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

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Objectives: Although medications for opioid use disorder (MOUD) save lives, treatment retention remains challenging. Identification of interventions to improve MOUD retention is of interest to policymakers and researchers. On behalf of the Agency for Healthcare Research and Quality, we conducted a rapid evidence review on interventions to improve MOUD retention.

Methods: We searched MEDLINE and the Cochrane Library from February 2009 through August 2019 for systematic reviews and randomized trials of care settings, services, logistical support, contingency management, health information technology (IT), extended-release (XR) formulations, and psychosocial interventions that assessed retention at least 3 months.

Results: Two systematic reviews and 39 primary studies were included; most did not focus on retention as the primary outcome. Initiating MOUD in soon-to-be-released incarcerated people improved retention following release. Contingency management may improve retention using antagonist but not agonist MOUD. Retention with interventions integrating medical, psychiatric, social services, or IT did not differ from in-person treatment-as-usual approaches. Retention was comparable with XR- compared to daily buprenorphine formulations and conflicting with XR-naltrexone monthly injection compared to daily buprenorphine. Most psychosocial interventions did not improve retention.

Discussion: Consistent but sparse evidence supports criminal justice prerelease MOUD initiation, and contingency management interventions for antagonist MOUD. Integrating MOUD with medical, psychiatric, social services, delivering through IT, or administering via XR-MOUD formulations did not worsen retention. Fewer than half of the studies we identified focused on retention as a primary outcome. Studies used different measures of retention, making it difficult to compare effectiveness. Additional inquiry into the causes of low retention would inform future interventions.

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Key Words: medications for opioid use disorder, opioid use disorder, retention

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Opioid use disorder (OUD) is a national health crisis. In 2018, an average of 128 people in the US died each day of opioid overdose.[1] There is clear evidence, including a recent report by the National Academies of Science, Engineering, and Medicine (NASEM), that people with OUD who receive medications for opioid use disorder (MOUD) are less likely to die from overdose,[2,3] engage in less illicit opioid use, and experience improved quality of life.[4] Three medications—methadone, buprenorphine, and naltrexone—are approved by the US Food and Drug Administration for the treatment of OUD.[5] Although remission from opioid use may be most protective against overdose and morbidity, remission is not always achievable due to treatment gaps along the OUD cascade of care continuum (ie, diagnosis, engagement, initiation of MOUD, retention, and remission).[4] Longer retention on MOUD is associated with improved mortality; however, retention rates are low and variable, with 30% to 50% reported in most settings.[5–7] Possible explanations for poor retention rates include barriers to treatment access, particularly in rural

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settings[8] or among vulnerable populations (eg, people who experience incarceration),[9] stigma toward individuals with OUD and MOUD,[10] fragmented care (eg, separate addiction treatment systems and medical or psychiatric care systems),[4] cost of MOUD,[11] and logistical challenges associated with MOUD prescribing (eg, frequent visits and diversion surveillance).[4,8,9]

Multiple interventions attempt to address these barriers but their impact on retention is unknown.[12] Identifying which interventions are effective at improving retention is of high priority for policy makers and researchers. Therefore, the Agency for Healthcare Research and Quality (AHRQ) commissioned this rapid evidence review on interventions to improve MOUD retention to assist the Office of the Assistant Secretary for Health, Department of Health and Human Services and other federal agency stakeholders in their decision-making and current work. Rapid evidence reviews "accelerate or streamline traditional [systematic review] processes" to meet the needs and timelines of the end-users (eg, "government policymakers, health care institutions, health professionals, and patient associations")[13] The following key questions and analytic framework (Fig. 1) guided our review:

Key Question 1: What is the effectiveness and comparative effectiveness of strategies to improve retention in MOUD among nonpregnant adults with OUD?
Key Question 2: What are the harms of retention strategies for MOUD?
Key Question 3: Does the effectiveness of the MOUD retention strategy vary by participant characteristics (eg, age, gender, socioeconomic status, geographic region, polysubstance use)?

METHODS

The protocol was registered in the PROSPERO database (CRD42019134739).[10] The draft report was posted on the AHRQ website for public comment. The detailed methods including search strategies are available in the full report at https://effectivehealthcare.ahrq.gov/.[11] We followed rapid review methods published by the World Health Organization (WHO)[12] and PRISMA reporting guidance.[13]

Data Sources and Searches

We searched OVID MEDLINE and the Cochrane Database of Systematic Reviews from February 12, 2009 to June 16, 2019. We conducted an additional gap search through August 20, 2019.

Study Selection

One investigator reviewed abstracts and full-text articles for inclusion with 25% independent review by a second investigator. Appendix Table 1, http://links.lww.com/JAM/A213 details study inclusion criteria. We included existing systematic reviews (SRs) if they searched more than 2 databases; performed quality assessment; used predetermined inclusion/exclusion criteria; and described the search strategy.

We included randomized controlled trials (RCT) that compared MOUD retention strategies against each other or against treatment as usual (TAU) if TAU included the use of, or access to MOUD (ie, we excluded placebo-controlled studies or trials of abstinence based interventions). In the absence of an established definition, we defined retention as continued treatment or medication engagement for at least 3 months, which our stakeholders considered the minimum clinically-relevant treatment duration. We were purposefully inclusive in how retention was assessed (eg, by self-report, medication adherence, or documented visits). We included observational studies when there were no RCTs for a particular intervention. We included studies of interventions conducted internationally if they had potential for implementation in US, but excluded studies of interventions that used non-Food and Drug Administration-approved MOUD formulations.

