Factors Associated with Long-Term Retention in Buprenorphine-Based Addiction Treatment Programs: a Systematic Review

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BACKGROUND: The average length of buprenorphine treatment for opioid use disorder is less than 6 months.
OBJECTIVE: We conducted a systematic review to determine what factors were associated with longer retention in buprenorphine treatment.
DESIGN: We searched Medline, Embase, and Cochrane Database of Systematic Reviews in February 2018. Articles were restricted to randomized controlled trials on human subjects, written in English, which contained ≥ 24 weeks of objective data on retention in buprenorphine treatment.
MAIN MEASURES: We assessed whether dose of buprenorphine, treatment setting, or co-administration of behavioral therapy was associated with retention rates.
KEY RESULTS: Over 14,000 articles were identified. Thirteen articles (describing 9 studies) met inclusion criteria. Measures of retention varied widely. Three studies compared doses of buprenorphine between 1 and 8 mg and showed significantly higher rates of retention with higher doses (p values < 0.01). All other studies utilized buprenorphine doses between 8 and 24 mg daily, without comparison. No study found a significant difference in retention between buprenorphine alone and buprenorphine plus behavioral therapy (p values > 0.05). Initiating buprenorphine while hospitalized or within criminal justice settings prior to outpatient treatment programs was significantly associated with retention in buprenorphine treatment (p values < 0.01 respectively).
CONCLUSIONS: Setting of treatment initiation and a higher buprenorphine dose are associated with improved long-term treatment retention. More objective data on buprenorphine treatment programs are needed, including a standardized approach to defining retention in buprenorphine treatment programs.
REGISTRATION: This review was registered with PROSPERO (#CRD42019120336) in March 2019.

KEY WORDS: systematic review; buprenorphine; opioid use disorder; retention; long-term.

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INTRODUCTION

Millions of Americans live with opioid use disorder (OUD)[1]. When untreated, OUD leads to significant health consequences[2–4] and higher mortality than that observed in the general population[5, 6]. Buprenorphine is an evidence-based, first-line medication to treat OUD[7]. Not only does buprenorphine improve abstinence rates among individuals with OUD[8, 9], but it is also associated with improved morbidity and mortality for individuals on active treatment[10]. Buprenorphine is a medication used to treat OUD in the outpatient setting, as it can be prescribed by physicians, nurse practitioners, and physician assistants who have received a special waiver from the Drug Enforcement Agency.

Despite the benefits of buprenorphine in the treatment for OUD, the average length of treatment is less than 6 months, with only a minority of individuals remaining on the medication at 1 year[11–13]. Return to drug use is common after buprenorphine discontinuation[14], with high rates of overdose among those lost to follow-up[15]. Retaining individuals in buprenorphine treatment (e.g., regular follow-up visits, long-term continuation of therapy) is critical to improve health outcomes for individuals with OUD.

Prior research has demonstrated highly variable retention rates of medication treatment for OUD ranging from 19 to

Prior Presentations *Preliminary results from this study were presented in abstract form at the Society of General Internal Medicine Annual Meeting in Washington D.C. in May 2019 and as an oral abstract at the Association for Multidisciplinary Education and Research in Substance Use and Addiction National Meeting in November 2019.*

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94%, 3 to 88%, and 37 to 91% at 3, 6, and 12 months, respectively[16]. Low retention may reflect the variability in treatment programs or types of medication therapy for OUD, and could also reflect the lack of consistency in measurement of retention. Prior systematic reviews on this topic have focused on assessing quality metrics[17] and retention in all types of medication treatment programs[16]. Though buprenorphine is rapidly becoming a common medication for office-based treatment of OUD, less is known regarding what specific factors are associated with long-term buprenorphine retention. This is especially true regarding studies in which retention is measured objectively. In this systematic review, we analyzed factors associated with long-term retention in office-based buprenorphine treatment for OUD.

METHODS

This review was registered with PROSPERO (#CRD42019120336) in March 2019.

Data Sources and Searches

We searched Medline, Embase, and the Cochrane Database of Systematic Reviews in February 2018 using the terms "buprenorphine agonists," "addiction/substance abuse/opiate-opioid use," and "opiate substitution treatment." Our search string was developed and executed using the input of four co-authors (J.M.L., J.S.M., C.B.W., and A.J.K.), one of whom (C.B.W.) is a librarian with expertise in systematic reviews (see Appendix 1 for full search string). Search results were downloaded into an Endnote library, where duplicates were removed. Results were then uploaded to the DistillerSR (Evidence Partners) software program for review and screening.

