76% male mean age 36 years	Network therapy led to significantly more negative urine toxicologies and more network therapy than medication management patients had positive outcome relative to secondary heroin use by the end of treatment

Model name Author, year	Comparators	Followup	N	Country	Population Characteristics	Findings
Moore, 2012[98]	Buprenorphine and physician management (15 minute sessions weekly) vs. buprenorphine and physician management plus CBT (45 minute sessions weekly, depending on therapist availability)	12 weeks	55	France	74% male mean age 39 years	Analyses adjusting for baseline characteristics showed no significant differences between groups on retention or drug use based on self-report or urines. Patient satisfaction was high across conditions, indicating acceptability of CBT counseling with observed medication. The number of CBT sessions attended was significantly associated with improved outcome, and session attendance was associated with a greater abstinence the following week.
Sullivan, 2006[48] (also a model of care)	Buprenorphine/naloxone and physician management (brief, biweekly) vs. buprenorphine/naloxone and physician management plus once-weekly drug counseling and adherence management	12 weeks	16	USA	94% male mean age 47 years 29% reported one or more days of alcohol use in past 30 days 100% HIV positive 81% HCV positive	There was no difference in treatment retention or illicit drug use by counseling group; Overall, the proportion of opioid-positive weekly urine screens decreased substantially over trial; CD4 counts remained stable; viral load declined significantly; demonstrated feasibility of integrating buprenorphine into HIV clinical care for treatment of opioid dependence
Tetrault, 2012[100]	Physician management (brief, once every 2 weeks) vs. physician management plus enhanced medical management (45 minutes weekly; focused on drug counseling and adherence to anti-retroviral treatment); used buprenorphine/naloxone	12 weeks	47	USA	39% male mean age 47 years mean 4 days of alcohol use in past 30 days mean 12 years duration of HIV diagnosis 26% HCV positive	At end of trial, no difference between groups in percentage of opioid negative urines, maximum duration of continuous abstinence, or retention; the percentage of subjects with detectable viral loads decreased from baseline across both groups similarly; overall, providing extended counseling in this setting is feasible but does not provide detectable improvement in outcomes
Weiss, 2011[101] Prescription Opioid Addiction Treatment Study (POATS)	Phase 1: Standard medication management (after initial session,15-20 minute s weekly, then biweekly sessions with a physician) with buprenorphine/ naloxone vs. standard medication management with buprenorphine/ naloxone plus opioid dependence counseling (45-60 minute sessions with a counselor, twice weekly then biweekly) Phase 2 (extended treatment for those who relapsed): Standard medication management (2 visits first week, then weekly) with buprenorphine/ naloxone vs. standard medication management with buprenorphine/ naloxone plus opioid dependence counseling (twice weekly then biweekly)	Phase 1: 12 weeks Phase 2: 24 weeks	653	USA	60% male mean age 33 years 27% alcohol dependence during lifetime	During phase 1, only 6.6% of patients had successful outcomes, with no difference between standard medical management or standard medical management plus opioid dependence counseling. During phase 2, 49% attained successful outcomes, with no difference between groups. Success rates 8 weeks after completing the buprenorphine-naloxone taper (phase 2, week 24) dropped to 8.6%, again with no difference between groups.
Weiss, 2015[102] Prescription Opioid Addiction Treatment Study (POATS)	See above	9 month treatment; 42 month followup	375	USA	56% male mean age 33 years old 3.7% with alcohol dependence in past year	Few participants had successful opioid outcomes in phase 1; almost half had successful opioid treatment in phase 2; addition of opioid dependence counseling to medication did not improve outcomes; one third of those in followup abstained and were not on agonist medication, one third were abstinent on agonist therapy and another third were using opioids (followup outcomes not described by group)

Model name Author, year	Comparators	Followup	N	Country	Population Characteristics	Findings
Pharmacological Therapies						
Carrieri, 2014[116] See also Roux, 2012[117]	Induction of methadone in primary care vs. specialty care	12 months	221	France	84% male median age 32 years 33% had hazardous alcohol consumption 2% HIV-positive 19% HCV-positive	Under appropriate conditions, methadone induction in primary care is feasible and acceptable to both physicians and patients. It is as effective as induction in specialized care in reducing street-opioid use and ensuring engagement and retention in treatment for opioid dependence.
Fiellin, 2001[118]	Primary care-based methadone (weekly physician sessions and monthly counseling session) vs. narcotic treatment program-based methadone (1 to 3 sessions per week dose, weekly group counseling, and monthly individual counseling)	6 months	46	USA	65% male mean age 42 years 17% HIV-positive	There was no significant between-group difference on illicit drug use or patients with clinical instability; Significantly more office-based patients thought that quality of care was excellent; There were no group differences in functional status or use of health, legal, or social services; Overall, results supported feasibility and efficacy of transferring stable opioid-dependent patients to primary care for methadone maintenance
Fudala, 2003[103]	Daily buprenorphine/naloxone vs. buprenorphine vs. placebo All participants received HIV counseling and up to 1 hour of individualized counseling per week; emergency counseling and referrals provided	4 weeks for efficacy; 52 weeks for safety	323 for efficacy; 472 for safety	USA	65% male mean age 38 years	Efficacy study terminated early due to greater efficacy of buprenorphine/naloxone and buprenorphine vs. placebo; Proportion of opiate-negative urine samples significantly less among both MAT groups vs. placebo; MAT groups reported significantly less opiate craving than placebo; Rates of adverse events similar in active-treatment and placebo groups; findings from open-label followup indicated combined treatment was safe and well tolerated
King, 2006[119]	Routine care (methadone dispensing window for weekly doses and monthly counseling for 20 minutes) vs. methadone maintenance clinic (monthly observed dose, take home supply, monthly 20 minute counseling session with medical provider) vs. primary care based-methadone (monthly observed dose, take home supply, monthly 20 minute counseling session with office physician)	12 months	92	USA	62% male mean age 44 years	Generally low rates of drug use or failed medication recall with good study retention; No between-group differences on ASI scores; Treatment satisfaction was high in all groups and patients in all groups rated strong quality of therapeutic alliance; methadone medical maintenance patients in both office and clinic-based care initiated more new employment or social/family activities than routine care; most methadone medical maintenance patients reported a preference for office-based care compared with clinic-based
Lintzeris, 2004[104]	Methadone vs. buprenorphine administered under naturalistic conditions by 18 community-based and 1 specialist-based sites by general practitioners and community pharmacists (Buprenorphine Implementation Trial)	12 months	139	Australia	58% male mean age 30 years	Among methadone stabilized patients, mean retention time was similar between groups; among heroin users, there was a trend towards improved retention among those taking methadone compared with those on buprenorphine, though this was not statistically significant; There were significant reductions in heroin use in all groups over time and a trend toward lower heroin use among heroin users on buprenorphine

ASI = Addiction Severity Index; CBT = cognitive behavioral therapy; ED = emergency department, MAT = medication-assisted treatment

Table 5. Cochrane Systematic Reviews for Guiding Question 3

Author, Year	Intervention Characteristics	Population and Setting	Countries	Types of Studies Included	No. of Included Studies No. of Patients	Findings	Limitations
Amato, 2011[95]	Any psychosocial intervention plus any agonist vs. any agonist alone; methadone, buprenorphine, LAAM; models of care not described	OUD due to opiates (not specified); setting not described (appears mostly specialist centers)	USA, Germany, Malaysia, China, Scotland	RCTs, CCTs	35 studies 4319 patients	Comparing any psychosocial intervention plus maintenance pharmacological treatment to standard maintenance treatment, shows no significant advantage of adding psychosocial interventions for retention in treatment and at followup, abstinence from opiates during treatment or at followup, compliance, psychiatric symptoms, and depression. Also, there was no significant difference in outcomes comparing psychosocial approaches. Of note, standard pharmacological treatment generally offers counseling services.	Focused on effectiveness of psychotherapy interventions in addition to standard interventions; setting not described (appears mostly specialist centers); 31 studies in USA
Ferri, 2013[120]	Slow-release oral morphine vs. other MAT medications; models of care not described	OUD due to heroin; Setting not described	Australia and Austria	RCTs, quasi-randomized (one study only provided conference abstract)	3 studies 195 patients	Limited evidence that sustained-release oral morphine is at least similar to other MAT medications for retention and other clinical outcomes	Focused on effectiveness of medications; trials with no description of setting; no studies in USA
Gowing, 2011[123]	Buprenorphine, methadone, or LAAM for substitution therapy (alone or vs. others); models of care not described	OUD due to heroin; majority injecting drug users or with recent history (last 3 months); users of other injectable drugs also included; mostly specialist treatment centers	USA, UK, Australia, Italy, Germany, Canada, Malaysia, Ukraine with one study in multiple countries	RCTs, observational prospective studies, cross-sectional studies	38 studies 12400 patients	Oral substitution treatment with methadone or buprenorphine is associated with significant reductions in illicit opioid use, injecting use, and sharing of injecting equipment; also led to fewer drug users reporting multiple sex partners or exchanges of sex for money or drugs but no change in condom use; reduced drug risk behaviors led to reduced HIV; one study partially done in primary care showed significant reductions in proportion injecting, sharing injecting equipment, and having unprotected sex in those on methadone treatment.	Focused on effectiveness of medications on HIV and behaviors; 2 studies included primary care settings; 26 studies in USA
Lobmaier, 2008[108]	Three depot and two implant formulations of naltrexone (10 of 17 depot studies used sustained release form) vs. placebo, different naltrexone doses, oral naltrexone, or methadone; in addition to medication, all patients offered relapse prevention therapy	OUD not specified; effectiveness study in outpatient setting	Australia, Germany, USA, Norway, Spain, UK	RCTs for effectiveness; prospective controlled and uncontrolled trials, case-series, and record-linkage for safety evaluation	1 study for effectiveness 60 patients for effectiveness	One study found high-dose naltrexone depot injections significantly increased days in treatment vs. placebo and vs. low-dose with no group differences on patients retained in treatment;	Focused on effectiveness and adverse events of medications; effectiveness study in outpatient setting (no further details); effectiveness study and most safety studies done in USA

Author, Year	Intervention Characteristics	Population and Setting	Countries	Types of Studies Included	No. of Included Studies No. of Patients	Findings	Limitations
Mattick, 2009[18]	Methadone maintenance vs. placebo or other nonpharmacological therapy (wait-list control, drug-free rehabilitation, detoxification); models of care not described (some studies included counseling in the intervention but this was not described)	OUD due to opioids (not specified); most studies done in specialist medical or research facilities (3 in prison setting)	USA, Australia, Hong Kong, Thailand, Sweden	RCTs	11 studies 1969 patients	Methadone was significantly more effective than nonpharmacological approaches in treatment retention and suppression of heroin use but not different in criminal activity or mortality	Focused on effectiveness of medication; no studies appear to be have been done in primary care; 6 studies in USA
Mattick, 2014[17]	Buprenorphine maintenance vs. placebo or methadone; models of care not described	OUD due to heroin or other opioids; settings not described	North America, Europe, Asia, Middle East, Australia	RCTs	31 studies 5430 patients	Buprenorphine was superior to placebo in participant retention at all doses; only high-dose buprenorphine (not low- or moderate-dose) was more effective than placebo in suppressing illicit opioid use; flexible dosed buprenorphine was less effective than methadone in participant retention with no group differences in suppression of opioid use; low-dose methadone was more likely to retain participants and limit opioid use than low-dose buprenorphine but high and medium-dose methadone were not more effective than high and medium-dose buprenorphine for participant retention and illicit opioid use	Focused on effectiveness of medications; setting not described; 15 studies from North America
Minozzi, 2009[127]	Any maintenance treatment alone or in combination with psychological intervention vs. no intervention, other pharmacological or psychosocial intervention; models of care not described	OUD due to heroin; adolescents; outpatient	USA	RCTs and controlled clinical trials	2 studies 187 patients	Limited evidence that maintenance treatment was superior in patient retention but not in reducing illicit opioid use; Opioid use at 1 year followup was significantly lower in the maintenance group and more patients in this group were enrolled in other addiction treatment at followup	Focused on effectiveness of medications; outpatient setting (unclear if primary care); all trials done in USA

Author, Year	Intervention Characteristics	Population and Setting	Countries	Types of Studies Included	No. of Included Studies No. of Patients	Findings	Limitations
Minozzi, 2011[107]	Oral naltrexone alone or in combination with psychosocial treatments vs. placebo, no intervention, other pharmacological treatments, or psychosocial treatments; models of care not described	OUD due to heroin alone or multiple drugs; outpatient only	USA, Israel, Russia, Italy, Spain, China, Malaysia, Germany	RCTs	13 studies 1158 patients	Oral naltrexone did not perform better than treatment with placebo or no agent with respect to abstinence and relapse, though naltrexone was favored for number of people reincarcerated. Naltrexone was not superior to benzodiazepines and buprenorphine for retention, abstinence, and side effects, though numbers retained in studies were generally low. In single study of naltrexone vs. psychotherapy, there was no statistically significant difference for abstinence and reincarceration. Overall, studies inadequate to evaluate oral naltrexone treatment for opioid dependence.	Focused on effectiveness of medications /interventions; includes psychotherapy as an intervention; outpatient trials (unclear if primary care); 4 trials in USA
Minozzi, 2013[121]	Methadone vs. buprenorphine or slow-release morphine; models of care not described	Opiate addicted pregnant women (OUD not specified); inpatient and outpatient settings	Austria, USA, one multicounty trial (Austria, Canada, USA)	RCTs	4 studies 271 patients	Limited evidence of no significant differences between methadone and buprenorphine or slow-release morphine for all outcomes (child health status, neonatal mortality, treatment retention, and reducing substance use)	Focus on effectiveness of medications; 3 studies in outpatient setting (no further details); 2 studies done in USA
Nielsen, 2016[126]	Methadone vs. buprenorphine; also, buprenorphine maintenance vs. either buprenorphine taper (in addition to psychological treatment) or brief intervention and referral to treatment	OUD due to pharmaceutical opioids; 5 studies conducted in outpatient settings, 1 study hospital-based treatment vs. brief hospital intervention and treatment referral	USA (5 studies) and Iran (1 study)	RCTs	6 studies 607 patients	Methadone or buprenorphine appeared equally effective on opioid use and treatment retention; Maintenance treatment with buprenorphine appeared more effective than detoxification or psychological treatments on opioid use and treatment retention	Use of open label study designs; most studies conducted in outpatient settings

Author, Year	Intervention Characteristics	Population and Setting	Countries	Types of Studies Included	No. of Included Studies No. of Patients	Findings	Limitations
Rahimi-Movaghar, 2013[128]	Various pharmacological therapies (alone or in combination with psychosocial interventions) compared with no intervention, detoxification, different doses of the same intervention, other pharmacologic interventions and any psychosocial interventions; models of care not described	OUD due to heroin; outpatient	Iran	RCTs	3 studies 870 patients	Higher doses of buprenorphine significantly increased the treatment retention rate compared with lower doses; No significant difference in maintenance retention rate between baclofen vs. placebo post detoxification.	Focused on effectiveness of medications; outpatient setting (unclear if primary care); no trials in USA (appears Asia-focused)

CCT = controlled clinical trial; LAMM = levo-alpha-acetylmethadol; OUD = opioid use disorder; RCT = randomized controlled trial

Guiding Question 4. Future Directions

New and Innovative Strategies

Key Informants uniformly noted that the most promising models of care are those that emphasize the integration of management of OUD with primary care and other medical and psychological needs. The chronic disease management paradigm is particularly suitable for populations with OUD who also have other conditions that require ongoing care, such as HIV or HCV infection.[129] The BHIVES model was specifically designed to integrate office-based treatment with buprenorphine/naloxone with HIV management. Some important innovations in implementation of MAT models of care include the use of a nonphysician glue person (e.g., OBOT [Yale], Massachusetts Nurse Care Manager model, ECHO Project), integration of more comprehensive psychosocial services (e.g., One Stop Shop, Medicaid Health Home Model), coordination and integration of office-based management with centralized centers of excellence (e.g., Hub and Spoke, Co-OP), and identification and initial treatment in ED, inpatient, or prenatal settings. Peer-delivered recovery support services are promising and could be integrated into primary care settings;[130] as of 2007, such services are Medicaid reimbursable. Several Key Informants noted that models of care that also integrate education, training, and outreach, such as the Massachusetts Nurse Care Manager model, are important for increasing the pool of buprenorphine-waivered physicians, decreasing stigma, and increasing uptake of MAT, while also promoting higher-quality care. Existing resources such as PCSS-MAT, which provides physician training and access to a national network of experts in MAT who can provide mentoring to those less experienced in prescribing buprenorphine, could be leveraged by models of care that lack resources for their own educational and training component; such resources were used successfully in the initial dissemination and expansion of office-based buprenorphine in the United States. Utilization of existing training and educational resources would also be more efficient than developing new resources in each implementation setting.