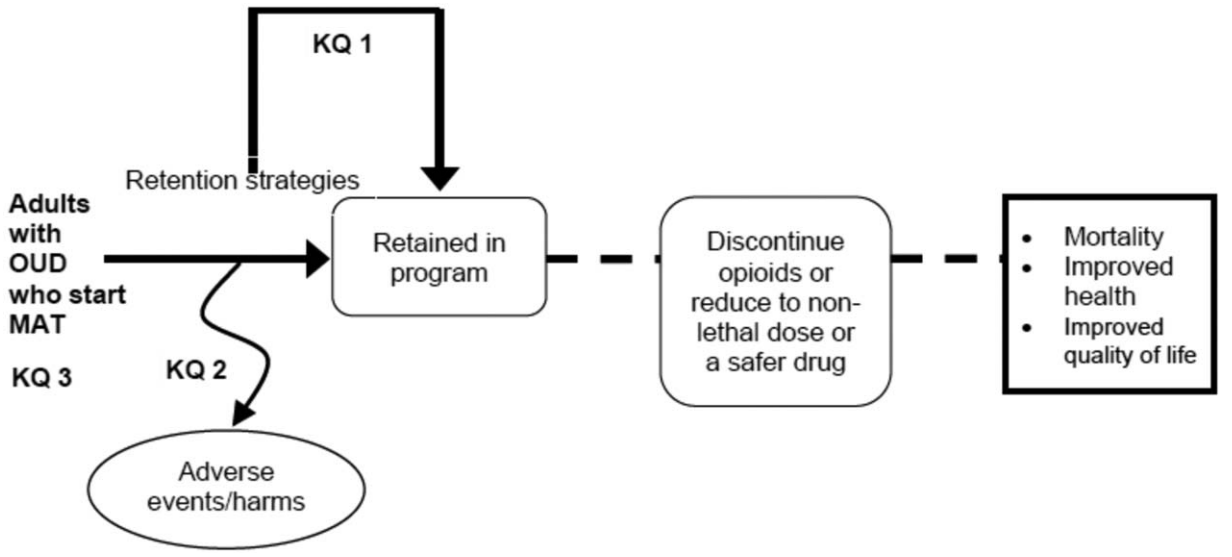

FIGURE 1. Analytic framework for improving retention in medications for opioid use disorder for opioid use disorder.

With input from our stakeholders, we assessed the effectiveness of the following categories of interventions: (1) provision of MOUD in novel care settings or with integrated medical, psychiatric, or social services, or evaluations of changes in current prescribing practices in traditional care settings; (2) contingency management; (3) MOUD coupled with psychosocial counseling; (4) use of health information technology (IT); (5) extended-release (XR) MOUD formulations; and (6) financial support interventions (eg, transportation).[4,14–16] No studies of financial interventions met our inclusion criteria.

Data Extraction and Quality Assessment

One investigator abstracted details on study design, setting, population, intervention, outcomes, and harms. Two reviewers independently rated study quality using criteria developed by the US Preventive Services Task Force.[17] We did not downgrade studies for high attrition because it related to the primary outcome of MOUD retention.

We evaluated the quality of individual studies. We relied on high-quality published SRs and, when those existed, we used the quality ratings provided by the SR, which meant that quality assessment tools could differ. We did not conduct formal grading of the body of evidence for outcomes.

Data Synthesis and Analysis

We reported retention outcomes of intention-to-treat (ITT) analyses; if studies did not report retention using ITT, we calculated this if data were available. We synthesized findings across interventions qualitatively. Due to the small number of studies in each category, variation in types of interventions, populations, or settings, as well as methodological differences among studies, we did not perform quantitative analyses.

Role of Funding Source

AHRQ commissioned this rapid evidence review on behalf of HHS. Investigators worked with AHRQ and HHS to develop the scope and key questions. AHRQ staff provided project oversight and reviewed and made comments on drafts of the report and distributed the draft for peer review and public comment.

RESULTS

Of 1580 titles and abstracts retrieved, we reviewed 258 full text articles and included two SRs and 39 primary studies (Fig. 2). Duration of follow-up ranged from 3 to 24 months. Thirty-eight percent of the included studies reported retention as the primary outcome. Table 1 summarizes the included studies organized by intervention category and provides retention outcomes. Appendix Tables 7 to 11, http://links.lww.com/JAM/A213 report risk of bias assessments.

Care Settings, Services, and Logistical Support

One good-quality SR[18] and 11 primary studies, 1 good-[19]; 9 fair-[20–28]; and 1 poor-quality[29]; evaluated the effect of care setting/logistical support interventions on retention (Appendix Table 2, http://links.lww.com/JAM/A213).