Study Selection

Inclusion Criteria. Participants were limited to adolescents and adults (aged > 12 years old) with diagnosed OUD who sought buprenorphine treatment at an outpatient treatment program. Studies from all settings where buprenorphine initiation occurred, including both inpatient and outpatient settings, were included in our analysis. There were no restrictions regarding date of publication. Articles were restricted to peer-reviewed, randomized controlled trials (RCTs) on human subjects, written in English that contained at least 24 weeks of objective data on retention in buprenorphine treatment. A minimum of 24 weeks was chosen for retention as we were most interested in long-term retention (i.e., 6 months to 1 year or longer). We defined an objective measure for retention in treatment as any outcome that listed data such as days retained in care, treatment days, study days, documented buprenorphine via blood or urine testing, or buprenorphine prescription fills.

Exclusion Criteria. We excluded articles if they comprised primarily minors (aged < 13 years old), if they had no objective data on treatment retention, or if the study outcome was unrelated to treatment of OUD (e.g., neonatal abstinence syndrome, hepatitis C, HIV, tobacco use). We also excluded articles that did not describe buprenorphine as a treatment for OUD (i.e., if buprenorphine was administered only for pharmacokinetics, withdrawal, or detoxification) and those that contained no patient-level data (i.e., contained provider-only data, or were cost-effectiveness analysis or program evaluations). Though the majority of articles included buprenorphine co-formulated with naloxone, we did not exclude studies that assessed buprenorphine alone as treatment for OUD.

Data Collection. One author (A.J.K.) conducted an initial title screen on all articles. Four authors (A.J.K., R.L., M.R., and D.O.) performed an abstract and a full-text screen on the remaining articles (two authors per abstract). Any conflicts among authors in either the abstract or full-text review were resolved by the primary investigator (A.J.K.), along with the senior authors (J.S.M. and J.M.L.). A full description of screening questions by level is available in Appendix 2.

Data Extraction and Strength of Evidence

Data was extracted from each of the included studies using outcomes previously reported in the literature[16, 17], as well as a priori criteria iteratively determined by three of the authors (A.J.K., J.S.M., J.M.L.). Four authors (A.J.K., I.H., K.D., R.L.) independently performed data extraction (two authors per article) on all the included studies. Study authors were contacted for additional information or clarification if needed. All manuscripts describing data from the same study were utilized during this extraction (e.g., protocol and results papers).

Variables. Data items included sample description, study design, study duration, retention in OUD treatment, method of statistical analysis, and outcomes. Sample description included location of study, number of participants, and participant inclusion and exclusion criteria. Study design included the primary outcome, co-interventions, presence of a prior protocol paper, and type and frequency of behavioral intervention, if behavioral intervention was included. Study duration included number of weeks of intervention and duration of data collection/follow-up. The results included primary outcomes of the study and retention results, including how retention was measured if retention was not the primary outcome of the study. Data was included on illicit opioid use and how it was measured.

Strength of Evidence. We assessed for selection, performance, detection, attrition, and reporting bias utilizing the Cochrane Risk of Bias Tool for randomized controlled trials[18]. Four authors (I.H., K.D., R.L., D.O.) independently assessed the studies (two authors per article). The primary

investigator (A.J.K.) compared the risk of bias ratings and data extraction results and resolved any discrepancies with consultation from senior authors (J.S.M. and J.M.L.) when needed.

Data Synthesis and Analysis. Data were evaluated descriptively as the heterogeneity of the studies did not allow for a formal meta-analysis to be performed.

Role of Funding Source. This study was not directly supported by funding.

RESULTS

Study Selection

We identified 14,096 unique publications through February 2018; 4199 articles were screened at the abstract level and 610 at the full-text level. A total of 13 articles met final inclusion criteria, describing a total of 9 unique randomized controlled trials (Fig. 1) (19–27). All ($n = 9$, 100%) studies had greater than 100 participants. A majority of trials were single center (n = 7, 78%) and from the USA (n = 6, 67%). Most trials (n = 7, 78%) excluded patients with co-morbid severe psychiatric disorders, and 5 (55%) trials excluded pregnant women or required reproductive aged women to be on contraception (Table 1). All but one study (n = 8, 89%) included some form of behavioral therapy for OUD.