Recent MAT models focus on the identification of patients with OUD and initiation of treatment in the ED, inpatient, and prenatal settings. These strategies can help identify patients with OUD who otherwise might not have access to primary care, have a higher prevalence of OUD (e.g., in the ED and inpatient settings), or facilitate initiation and engagement in treatment. Ideally, such models of care would be linked to an integrated, office-based model that can provide ongoing management.

In rural settings, major barriers to MAT include the lack of addiction and psychiatric expertise, distances that patients must travel to access care, lack of buprenorphine-waivered physicians, and negative attitudes and beliefs regarding MAT. Strategies to overcome these barriers include Web-based learning networks (e.g., Project ECHO), use of telemedicine for consultation with experts, utilization of nonphysician providers in key roles (e.g., screening, counseling, coordination of care, provision of primary care), and educational and outreach efforts. In the Southern Oregon Model, for example, local stakeholders meet regularly and discuss issues in management of OUD and develop practice standards using a collaborative model. One Key Informant has developed and evaluated computer-assisted delivery of cognitive behavioral therapy for addiction.[131,132] Resources such as these could supplement face-to-face psychosocial services and would not be constrained by geographical barriers. In rural settings, the availability of extended-release formulations (e.g., currently approved extended-release naltrexone and emerging products such as implantable and injectable buprenorphine preparations) could potentially reduce the need for frequent visits, particularly in less complex

patients who have long distances to travel, and if coupled with psychosocial services conducted over the phone or via the Web.

MAT models of care in primary care settings could also integrate pharmacist-based management strategies. A recent small (n=12 patients) pilot project evaluated a physician-pharmacist collaborative model in which patients were managed using a drug therapy management model.[133] The pharmacist conducted intake assessments and followup appointments and documented each interaction after debriefing with a physician, who appended additional notes as needed and cosigned records. The pharmacist was responsible for gathering data from outside providers and pharmacies regarding prescribed medications and results of urine drug testing. Prescriptions were written by the physician or called in by the pharmacist. In addition, the pilot study projected that the model would be cost savings for the health system. Another 2-year pilot study in San Francisco evaluated a tiered model with centralized induction and stabilization followed by management in a community-based center, with buprenorphine dosing and dispensing provided through a designated pharmacy.[134] The pharmacist at the dispensing pharmacy worked in collaboration with the clinicians at the community center, with a secure database specifically designed to facilitate communication. However, for both models, details regarding the provision of psychosocial services and coordination of care within this model are limited.

Implications for Diffusion of Medication-Assisted Treatment

Key Informants consistently noted that MAT is effective in office-based settings, but access remains limited, particularly in rural settings. Increasing the number of buprenorphine waivered physicians as well as the number of buprenorphine waivered physicians who actually prescribe are critical for increasing the diffusion of MAT. Enhanced use of extended-release naltrexone could also increase diffusion of MAT since it does not require a waiver to prescribe and provides patients with additional options. As an opioid antagonist, naltrexone may be preferred by patients who do not wish to use opioid agonist or partial agonist therapy.

This report describes a number of MAT models of care viewed as effective or promising by Key Informants. Although evidence is lacking with regard to how one model of care performs compared with another, comparative effectiveness research may not be the most important determinant for informing further diffusion of MAT. Rather, the most effective model of care is likely to depend in part on the specific implementation setting, including unique characteristics of the target patient population (e.g., HIV infection, pregnant, or adolescent), what resources are available locally, and financing options. Implementation of the Hub and Spoke or Co-OP models, for example, requires a relatively local center of expertise in addiction that is willing to partner with community centers in an integrated model. A model developed for patients with HIV infection requires expertise in both OUD and HIV care. In rural settings, models of care that integrate Web-based training, consultation, and mentorship may be needed to overcome the lack of local expertise. One support model, for example, is the Oregon Addiction Education and Prevention Initiative, in which academic medical center addiction medicine specialists partner with accountable care organizations to conduct DATA 2000 waiver training for rural primary care providers, who are then linked to PCSS and offered personal ongoing phone consultation support in MAT management. In some cases, effective diffusion of MAT may involve adaptation of an established model of care to the needs of the particular setting. For example, the Massachusetts Nurse Care Manager model represents an adaptation of the OBOT model developed at Yale and the BHIVES model represents an adaptation of the OBOT model for

patients with OUD and HIV infection. Models of care could also integrate models that target different parts of the treatment process. For example, models that involve ED or inpatient screening for OUD and initiation of treatment could be integrated with models that provide ongoing care based on the Massachusetts Nurse Care Manager or Hub and Spoke models.

Given the barriers to implementing MAT in primary care settings, effective strategies for implementation are likely to require multifactorial interventions that involve partnerships between payers and clinics that use financing, contracting, policy change, process improvement to improve workflow, and customer input to facilitate organizational change. Although one such intervention (Advancing Recovery) has been shown to increase access to MAT in addiction treatment settings,[135] studies on the effects of Advancing Recovery in primary care settings are not yet available. Several Key Informants also commented that with increased diffusion of MAT comes the possibility for suboptimal provision of care. They noted the need for clear standards to measure the quality of care and ensure that care is adequate. Key Informants also noted that there is a general lack of knowledge regarding treatment of addiction in primary care, and that dissemination of addiction education into primary care could help with diffusion of MAT in primary care.

Ethical, Equity, and Cost Issues

Key Informants noted equity issues with regard to access to MAT in rural areas due to lack of prescribing physicians, ongoing stigma, and lack of policy and funding support. Efforts to expand MAT in Medicaid programs and Federally Qualified Health Centers represent an opportunity to increase equity. Although evidence indicates that OUDs often begin during adolescence, no models of care have been developed to address adolescent populations.[136] A multi-site clinical trial documented improved short-term outcomes for adolescents and young adults supported on buprenorphine/naloxone compared with those who completed a brief taper.[122]

Key Informants consistently noted that MAT is effective when, and it is important from an ethical standpoint that, patients have access to these treatments and be provided with accurate information about the risks and benefits of MAT and alternative treatments. Although substance use disorder benefits are included as Essential Health Benefits in the Affordable Care Act, insurers may try to avoid paying for MAT medications through onerous prior authorization requirements or arbitrarily limit the duration or dose of therapy.[137] Key Informants noted that prevention of buprenorphine diversion has been a major concern of some payers and providers and in some cases has impacted the ability to provide MAT, due to the effects of efforts to prevent diversion.

Financing remains a major issue in many settings. They noted that some models have been run largely by volunteers or are unable to remain financially viable due to inadequate reimbursement and a lack of state or other financial support. One Key Informant noted that some private clinics have gone bankrupt trying to work with Medicaid. Some Key Informants noted that the 100-patient limit for prescribing buprenorphine may make provision of MAT noneconomically viable for some physicians. Other Key Informants noted that some for-profit clinics involve several physicians banding together to increase the number of patients treated and increase economic viability, but this could result in provision of MAT which may not meet quality of care standards. Key Informants noted that showing that MAT is cost-effective or even cost-savings in the long run would be very helpful for convincing policymakers and clinicians to support and use MAT.

Areas of Uncertainty and Future Research Needs

Based on our review of the literature and Key Informant input, we identified a number of important areas of uncertainty regarding MAT that warrant additional research. These include:

- Research to identify factors associated with high-quality care and how to measure it. With improved access to MAT, it is also critical to insure that the quality of care that is delivered is high. This will require development of new quality of care indicators for use of MAT in primary care settings.
- Research on management of patients with OUD and concomitant chronic noncancer or cancer pain,[138,139] benzodiazepine use, and/or alcohol use disorder (e.g., use of buprenorphine/naloxone for transitioning off high doses of opioids in patients with chronic pain). Treatment of OUD in patients who also have pain is a major challenge given the high prevalence of opioid prescribing. A systematic review of 10 studies of limited quality evaluated the role of buprenorphine for management of chronic pain, but only one study was conducted in primary care.[140]
- Research on effectiveness of MAT in patients with prescription OUD. Most research on MAT has focused on patients with heroin use disorder. Research would be helpful for determining the degree to which evidence on MAT for heroin use disorder can be extrapolated to those with prescription OUD.
- Research on effectiveness and safety of mid-level prescribing of buprenorphine, such as by nurse practitioners and physician assistants. Currently, DATA 2000 only permits physicians to prescribe buprenorphine for OUD. Allowing mid-level providers to prescribe buprenorphine could help improve access in rural areas with few or no physicians.
- Research to identify patients more likely to benefit from more intensive psychosocial services, and methods for effectively targeting specific types of psychosocial services. The need for more intensive psychosocial services is likely to vary. Understanding which patients require which services would be very helpful for designing and implementing effective models of care.
- Research on effectiveness of peer-delivered support services as part of MAT in primary care settings.[130]
- Research to understand optimal methods for coordination and integration of care. Although Key Informants consistently noted that this is a critical component of successful MAT models of care, methods for coordination and integration of care varied among models and no study evaluated the effectiveness of different coordination and integration methods.
- Research to better understand the costs and cost-effectiveness of implementing MAT models of care. Although long-term treatment with buprenorphine/naloxone in office-based settings appears to be cost-effective[141] and provision of MAT using the Hub and Spoke model in Vermont is associated with decreased health care utilization and costs than treatment of OUD without medication,[142] there are relatively few cost- and cost-effectiveness studies and analyses have not compared different MAT models of care or evaluated the use of newer pharmacological therapies. Such research would be of particular importance for policymakers, and that such research should address societal outcomes impacted by OUD (e.g., ability to work, criminal activity) in addition to impacts on drug use.

- Research on effective methods implementation of MAT models of care in primary care settings and increasing uptake of MAT. Although some multicomponent implementation strategies appear to be effective for enhancing access, they have not yet been studies in primary care settings.[135]
- Research to better understand optimal duration and doses of treatment. This is particularly important because otherwise payers may (and sometimes do) impose arbitrary duration limits for MAT.
- Research on effectiveness of telehealth and Web-based training, mentoring, and educational resources. These would be particularly useful in rural and other settings where addiction and other expertise are not available locally. As noted elsewhere in this report, one Key Informant described a Web-based cognitive-behavioral resource that has been developed[131,132,143] and another described psychiatric consultation using computer tablets.
- Research on effectiveness of alternative medications or formulations (e.g., implantable and injectable buprenorphine preparations). Such formulations could reduce the frequency of followup, increase uptake and compliance, and mitigate barriers related to long travel distance. However, there is almost no evidence on injectable buprenorphine used in primary care settings.
- Research on effectiveness of methods for reducing diversion (e.g., use of extended-release medications, thrice weekly observed dispensing, or pharmacy-based dispensing). Pharmacy-based dispensing is done in Canada and Europe for buprenorphine and methadone prescribed in primary care and has been piloted in small studies in the United States.[133,134] Key Informants noted that preventing diversion has been a major concern of some payers and policymakers.
- Research to understand why buprenorphine waivered physicians don't prescribe, factors associated with prescribing, and methods to increase prescribing. The gap between the number of waivered physicians and the number prescribing indicates that that there is substantial untapped capacity to prescribe buprenorphine.[92]
- Research to better understand patients who are appropriate for office-based treatment versus those who require treatment in an OTP. Key Informants noted that current methods to determine who is appropriate for office-based treatment are largely based on anecdotal experience.
- Research on patients who are more likely to benefit from extended-release naltrexone, comparative effectiveness of buprenorphine/naloxone versus extended-release naltrexone, and optimal models of care for provision of extended-release naltrexone. Most models of care have focused on provision of buprenorphine/naloxone, and there is very little evidence on use of extended-release naltrexone in primary care settings. Although there is evidence supporting the efficacy of extended-release naltrexone, Key Informants reported the perception that this treatment was not in high demand by patients and that some patients might not do well with opioid antagonist therapy. In addition, a recent study found a low rate of linkage to ongoing treatment with extended-release naltrexone following an initial injection during inpatient opioid detoxification.[144] On the other hand, expanding the medication choices for patients could increase uptake and that extended-release naltrexone may be associated with less stigma by some patients and providers.

- Research on effectiveness of methadone for office-based treatment. Methadone is not authorized under DATA 2000 but has been evaluated in office-based settings in some clinical trials[118,119] and observational studies in the United States,[145-147] and is used in primary care settings in other countries. Primary care providers in Canada, parts of Europe, and some other countries prescribe methadone for directly observed daily dispensing in local pharmacies. This model has not been tested in the United States, but could expand access to OUD treatment while limiting diversion.
- Research to understand optimal MAT models of care in adolescents and children,[122,136] who often differ from adults in their treatment needs.[148] In 2014, an estimated 18,000 adolescents had heroin use disorder and 168,000 had OUD related to prescription opioids,[3] but data indicate that treatment for OUD is markedly underused in this population.[149]

Ongoing Studies

We identified several ongoing randomized trials of MAT models of care in primary care settings that may address some of the research gaps described above (**Table 6**). One ongoing trial compared effects of an organizational readiness intervention (including implementation tools and activities) plus an integrated collaborative care service delivery intervention (based on a chronic care model) versus usual care for implementing substance use disorder treatment in primary care.[150] Two ongoing trials focused on MAT models of care that involve screening and initiation of MAT in emergency department[151] or inpatient[152] settings. One other trial compared effects of group visits (5 to 10 patients with primary care provider and behavioral specialists) versus usual care (individual visits) in patients receiving buprenorphine/naloxone.[153] Another trial compared a strategy of an interim bridging buprenorphine treatment intervention for patients on a waitlist for MAT.[154] An AHRQ-funded demonstration project is focused on improving access to MAT in rural primary care practices.[155]