MOUD for Soon-to-be-released Incarcerated Populations

The existing SR[18] of 21 studies (6 RCTs and 15 observational studies) and 2 additional RCTs[20,29] examined interventions that initiated MOUD in soon-to-be-released incarcerated people with OUD. The SR reported that initiating MOUD in prison was associated with higher rates of postrelease treatment retention compared with TAU controls (50% [range 27%–75%] vs 5% [range 0%–9%]).[18] Two additional RCTs similarly reported improved retention with prerelease initiation of MOUD. One was a small poor-quality study (n = 15) that randomized inmates to XR-naltrexone monthly injection versus TAU and found that more than 20% of prerelease participants continued receiving treatment at 6 months versus none in the postrelease group.[29] The second was a fair-quality study (n = 213) that assessed the effectiveness of prerelease initiation of buprenorphine compared with referral to begin an office-based buprenorphine treatment program after release and found higher retention in the prerelease group, measured as mean number of days in treatment at 12 months (65.9 days vs 21.8 days, $P = 0.005$).[20]

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

Three small (n range = 94–316) fair-quality RCTs provide conflicting evidence on the effectiveness of integrating primary or psychiatric services with OUD treatment to improve retention on MOUD.[21–23] Two studies conducted in the US integrated methadone and buprenorphine treatment, respectively, with psychiatric care. The larger study (n = 316) found no difference in retention at 12 months (41% vs 41%, $P = 0.96$).[22] The smaller study (n = 94), which included a third experimental arm involving MOUD treatment integrated with psychosocial therapy, reported improved retention at 20 weeks for both treatment groups compared with TAU alone (33.3% vs 51.5% vs. 21.4%, $P = 0.05$).[23] The third study was a French trial of methadone treatment integrated within primary care, a practice not currently available in the US, versus TAU and found no statistically significant difference in retention at 12 months (n = 195, 88% vs 69%, $P = 0.13$).[21]

MOUD Initiation in Emergency Department (ED)/Hospital Settings

Two fair-quality RCTs examined retention after initiating MOUD in ED or hospital settings.[24,27] One study, conducted at a US safety-net hospital (n = 139), compared an intervention that started patients on buprenorphine while inpatients, with linkage to outpatient treatment within 7 days of discharge versus TAU (medically supervised opioid withdrawal followed by referral to a community-based treatment program). Both groups experienced low retention rates but, at 6-month follow-up, the intervention group had higher retention compared to TAU (16.7% vs 3.0%, $P = 0.007$).[24] The second study was a follow-up of a US-based, three-arm RCT (n = 290) that randomized participants to either buprenorphine treatment initiated during an ED visit with linkage to primary care (PC) within 72 hours, brief counseling intervention in ED, or referral to outpatient treatment (TAU). The