Retention in Buprenorphine Treatment

All 9 RCTs provided objective measures of retention. Retention results varied among our studies (6-month retention, 10–69%; 1-year retention, 49–59%) (Table 2). There was significant heterogeneity in measurement of retention (Table 2). Measures included days in treatment (n = 6), retention at end of study (n = 2), urine drug testing for buprenorphine (n = 1), and medication monitoring (n = 1) (some studies used multiple methods to define treatment retention).

Types of Studies

We were able to further characterize the 9 RCTs that met the inclusion criteria in our review. Three of the studies compared doses of buprenorphine, 3 compared adjunctive behavioral therapy, and 4 looked at setting of care/frequency of dosing of buprenorphine.

Buprenorphine Dose Trials

Three trials, all performed in Iran between 2002 and 2004, compared doses of buprenorphine between 1 and 8 mg and showed significantly higher rates of retention with higher doses (63–78% retained in care for 4–8 mg doses vs. 17–46% for 1–3 mg doses; p values < 0.01; see Table 2 retained in care)[19–21]. When data from the three studies were combined, retention appeared to increase with buprenorphine dose (Digital Appendix 3). All other included trials utilized maintenance buprenorphine doses between 8 and 24 mg daily; none was designed to assess buprenorphine dose as an outcome (Table 2).

Adjunctive Behavioral Therapy Trials

Of the included trials, three compared buprenorphine with standard counseling versus buprenorphine plus intensive behavioral therapy[22–24]. One trial examined standard versus longer duration counseling sessions[22], one examined standard counseling versus cognitive behavioral therapy (CBT)[24], and one trial assessed standard counseling versus intensive outpatient therapy(IOP)[23]. No study found a significant difference in retention between buprenorphine with standard counseling (43–59% retained in care) and buprenorphine plus intensive behavioral therapy (39–57% retained in care) (p values > 0.05) (Table 2).

Setting of Care Trials

There were 4 trials that compared location and/or frequency of buprenorphine administration[22, 25–27]. Two trials assessed frequency of dosing of buprenorphine (once-daily dosing up to once-weekly dosing)[22, 27], one trial compared starting buprenorphine in criminal justice settings versus outpatient settings[25], and one trial compared inpatient induction of buprenorphine and linkage of care versus standard referral and outpatient initiation (Table 1)[26]. Frequency of dosing of buprenorphine was not associated with retention in buprenorphine treatment (43–73% retention at 24 weeks for less frequent dosing compared to 39–69% for more frequent dosing), but starting buprenorphine prior to initiation in outpatient treatment programs (inpatient induction or within criminal justice settings) was significantly associated with retention in buprenorphine treatment (p values < 0.01) (Table 2).

Cochrane Risk of Bias

Overall, all trials had 1 or more domains that were at unclear to high risk of bias on the Cochrane Risk of Bias Score (Table 3). Four trials (44%) had at least one domain considered to be at high risk of bias, and 7 trials (78%) had two or more domains with an unclear risk of bias. The most common domains to have unclear or high risk of bias were blinding participants and personnel (n = 7, 78%) and incomplete outcome data (n = 8, 89%).

DISCUSSION

In this systematic review of randomized controlled trials of buprenorphine treatment programs for OUD, we found limited clinical trial data on factors associated with long-term retention. Of over 14,000 articles identified, only 9 met our criteria, with the majority of articles excluded for lack of long-term