Table 6. Ongoing studies of MAT for OUD

Reference	Setting	Study design, Interventions	Outcomes
Bogenschutz, M. Comparing interventions for opioid dependent patients presenting in medical emergency departments. https://clinicaltrials.gov/ct2/show/NCT02586896?term=NCT02586896&rank=1[151]	Opioid dependent patients in medical emergency departments	RCT Brief strengths-based case management vs. screening, assessment and referral alone	Initiation of and engagement in treatment for opioid dependence Opioid and other substance use Initiation and engagement in participants with higher levels of environmental instability at baseline Quality of life
Fox, A. Buprenorphine group medical visits in primary care. https://clinicaltrials.gov/ct2/show/NCT02526212?term=NCT02526212&rank=1[153] *Group Buprenorphine Maintenance Treatment (G-BMT) Study*	Primary care	RCT Group visits (90 minutes; 5-10 patients simultaneously receive care from a multidisciplinary team of a generalist physician and a behavioral specialist) vs. treatment as usual in primary care (individual visits including protocol of BMT intensification, which includes increased visit frequency, referral for mental health counseling, and referral to addiction treatment specialist); both buprenorphine	Opioid abstinence Retention in treatment HIV risk behaviors Acceptability Feasibility
Ober, AJ. An organizational readiness intervention and randomized controlled trial to test strategies for implementing substance use disorder treatment into primary care: SUMMIT study protocol. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4432875/[150] Watkins, K. Integrated collaborative care for substance use disorders. https://clinicaltrials.gov/ct2/show/NCT01810159[156] *Substance Use Motivation Medication Integrated Treatment (SUMMIT) Study*	Federally-qualified health center and Venice Family Clinics	RCT Integrated collaborative care vs service as usual Details: combined effect of both an organizational readiness intervention, consisting of implementation tools and activities and an integrated collaborative care service delivery intervention, based on the Chronic Care Model Also, mixed methods study (pre-post analysis)	Service system outcomes: patient-centered care, utilization of substance use disorder treatment, utilization of health care services and adoption and sustainability of evidence-based practices Patient outcomes: substance use, consequences of use, health and mental health, and satisfaction with care
Sigmon, S. Interim buprenorphine: leveraging medication and technology to bridge delays in treatment access (IBT). https://clinicaltrials.gov/ct2/show/NCT02360007[154]	Patients on a waitlist for clinic treatment placement	RCT Strategy of an interim bridging buprenorphine treatment intervention for patients on a waitlist for MAT including buprenorphine, computerized adherence monitoring, mHealth clinical support delivered via interactive voice response, automated random call-backs for urinalysis and adherence monitoring, and HIV and hepatitis education delivered via iPad vs. waitlist control condition	Illicit opioid abstinence Addiction severity index subscale scores

Reference	Setting	Study design, Interventions	Outcomes
Stein, M. Linking opioid-dependent patients from inpatient detoxification to primary care. https://wwwcf.nlm.nih.gov/hsr_project/view_hsrproj_record.cfm?NLMUNIQUE_ID=20132453&SEARCH_FOR=(((%22primary%20care%22))%20AND(buprenorphine))%20OR(naltrexone)[152]	Recruiting illicit opioid users during detoxification and linking them to primary care-based treatment	RCT Buprenorphine, initiated during inpatient detoxification and continued after discharge vs. buprenorphine detoxification	Illicit opioid use Emergency department and hospital utilization

MAT = medication-assisted treatment; OUD = opioid use disorder; RCT = randomized controlled trial

Summary and Implications

A number of MAT models of care have been developed and implemented in primary care settings. Key Informants noted that MAT models of care could be described using a framework focusing on the following four components: (1) pharmacological therapy; (2) psychosocial services; (3) integration of care; and (4) education and outreach. This report describes 12 representative/key models of care utilizing a framework based on these four components. Although other models of care have been developed, in many cases sources to understand their components could not be identified, or it was difficult to determine how they differed from the representative models. A challenge in understanding current MAT models of care is the limited published data on most models. No study has compared the effectiveness of one MAT model of care in primary care versus another; rather, most trials have focused on specific components, in particular which medication was used and the type of psychosocial services provided. However, the ideal model of care for a particular setting is likely to depend on a number of local factors, such as the expertise available, the population being served, proximity to an addiction center of excellence, reimbursement policies, geographic factors, and others. Several Key Informants noted that efforts to implement MAT have often failed due to poor reimbursement or because the model was financially unsustainable for other reasons. Therefore, decisions about MAT models of care may best be individualized to address the unique milieu of each implementation setting. In some situations, it may be appropriate to use elements of different models of care (e.g., implement nurse care manager-based coordination of care within a Hub and Spoke model of care) or to link models of care (e.g., ED or inpatient based screening and initiation of treatment linked with an office-based model of care for ongoing management).

Regarding the pharmacological therapy component, most MAT models of care in primary care settings to date have focused on provision of sublingual buprenorphine/naltrexone. Although implantable buprenorphine was approved by the FDA in 2016, research on its use in primary care settings is lacking. Similarly, although extended-release naltrexone has been shown to be effective in addiction treatment settings, research on its use in primary care settings is extremely sparse. Provision of additional pharmacological therapy choices for MAT has potential advantages in terms of expanding patient choices, reducing risk of diversion, and decreasing need for frequent followup in appropriate patients.

Key Informants consistently noted that the psychosocial services component is critical for any MAT model of care, but there is uncertainty about whether brief counseling (as required by DATA 2000) is sufficient, or whether more extensive psychosocial services should be routinely available. In addition, many different types of psychosocial services beyond brief counseling are available and it is uncertain which services should be prioritized when implementing a model of care. Although most evidence suggests that more intensive psychosocial services are not associated with superior outcomes to standard counseling, Key Informants noted that some patients require more intensive psychosocial services and that research is needed to identify higher-risk patients who would benefit from such services. Although Key Informants generally agreed that psychosocial services are best provided on-site, some models of care use services via an affiliated OTP or through telehealth/Web-based resources.

A core component of successful MAT models of care is the integration/coordination component, in order to manage issues related to OUD as well as psychological, medical, and primary care needs. Key Informants viewed successful integration of care as critical for the success of any MAT model of care. The MAT models of care that were viewed as particularly successful used a designated nonphysician staff member in the integration/coordination role,

reducing the burden on the physician while increasing practice efficiency and permitting more patients to be effectively and safely treated.

Although the education and outreach component was not as well-defined in some models, this was viewed by Key Informants as critical for reducing stigma associated with MAT, increasing the pool of prescribing physicians, and increasing uptake, particularly in settings in which stigma is still high. Education was also viewed as critical for improving standards and quality of care. Our survey of MAT models of care indicated a number of approaches to education and outreach, including a Web-based learning network and educational resources, internet-based mentoring by more experienced physicians, meetings of community stakeholders, in-person educational sessions with patient and clinician educational sessions, and others.

Particular challenges in rural settings include a lack of waivered buprenorphine physicians, limited access to addiction expertise, persistent stigma associated with MAT, and long travel times for patients. Models of care developed in rural settings have attempted to address some of these issues by utilizing a Web-based learning network and accessing a national network of mentoring physicians. Other strategies that could be helpful include use of longer-acting medication formulations to reduce the number of followup visits in appropriate patients, use of telemedicine, engagement of community stakeholders, use of online interventions such as Web-based cognitive-behavioral therapy, and use of mid-level providers for administration of MAT.

We identified a number of important areas of uncertainty with regard to MAT models of care in primary care settings, including methods for measuring quality of care, how to assess patients to better individualize care, optimal psychosocial components of MAT, effectiveness of mid-level prescribing, enhancing access to and uptake of MAT in primary care settings, effectiveness of newer or alternative medications for OUD, optimal medications dosing strategies, cost and cost effectiveness, methods for reducing diversion, effective implementation methods, optimal methods for coordination and integration of care, and effectiveness of telehealth and telemedicine approaches. Research in these areas would be helpful for informing future efforts at dissemination and expansion of MAT in primary care settings. In the meantime, this technical brief describes a number of MAT models of care that have been developed and implemented in such settings, which may help inform further efforts at individualized implementation of MAT.

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Appendix A. Sample Questions for Key Informants

Key Informant Perspective	Sample Questions
Researchers and Clinicians (including Professional Societies and Organizations)	Guiding Questions 1, 2, and 4. In addition: 1. What outcomes should be prioritized? 2. In your experience, what MAT models of care have been particularly successful and why? 3. Are there models of care that are particularly suited (e.g., feasibility, applicability) for rural or other underserved settings? 4. How would you categorize the components of MAT models of care? 5. What MAT models of care components are most critical for effectiveness? 6. What are barriers to implementation of MAT in primary care settings? 7. What are specific barriers to implementation of community-based psychosocial programs in MAT? 8. How could barriers to implementation be overcome? 9. Are you aware of new or innovative models of care that warrant additional research? 10. What are key research needs to understand effectiveness and implementation of MAT models of care? 11. What types of study designs would be useful for studying new or innovative MAT models of care? 12. What is a meaningful length of followup? 13. Are there specific areas related to effectiveness or implementation of MAT models of care that have been sufficiently studied to warrant a systematic evidence review?
Health Policy and Implementation Arenas	1. What outcomes of MAT are important from a health policy/payer perspective? 2. What policies do payers put in place to influence use of MAT for treatment of opioid use disorder? 3. How are decisions to cover or implement MAT made at a policy level or at an institutional/clinical setting level? 4. What are some research questions about MAT that you would like answered to inform policy and implementation decisions? 5. Are you considering new policies to improve the use of MAT, particularly in primary care, including rural or other underserved populations? 6. What are cost and/or economic efficiency considerations that impact diffusion, decision-making, and/or conceptual thinking around MAT?
Patient Perspective	1. What values do patients place on various non-substance-use-related outcomes and how do patients weigh trade-offs related to different pharmacological and non-pharmacological approaches? 2. What factors or themes are most important to patients receiving MAT? 3. What components of MAT are important for patients to know, that they may not be aware of? 4. What common experiences do patients in MAT programs describe? 5. Should the use of MAT programs be expanded; and if so, what settings for patients are most amenable to the implementation of MAT? 6. What barriers do patients experience in obtaining MAT? 7. What suggestions do patients have for improving MAT models of care? 8. What are ethical, privacy, equity, or cost considerations that impact patient's use of MAT?

MAT = medication-assisted treatment

Appendix B. Search Strategies for Guiding Question 3

Database: Ovid MEDLINE

1 exp Opiate Substitution Treatment
2 exp Opioid-Related Disorders/dt, pc, px, rh, th
3 methadone.mp. or exp Methadone
4 buprenorphine.mp. or Buprenorphine
5 naltrexone.mp. or Naltrexone
6 suboxone.mp.
7 3 or 4 or 5 or 6
8 2 and 7
9 (medicat* adj3 assist* adj3 (treat* or therap* or regimen* or interven* or program*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab.
11 9 or 10
12 2 and 11
13 1 or 8 or 12
14 limit 13 to english language
15 exp Comprehensive Health Care/
16 exp Community Health Services/
17 exp Outpatients/
18 exp Ambulatory Care/
19 exp Ambulatory Care Facilities/
20 exp General Practice/
21 general practitioners/ or physicians, family/ or physicians, primary care/
22 exp Health Services Accessibility/
23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 (((primary or ambulatory) adj3 care) or ((family or general) adj3 (medicine or practice* or physician* or doctor* or practitioner* or provider*)) or outpatient* or ((communit* or comprehensiv*) adj3 (health* or care))).mp.
25 (rural* or underserv* or frontier* or (geograph* adj3 (isolat* or remot*))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
26 24 or 25
27 23 or 26
28 14 and 27
29 limit 28 to yr="2005 -Current"
30 limit 28 to yr="1902 - 2004"
31 limit 14 to systematic reviews
32 limit 14 to (controlled clinical trial or guideline or randomized controlled trial)
33 exp epidemiologic study/
34 14 and 33
35 Comparative Study/
36 14 and 35
37 exp "Outcome and Process Assessment (Health Care)"/
38 14 and 37
39 mo.fs.
40 exp Death/
41 exp Vital Statistics/
42 39 or 40 or 41
43 14 and 42
44 exp Evaluation Studies as Topic/
45 14 and 44
46 exp "costs and cost analysis"/

47 14 and 46
48 exp Sociological Factors/
49 14 and 48
50 exp quality of life/
51 14 and 50
52 exp health behavior/
53 14 and 52
54 exp attitude to health/
55 14 and 54
56 31 or 32 or 34 or 36 or 38 or 43 or 45 or 47 or 49 or 51 or 53 or 55
57 28 or 56

Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 [exp Opiate Substitution Treatment/]
2 [exp Opioid-Related Disorders/dt, pc, px, rh, th]
3 methadone.mp. or exp Methadone/
4 buprenorphine.mp. or Buprenorphine/
5 naltrexone.mp. or Naltrexone/
6 suboxone.mp.
7 3 or 4 or 5 or 6
8 2 and 7
9 (medicat* adj3 assist* adj3 (treat* or therap* or regimen* or interven* or program*)).mp.
10 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab.
11 9 or 10
12 1 or 8 or 11

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp Opiate Substitution Treatment/
2 exp Opioid-Related Disorders/dt, pc, px, rh, th
3 methadone.mp. or exp Methadone/
4 buprenorphine.mp. or Buprenorphine/
5 naltrexone.mp. or Naltrexone/
6 suboxone.mp.
7 3 or 4 or 5 or 6
8 2 and 7
9 (medicat* adj3 assist* adj3 (treat* or therap* or regimen* or interven* or program*)).mp.
10 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab.
11 9 or 10
12 1 or 8 or 11

Database: PsycINFO
1 exp opiates/
2 exp drug rehabilitation/
3 exp drug dependency/
4 2 or 3
5 exp drug therapy/
6 exp methadone maintenance/
7 methadone.mp. or exp Methadone/
8 buprenorphine.mp. or Buprenorphine/
9 naltrexone.mp. or Naltrexone/
10 suboxone.mp.
11 5 or 6 or 7 or 8 or 9 or 10
12 1 and 4 and 11
13 (medicat* adj3 assist* adj3 (treat* or therap* or regimen* or interven* or program*)).mp.