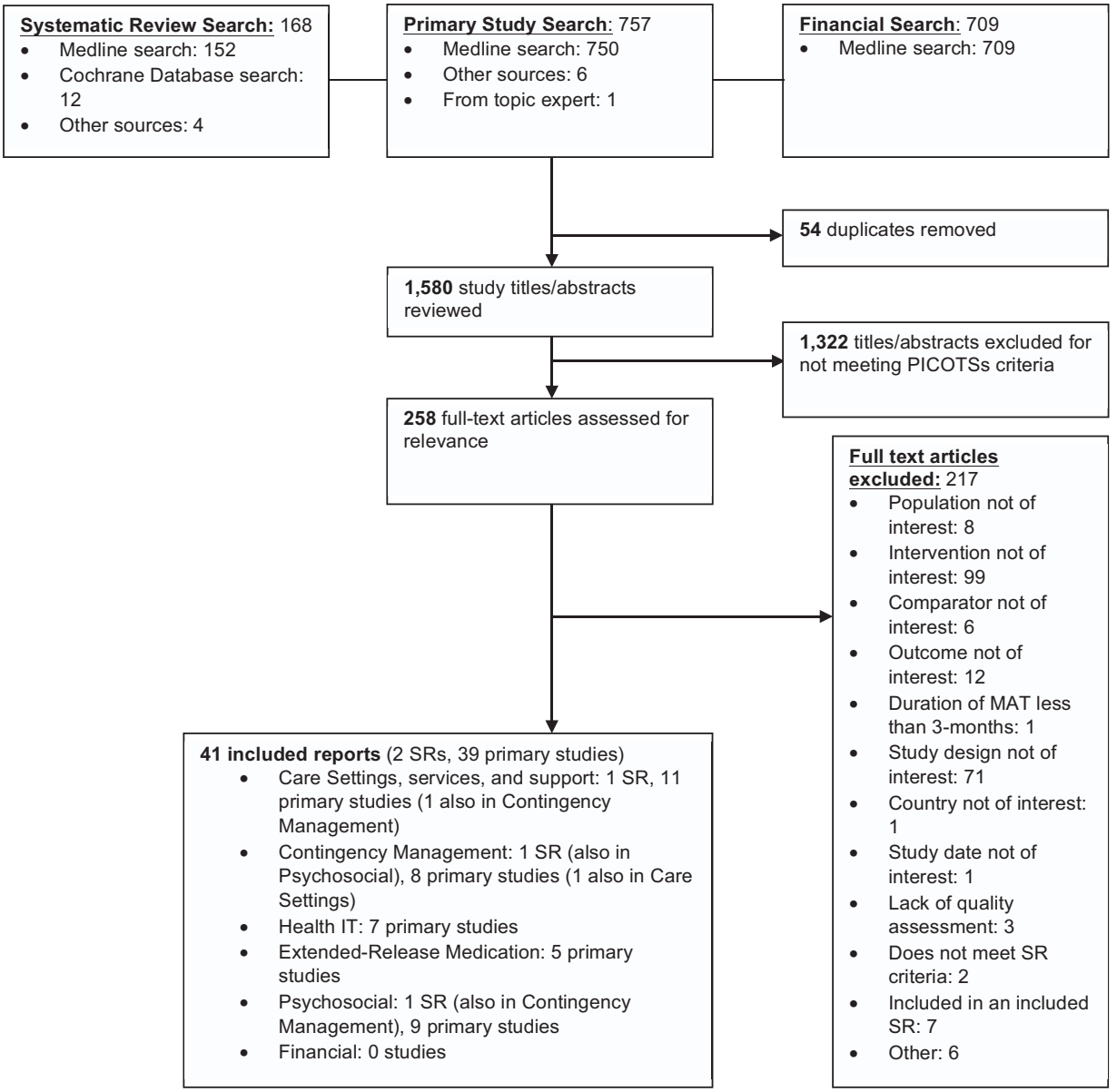

FIGURE 2. Literature flow diagram.

study found no difference in retention, defined as self-reported engagement in OUD treatment, between the 3 groups at 6 months (53% vs 51% vs 60%, $P = 0.55$) or at 12 months (49% vs. 63% vs 49%, $P = 0.14$).[27]

Logistical Support Interventions

We identified one good- and 3 fair-quality RCTs that assessed interventions that either streamlined the initiation of MOUD treatment, (''low-threshold'' MOUD), expedited enrollment in MOUD (''Script in a Day''), or combined OUD treatment with housing assistance and social care services.[19,25,26,28] One trial (n = 300) of a low-threshold, patient-centered methadone treatment delivery intervention that allowed for nonmandatory counseling and did not discharge from treatment for administrative violations, found no differences in retention between the experimental and control groups at 12 months (48.6% vs 46.3%, $P =$ not reported (NR)).[19] Similarly, another trial (n = 212) that assessed the effectiveness of a low-threshold MOUD initiation with reduced counseling frequency found no statistically significant differences in retention at 90 (35% vs 31%, $P =$ not significant (NS)), and 180 days of treatment (37% vs 29%, $P =$ NS).[26] A UK based study (n = 100) of an intervention offering immediate initiation of methadone treatment through a syringe exchange program followed by facilitated enrollment into office-based methadone treatment similarly found no difference in retention at 3 months compared to TAU (51% vs 47%, $P =$ NR).[28] Finally, in a Canadian trial (n = 97) of a

TABLE 1. Summary of Included Studies for Strategies to Improve Retention in MOUD

Intervention	Comparator	Number of Studies	Number of Participants	Quality of Evidence	Summary of Retention Results
Care settings, services, logistical support:					
MAT for soon-to-be-released incarcerated populations	No MOUD in prison	1 SR[18] + 2 additional RCTs[20,29]	SR: n = 834 (range: 32–446)	SR: good;	Benefit with prerelease MOUD in all studies
			2 RCTs: n = 228 (15 and 213)	1 fair; 1 poor	
Psychiatric & primary care (PC) services	Specialty outpatient setting	3 RCTs[21–23]	n = 631 (range: 94–316)	3 fair	Inconsistent (2 psychiatric studies, benefit in one and no difference than traditional setting in other; 1 study in PC, no difference from traditional setting)
Emergency department (ED) / hospital setting	Treatment as usual	2 RCTs[24,27]	n = 429 (139 and 290)	2 fair	ED no worse than traditional (1 study with no difference; 1 study with benefit for hospital-initiated MOUD)
Logistical support	Treatment as usual	4 RCTs[19,25,26,28]	n = 709 (range:97–300)	1 good: 3 fair	No difference
Contingency management:					
Opioid receptor antagonist MOUD	Non-contingent access to a reward	3 RCTs[30–32]	n = 140 (range:35–67)	3 fair	Benefit for contingency management in all studies
Opioid receptor agonist/ partial agonist MOUD	Non-contingent access to a reward	1 SR*,[14] + 4 additional RCTs[26,33–35]	SR: n = 1616	SR: good;	No difference
			4 RCTs: n = 698 (range:98–252)	1 good; 3 fair	
Health IT:					
Telehealth	Treatment as usual	3 cohort studies[41–43]	n = 3965 (range:55–3733)	3 fair	Telehealth no worse than in-person (2 studies with no difference, 1 study with benefit for telehealth)
Computer-based education &/or support	Treatment as usual	3 RCTs[37,39,40]	n = 262 (range:20–160)	2 fair: 1 poor	No difference
Multicomponent mobile and computer-based program	Treatment as usual	1 RCT[38]	n = 1426	1 fair	No difference
Extended-release medication based treatments:					
Naltrexone extended-release 1-month injection	Daily naltrexone	1 RCT[46]	n = 60	1 fair	Benefit for XR injection
Buprenorphine extended-release 1-month injection	Daily SL-buprenorphine/ naloxone	1 RCT[47]	n = 428	1 fair	No difference
Buprenorphine extended-release 6-month implant	Daily SL-buprenorphine	1 RCT[49]	n = 177	1 good	No difference
Naltrexone extended-release 1-month injection	Daily SL-buprenorphine/ naloxone	2 RCTs[45,48]	n = 729 (159 and 570)	1 good; 1 fair	Inconsistent (1 study no difference, 1 study with benefit for SL buprenorphine/naloxone)
Psychosocial Support:					
Including behavioral, psychoanalytic and counseling interventions	Treatment as usual	1 SR*,[14] + 9 additional RCTs[50–58]	SR: n = 3124 (range: 14–542)	SR: good	No difference in all but one poor quality study. Many of the studies reviewed included some form of counseling in the control groups.
			9 RCTs: n = 2483 (range:49–653)	2 good; 4 fair; 3 poor	