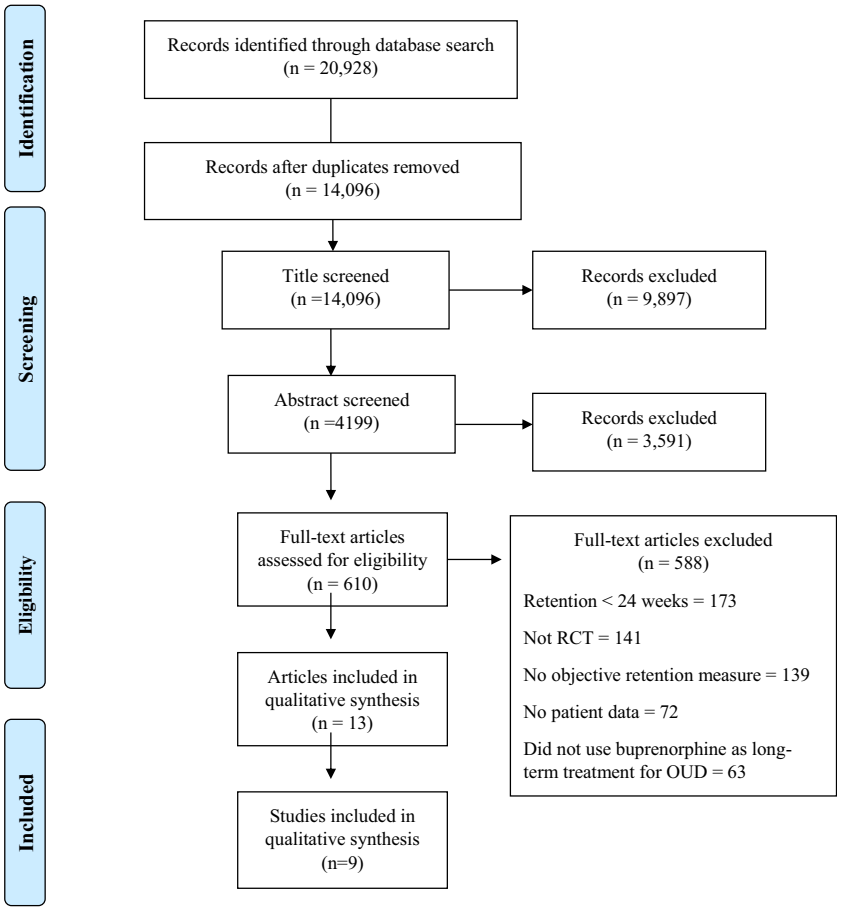


Figure 1 Flow diagram of selection process for randomized controlled studies assessing ≥ 24-week retention in buprenorphine treatment programs.

follow-up and inconsistency in their measurement of retention results.

Retention in buprenorphine treatment was low for all RCTs included in our review. Almost half of all participants were no longer receiving treatment at 24 weeks. This is in line with prior studies on medication for OUD[16]. In Timko et al.'s (2016) review, RCTs evaluating retention in medication treatment programs for OUD (buprenorphine, naltrexone, and methadone) demonstrated extremely variable follow-up results: 19 to 94% at 3 months; 3 to 88% at 24 weeks; and 37 to 91% at 12 months[16]. The patient populations and settings of care in our included studies were diverse, illustrating that retention in buprenorphine treatment is challenging across multiple settings. It is important to note that our systematic review focused on RCTs, which, given their rigorous recruitment and retention efforts, likely represent higher-than-average "real world" rates of retention. These data highlight the critical need to improve retention in buprenorphine treatment programs. More research is needed regarding what factors, both clinic level and patient level, are associated with retention in care.

Though limited by the rigor of the included studies, higher doses of buprenorphine did significantly increase retention in outpatient OUD programs. Though these trials were all completed in Iran in the early 2000s, with doses of buprenorphine between 1 and 8 mg daily, their outcomes are in line with prior research, which has shown that higher doses of buprenorphine (up to 32 mg daily), with flexibility in dosing, have better outcomes than strict adherence to lower doses[13, 28].

One notable finding of this review was that two RCTs found that initiating buprenorphine prior to establishment in an outpatient treatment program significantly increased retention in care[25, 26]. In Liebschutz et al.'s (2014) trial, buprenorphine initiation in the hospital significantly improved retention, though the overall rates of retention in both arms of the trial were poor (total study 6-month retention was only 10–17% in the linkage group and 3% in non-linkage group, respectfully)[26]. These low retention rates are considerably lower than those in the other studies in our review, which the authors suggest could reflect the complexities of hospitalized OUD patients, who often deal with