14 ((opiate* or opioid* or narcotic*) adj2 (substitut* or replac* or maint*) adj2 (treatment* or therap* or regimen* or program* or interven*)).ti,ab.
15 13 or 14
16 1 and 4 and 15
17 12 or 16
18 limit 17 to english language
19 exp Primary Health Care/
20 exp community services/
21 exp Outpatients/
22 exp outpatient treatment/
23 exp Maintenance Therapy/
24 exp Ambulatory Care/
25 exp Ambulatory Care Facilities/
26 exp General Practitioners/
27 exp Family Medicine/
28 exp Family Physicians/
29 exp Treatment Barriers/
30 exp health disparities/
31 exp health care utilization/
32 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33 (((primary or ambulatory) adj3 care) or ((family or general) adj3 (medicine or practice* or physician* or doctor* or practitioner* or provider*)) or outpatient* or ((communit* or comprehensiv*) adj3 (health* or care))).mp.
34 (rural* or underserv* or frontier* or (geograph* adj3 (isolat* or remot*))).mp.
35 33 or 34
36 32 or 35
37 18 and 36
38 limit 18 to systematic reviews
39 exp treatment outcomes/ or exp treatment effectiveness evaluation/
40 18 and 39
41 exp "Death and Dying"/
42 exp mortality rate/
43 41 or 42
44 18 and 43
45 exp "costs and cost analysis"/
46 18 and 45
47 exp Sociocultural Factors/
48 exp socioeconomic status/
49 47 or 48
50 18 and 49
51 exp quality of life/
52 18 and 51
53 exp health behavior/
54 18 and 53
55 exp attitudes/
56 18 and 55
57 38 or 40 or 44 or 46 or 50 or 52 or 54 or 56
58 37 or 57

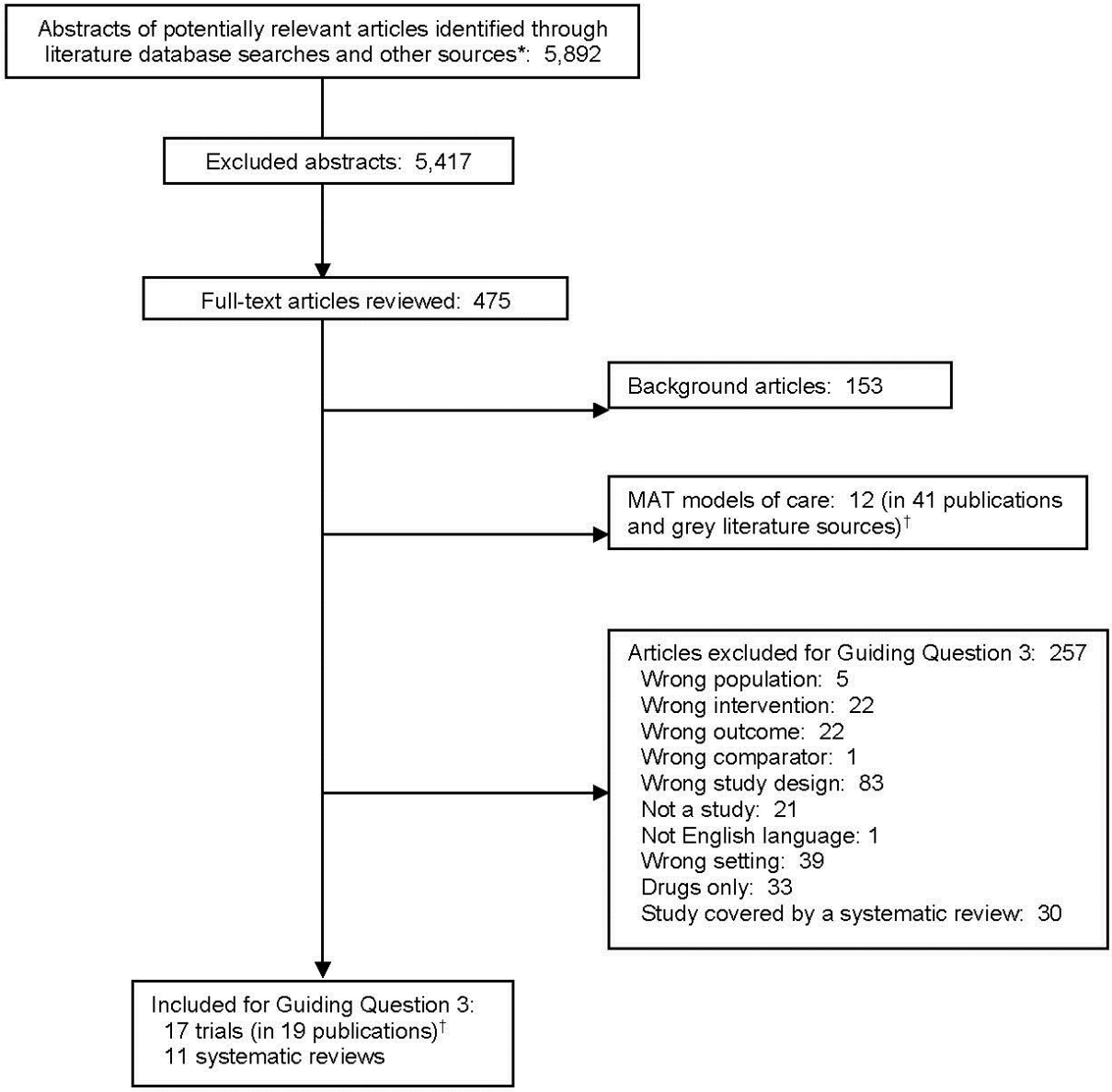
CINAHL
S1 (MH "Substance Use Disorders+")
S2 (MH "Narcotics+")
S3 S1 AND S2
S4 "methadone"
S5 "buprenorphine"
S6 "naltrexone"
S7 suboxone

S8 S4 OR S5 OR S6 OR S7
S9 S1 AND S8
S10 (medicat* n3 assist* n3 (treat* or therap* or regimen* or interven* or program*))
S11 ((opiate* or opioid* or narcotic*) n2 (substitut* or replac* or maint*) n2 (treatment* or therap* or regimen* or program* or interven*))
S12 S10 OR S11
S13 S1 AND S12
S14 S3 OR S9 OR S13
S15 S3 OR S9 OR S13
S16 (MH "Primary Health Care")
S17 (MH "Community Health Services+")
S18 (MH "Outpatients") OR (MH "Outpatient Service") OR (MH "Ambulatory Care Facilities+")
S19 (MH "Family Practice")
S20 (MH "Physicians, Family")
S21 (MH "Health Services Accessibility+")
S22 S16 OR S17 OR S18 OR S19 OR S20 OR S21
S23 (((primary or ambulatory) n3 care) or ((family or general) n3 (medicine or practice* or physician* or doctor* or practitioner* or provider*)) or outpatient* or ((communit* or comprehensiv*) n3 (health* or care)))
S24 (rural* or underserv* or frontier* or (geograph* n3 (isolat* or remot*)))
S25 S23 OR S24
S26 S22 OR S25
S27 S15 AND S26
S28 (MH "Systematic Review")
S29 (MH "Meta Analysis")
S30 (MH "Practice Guidelines") OR (MH "Guideline Adherence")
S31 (MH "Randomized Controlled Trials")
S32 (MH "Epidemiological Research+")
S33 (MH "Prospective Studies+")
S34 S28 OR S29 OR S30 OR S31 OR S32 OR S33
S35 S15 AND S34
S36 (MH "Outcomes (Health Care)+")
S37 (MH "Vital Statistics+")
S38 (MH "Evaluation Research+")
S39 (MH "Costs and Cost Analysis+")
S40 (MH "Socioeconomic Factors+")
S41 (MH "Cultural Values")
S42 (MH "Quality of Life+")
S43 (MH "Quality-Adjusted Life Years")
S44 (MH "Health Behavior+")
S45 (MH "Attitude+")
S46 S36 OR S37 OR S38 OR S42 OR S43
S47 S15 AND S46
S48 S15 AND S46
S49 S15 AND S34
S50 s48 NOT s49

SocINDEX
S1 (MH "Substance Use Disorders+")
S2 (MH "Narcotics+")
S3 S1 AND S2
S4 "methadone"
S5 "buprenorphine"
S6 "naltrexone"
S7 suboxone
S8 S4 OR S5 OR S6 OR S7
S9 S1 AND S8

S10 (medicat* n3 assist* n3 (treat* or therap* or regimen* or interven* or program*))
S11 ((opiate* or opioid* or narcotic*) n2 (substitut* or replac* or maint*) n2 (treatment* or therap* or regimen* or program* or interven*))
S12 S10 OR S11
S13 S9 OR S12

Appendix C. Literature Flow Diagram for Guiding Question 3



MAT=medication-assisted treatment for opioid use disorder
*Other sources include references lists, referrals from experts, and grey literature searches
†6 trials were used as sources for the models and were also included for Guiding Question 3

Appendix D. Included Studies List

Trials

Carrieri PM, Michel L, Lions C, et al. Methadone induction in primary care for opioid dependence: a pragmatic randomized trial (ANRS Methaville). PLoS ONE. 2014;9(11):e112328. PMID: 25393311.

Christensen DR, Landes RD, Jackson L, et al. Adding an Internet-delivered treatment to an efficacious treatment package for opioid dependence. J Consult Clin Psychol. 2014;82(6):964-72. PMID: 25090043.

D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. JAMA. 2015;313(16):1636-44. PMID: 25919527.

Fiellin DA, O'Connor PG, Chawarski M, et al. Methadone maintenance in primary care: a randomized controlled trial. JAMA. 2001;286(14):1724-31. PMID: 11594897.

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Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Engl J Med. 2006;355(4):365-74. PMID: 16870915.

Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. Am J Med. 2013;126(1):74.e11-7. PMID: 23260506.

Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003;349(10):949-58. PMID: 12954743.

Galanter M, Dermatis H, Glickman L, et al. Network therapy: decreased secondary opioid use during buprenorphine maintenance. J Subst Abuse Treat. 2004;26(4):313-8. PMID: 15182896.

King VL, Kidorf MS, Stoller KB, et al. A 12-month controlled trial of methadone medical maintenance integrated into an adaptive treatment model. J Subst Abuse Treat. 2006;31(4):385-93. PMID: 17084792.

Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. JAMA Intern Med. 2014;174(8):1369-76. PMID: 25090173.

Lintzeris N, Ritter A, Panjari M, et al. Implementing buprenorphine treatment in community settings in Australia: experiences from the Buprenorphine Implementation Trial. Am J Addict. 2004;13 Suppl 1:S29-41. PMID: 15204674.

Lucas GM, Chaudhry A, Hsu J, et al. Clinic-based treatment of opioid-dependent HIV-infected patients versus referral to an opioid treatment program: A randomized trial. Ann Intern Med. 2010;152(11):704-11. PMID: 20513828.

Moore BA, Barry DT, Sullivan LE, et al. Counseling and directly observed medication for primary care buprenorphine maintenance: a pilot study. J Addict Med. 2012;6(3):205-11. PMID: 22614936.

Roux P, Michel L, Cohen J, et al. Methadone induction in primary care (ANRS-Methaville): a phase III randomized intervention trial. BMC Public Health. 2012;12:488. PMID: 22741944. (pilot study to Carrieri et al, 2014)

Sullivan LE, Barry D, Moore BA, et al. A trial of integrated buprenorphine/naloxone and HIV clinical care. Clin Infect Dis. 2006;43 Suppl 4:S184-90. PMID: 17109305.

Tetrault JM, Moore BA, Barry DT, et al. Brief versus extended counseling along with buprenorphine/naloxone for HIV-infected opioid dependent patients. J Subst Abuse Treat. 2012;43(4):433-9. PMID: 22938914.

Weiss RD, Potter JS, Fiellin DA, et al. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial. Arch Gen Psychiatry. 2011;68(12):1238-46. PMID: 22065255.

Weiss RD, Potter JS, Griffin ML, et al. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. Drug Alcohol Depend. 2015;150:112-9. PMID: 25818060

Systematic Reviews

Amato L, Minozzi S, Davoli M, et al. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database Syst Rev. 2011(10):CD004147. PMID: 21975742.

Ferri M, Minozzi S, Bo A, et al. Slow-release oral morphine as maintenance therapy for opioid dependence. Cochrane Database Syst Rev. 2013;6:Cd009879. PMID: 23740540.

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Mattick RP, Breen C, Kimber J, et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev. 2009(3):CD002209. PMID: 19588333.

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Minozzi S, Amato L, Vecchi S, et al. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev. 2011(4):Cd001333. PMID: 21491383.

Minozzi S, Amato L, Bellisario C, et al. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev. 2013;12:CD006318. PMID: 24366859.

Nielsen S, Larance B, Degenhardt L, et al. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database Syst Rev. 2016(5):CD011117. PMID: 27157143.

Rahimi-Movaghar A, Amin-Esmaeili M, Hefazi M, et al. Pharmacological therapies for maintenance treatments of opium dependence. Cochrane Database Syst Rev. 2013;1:Cd007775. PMID: 23440817.

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Appendix E. Excluded Studies List

Counseling Conditons for Thrice Weekly BUP in a PCC. PMID: SN029405. Excluded for not a study/systematic review.

Opiate Dependence: Combined Naltrexone/behavior Therapy. PMID: SN097696. Excluded for not a study/systematic review.

Buprenorphine combined with counseling found effective in reducing relapse. Alcoholism & Drug Abuse Weekly. 2003;3(10). PMID: 106876227. Excluded for not a study/systematic review.

Aalto M, Visapaa JP, Halme JT, et al. Effectiveness of buprenorphine maintenance treatment as compared to a syringe exchange program among buprenorphine misusing opioid-dependent patients. Nord J Psychiatry. 2011;65(4):238-43. PMID: 21047194. Excluded for wrong study design for Key Question.

Ahamad K, Milloy MJ, Nguyen P, et al. Factors associated with willingness to take extended release naltrexone among injection drug users. Addict Sci Clin Pract. 2015;10:12. PMID: 25935714. Excluded for wrong outcome.

Allen MA, Jewers H, McDonald JS. A Framework for the Treatment of Pain and Addiction in the Emergency Department. JEN. 2014;40(6). PMID: 103858648. Excluded for wrong intervention.

Amass L, Pukeleviciene V, Subata E, et al. A prospective, randomized, multicenter acceptability and safety study of direct buprenorphine/naloxone induction in heroin-dependent individuals. Addiction. 2012;107(1):142-51. PMID: 21749526. Excluded for drugs only.

Amato L, Davoli M, Minozzi S, et al. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev. 2013;2:Cd003409. PMID: 23450540. Excluded for wrong intervention.

Amato L, Minozzi S, Davoli M, et al. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database Syst Rev. 2004(4):CD004147. PMID: 15495081. Excluded as a study covered by a systematic review.

Anonymous. Treatment of opiate dependence in hands of primary care providers. Public Health Rep. 2003;118(1):76. PMID: 12622131. Excluded for not a study/systematic review.

Anonymous. Public policy statement on Office-Based Opioid Agonist Treatment (OBOT). J Addict Dis. 2005;24(3):153-61. PMID: 16186090. Excluded for not a study/systematic review.

Apelt SM, Scherbaum N, Golz J, et al. Safety, effectiveness and tolerance of buprenorphine-naloxone in the treatment of opioid dependence: results from a nationwide non-interventional study in routine care. Pharmacopsychiatry. 2013;46(3):94-107. PMID: 23293011. Excluded for wrong study design for Key Question.

Aszalos R, McDuff DR, Weintraub E, et al. Engaging hospitalized heroin-dependent patients into substance abuse treatment. J Subst Abuse Treat. 1999;17(1-2):149-58. PMID: 10435263. Excluded for wrong study design for Key Question.

Barnett PG, Masson CL, Sorensen JL, et al. Linking opioid-dependent hospital patients to drug treatment: Health care use and costs 6 months after randomization. Addiction. 2006;101(12):1797-804. PMID: 17156179. Excluded for wrong setting.

Barry DT, Moore BA, Pantalon MV, et al. Patient satisfaction with primary care office-based buprenorphine/naloxone treatment. J Gen Intern Med. 2007;22(2):242-5. PMID: 17356993. Excluded for wrong outcome.

Bassuk EL, Hanson J, Greene RN, et al. Peer-Delivered Recovery Support Services for Addictions in the United States: A Systematic Review. J Subst Abuse Treat. 2016 Apr;63:1-9. PMID: 26882891. Excluded for wrong setting.

Berger R, Pulido C, Lacro J, et al. Group medication management for buprenorphine/naloxone in opioid-dependent veterans. J Addict Med. 2014;8(6):415-20. PMID: 25275875. Excluded for wrong study design for Key Question.

Bonhomme J, Shim RS, Gooden R, et al. Opioid addiction and abuse in primary care practice: a comparison of methadone and buprenorphine as treatment options. J Natl Med Assoc. 2012;104(7-8):342-50. PMID: 23092049. Excluded as a study covered by a systematic review.

Brands B, Blake J, Marsh D. Changing patient characteristics with increased methadone maintenance availability. Drug Alcohol Depend. 2002;66(1):11-20. PMID: 11850131. Excluded for wrong intervention.

Bryson WC, McConnell J, Korthuis PT, et al. Extended-release naltrexone for alcohol dependence: persistence and healthcare costs and utilization. Am J Manag Care. 2011;17 Suppl 8:S222-34. PMID: 21761949. Excluded for wrong study design for Key Question.

Burns L, Mattick RP, Lim K, et al. Methadone in pregnancy: treatment retention and neonatal outcomes. Addiction. 2007;102(2):264-70. PMID: 17222281. Excluded for wrong study design for Key Question.