*SR applicable to 2 intervention types.
IT, information technology; MOUD, medications for opioid use disorder; RCT, randomized controlled trial; SL, sublingual; SR, systematic review; XR, Extended-release.

Housing First intervention, patients with OUD experiencing homelessness were randomized to an intervention that provided housing combined with various healthcare and social services or TAU, which included referrals to housing assistance combined with outpatient specialty treatment programs. Treatment retention, measured using medication possession ratio (MPR) over a 2-year study period, did not differ between groups (MPR 0.52 vs 0.57, $P = 0.60$).[25]

Harms and Patient Characteristics

Only 4 trials reported serious harms or adverse events, 2 without specifying in which arm the events occurred. The low-threshold, patient-centered methadone treatment intervention reported 67 nonstudy-related hospitalizations and two nonstudy-related deaths, including one from methadone overdose among 149 intervention participants compared with 59 hospitalizations and four nonstudy-related deaths (2 from overdose) among 151 TAU participants.[19] In the study of prerelease initiation of XR-naltrexone, 6 patients in the prerelease MOUD arm reported adverse events (2 serious, not specified) compared with 2 (none serious) in the control arm.[29]

The majority of studies did not examine population characteristics that affected retention outcomes. One study of prerelease MOUD initiation with linkage to office-based buprenorphine found no gender differences in retention outcomes.[20]

Contingency Management

One SR[14] that included 14 relevant RCTs, and 7 additional fair-[26,30–34] to good-quality[35] RCTs, with one follow-up analysis[36] assessed the effectiveness of contingency management interventions on MOUD retention (Appendix Table 3, http://links.lww.com/JAM/A213).

All RCTs included in the SR implemented a contingency management intervention that rewarded abstinence from illicit opioids in participants receiving either full agonist (methadone or levo-alpha acetyl methadol [LAAM]) or partial agonist (buprenorphine)) forms of MOUD. Rewards for abstinence ranged from nonmonetary vouchers to take-home medication privileges. Meta-analysis of these trials showed no differences in retention (RR 1.02, 95% CI 0.96–1.08).[14]

Among the additional 7 RCTs we included, 4 assessed contingency management with full or partial agonist forms of MOUD and, similar to the SR findings, found no differences in retention between groups.[26,33–35] The remaining 3 studies assessed contingency management with antagonist MOUD.[30–32] Two of these studies (total n = 73) provided access to a workplace where study participants could earn vouchers to exchange for goods and services contingent upon receipt of XR-naltrexone monthly injections, and found that nearly twice as many intervention group participants received all scheduled monthly injections compared to controls who had noncontingent access to the workplace (66% vs 35%, $P = 0.026$[30]; and 74% vs 26%, $P = 0.004$[31]). The third study (n = 67) also provided access to the workplace contingent upon acceptance of daily naltrexone formulation, and similarly showed improved retention in the intervention group at 26 weeks (54% vs 16%, $P < 0.01$).[32] A follow-up analysis conducted 6 month after completion of the study found no difference in medication adherence between the 2 groups (31% noncontingent vs 17% contingent, $P = 0.66$).[32]

Health Information Technology

Four RCTs (3 fair-quality[37–39] and 1 poor[40]) and 3 fair-quality retrospective cohort studies[41–43] assessed the effectiveness of Health IT (IT) interventions to improve retention on MOUD (Appendix Table 4, http://links.lww.com/JAM/A213). Figure 3 presents a graphic framework for how IT may help increase MOUD retention and summarizes the details of included studies.

All RCTs found IT interventions to be no less effective than in-person delivered TAU. The largest study was a fair-quality industry-sponsored RCT (n = 1426) that enrolled all patients into office-based buprenorphine treatment and randomized them to receive ''Here-To-Help'' (HTH) patient phone support intervention that provided coaching for medication adherence and access to online educational materials compared to office-based buprenorphine treatment alone (TAU). At 12 months, ITT analysis found no differences in retention between groups (55.5% HTH vs 56.1% TAU, P = NR). However, planned posthoc analyses reported that intervention participants who completed more phone coaching sessions had higher treatment retention compared to TAU (64.4% vs 56.1%, $P < 0.025$).[38]