Table 1 Study Type of Randomized Controlled Trials of Buprenorphine Retention

Author, year	*N*	Location	Study description	Bup dose	Inclusion and exclusion criteria	Study retention*	Behavioral therapy	Comment
Dosage of buprenorphine trials								
Ahmadi, 2002	420	International, urban, single site Shiraz, Iran	1 mg vs. 2 mg vs. 4 mg Bup daily	1–4 mg Bup	Inclusion: DSM-IV for OUD, daily opium use for 12 months Exclusion: serious medical or psychiatric condition, AUD, use of methadone or anticonvulsants	24 W	Offered weekly, 1-h counseling with addiction psychiatrist	Opium dependent only
Ahmadi, 2003	123	International, urban, single site Shiraz, Iran	1 mg vs. 3 mg vs. 8 mg Bup daily	1–8 mg Bup	Inclusion: DSM-IV for OUD, daily heroin use for 6 months Exclusions: serious medical or psychiatric condition, AUD, use of methadone or anticonvulsants	12 M	Offered weekly, 1-h counseling with addiction psychiatrist	Heroin dependent only
Amadi, 2004	513	International, urban, single site Shiraz, Iran	1 mg vs. 3 mg vs. 8 mg Bup daily	1–8 mg Bup	Inclusion: DSM-IV for OUD, opium dependence Exclusions: age < 18 or > 85 years, serious medical or psychiatric condition, AUD, use of methadone or anticonvulsants	6 M	Offered weekly, 1-h counseling with addiction psychiatrist	Opium dependent only
Adjunctive therapy trials								
Fiellin, 2006†	166	USA, urban, single site, primary care Yale, New Haven, CT	SM/1 weekly vs. SM/3 weekly vs. EM/3 weekly	16–24 mg Bup/Na	Inclusion: OUD on OAT Exclusion: AUD, BUD, serious medical or psychiatric condition, women of child-bearing age not on contraception	24 W	SM: 20-min weekly sessions EM: 45-min weekly session All counseling by primary care nurses	Could transfer care if unremitting drug use
Mitchell, 2013	300	USA, urban, multi-site, CHC, OTP	Bup and OP or Bup and IOP	8–24 mg Bup/Na	Inclusion: African American, Bup treatment for OUD Exclusion: serious medical or psychiatric condition, pregnancy	6 M	OP: 2–8 h weekly counseling IOP: 9+ h weekly counseling	African-American only IOP was 5 h/week
Moore, 2016	140	USA, urban, single site, primary care Yale, New Haven, CT	Bup alone vs. Bup plus CBT	16–24 mg Bup/Na	Inclusion: DSM-IV for OUD Exclusion: AUD, BUD, CUD, serious medical or psychiatric condition, women of child-bearing age not on contraception	26 W	Bup: 20-min counseling with IM physicians CBT: 12 weeks of 50-min CBT sessions with master's or doctoral level clinician	
Setting of care trials								
Fiellin, 2006†	166	USA, urban, single site, primary care Yale, New Haven, CT	SM/1 weekly vs. SM/3 weekly vs. EM/3 weekly	16–24 mg Bup/Na	Inclusion: OUD on OAT Exclusion: AUD, BUD, serious medical or psychiatric condition, women of child-bearing age not on contraception	24 W	SM: 20-min weekly sessions EM: 45-min weekly sessions All by primary care nurses.	Could transfer care if unremitting drug use
Gordon, 2017	211	USA, urban, multisite, prisons, OTPs, CHCs Baltimore, MD	Prison Bup+OTP referral Prison Bup+CHC referral Prison counseling +OTP referral Prison counseling +CHC referral	8 mg Bup/Na	Inclusion: DSM-IV for OUD, > 18 years, within 3–6 months of release, living in Baltimore post-release Exclusion: liver or kidney disease, psychosis, pending parole hearing, un-adjudicated charges	12 M	Initial assessment and 12 weekly group counseling sessions	Bup initiation in criminal justice setting
	139			16 mg		6 M	Does not specify	

(continued on next page)

Table 1. (continued)

Author, year	N	Location	Study description	Bup dose	Inclusion and exclusion criteria	Study retention*	Behavioral therapy	Comment
Liebschutz, 2014		USA, urban, single-site, hospital and primary care, Boston, MA	Inpatient Bup + linkage vs. Bup detox and no linkage	Bup/Na	Inclusion: hospitalized, opioid-dependent, age > 18 years Exclusion: prior Bup or methadone, AUD, BUD, self-harm, surgery or jail time pending, uncontrolled pain, pregnancy			Bup initiation in hospital patients
Marsch, 2005	134	USA, single site, OTP, VT	Daily vs. 2 weekly vs. 3 weekly Bup dosing	4-12 mg Bup	Inclusion: DSM-IV for OUD, age > 18 Exclusion: serious medical or psychiatric condition, pregnancy	24 W	1-h counseling/ week with master's level therapist	