Caldiero RM, Parran TV, Jr., Adelman CL, et al. Inpatient initiation of buprenorphine maintenance vs. detoxification: can retention of opioid-dependent patients in outpatient counseling be improved? Am J Addict. 2006;15(1):1-7. PMID: 16449087. Excluded for wrong study design for Key Question.

Carroll KM, Ball SA, Martino S, et al. Computer-assisted delivery of cognitive-behavioral therapy for addiction: a randomized trial of CBT4CBT. Am J Psychiatry. 2008;165(7):881-8. PMID: 18450927. Excluded for wrong population.

Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. SAMHSA/CSAT Treatment Improvement Protocol (TIP) Series, No. 43. HHS Publication No. (SMA) 12-4214. Rockville, MD. 2005. PMID: 22514849. Excluded for wrong setting.

Chawarski MC, Mazlan M, Schottenfeld RS. Behavioral drug and HIV risk reduction counseling (BDRC) with abstinence-contingent take-home buprenorphine: a pilot randomized clinical trial. Drug Alcohol Depend. 2008;94(1-3):281-4. PMID: 18164145. Excluded as a study covered by a systematic review.

Chua SM, Lee TS. Abuse of prescription buprenorphine, regulatory controls and the role of the primary physician. Ann Acad Med Singapore. 2006;35(7):492-5. PMID: 16902726. Excluded as a study covered by a systematic review.

Clay E, Khemiri A, Zah V, et al. Persistence and healthcare utilization associated with the use of buprenorphine/naloxone film and tablet formulation therapy in adults with opioid dependence. J Med Econ. 2014;17(9):626-36. PMID: 24841329. Excluded for wrong study design for Key Question.

Colameco S, Armando J, Trotz C. Opiate dependence treatment with buprenorphine: one year's experience in a family practice residency setting. J Addict Dis. 2005;24(2):25-32. PMID: 15784521. Excluded for wrong study design for Key Question.

Colson J, Helm S, Silverman SM. Office-based opioid dependence treatment. Pain physician. 2012;15(3 Suppl):ES231-6. PMID: 22786460. Excluded as a study covered by a systematic review.

Connery HS. Medication-assisted treatment of opioid use disorder: review of the evidence and future directions. Harv Rev Psychiatry. 2015;23(2):63-75. PMID: 25747920. Excluded as a study covered by a systematic review.

Copenhaver MM, Bruce RD, Altice FL. Behavioral counseling content for optimizing the use of buprenorphine for treatment of opioid dependence in community-based settings: a review of the empirical evidence. Am J Drug Alcohol Abuse. 2007;33(5):643-54. PMID: 17891657. Excluded as a study covered by a systematic review.

Cozzolino E, Guglielmino L, Vigezzi P, et al. Buprenorphine treatment: a three-year prospective study in opioid-addicted patients of a public out-patient addiction center in Milan. Am J Addict. 2006;15(3):246-51. PMID: 16923672. Excluded for wrong setting.

Cunningham C, Giovanniello A, Sacajiu G, et al. Buprenorphine treatment in an urban community health center: what to expect. Fam Med. 2008;40(7):500-6. PMID: 18928077. Excluded for drugs only.

Cunningham CO, Giovanniello A, Li X, et al. A comparison of buprenorphine induction strategies: patient-centered home-based inductions versus standard-of-care office-based inductions. J Subst Abuse Treat. 2011;40(4):349-56. PMID: 21310583. Excluded for wrong study design for Key Question.

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Daniels AM, Salisbury-Afshar E, Hoffberg A, et al. A novel community-based buprenorphine program: client description and initial outcomes. J Addict Med. 2014;8(1):40-6. PMID: 24394496. Excluded for wrong setting.

Davies D. Buprenorphine versus methadone--safety first? Br J Gen Pract. 2005;55(512):232-3. PMID: 15808047. Excluded for not a study/systematic review.

De Ducla M, Gagnon A, Mucchielli A, et al. Comparison of high dose buprenorphine treatments of opiate dependent outpatients in four healthcare networks. Ann Med Interne (Paris). 2000;151 Suppl B:B9-15. PMID: 11104938. Excluded for wrong study design for Key Question.

DeFulio A, Everly JJ, Leoutsakos JM, et al. Employment-based reinforcement of adherence to an FDA approved extended release formulation of naltrexone in opioid-dependent adults: a randomized controlled trial. Drug Alcohol Depend. 2012;120(1-3):48-54. PMID: 21782353. Excluded for wrong setting.

Donaher PA, Welsh C. Managing opioid addiction with buprenorphine. Am Fam Physician. 2006;73(9):1573-8. PMID: 16719249. Excluded as a study covered by a systematic review.

Doolittle B, Becker W. A case series of buprenorphine/naloxone treatment in a primary care practice. Substance abuse. 2011;32(4):262-5. PMID: 22014257. Excluded for drugs only.

Drainoni ML, Farrell C, Sorensen-Alawad A, et al. Patient perspectives of an integrated program of medical care and substance use treatment. AIDS Patient Care STDS. 2014;28(2):71-81. PMID: 24428768. Excluded for wrong study design for Key Question.

Ducharme S, Fraser R, Gill K. Update on the clinical use of buprenorphine: in opioid-related disorders. Can Fam Physician. 2012;58(1):37-41. PMID: 22267618. Excluded as a study covered by a systematic review.

Everly JJ, DeFulio A, Koffarnus MN, et al. Employment-based reinforcement of adherence to depot naltrexone in unemployed opioid-dependent adults: a randomized controlled trial. Addiction. 2011;106(7):1309-18. PMID: 21320227. Excluded for wrong setting.

Fals-Stewart W, O'Farrell TJ. Behavioral family counseling and naltrexone for male opioid-dependent patients. J Consult Clin Psychol. 2003;71(3):432-42. PMID: 12795568. Excluded for wrong setting.

Fareed A, Eilender P, Ketchen B, et al. Factors affecting noncompliance with buprenorphine maintenance treatment. J Addict Med. 2014;8(5):345-50. PMID: 25072677. Excluded for wrong study design for Key Question.

Fareed A, Vayalapalli S, Casarella J, et al. Treatment outcome for flexible dosing buprenorphine maintenance treatment. Am J Drug Alcohol Abuse. 2012;38(2):155-60. PMID: 22175698. Excluded for drugs only.

Ferner RE, Daniels AM. Office-based treatment of opioid-dependent patients. N Engl J Med. 2003;348(1):81-2; author reply -2. PMID: 12510051. Excluded for not a study/systematic review.

Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. Cochrane Database Syst Rev. 2011(12):Cd003410. PMID: 22161378. Excluded for wrong intervention.

Ferri M, Finlayson AJ, Wang L, et al. Predictive factors for relapse in patients on buprenorphine maintenance. Am J Addict. 2014;23(1):62-7. PMID: 24313243. Excluded for wrong setting.

Fiellin DA. Buprenorphine: effective treatment of opioid addiction starts in the office. Am Fam Physician. 2006;73(9):1513-4. PMID: 16719242. Excluded as a study covered by a systematic review.

Fiellin DA, O'Connor PG. Office-Based Treatment of Opioid-Dependent Patients. PMID: 7298856. Excluded for not a study/systematic review.

Fiellin DA, O'Connor PG. Clinical practice Office-based treatment of opioid-dependent patients. N Engl J Med. 2002;9(12). PMID: 106819223. Excluded for not a study/systematic review.

Fiellin DA, O'Connor PG, Chawarski M, et al. Processes of care during a randomized trial of office-based treatment of opioid dependence in primary care. Am J Addict. 2004;13 Suppl 1:S67-78. PMID: 15204676. Excluded for wrong study design for Key Question.

Fiellin DA, Schottenfeld RS, Cutter CJ, et al. Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern Med. 2014;174(12):1947-54. PMID: 25330017. Excluded for drugs only.

Fingerhood MI, King VL, Brooner RK, et al. A comparison of characteristics and outcomes of opioid-dependent patients initiating office-based buprenorphine or methadone maintenance treatment. Substance abuse. 2014;35(2):122-6. PMID: 24821346. Excluded for wrong study design for Key Question.

Fischer G, Etzersdorfer P, Eder H, et al. Buprenorphine maintenance in pregnant opiate addicts. Eur Addict Res. 1998;4 Suppl 1:32-6. PMID: 9767205. Excluded for wrong study design for Key Question.

Fischer G, Johnson RE, Eder H, et al. Treatment of opioid-dependent pregnant women with buprenorphine. Addiction. 2000;95(2):239-44. PMID: 10723852. Excluded for drugs only.

Fischer G, Ortner R, Rohrmeister K, et al. Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. Addiction. 2006;101(2):275-81. PMID: 16445556. Excluded for wrong setting.

Fishman MJ, Winstanley EL, Curran E, et al. Treatment of opioid dependence in adolescents and young adults with extended release naltrexone: preliminary case-series and feasibility. Addiction. 2010;105(9):1669-76. PMID: 20626723. Excluded for wrong study design for Key Question.

French MT. Cost-effectiveness of buprenorphine maintenance versus methadone maintenance. Addiction. 2001;96(10):1515-7. PMID: 11599513. Excluded as a study covered by a systematic review.

George S. Review: methadone increases retention and reduces heroin use compared with non-pharmacological maintenance. Evidence Based Mental Health. 2010;13(1). PMID: 105126642. Excluded for not a study/systematic review.

Giacomuzzi SM, Riemer Y, Ertl M, et al. Buprenorphine versus methadone maintenance treatment in an ambulant setting: a health-related quality of life assessment. Addiction. 2003;98(5):693-702. PMID: 12751987. Excluded for wrong study design for Key Question.

Gordon AJ, Trafton JA, Saxon AJ, et al. Implementation of buprenorphine in the Veterans Health Administration: results of the first 3 years. Drug Alcohol Depend. 2007;90(2-3):292-6. PMID: 17493771. Excluded for wrong outcome.

Gossop M, Marsden J, Stewart D, et al. The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. Addiction. 2003;98(3):291-303. PMID: 12603229. Excluded for wrong study design for Key Question.

Gossop M, Marsden J, Stewart D, et al. Methadone treatment practices and outcome for opiate addicts treated in drug clinics and in general practice: results from the National Treatment Outcome Research Study. Br J Gen Pract. 1999;49(438):31-4. PMID: 10622013. Excluded for wrong study design for Key Question.

Gossop M, Stewart D, Browne N, et al. Methadone treatment for opiate dependent patients in general practice and specialist clinic settings: Outcomes at 2-year follow-up. J Subst Abuse Treat. 2003;24(4):313-21. PMID: 12867205. Excluded for wrong study design for Key Question.

Gourevitch MN, Chatterji P, Deb N, et al. On-site medical care in methadone maintenance: associations with health care use and expenditures. J Subst Abuse Treat. 2007;32(2):143-51. PMID: 17306723. Excluded for wrong study design for Key Question.

Haddad MS, Zelenev A, Altice FL. Integrating buprenorphine maintenance therapy into federally qualified health centers: real-world substance abuse treatment outcomes. Drug Alcohol Depend. 2013;131(1-2):127-35. PMID: 23332439. Excluded for wrong study design for Key Question.

Haddad MS, Zelenev A, Altice FL. Buprenorphine maintenance treatment retention improves nationally recommended preventive primary care screenings when integrated into urban federally qualified health centers. J Urban Health. 2015;92(1):193-213. PMID: 25550126. Excluded for wrong study design for Key Question.

Harris KA, Jr., Arnsten JH, Joseph H, et al. A 5-year evaluation of a methadone medical maintenance program. J Subst Abuse Treat. 2006 Dec;31(4):433-8. PMID: 17084798. Excluded for wrong study design for Key Question.

Herman M, Gourevitch MN. Integrating primary care and methadone maintenance treatment: implementation issues. J Addict Dis. 1997;16(1):91-102. PMID: 9046446. Excluded as a study covered by a systematic review.

Hersh D, Little SL, Gleghorn A. Integrating buprenorphine treatment into a public healthcare system: the San Francisco Department of Public Health's office-based Buprenorphine Pilot Program. J Psychoactive Drugs. 2011;43(2):136-45. PMID: 21858959. Excluded for wrong study design for Key Question.

Hulse GK. Subcutaneous naltrexone implants reduce opioid use in opiate dependent patients. Evid Based Ment Health. 2010;13(1):25. PMID: 105126640. Excluded for not a study/systematic review.

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Appendix F. Details of Trials for Guiding Question 3

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
MAT Models of Care								
D'Onofrio, 2015[1]	Screening and referral to treatment (referral) vs. screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention) vs. screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week followup (buprenorphine)	30 days	329	USA; 76.3% male; 75.4% white; mean age 31.4 years (SD 10.6); study done in USA; 34.3% use alcohol to intoxication; 47.4% used sedatives in past month; 52.9% used cannabis in past month; 55.3% used cocaine in past month; 88.1% used cigarettes in past month; 51.1% had received psychiatric treatment in the past; 26.1% had received in-patient psychiatric treatment; 41.9% had received out-patient psychiatric treatment; 12.2% had received treatment for depression in the past month; 24.9% used prescription opioids; 75.1% used heroin; 52.9% were IV drug users	Buprenorphine group given treatment for 10 weeks before transferred to community program or detoxification for 2 weeks; Referral group received information for treatment programs only; brief intervention program received a brief 10- to 15-minute manual-driven audio-taped brief negotiation interview from a research associate who linked them with a referral; buprenorphine group received a Brief Negotiation Interview and if they exhibited moderate to severe opioid withdrawal received ED-initiated treatment and sufficient take-home daily doses to get through to next appointment, those without opioid withdrawal were given unobserved inducted with detailed self-medication guide, then office based buprenorphine treatment, and ongoing opioid agonist maintenance treatment or detoxification	Urban teaching hospital; Research associate performed ED visits, interviews, and referrals. Physicians and nurses managed buprenorphine dosages	Engagement in treatment assessed by direct contact with the facility, clinicians, or both; self-reported number of days of illicit opioids use in the past 7 days; urine toxicology for illicit opioid use; HIV risk-taking behavior using an 11-item validated scale for drug use and sexual behavior; and use of addiction treatment services.	Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk. These findings require replication in other centers before widespread adoption.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2002[2]	Buprenorphine and medication management (thrice-weekly sessions with a nurse and a monthly meeting with a physician) vs. buprenorphine and medication management plus drug counseling (not described)	13 weeks	14	USA; 71% male; 93% white, mean age 36 years; 50% current IV drug user; mean 7 years heroin use; 79% with history/current alcohol dependence; 79% with history/current cocaine dependence	Buprenorphine given 3 times per week following one week induction with dose escalation as needed for positive urine screen or withdrawal. Medication management group had brief monthly counseling sessions with physicians and 3 times per week manual-guided counseling sessions with nurses covering recent drug use, abstinence efforts, attendance at self-help groups with support and advice for efforts to reduce drug use or remain abstinent. Medication management plus manual-guided drug counseling sessions met weekly (no details provided)	Urban academically affiliated medical center; primary care; medical management provided by nurses and physicians (counseling issues reviewed weekly with physician and clinical psychologist)	Illicit drug use: urine toxicology and self report Retention/adherence: attendance at visits Overall health:SF-36 Patient satisfaction	Overall, patients reduced opioid-positive urine toxicology tests and good retention through maintenance; less patients in medication management group vs. medication management plus counseling group achieved greater than or equal to one week of opioid-free urine screens, though this difference was not statistically significant; A greater proportion of the medication management plus counseling group had opioid-free urine screens compared with the medication management alone group, though this difference was not statistically significant