A retrospective cohort study conducted in Ontario, Canada (n = 3733) tested the effectiveness of a telemedicine intervention on MOUD retention in areas with limited treatment access. The intervention allowed methadone-stabilized patients to receive care with an off-site physician via videoconference, while on-site nurses delivered guideline-concordant care. Just under half (47%) of patients received >75% of services in-person, 42% received >75% of services through IT, and 11% through a mix, with 25% to 75% of the therapy delivered via telemedicine. Compared to the mostly in-person group (39% retention), patients receiving mostly IT visits and patients who received a mix of IT visits were more likely to be retained in MOUD at 1 year (50% retention, aOR 1.27; 95% CI 1.14 to 1.41; 47% retention, aOR 1.27; 95% CI 1.08 to 1.47, respectively).[42]

Few studies reported harms associated with IT interventions. One RCT that assessed the effectiveness of combining methadone treatment with an adjunct phone-based cognitive behavioral therapy intervention reported 12 adverse events among 82 study participants (17% in the intervention group and 12% in TAU, P = NR). None were related to the intervention.[37]

None of the studies assessed whether the effectiveness of IT interventions varied by patient characteristics. Findings of a secondary analysis within an RCT that compared in-person counseling versus a combination of in-person and computer-based counseling (Therapeutic Educational System), found that counseling delivered using this combination may improve treatment retention among patients who are employed, highly anxious, ambivalent about opioid abstinence, and who have a history of crack cocaine use in the past 30 days.[44]

Extended-release Compared With Daily MOUD Formulations

Five RCTs (3 fair[45–47]; 2 good quality[48,49]) compared XR-MOUD formulations (buprenorphine injection/implant, naltrexone injection) head-to-head against daily MOUD formulations (naltrexone, buprenorphine/naloxone, buprenorphine, and methadone) (Appendix Table 5, http://links.lww.com/JAM/A213).

One (n = 60) fair-quality study compared treatment retention between XR-naltrexone monthly injections and

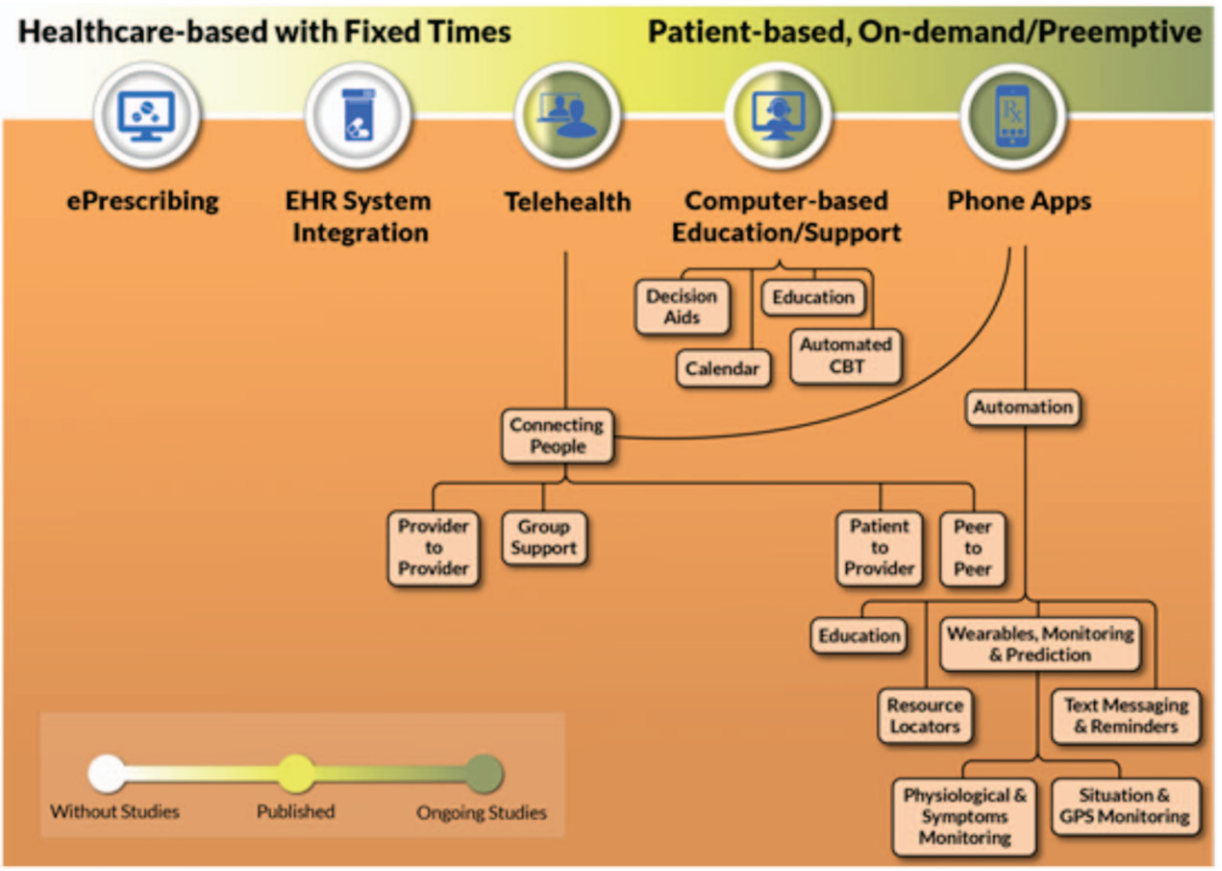

FIGURE 3. Spectrum of IT interventions proposed to increase MOUD retention. Apps, applications; CBT, cognitive behavioral therapy; GPS, global positioning system; HER, electronic health record; This figure adapted from the Office of the National Coordinator for Health IT Playbook definition and categorization of health IT[16].