*Retention reported in weeks or months, depending on individual clinical trial
†Fiellin study included both adjunctive therapy trial and setting of care trial
Abbreviations: N, number; AUD, alcohol use disorder; BUD, benzodiazepine or sedative use disorder; Bup, buprenorphine; Bup/Na, buprenorphine-naltrexone; CBT, cognitive behavioral therapy; CHC, community health center; CUD, cocaine use disorder; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EM, enhanced medical; IM, internal medicine; IOP, intensive outpatient therapy; min, minute; M, month; SM, standard medical; OAT, opioid agonist therapy; OTP, opioid treatment program; OP, standard outpatient therapy; OUD, opioid use disorder; W, week

more serious medical conditions than those traditionally starting in outpatient buprenorphine treatment. In a different venue, Gordon et al. (2017) found that persons who started buprenorphine within criminal justice settings had higher 1-year rates of retention in outpatient treatment than those who were referred after discharge[25], which is consistent with prior research. Studies assessing short-term outcomes of starting buprenorphine in criminal justice settings have been similarly effective[29–31]. Though promising, more research is needed to determine if these results hold true in larger studies.

A subset of the RCTs in our review assessed buprenorphine treatment with and without adjunctive behavioral therapy. All three studies showed that the addition of behavioral therapy had no association with retention in care. Though these studies varied widely in the type of therapy offered (CBT vs. IOP vs. intensive counseling), they do add to other published works that suggest that behavioral therapy in conjunction with medication therapy may not significantly improve patient outcomes[32]. Though behavioral therapy is important in many people's recovery process, our results suggest adding behavioral therapy to buprenorphine treatment may not impact retention rates.

Importantly, this review highlights the lack of objective data on long-term retention in buprenorphine treatment. Retention was measured in a variety of ways in our trials, and a large number of excluded studies either did not describe how they measured retention or used only self-reported data. Of those studies included, there was significant heterogeneity in how retention was measured (days in treatment, retention at end of study, medication monitoring). More objective measures of retention, such as urine screens for buprenorphine or documented prescription fills, are needed to better capture true retention in care. Now that prescription drug monitoring programs are in place throughout the majority of the country, documentation of prescription fills would be relatively straightforward and could be added to a clinical variable, such as days in treatment, to better capture true retention. As with other fields of research in which retention is an important outcome, such as HIV[33], standardization in methodology is an important area for further development[17, 34].

Our review did have significant limitations. Given the heterogeneity of the trial outcomes, we were unable to perform a meta-analysis of all included studies. We chose to focus on the highest quality of evidence (RCTs), but this means we excluded observational data, which may have limited the data available to answer our question. We had only a small number of studies that met our inclusion criteria, many of which were performed over a decade ago, which made it difficult to apply their results within the current context of the opioid epidemic.

In future work, we plan to compare outcomes of long-term buprenorphine retention with that of methadone and naltrexone treatment programs. Novel programs, such as initiation of treatment outside of the clinic setting, need to be evaluated, as the current standard of care is not working. This review highlights the lack of high-quality studies on buprenorphine retention and the need for objective measures of retention to be standardized.