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2006[3]	Standard medical management (20 minutes with a nurse) and once-weekly medication dispensing (buprenorphine-naloxone) vs. standard medical management and thrice-weekly medication dispensing vs. enhanced (45 minutes with a nurse) medical management and thrice-weekly medication dispensing All groups met monthly with a physician	24 weeks	166	USA; 78% male; 77% white; mean age 36 years; mean duration of opioid dependence 8 years; 17% prescription drug use; 31% history of intravenous drug use; 20% cocaine-positive urine specimen at treatment entry; 66% previously attempted detoxification; 32% history of participation in methadone-maintenance program	Nurses dispensed buprenorphine-naloxone and provided standard (20 minutes; sessions covered recent drug use or efforts to achieve or maintain abstinence, attendance in self-help groups, support for efforts to reduce drug use or remain abstinent, advice for the achievement or maintenance of abstinence, and the results of analysis of weekly urine specimens) or enhanced (45 minutes; sessions covered similar issues but provided more in-depth drug counseling) medical management Physicians met with patients monthly (20 minutes; sessions paralleled that of the standard sessions, with the addition of an assessment of employment, legal, family or social, medical, and psychiatric problems related to addiction) The nurses, a physician, and a psychologist met weekly to review the counseling	Trained primary care nurses without previous addiction treatment, physician, psychologist Primary care center	Illicit opioid use: urine toxicology and self-report Abstinence: measured in consecutive weeks	The efficacy of brief weekly counseling and once-weekly medication dispensing did not differ significantly from that of extended weekly counseling and thrice-weekly dispensing
Liebschutz, 2014[4]	Detoxification plus referral vs. induction plus contact from long-term opioid agonist treatment staff that facilitated linkage to hospital-associated primary care buprenorphine treatment	6 months	139	USA; 71.2% male; mean age 40.5 (SD 11.8); mean illicit opioid use per 30 followup days 20.8 (SD 9.7)	Both groups received buprenorphine and naloxone up to 4 times for the first day in the hospital. Detoxification group received 4 additional days of tapering buprenorphine and naloxone, then treatment referral information; linkage group received buprenorphine and naloxone for hospitalization with enough given at discharge to get through to clinic appointment, before discharge research staff facilitated linkage to hospital-associated primary care buprenorphine treatment	Hospital and medical center; Research staff, which included an addiction nurse specialist, hospital nursing staff administered medication in hospital	Entry into opioid agonist treatment program, length of illicit opioid use defined as number of days of reported opioid use in the 30 days before visits, time to entry into buprenorphine program, number of self-reported prescribed opioid agonist treatment in the 30 days before visits, mortality.	Compared with an inpatient detoxification protocol, initiation of and linkage to buprenorphine treatment is an effective means for engaging medically hospitalized patients who are not seeking addiction treatment and reduces illicit opioid use 6 months after hospitalization. However, maintaining engagement in treatment remains a challenge.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Lucas, 2010[5]	Clinic-based, nurse-administered treatment with buprenorphine-naloxone vs. case management and referral to an intensive opioid treatment program (referred treatment)	12 months	93	USA; 72% male; 98% black; median ages 45-46 years; median years of opioid use 18-20 years; 96% heroin used in previous month; 27% prescription opioid used in previous month; 72% used cocaine in previous month; 60% injection drug use in previous month; 73% positive for hepatitis C antibody; 10% AIDS-defining opportunistic condition in previous 3 months; 53% receiving ART	Clinic-based group was managed and seen weekly by a nurse (10-40 minutes; sessions included unstructured individual counseling, urine samples, observed buprenorphine doses, and provision of take-home supplies of buprenorphine to last until their next visit), and met with a physician 4-6 weeks after initiation of therapy and at other times as indicated. A treatment team, comprising the nurse and 2 to 5 buprenorphine prescribing physicians, met weekly to discuss participants' progress in treatment. The treatment team set reporting frequencies, which ranged from 3 times weekly to monthly, according to drug test results and other factors. Participants assigned to referred treatment were enrolled in an intensive case management program that has operated in the same clinic. A social worker or registered nurse in the case management program met with referred treatment participants shortly after randomization and made treatment plans that were primarily focused on linking participants to opioid treatment programs, but may have included such issues as food and housing needs	Licensed practical nurse with training and experience as a substance counselor, buprenorphine prescribing physicians HIV clinic	Drug use: urine toxicology Participation in opioid agonist therapy at study visits: self-reported Also, visits with primary HIV providers, months of ART use, changes in HIV RNA levels and CD4 cell counts, and proportion of participants with emergency department visits or hospitalizations (methods NR)	Participation in opioid agonist therapy was significantly higher in clinic-based buprenorphine than for referred treatment. Positive test results for opioids and cocaine were significantly less frequent in clinic-based buprenorphine than in referred treatment, and study participants receiving clinic-based buprenorphine attended significantly more HIV primary care visits than those receiving referred treatment. Use of antiretroviral therapy and changes in HIV RNA levels and CD4 cell counts did not differ between the 2 groups.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Sullivan, 2006[6]	Buprenorphine/ naloxone and physician management (brief, biweekly) vs. buprenorphine/ naloxone and physician management plus once-weekly drug counseling and adherence management	12 weeks	16	USA; 94% male; 31% white, 44% Black, 25% Hispanic; mean age 47 years; mean 17 years opioid dependence; 56% with injection drug use; 29% reported one or more days of alcohol use in past 30 days; 36% reported one or more days of cocaine use in past 30 days; 100% HIV positive; mean 13 years since HIV diagnosis; 63% currently on ART; 81% HCV positive	Buprenorphine/naloxone stabilization over 2-weeks with clinic visits 3 times per week and 1 and 2-day take home doses then 10-week maintenance period with once weekly clinic visits and 6 take home doses then offered 2-week taper or extension phase; all patients received brief, bi-weekly, manual-guided physician management that focused on symptoms, drug use, and progress; half of patients received physician management plus once-weekly drug counseling and adherence management focused on addiction-specific topics like triggers, relationships, and craving and strategies to increased adherence to antiretroviral treatment	HIV clinics; Buprenorphine and physician management provided by physician specialized in addiction medicine and experienced in HIV care; drug counseling and adherence management provided by trained nursing staff (issues reviewed with supervising physician and clinical psychologist)	Treatment retention Illicit drug use: urine toxicology and self-report Laboratory parameters: CD4 count, viral load, and liver function tests Adherence to MAT and ART: Medication Event Monitoring System (caps that record the date and time the pill bottle was opened) HIV transmission risk behaviors: HIV/AIDS Risk Inventory Health status: SF-36 Patient satisfaction: 5-point Likert scale questionnaire	There was no difference in treatment retention or illicit drug use by counseling group; Overall, the proportion of opioid-positive weekly urine screens decreased substantially over trial; CD4 counts remained stable; viral load declined significantly; demonstrated feasibility of integrating buprenorphine into HIV clinical care for treatment of opioid dependence
Psychosocial Interventions								
Christensen, 2014[7]	Buprenorphine and individual counseling plus contingency management (based on urine results linked to points for gift cards or money) vs. buprenorphine and individual counseling and contingency management plus internet-based community reinforcement approach Both groups had individual counseling every 2 weeks	12 weeks	170	USA; 54% male, 95% white, mean age 34 years; 13% with concurrent alcohol dependence, 5% with concurrent cocaine dependence, 12% with concurrent sedative dependence, 29% with concurrent cannabis dependence; 46% had prior treatment; 14% with injection drug use	Buprenorphine given 3 times per week with extra dose for days in between; contingency management based on urine results linked to points for gift cards or money; community reinforcement approach completed set of topics on community reinforcement approach at each clinic visit; both groups had individual counseling every 2 weeks	Clinic setting at university research center; Buprenorphine from study physician; therapist for community reinforcement approach and counseling	Retention: number of days from start of intervention until participant left trial or completed trial Abstinence: number of negative urine specimens overall and over longest continuous period with missed visits equal to positive result Addiction-related severity: ASI	Compared to those receiving contingency management-alone, community reinforcement approach recipients had more total days of abstinence and were less likely to drop out of treatment; prior treatment for opioid dependence moderated the additional improvement of community reinforcement approach for longest continuous days of abstinence

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2002[2] (also a model of care	Buprenorphine and medication management (thrice-weekly sessions with a nurse and a monthly meeting with a physician) vs. buprenorphine and medication management plus drug counseling (not described)	13 weeks	14	USA; 71% male; 93% white, mean age 36 years; 50% current IV drug user; mean 7 years heroin use; 79% with history/current alcohol dependence; 79% with history/current cocaine dependence	Buprenorphine given 3 times per week following one week induction with dose escalation as needed for positive urine screen or withdrawal. Medication management group had brief monthly counseling sessions with physicians and 3 times per week manual-guided counseling sessions with nurses covering recent drug use, abstinence efforts, attendance at self-help groups with support and advice for efforts to reduce drug use or remain abstinent. Medication management plus manual-guided drug counseling sessions met weekly (no details provided)	Urban academically affiliated medical center; primary care; medical management provided by nurses and physicians (counseling issues reviewed weekly with physician and clinical psychologist)	Illicit drug use: urine toxicology and self report Retention/adherence: attendance at visits Overall health:SF-36 Patient satisfaction	Overall, patients reduced opioid-positive urine toxicology tests and good retention through maintenance; less patients in medication management group vs. medication management plus counseling group achieved greater than or equal to one week of opioid-free urine screens, though this difference was not statistically significant; A greater proportion of the medication management plus counseling group had opioid-free urine screens compared with the medication management alone group, though this difference was not statistically significant

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2006[3] (also a model of care)	Standard medical management (20 minutes with a nurse) and once-weekly medication dispensing (buprenorphine-naloxone) vs. standard medical management and thrice-weekly medication dispensing vs. enhanced (45 minutes with a nurse) medical management and thrice-weekly medication dispensing All groups met monthly with a physician	24 weeks	166	USA; 78% male; 77% white; mean age 36 years; mean duration of opioid dependence 8 years; 17% prescription drug use; 31% history of intravenous drug use; 20% cocaine-positive urine specimen at treatment entry; 66% previously attempted detoxification; 32% history of participation in methadone-maintenance program	Nurses dispensed buprenorphine-naloxone and provided standard (20 minutes; sessions covered recent drug use or efforts to achieve or maintain abstinence, attendance in self-help groups, support for efforts to reduce drug use or remain abstinent, advice for the achievement or maintenance of abstinence, and the results of analysis of weekly urine specimens) or enhanced (45 minutes; sessions covered similar issues but provided more in-depth drug counseling) medical management Physicians met with patients monthly (20 minutes; sessions paralleled that of the standard sessions, with the addition of an assessment of employment, legal, family or social, medical, and psychiatric problems related to addiction) The nurses, a physician, and a psychologist met weekly to review the counseling	Trained primary care nurses without previous addiction treatment, physician, psychologist Primary care center	Illicit opioid use: urine toxicology and self-report Abstinence: measured in consecutive weeks	The efficacy of brief weekly counseling and once-weekly medication dispensing did not differ significantly from that of extended weekly counseling and thrice-weekly dispensing

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2013[8]	Physician management (15-20 minutes weekly for the first 2 weeks, every 2 weeks for the next 4 weeks, and then monthly) with buprenorphine-naloxone or physician management with buprenorphine-naloxone plus CBT (up to 12 50-minute weekly sessions during the first 12 weeks of treatment)	24 weeks	141	USA; 74% male; 90% white; mean age 34 years; mean time opioid dependent 8 years; 35% prescription drug use; 32% current injection drug use; 45% prior attempted detoxification; 59% prior substance abuse treatment; mean 1.3 days of use of cocaine in previous 30 days	Physician management (15-20 minutes; sessions occurred weekly for the first 2 weeks, every 2 weeks for the next 4 weeks, and then monthly). The physician followed a structured note that reviewed the patient's recent drug use; provided brief advice on how to achieve or maintain abstinence; supported efforts to reduce drug use or remain abstinent; reviewed medical and psychiatric symptoms; assessed social, work, and legal function; discussed weekly urine toxicology results; and reviewed attendance at self-help groups.CBT was provided using a CBT manual adapted for cocaine dependence. Fidelity measures were taken and supervision provided. Patients were offered up to 12 50-minute weekly sessions during the first 12 weeks of treatment. The main components of counseling focused on performing a functional analysis of behavior, promoting behavioral activation, identifying and coping with drug cravings, enhancing drug-refusal skills, enhancing decision-making about high-risk situations, and improving problem-solving skills.	Internal medicine physicians with experience providing buprenorphine, trained masters and doctoral-level clinicians Primary care clinic	Frequency of illicit opioid use: self-report Maximum number ofconsecutive weeks of abstinence from illicit opioids: urine toxicology and self-report Also, the proportion of patients remaining in the study (the percentage of patients who did not meet the criteria for protective transfer, did not miss medication for 7 days, or did not miss 3 physician management sessions), the number of days of the study that were completed, and self-reported abstinence from cocaine use (verifiedby urinalysis)	The effectiveness of physician management did not differ significantly from that of physician management plus CBT.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Galanter, 2004[9]	Buprenorphine plus medication management (2 individual sessions per week) vs. buprenorphine plus network therapy (1 individual and 1 group counseling session per week)	18 weeks	66	USA; 76% male; 59% white, 24% Hispanic, 12% Black, 5% Asian/other; mean age 36 years; mean 12 years of heroin use; 33% had injection drug use in past 30 days; 73% had history of treatment for heroin addiction, 30% had history of methadone maintenance treatment	Patients underwent induction on buprenorphine/naloxone, maintenance phase, and taper off over 15 weeks, doses given daily aside for weekend take-home dosing Network therapy had one group and one individual session per week; Network therapy trains network members to provide supportive environment for patient's adherence to avoidance of illicit drug use, joint sessions with support network members as well as individual sessions organized; Medication management had two individual sessions per week; medication management focused on medication response and adherence monitoring and the establishment of therapeutic relationship	Office-based; Therapies provided by psychiatry resident physicians	Illicit drug use: urine toxicologies, percentage of negative screens (goal of adherence to abstinence expectation) and whether or not last 3 scheduled urines in study were negative (goal of opiate-free state by end of treatment)	Network therapy led to significantly more negative urine toxicologies and more network therapy than medication management patients had positive outcome relative to secondary heroin use by the end of treatment
Moore, 2012[10]	Buprenorphine and physician management (15 minute sessions weekly) vs. buprenorphine and physician management plus CBT (45 minute sessions weekly, depending on therapist availability)	12 weeks	55	France; 74% male; mean age 39 years; 72% white; mean opioid dependence 9 years; 45% prescription drug use; 16% history of IV drug use; 41% prior attempted detoxification	Physician management included weekly buprenorphine dispensing, 15 minutes per session Other arm included physician management and thrice weekly directly observed buprenorphine therapy plus weekly CBT, 45 minutes per session, based on therapist availability	Adult primary care center of an urban teaching hospital; Physician management provided by primary care internal medicine physician with experience in office-based buprenorphine treatment. CBT provided by trained therapists (2 master's level and 3 doctoral-level) with at least 3 years of experience. Induction performed by trained nursing staff.	Drug use: urine toxicology and self-report Treatment completion: continued participation through the 14th week; Treatment retention: number of weeks; Patient satisfaction: Primary Care Buprenorphine Satisfaction Scale	Analyses adjusting for baseline characteristics showed no significant differences between groups on retention or drug use based on self-report or urines. Patient satisfaction was high across conditions, indicating acceptability of CBT counseling with observed medication. The number of CBT sessions attended was significantly associated with improved outcome, and session attendance was associated with a greater abstinence the following week.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Sullivan, 2006[6] (also a model of care)	Buprenorphine/naloxone and physician management (brief, biweekly) vs. buprenorphine/naloxone and physician management plus once-weekly drug counseling and adherence management	12 weeks	16	USA; 94% male; 31% white, 44% Black, 25% Hispanic; mean age 47 years; mean 17 years opioid dependence; 56% with injection drug use; 29% reported one or more days of alcohol use in past 30 days; 36% reported one or more days of cocaine use in past 30 days; 100% HIV positive; mean 13 years since HIV diagnosis; 63% currently on ART; 81% HCV positive	Buprenorphine/naloxone stabilization over 2-weeks with clinic visits 3 times per week and 1 and 2-day take home doses then 10-week maintenance period with once weekly clinic visits and 6 take home doses then offered 2-week taper or extension phase; all patients received brief, bi-weekly, manual-guided physician management that focused on symptoms, drug use, and progress; half of patients received physician management plus once-weekly drug counseling and adherence management focused on addiction-specific topics like triggers, relationships, and craving and strategies to increased adherence to antiretroviral treatment	HIV clinics; Buprenorphine and physician management provided by physician specialized in addiction medicine and experienced in HIV care; drug counseling and adherence management provided by trained nursing staff (issues reviewed with supervising physician and clinical psychologist)	Treatment retention Illicit drug use: urine toxicology and self-report Laboratory parameters: CD4 count, viral load, and liver function tests Adherence to MAT and ART: Medication Event Monitoring System (caps that record the date and time the pill bottle was opened) HIV transmission risk behaviors: HIV/AIDS Risk Inventory Health status: SF-36 Patient satisfaction: 5-point Likert scale questionnaire	There was no difference in treatment retention or illicit drug use by counseling group; Overall, the proportion of opioid-positive weekly urine screens decreased substantially over trial; CD4 counts remained stable; viral load declined significantly; demonstrated feasibility of integrating buprenorphine into HIV clinical care for treatment of opioid dependence