daily naltrexone. Retention was assessed by documented clinical contact at 6 months and favored XR-naltrexone (57.1% vs 28.1%, HR = 2.18, 95% CI 1.07–4.43).[46]

Two studies compared retention between XR and daily buprenorphine formulations.[47,49] One multi-site trial (n = 177) randomized patients who were clinically stable on daily buprenorphine before enrollment to either XR-buprenorphine 6-month implant or continued daily buprenorphine and found similar high rates of retention at 6 months (93.1% vs 94.3%, P = NR).[49] Another trial (n = 428) randomized treatment-seeking patients to weekly, followed by monthly, XR-buprenorphine monthly injection versus daily buprenorphine/naloxone and also reported similar retention between groups at 24 weeks (56.8% vs 58.1%, P = NR).[47]

Two studies comparing XR-naltrexone monthly injection with daily buprenorphine/naloxone reported conflicting results.[45,48] One good-quality Norwegian trial (n = 159) recruited patients from outpatient and inpatient settings, randomized them following completion of medically-supervised opioid withdrawal, and reported no difference in retention measured as mean days on study medication (mean [SD]: 69.3 [25.9] vs 63.7 [29.9] days, P = 0.33).[48] Another multisite fair-quality US trial (n = 570) recruited patients from inpatient detox programs, randomized them before completing medically-supervised opioid withdrawal, and found lower retention rates in the XR-naltrexone group at 3 months (33.9% vs 40.0%, P = NR), in part due to decreased treatment initiation in the XR-NTX group.[45]

All studies of XR versus daily MOUD formulations reported adverse events. One study (n = 60) reported 2 severe drug related adverse events (hives and increased anxiety and alcohol use) which resulted in removing two XR-naltrexone group participants from the study.[46] Another trial (n = 570) of XR-naltrexone injection versus daily buprenorphine/naloxone reported a total of 28 elicit opioid-related overdose events among 23 participants. Eighteen overdoses (64%) were in the XR-naltrexone arm and included 8 participants who failed treatment induction and never received an injection. Five overdose events were fatal (2 in the XR-naltrexone group and three in the daily buprenorphine/naloxone group).[45] None of the studies assessed whether the effectiveness of XR-MOUD formulations to improve retention varied by participant characteristics.

Psychosocial Interventions

One good-quality SR[14] (26 relevant RCTs) and nine additional RCTs[50–58] (n = 49[57]–653[58]), 2 of good quality,[51,57] 4 of fair quality,[53,55,56,58] and 3 of poor quality,[50,52,54]

examined psychosocial interventions (eg, psychiatric care, psychotherapy, counseling, social work services)[14] to improve MOUD retention (Appendix Table 6, http://links.lww.com/JAM/A213).

The existing SR meta-analysis found combining MOUD treatment with psychosocial interventions did not improve retention (n = 3124, RR 1.03, 95% CI 0.98–1.07).[14] Of the 9 additional RCTs we identified, 8 also found no difference in MOUD retention.[39,51–55,57,58] The 1 positive study was a poor-quality (n = 170) study of a community reinforcement approach (CRA+) that utilized participants' social networks to increase MOUD program retention plus contingency management, versus contingency management alone, and reported increased retention in the CRA+ group (80% vs 64%; OR 2.3, CI 1.15–4.60).[50]

Few studies reported significant harms of psychosocial interventions. One study (n = 542) of pharmacist-delivered motivational interviewing versus standard methadone treatment found that intervention group participants reported poorer physical health.[52]

Few studies assessed which patient subgroups were most likely to benefit from the addition of psychosocial interventions. A study (n = 125) of XR-naltrexone coupled with a Behavioral Naltrexone Therapy compared to XR-naltrexone coupled with Compliance Enhancement intervention reported higher retention at 6-months in the Behavioral Naltrexone Therapy group among patients with low-severity OUD (<6 bags of heroin/day; 60% vs 24%, $P = 0.03$).[56]

DISCUSSION

It is clear that longer retention on MOUD reduces morbidity and mortality,[59–61] but improving retention is difficult.[6] This review summarized recent evidence on interventions to improve retention on MOUD and found limited evidence regarding which interventions are effective. We found that prerelease initiation of MOUD in incarcerated individuals with OUD, and contingency management interventions using antagonist, but not agonist, forms of MOUD, improved retention. Combining OUD treatment with medical, psychiatric, or social services, decreasing prescribing barriers to MOUD treatment, IT interventions, and XR formulations of MOUD did not worsen retention compared to TAU approaches but requires further study. Few studies reported intervention-related harms, the exception being studies of XR formulations that reported similar rates of adverse events between groups. Fewer studies assessed whether the effectiveness of different interventions to improve MOUD retention varied by patient subpopulation.