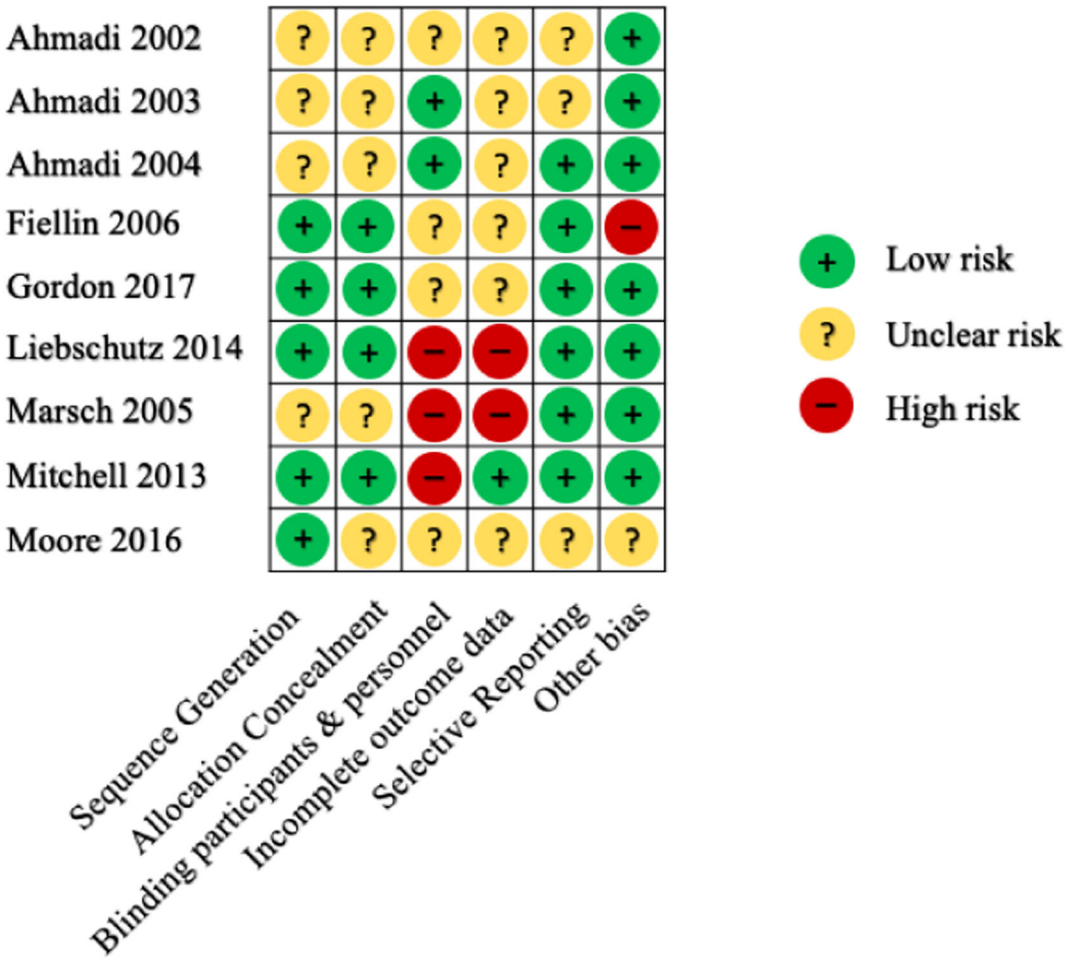
In conclusion, this systematic review found limited evidence on long-term retention in buprenorphine treatment programs. Of the 9 RCTs in our review, setting of treatment initiation and a higher buprenorphine dose were associated with improved long-term treatment retention, while adjunctive

Table 2 Outcome Measures of Randomized Controlled Trials of Buprenorphine Retention