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Tetrault, 2012[11]	Physician management (brief, once every 2 weeks) vs. physician management plus enhanced medical management (45 minutes weekly; focused on drug counseling and adherence to anti-retroviral treatment)	12 weeks	47	USA; 39% male; 29% white; mean age 47 years; mean 4 days of alcohol use in past 30 days; mean 5 days of cocaine use in past 30 days; mean 17 years of opioid dependence; 87% with primary heroin use; 49% with injection drug use; mean 12 years duration of HIV diagnosis; 61% receiving ART, 26% HCV positive	Physician management group had physician visit once every 2 weeks where they took medication under observation and were given a supply to take-home; physician management was brief, manual-guided, medically focused counseling intervention that focused on drug use, symptoms, side effects. Enhanced medical management group had clinic weekly, took medication under observation, and given supply to take home; enhanced medical management was a manual-guided counseling intervention lasting 45 minutes focused on drug counseling and adherence to ART	HIV clinic; Physicians for medication and physician management; nurses delivered enhanced medical management	Illicit drug use: percentage of opioid-negative urine specimens, drug urine screen; and self-report Abstinence: self-report Study completion: not meeting criteria for protective transfer (3 consecutive positive urine tests after buprenorphine dose increased), continued research visits and medication dispensing through week 12 MAT and ART adherence: computerized bottle caps HIV clinical data: CD-4 and viral load HIV risk behaviors: AIDS Risk InventoryImpact of opioid treatment and counseling into HIV setting: buprenorphine/naloxone dose, number of sessions attended, length of visits, number of sessions missed	At end of trial, no difference between groups in percentage of opioid negative urines, maximum duration of continuous abstinence, or retention; the percentage of subjects with detectable viral loads decreased from baseline across both groups similarly; overall, providing extended counseling in this setting is feasible but does not provide detectable improvement in outcomes

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Weiss, 2011[12] Prescription Opioid Addiction Treatment Study (POATS)	Phase 1: Standard medication management (after initial session,15-20 minute s weekly, then biweekly sessions with a physician) with buprenorphine/ naloxone vs. standard medication management with buprenorphine/ naloxone plus opioid dependence counseling (45-60 minute sessions with a counselor, twice weekly then biweekly) Phase 2 (extended treatment for those who relapsed): Standard medication management (2 visits first week, then weekly) with buprenorphine/ naloxone vs. standard medication management with buprenorphine/ naloxone plus opioid dependence counseling (twice weekly then biweekly)	Phase 1: 12 weeks Phase 2 (for patients with unsuccessful outcomes): 24 weeks	653	USA; 60% male; 91% white; mean age 33 years; 27% alcohol dependence during lifetime; 18% cocaine dependence during lifetime; 5 mean years of opioid use; 23% used heroin ever; 32% previous treatment for OUD; 42% current chronic pain	Physicians provided manual-based, standard medical management. During the initial sessions (45-60 minutes in phase 1 and 30-60 minutes in phase 2), the physician reviewed the patient's medical, psychiatric, and substance use problems; recommended abstinence; and referred the patient to self-help groups. In subsequent visits (15-20 minutes), the physician assessed substance use, craving, and buprenorphine-naloxone response; recommended abstinence and self-help participation; and prescribed buprenorphine-naloxone.The comparison group received standard medical management and manual-based opioid dependence counseling (45-60 minute sessions). Opioid dependence counseling was based on drug counseling manuals with demonstrated efficacy, modified for this study of prescription opioid dependence treatment with buprenorphine. Counselors educated patients about addiction and recovery, recommended self-help groups, and emphasized lifestyle change. Using a skills-based format with interactive exercises and take-home assignments, opioid dependence counseling covered a wider range of relapse prevention issues in greater depth than did standard medication management, including coping with high-risk situations, managing emotions, and dealing with relationships.	Physicians certified to prescribe buprenorphine, trained substance abuse or mental health professionals10 study/treatment sites	Opioid use: urine toxicology and self-reportPhase 1 successfuloutcome: completing week 12 with opioid use on no more than 4 days in a month, absence of 2 consecutive opioid-positive urine test results, no additional substance use disorder treatment, and no more than 1 missing urine sample during the 12 weeks Phase 2 successful outcome:abstaining from opioids during week 12 and during at least 2 of the previous 3 weeks	During phase 1, only 6.6% of patients had successful outcomes, with no difference between standard medical management or standard medical management plus opioid dependence counseling. During phase 2, 49% attained successful outcomes, with no difference between groups. Success rates 8 weeks after completing the buprenorphine-naloxone taper (phase 2, week 24) dropped to 8.6%, again with no difference between groups.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Weiss, 2015[13] Prescription Opioid Addiction Treatment Study (POATS)	See above	9 month treatment; 42 month followup	375	USA; 56% male; 90% white; mean age 33 years old; 3.7% with alcohol dependence in past year; 5.9% with cannabis dependence in past year; 3.2% with cocaine dependence in past year; 3.5% with other stimulant dependence in past year; 4.8% with sedative-hypnotic dependence in past year; mean 5 years of opioid use; 22% had ever used heroin; 78% used opioids through route other than sublingually/ swallowed	Standard medication management included weekly visits with physician, combining medication administration with medication-focused counseling; phase 1 was 4-week medication taper; phase 2 for those who relapsed included medication for 12 weeks then 4-week taper Opioid dependence counseling focused on relapse prevention, skill-building, and lifestyle change opioid dependence counseling twice weekly for six weeks then once weekly for 6 weeks	Office-based; primary care; Physicians for medication management and counseling Opioid dependence counseling providers not described but appear to be physicians; research assistants conducted followup phone interviews	Followup measures: phone calls at 18, 30, and 42 months and included the Composite International Diagnostic Interview for opioid diagnosis, the ASI for substance use severity, four items from SF-36 for general health and pain, the Fagerstrom Test for Nicotine Dependence for smoking dependence severity, subset from the Pain and Opiate Analgesic Use History	Few participants had successful opioid outcomes in phase 1; almost half had successful opioid treatment in phase 2; addition of opioid dependence counseling to medication did not improve outcomes; one third of those in followup abstained and were not on agonist medication, one third were abstinent on agonist therapy and another third were using opioids (followup outcomes not described by group)

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Pharmacological Therapies								
Carrieri, 2014[14]	Induction of methadone in primary care vs. specialty care	12 months	221	France; 84% male; median age 32 years (IQR: 27-38); 27% used cocaine; 72% used street opioids; 20% used psychotropic drugs; 15% drug injection users; 64% drug snorting users; 18% were daily cannabis users; 33% had hazardous alcohol consumption; 12% history of drug overdose; 17% history of suicide attempt,;2% HIV-positive, 19% HCV-positive; 49% history of drug injection	Evaluation of implementation strategy of 14-day supervised methadone induction, with starting dose of 30-40 mg, with 10 mg increases every 2-4 days, until dose stabilization. Took into account those who switched from buprenorphine to methadone at enrollment.	Physicians in 10 sites; specialty care and primary care physicians with field experience in care for opioid dependence and/or training in care for drug dependence	Abstinence from street-opioids at 12 months using a validated question administered during phone interviews, engagement in treatment computed as the proportion of patients who actually started methadone and remained in the trial until the stabilization of dosages, retention in methadone maintenance treatment only for patients who actually started methadone treatment recorded as the time between the first day of methadone induction and the last known date that the patient was still receiving treatment, and patient satisfaction on a 5-point Likert scale that was dichotomized as very satisfied vs. other. Pharmacies and physicians recorded overdoses, signs of intoxication, and lost-to-followup. A list of 50 health-related symptoms was included in a questionnaire that helped document self-reported symptoms.	Under appropriate conditions, methadone induction in primary care is feasible and acceptable to both physicians and patients. It is as effective as induction in specialized care in reducing street-opioid use and ensuring engagement and retention in treatment for opioid dependence.

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
(Carrieri 2014 pilot study) Roux, 2012[15]	See above	2 weeks induction 12 months followup for outcomes	195	Study conducted in France, no other information provided	Induction model included: 1) study-specific pretraining for primary care physicians; 2) a shared care model, based on the patient primary care physicians-Center for Substance Abuse Prevention Association -pharmacist network; 3) the exclusion of patients with triple codependence on opioids/benzodiazepines/alcohol, as screened by Mini-International Neuropsychiatric Interview; 4) the daily supervision at the local pharmacy during the initiation phase for patients starting methadone in primary care; 5) patient accountability for treatment intake and appropriate storage	Primary care and medical center; Clinic visits and phone interviews; Trained primary care and Center for Drug Abuse Prevention Association physicians	Abstinence from street-opioids at 12 months using a validated question, retention in treatment, occurrence of overdoses, prevalence of other HCV risk transmission practices, depressive symptoms using CES-D, suicidal risk using Beck Hopelessness Scale, impulsivity using the Barratt Impulsiveness Scale, sensation seeking using the Brief Sensation Seeking Scale, tobacco dependence using the Fagerstrom test, alcohol consumption using the AUDIT questionnaire, pain assessment using the Brief Pain Inventory, adherence to methadone prescription, patient-health care provider relationship, opioid withdrawal, quality of life using SF-12, adult ADHD Self-Report Scale 6 item version, urinary drug screening, and socio-demographic information on history of incarceration and contact with associations.	NR

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fiellin, 2001[16]	Primary care-based methadone (weekly physician sessions and monthly counseling session) vs. narcotic treatment program-based methadone (1 to 3 sessions per week dose, weekly group counseling, and monthly individual counseling)	6 months	46	USA; 65% male; 78% white; mean age 42 years; 17% HIV-positive; 91% with prior detoxification attempt; 72% with history of IV drug use	Office-based group had weekly physician contact for medication dosing and 6 take-home doses plus monthly counseling session Narcotic treatment program group had 1 to 3 treatment center visits per week for methadone dose and take-home dosing plus weekly group and monthly individual counseling Note: patients who had a positive random urine sample or urine that did not show methadone and a repeat urine sample that was positive and did not show methadone were considered clinically unstable and care was escalated	Offices of general medicine internists who provided all office-based care (4/6 were certified in Addiction Medicine); Treatment center was site of narcotic treatment program; Physicians, counselors, social workers, and employment services provided narcotic treatment program	Illicit drug use: self-report, urine and hair toxicology Patient and clinician satisfaction: 5-point Likert scale questionnaire Functional status: SF-36, ASI and modified Treatment Services Review; Depression: Center for Epidemiologic Studies Depression Scale	There was no significant between-group difference on illicit drug use or patients with clinical instability; Significantly more office-based patients thought that quality of care was excellent; There were no group differences in functional status or use of health, legal, or social services; Overall, results supported feasibility and efficacy of transferring stable opioid-dependent patients to primary care for methadone maintenance

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
Fudala, 2003[17]	Daily buprenorphine/naloxone vs. buprenorphine vs. placebo All participants received HIV counseling and up to 1 hour of individualized counseling per week; emergency counseling and referrals provided	4 weeks for efficacy; 48-52 weeks for safety	323 for efficacy; 472 for safety	Efficacy sample: USA; 65% male; mean age 38 years; 61% white, 28% black, 7.1% Hispanic, 1.2% Native American, 2.2% Asian/Pacific Islander; median 84 month (range: 3 to 468) duration of heroin abuse; 51% with prior enrollment in methadone or LAAM program Safety sample: USA; 69% male; mean age 39 years; 50% white, 30% black, 17% Hispanic, 0.8% native American, 1.9% Asian/Pacific Islander; median 120 months (range: 3 to 468) duration of heroin abuse; 50% with prior enrollment in methadone or LAAM program	Provided daily MAT or placebo administered on site with take-home dosing for weekends/holidays; during open-label phase, up to 10-day supply of medication provided; all participants received HIV counseling and up to 1 hour of individualized counseling per week; emergency counseling and referrals provided	Physician's office in a clinical research program distinct from methadone clinic (provider type not described)	Opiate use: percentage of opiate-negative urine samples Opiate craving: self report Overall status: per participant and per clinicianIllicit drug use other than opiates: percentage of negative urine drug screens Subject retentionRates of adverse medical events Electrocardiography and laboratory findings	Efficacy study terminated early due to greater efficacy of buprenorphine/naloxone and buprenorphine vs. placebo; Proportion of opiate-negative urine samples significantly less among both MAT groups vs. placebo; MAT groups reported significantly less opiate craving than placebo; Rates of adverse events similar in active-treatment and placebo groups; findings from open-label followup indicated combined treatment was safe and well tolerated