Many interventions reviewed attempt to improve retention on MOUD by expanding access to OUD treatment among novel settings. Our findings suggest that interventions initiating MOUD in soon-to-be-released incarcerated people with OUD improved retention. Given the rates of OUD in criminal justice populations and high overdose risk within the first few weeks of reentry into the community,[62,63] these interventions have potential for high impact. Interventions initiating MOUD in hospital and emergency settings prior to discharge had comparable retention post-discharge as TAU; although one of the included studies and other nonrandomized evaluations found improved rates of short-term follow-up from these programs,[27,64,65] our findings suggest that more efforts may be necessary postdischarge to support longer-term retention.

Another approach to improving retention may be addressing care fragmentation and delivery of patient-centered care through integrating MOUD treatment with outpatient medical, mental health, or social service settings. One potential reason that these studies did not demonstrate improved retention over TAU may be sub-optimal implementation of the integrated services and low-uptake of interventions[66]—future studies are needed that report aspects of implementation fidelity and specify the level of psychiatric or medical comorbidity of participants.

Our finding that contingency management interventions improved retention when combined with antagonist MOUD, but not with agonist MOUD suggests different interventions may have varying levels of effectiveness depending on MOUD type. Prior reviews have shown improved retention with methadone compared to buprenorphine.[15] Several reasons for this include the effects of full-agonist compared to partial-agonist, sub-therapeutic levels of MOUD, differences in withdrawal syndromes, and past patient experience with MOUD.[16] The lack of self-reinforcing properties of antagonist MOUD may be a reason why contingency management interventions improved retention only when paired with naltrexone. Although it was beyond the scope of this review to compare differential effects of interventions by MOUD, future studies could include additional treatment arms that utilize different MOUD formulations and doses.

Recognizing that there are few addiction providers and that most are concentrated in urban areas,[17] IT-based interventions may be attractive for those in underserved and rural areas. The few studies we found showed similar retention rates with in-person approaches. Future studies of these interventions should be designed to assess long-term outcomes, be powered to demonstrate true equivalence, assess harms as well as benefits, and consider potential implementation challenges (eg, connectivity or software compatibility) to patients, clinicians, and systems.

Although XR-MOUD formulations are a conceptually-attractive intervention because of their ease of use, we found few studies comparing the effectiveness of XR versus daily MOUD formulations. Our synthesis extends prior reviews[15] by including studies comparing XR and daily buprenorphine formulations [47,49] which showed comparable treatment retention. On the other hand, there were conflicting results in retention with XR-naltrexone monthly injection compared with daily buprenorphine. Potential reasons for this include between-study differences in the comorbidity burden of study populations, in dosing of comparator buprenorphine, and in study design (randomization before medically-supervised withdrawal versus postwithdrawal). Further comparative effectiveness trials are necessary and are underway, including a Helping to End Addiction Long-term (HEAL) Initiative trial that will assess retention at 6 months and can provide much-needed evidence in this area.[67]

Our review of psychosocial support interventions (excluding contingency management) found no differences

in retention, consistent with a prior systematic review.[68] The lack of effect may due to heterogeneity of the interventions studied, difficulties assessing fidelity of such interventions, as well as inclusion of elements of psychosocial support in the control groups, as is standard of care.[18] Given these limitations, RCTs may not be the optimal study design to assess effectiveness and other evaluation methods may better assess the impact of these interventions on retention.

Future Directions

This review highlights a need to develop a consensus definition of retention for future research. Fewer than half of the studies included in this review reported retention as a primary outcome and were underpowered. We purposely defined retention broadly to include as many interventions as possible but this made comparisons and drawing conclusions difficult. Additionally, the wide differences in retention rates seen likely reflect enrollment of disparate populations and settings – future studies might use study designs that reflect ''real-world'' conditions to increase generalizability to the OUD population. Several on-going pragmatic trials, including the NIH NIDA Clinical Trials Network (CTN) ''Retention-Duration-Discontinuation'' trial (CTN-100 RDD Study)[69] may help answer the question of whether XR formulations can improve retention in MOUD.

Limitations

This review focused on MOUD interventions that are legal, available in the US, and of highest priority for stakeholders. Other interventions to address potential barriers to improved retention not addressed by our review include patient and system-level stigma towards use of MOUD[4]—educational interventions to overcome stigma may be effective. Athough financial barriers to MOUD are thought to affect MOUD retention, we did not identify any studies that assessed the impact of insurance or financial support and retention. Finally, our review was narrowly focused on the outcome of retention. When making healthcare or policy decisions, other outcomes (such as access to treatment, overdose, and quality of life, etc) are also important to consider.

CONCLUSIONS

Few studies of interventions to support MOUD retention assess retention as a primary outcome and even fewer assess intervention harms and patient characteristics associated with effectiveness. We found that retention in MOUD may be improved through several avenues, including use of integrated care settings with criminal justice populations, and use of contingency management interventions for patients on antagonist MOUD. Preliminary studies suggest that alternative means of care delivery (IT) and integration of medical, psychiatric, and social services with MOUD may yield similar retention outcomes to TAU. Although the few comparative effectiveness studies to date show no difference in retention between XR formulations and daily formulations, this evidence is evolving. Continued research on defining standard measures for retention and determining why low MOUD retention rates persist should guide future intervention development and testing.

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