Author, year	Retention measure	Retention results	Analysis comparison	Illicit opioid results
Dosage of buprenorphine trials				
Ahmadi, 2002	Urine screen for Bup	24 W retention* Total: *N* = 237/420 (56.%) 1 mg: 67/140 (48%) 2 mg: 78/140 (56%) 4 mg: 88/140 (63%)	4 mg Bup sig increased retention than 2 mg ($p < 0.05$) and 1 mg ($p < 0.01$) groups. No sex dif were observed ($p = 0.84$).	N/A
Ahmadi, 2003	Retention in study at 12 months	12 M retention Total: *N* = 49/123 (40%) 1 mg: *N* = 7/41 (17%) 3 mg: *N* = 16/41 (39%) 8 mg: *N* = 26/41 (63%)	8 mg Bup sig increased retention than 3 mg ($p = 0.03$) and 1 mg ($p < 0.01$). 3 mg Bup sig increased retention than 1 mg ($p = 0.03$).	N/A
Amadi, 2004	Retention in study at 12 months	12 M retention Total: *N* = 282/513 (55%) 1 mg: *N* = 46/171 (27%) 3 mg: *N* = 102/171 (60%) 8 mg: *N* = 134/171 (78%)	All groups sig differed from each other at $p < 0.01$.	N/A
Adjunctive therapy trials				
Fiellin, 2006†	Days in study, medication bottle monitoring	24 W retention* Total: *N* = 72/166 (43%) SM/1 weekly: *N* = 26/54 (48%) SM/3 weekly: *N* = 24/56 (43%) EM/3 weekly: *N* = 22/56 (39%)	Mean number of patients who completed study did not differ sig among the 3 groups ($p = 0.64$). Mean % of days adherent to Bup was 71+/-22%, did not differ sig among groups ($p = 0.87$).	No sig dif between groups in opioid use ($p = 0.73$), opioid-negative urine ($p = 0.82$), nor weeks abstinent ($p = 0.54$)
Mitchell, 2013	Days in clinic	6 M retention* Total: *N* = 174/300 (58%) Bup + OP: *N* = 91/155 (59%) Bup + IOP: *N* = 83/145 (57%)	No sig dif in retention in treatment (Bup + OP = 127.1 days vs. Bup + IOP = 126.9 days)($p = 0.84$).	No sig dif in OUD ($p = 0.67$) or CUD ($p = 0.63$) criteria
Moore, 2016	Days in study	26 W retention Total: *N* = 65/140 (46%) Bup alone: *N* = 34/70 (49%) Bup + CBT: *N* = 31/70 (44%)	No sig dif in weeks completing treatment ($p = 0.59$) or # of weeks in treatment ($p = 0.67$) between groups.	No sig dif in heroin use by treatment ($p = 0.33$). Sig dif in prescription opioid use by treatment ($p = 0.04$).
Setting of care trials				
Fiellin, 2006†	Days in study, medication bottle monitoring	24 W retention* Total: *N* = 72/166 (43%) SM/1 weekly: *N* = 26/54 (48%) SM/3 weekly: *N* = 24/56 (43%) EM/3 weekly: *N* = 22/56 (39%)	Mean number of patients who completed study did not differ sig among the 3 groups ($p = 0.64$). Mean % of days adherent to Bup was 71+/− 22%, did not differ sig among groups ($p = 0.87$).	No sig dif between groups in opioid use ($p = 0.73$), opioid-negative urine ($p = 0.82$), nor weeks abstinent ($p = 0.54$)
Gordon, 2017	Days in clinic	6 M retention‡ Total: *N* = 140/211 (66%) 12 M retention‡ Total: *N* = 124/211 (59%)	Initiating Bup in prison had sig higher days retained (mean 66) vs. initiating after release (mean 22) ($p < 0.01$) Women were sig more likely to have received Bup than men (29% vs. 10%, $p < 0.05$)	No sig dif in heroin use between groups.
Liebschutz, 2014	Days in clinic	6 M retention Total: *N* = 14/139 (10%) Inpt Bup+link: *N* = 12/72 (17%) Detox+no link: *N* = 2/67 (3%)	Sig higher 6-month retention in link than no link ($p < 0.01$) Link group had Bup for mean 65 days vs. 7 days for no link ($p < 0.01$)	Illicit opioid use was sig lower in link than no link ($p < 0.01$)
Marsch, 2005	Days in clinic	24 W retention* Total: *N* = 92/134 (69%) Daily Bup: *N* = 31/45 (69%) 2 weekly Bup: *N* = 29/45 (64%) 3 weekly Bup: *N* = 32/44 (73%)	No sig dif in retention at 24 weeks ($p = 0.74$)	No sig dif in opioid ($p = 0.38$) or cocaine ($p = 0.46$) use

**Participant retention numbers not listed in paper, inferred based on percentages listed, subject to rounding error*
†Fiellin study included both adjunctive therapy trial and setting of care trial
‡Study did not provide retention numbers for individual arms of study
Abbreviations: Bup, buprenorphine; CBT, cognitive behavioral therapy; CHC, community health center; CUD, cocaine use disorder; dif, difference; detox, buprenorphine detoxification; EM, enhanced medical; Inpt, inpatient; IOP, intensive outpatient therapy; link, linkage; M, month; Mod, moderate; N, number of participants; sig, significant; SM, standard medical; OTP, opioid treatment program; OP, standard outpatient therapy; OUD, opioid use disorder; W, week

Table 3 Cochrane Risk of Bias Assessment for Buprenorphine Retention Trials



behavioral therapy or counseling in combination with buprenorphine did not lead to better retention in treatment compared to buprenorphine alone. More high-quality randomized controlled trials on buprenorphine treatment programs are needed to understand what factors impact retention in care. Future clinical trials on this subject should include a standardized approach to define retention in treatment.

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Compliance with Ethical Standards:

Conflict of Interest: *The authors declare no conflict of interest.*

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