Model name Author, year	Comparators	Duration of Followup	N	Population Characteristics	Specifics of Model Components/ Implementation	Setting/ Provider Type/ Staffing	Types of Outcomes and Harms Examined and How They Were Measured	Findings
King, 2006[18]	Routine care (methadone dispensing window for weekly doses and monthly counseling for 20 minutes) vs. methadone maintenance clinic (monthly observed dose, take home supply, monthly 20 minute counseling session with medical provider) vs. primary care based-methadone (monthly observed dose, take home supply, monthly 20 minute counseling session with office physician)	12 months	92	USA; 62% male; 72% white; mean age 44 years; no patient included had submitted positive breath intoximeter readings in past year; mean 14 years of methadone treatment received over lifetime	Routine care group received 1-2 doses of methadone per week at dispensing window and 5-6 take-home doses with once-monthly appointments with the clinic counselorClinic-based methadone medical maintenance received one dose of methadone observed by nurse or physician and 27 days of take-home methadone every 4 weeks and monthly appointments with clinic counselor Office-based methadone medical maintenance received one dose of methadone observed by physician and 27 days of take-home doses every 4 weeks from physician's office and had monthly counseling session with physician Note: if found to have positive urine or failed medication recall, participant was stepped-up in care	Community primary health care center and one addiction treatment center as sites of office-based methadone medical maintenance; Physician provided medication and counseling Clinic-based methadone medical maintenance at two community-based methadone maintenance treatment programs; nurse or physician provided medication and counselor provided counseling	Illicit substance use: urine specimens Medication monitoring: random medication recalls Addiction-related issues in past 30 days: ASI Patient Satisfaction: Client Satisfaction Questionnaire Quality of therapeutic relationship: Helping Alliance Questionnaire for Patients Other measures: Post-study opinion survey Monthly hours in treatment: patient estimates of time spent engaged in treatment-based activities Engagement in employment, family/social, and personal activities: patient estimates	Generally low rates of drug use or failed medication recall with good study retention; No between-group differences on ASI scores; Treatment satisfaction was high in all groups and patients in all groups rated strong quality of therapeutic alliance; methadone medical maintenance patients in both office and clinic-based care initiated more new employment or social/family activities than routine care; most methadone medical maintenance patients reported a preference for office-based care compared with clinic-based
Lintzeris, 2004[19]	Methadone vs. buprenorphine administered under naturalistic conditions by 18 community-based and 1 specialist-based sites by general practitioners and community pharmacists (Buprenorphine Implementation trial [BIT])	12 months	139	Australia; 58% male; mean age 30 years; mean age of first heroin use 21 years; mean duration lifetime methadone treatment 27 months; 0-32% reported no heroin use in past month	Methadone treatment consistent with state guidelines with supervised dispensing at pharmacies and one take-away dose per week for stable patients; dose, frequency or review, counseling was tailored per patients; Buprenorphine treatment consisted of flexible dosing and at least monthly review, optional psychotherapy; daily dispensing at induction with alternate-day or 3-day dosing once stable	First intake of study conducted in specialist clinic; second intake of study conducted in community setting with primary care clinicians and pharmacists	Retention in treatment: pharmacy records Heroin use: Self report using Opiate Treatment Index	Among methadone stabilized patients, mean retention time was similar between groups; among heroin users, there was a trend towards improved retention among those taking methadone compared with those on buprenorphine, though this was not statistically significant; There were significant reductions in heroin use in all groups over time and a trend toward lower heroin use among heroin users on buprenorphine

ADHD = attention deficit hyperactivity disorder; ART = anti-retroviral treatment; ASI = addiction severity index; AUDIT = Alcohol Use Disorders Identification Test; BFC = behavioral family counseling; CBT = cognitive behavioral therapy; CD4 = cluster of differentiation 4 glycoprotein; CES-D = Center for Epidemiological Studies Depression; ED = emergency department; EMM = enhanced medical management; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IBT = individual based treatment; IV = intravenous; IQR = interquartile range; LAMM = levo-alpha-acetylmethadol; MAT = medication assisted treatment; NR = not reported; OUD= opioid use disorder; PM = physician management; RNA = ribonucleic acid; SD = standard deviation; SF-12 = Medical Outcomes Study Short-Form 12; SF-36 = Medical Outcomes Study Short-Form 36; USA = United States of America; vs. = versus

Appendix G. Details of Cochrane Systematic Reviews for Guiding Question 3

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Amato, 2011[20]	To evaluate the effectiveness of any psychological plus any agonist maintenance treatment vs. standard treatment for opiate dependence	Cochrane libraries, PUBMED, EMBASE, CINAHL, PsycINFO (through June 2011)	35	OUD due to opiates (not specified); setting not described (appears mostly specialist centers); USA, Germany, Malaysia, China, Scotland	Any psychosocial intervention plus any agonist vs. any agonist alone; medical interventions were methadone, buprenorphine, LAAM; models of care not described	RCTs, CCTs	Cochrane (Higgins, 2011)	GRADE; meta-analysis done	4319	Comparing any psychosocial intervention plus maintenance pharmacological treatment to standard maintenance treatment, shows no significant advantage of adding psychosocial interventions for retention in treatment and at followup, abstinence from opiates during treatment or at followup, compliance, psychiatric symptoms, and depression. Also, there was no significant difference in outcomes comparing psychosocial approaches. Of note, standard pharmacological treatment generally offers counseling services.	Not reported	Focused on effectiveness of psychotherapy interventions in addition to standard interventions; setting not described (appears mostly specialist centers); 31 studies in USA
Ferri, 2013[21]	To evaluate efficacy of slow-release oral morphine for treatment of opioid dependence	Cochrane libraries, MEDLINE, EMBASE (through April 2013)	3	OUD due to heroin; Setting not described; Australia and Austria	Slow-release oral morphine vs. other MAT medications; models of care not described	RCTs, quasi-randomized (one study only provided conference abstract)	Cochrane (Higgins, 2011)	GRADE; no meta-analysis	195	Limited evidence that sustained-release oral morphine is at least similar to other MAT medications for retention and other clinical outcomes	Limited evidence of no major differences in adverse events	Focused on effectiveness of medications; trials with no description of setting; no studies in USA

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Gowing, 2011[22]	To assess the effect of oral substitution treatment for opioid dependent injecting drug users on risk behaviors and rates of HIV	Cochrane libraries, MEDLINE, EMBASE, psycINFO (through May 2011)	38	OUD due to heroin; majority injecting drug users or with recent history (last 3 months); users of other injectable drugs also included; mostly specialist treatment centers; USA, UK, Australia, Italy, Germany, Canada, Malaysia, Ukraine with one study in multiple countries	Buprenorphine, methadone, or LAAM for substitution therapy (alone or vs. others); models of care not described	RCTs, observational prospective studies, cross-sectional studies	Cochrane (Higgins, 2008)	Unclear for quality; No meta-analysis	12400	Oral substitution treatment with methadone or buprenorphine is associated with significant reductions in illicit opioid use, injecting use, and sharing of injecting equipment; also led to fewer drug users reporting multiple sex partners or exchanges of sex for money or drugs but no change in condom use; reduced drug risk behaviors led to reduced HIV; one study partially done in primary care showed significant reductions in proportion injecting, sharing injecting equipment, and having unprotected sex in those on methadone treatment.	Not reported	Focused on effectiveness of medications on HIV and behaviors; 2 studies included primary care settings; 26 studies in USA

Author, Year	Purpose of Review	Databases Searched, Date of Last Search	Number of Included Studies	Population and Setting Characteristics	Intervention Characteristics	Types of Studies Included	Methods for Rating Method-ological Quality of Primary Studies	Methods for Synthes-izing Results of Primary Studies	Total Numbers of Patients	Findings	Adverse Events	Limitations
Lobmaier, 2008[23]	To evaluate the effectiveness of sustained-release naltrexone for opioid dependence and its adverse effects in different populations	Cochrane libraries, MEDLINE, EMBASE, CINAHL, LILACS, PsycINFO, ISI Web of Science, clinicaltrials.gov (through November 2007)	1 for effective-ness; 10 for safety in OUD	OUD not specified; effectiveness study in outpatient setting; Australia, Germany, USA, Norway, Spain, UK	Three depot and two implant formulations of naltrexone (10 of 17 depot studies used sustained release form) vs. placebo, different naltrexone doses, oral naltrexone, or methadone; in addition to medication, all patients offered relapse prevention therapy	RCTs for effectiveness; prospective controlled and uncontrolled trials, case-series, and record-linkage for safety evaluation	Cochrane (Higgins, 2006)	Unclear for quality; meta-analysis done for safety	60 for effectiveness; mean 168 (range: 5 to 894) for safety in OUD	One study found high-dose naltrexone depot injections significantly increased days in treatment vs. placebo and vs. low-dose with no group differences on patients retained in treatment;	Limited data showing side effects were significantly more frequent in naltrexone depot groups vs. placebo (mostly site-related); among OUD, no significant group differences in adverse events; most studies lacked systematic assessment of side effects and adverse events were rare	Focused on effectiveness and adverse events of medications; effectiveness study in outpatient setting (no further details); effectiveness study and most safety studies done in USA

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Mattick, 2009[24]	To evaluate the effects of methadone maintenance treatment compared with other treatment that did not involve opioid replacement therapy for opioid dependence	Cochrane libraries, EMBASE, PUBMED, CINAHL, Current Contents, PsycLIT, CORK, Alcohol and Drug Council of Australia, Australian Drug Foundation, Centre for Education and Information on Drugs and Alcohol, Australian Bibliographic Network, Library of Congress (through December 2008)	11	OUD due to opioids (not specified); most studies done in specialist medical or research facilities (3 in prison setting); USA, Australia, Hong Kong, Thailand, Sweden	Methadone maintenance vs. placebo or other nonpharmacological therapy (wait-list control, drug-free rehabilitation, detoxification); models of care not described (some studies included counseling in the intervention but this was not described)	RCTs	Cochrane - focus on randomization	GRADE; meta-analysis done	1969	Methadone was significantly more effective than nonpharmacological approaches in treatment retention and suppression of heroin use but not different in criminal activity or mortality	Not reported	Focused on effectiveness of medication; no studies appear to be have been done in primary care; 6 studies in USA

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Mattick, 2014[25]	To evaluate buprenorphine maintenance compared to placebo and to methadone maintenance in the management of opioid dependence, including its ability to retain people in treatment, suppress illicit drug use, reduce criminal activity, and mortality	Cochrane libraries, MEDLINE, EMBASE, Current Contents, PsycLIT, CORK, Alcohol and Drug Council of Australia, Australian Drug Foundation, Centre for Education and Information on Drugs and Alcohol, Library of Congress (through January 2013)	31	OUD due to heroin or other opioids; setting not described; North America, Europe, Asia, Middle East, Australia	Buprenorphine maintenance vs. placebo or methadone; models of care not described	RCTs	Cochrane (Higgins, 2011)	GRADE; meta-analysis done	5430	Buprenorphine was superior to placebo in participant retention at all doses; only high-dose buprenorphine (not low- or moderate-dose) was more effective than placebo in suppressing illicit opioid use; flexible dosed buprenorphine was less effective than methadone in participant retention with no group differences in suppression of opioid use; low-dose methadone was more likely to retain participants and limit opioid use than low-dose buprenorphine but high and medium-dose methadone were not more effective than high and medium-dose buprenorphine for participant retention and illicit opioid use	Limited evidence of no significant differences between methadone and buprenorphine (one result of more sedation among methadone users)	Focused on effectiveness of medications; setting not described; 15 studies from North America

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Minozzi, 2009[26]	Among adolescents (13-18 years old), to assess the effectiveness of any maintenance treatment alone or in combination with psychological intervention compared to no intervention, other pharma-cological or psychosocial intervention on retaining adolescents in treatment, reducing substance use, and reducing health and social status	Cochrane libraries, MEDLINE, EMBASE, CINHAL (through August 2008)	2	OUD due to heroin; outpatient; USA	Methadone maintenance vs. LAAM; buprenorphine-naloxone maintenance vs. buprenorphine detoxification; models of care not described	RCTs and controlled clinical trials	Cochrane (Higgins, 2008)	GRADE; no meta-analysis	187	Limited evidence that maintenance treatment was superior in patient retention but not in reducing illicit opioid use; Opioid use at 1 year followup was significantly lower in the maintenance group and more patients in this group were enrolled in other addiction treatment at followup	Limited evidence of no serious side effects or withdrawals attributable to bupren-orphine-naloxone	Focused on effectiveness of medications; outpatient setting (unclear if primary care); all trials done in USA

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Minozzi, 2011[27]	To evaluate the effects of naltrexone maintenance treatment vs. other treatments/ placebo in preventing relapse in opioid addicts after detoxification	Cochrane libraries, PubMed, CINAHL (through June 2010)	13	OUD due to heroin alone or multiple drugs; outpatient only; USA, Israel, Russia, Italy, Spain, China, Malaysia, Germany	Oral naltrexone alone or in combination with psychosocial treatments vs. placebo, no intervention, other pharmacological treatments, or psychosocial treatments; models of care not described	RCTs	Cochrane (Higgins, 2008)	GRADE (ratings not shown); meta-analysis	1158	Oral naltrexone did not perform better than treatment with placebo or no agent with respect to abstinence and relapse, though naltrexone was favored for number of people reincarcerated. Naltrexone was not superior to benzodiazepines and buprenorphine for retention, abstinence, and side effects, though numbers retained in studies were generally low. In single study of naltrexone vs. psychotherapy, there was no statistically significant difference for abstinence and reincarceration. Overall, studies inadequate to evaluate oral naltrexone treatment for opioid dependence.	Limited evidence of no significant differences in adverse events	Focused on effectiveness of medications /interventions; includes psychotherapy as an intervention; outpatient trials (unclear if primary care); 4 trials in USA

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Minozzi, 2013[28]	Among pregnant women, to assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological or psychosocial interventions for child health status, neonatal mortality, treatment retention, and reducing substance use	Cochrane libraries, PUBMED, CINAHL (through September 2013)	4	Opiate addicted pregnant women (OUD not specified); inpatient and outpatient settings; Austria, USA, one multicounty trial (Austria, Canada, USA)	Methadone vs. buprenorphine or slow-release morphine; models of care not described	RCTs	Cochrane (Higgins, 2011)	GRADE; meta-analysis done	271	Limited evidence of no significant differences between methadone and buprenorphine or slow-release morphine for all outcomes	One study showed no difference in side effects for the mother using methadone vs. buprenorphine and significantly less side effects for the infant on buprenorphine; one study showed no difference in side effects for the mother using methadone vs. slow-release morphine with one child in each group experiencing a serious side effect (apnea)	Focus on effectiveness of medications; 3 studies in outpatient setting (no further details); 2 studies done in USA

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Nielsen, 2016[29]	To assess the effects of maintenance agonist pharmacotherapy for the treatment of pharmaceutical opioid dependence	Cochrane Drugs and Alcohol Group's Specialised Register of Trials, Cochrane Central Register of Controlled Trials, PubMed, EMBASE, CINAHL, ISI Web of Science, PsycINFO (through May 2015)	6	OUD due to pharmaceutical opioids; 5 studies conducted in outpatient setting, 1 study hospital-based treatment vs. brief hospital intervention and treatment referral; USA (5 studies) and Iran (1 study)	Methadone vs. buprenorphine; also, buprenorphine maintenance vs. either buprenorphine taper (in addition to psychological treatment) or brief intervention and referral to treatment	RCTs	Cochrane (Higgens, 2011)	GRADE; meta-analysis done	607	Methadone or buprenorphine appeared equally effective on opioid use and treatment retention; Maintenance treatment with buprenorphine appeared more effective than detoxification or psychological treatments on opioid use and treatment retention	No difference between methadone and buprenorphine on adverse events; Evidence favored buprenorphine maintenance over detoxification or psychological treatment on adverse events	Use of open label study designs
Rahimi-Movaghar, 2013[30]	To evaluate the effectiveness and safety of various pharma-cological therapies on maintenance of opium dependence (alone or in combination with psychosocial interventions)	Cochrane libraries, MEDLINE, EMBASE, CINAHL, PsychINFO, regional databases (IMEMR and ASCI), national databases (Iranmedex and Iranpsych); through February 2012	3	OUD due to heroin; outpatient; Iran	Different doses of buprenorphine compared; one study of baclofen vs. placebo for maintenance post detoxification; models of care not described	RCTs	Cochrane (Higgins, 2011)	Unclear for quality; no meta-analysis	870	Higher doses of buprenorphine significantly increased the treatment retention rate compared with lower doses; No significant difference in maintenance retention rate between baclofen vs. placebo post detoxification.	Not reported	Focused on effectiveness of medications; outpatient setting (unclear if primary care); no trials in USA (appears Asia-focused)

CCTs = controlled clinical trials; GRADE = Grading of Recommendations; Assessment; Development and Evaluations; HIV = human immunodeficiency virus; LAMM = levo-alpha-acetylmethadol; MAT = medication-assisted treatment; OUD = opioid use disorder; RCT = randomized controlled trial; UK = United Kingdom; USA = United States of America; vs. = versus

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