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Retention in Medication-Assisted Treatment for Opiate Dependence: A Systematic Review

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Abstract

Retention in medication-assisted treatment (MAT) among opiate-dependent patients is associated with better outcomes. This systematic review (55 articles, 2010–2014) found wide variability in retention rates (i.e., 19%−94% at 3-month, 46%−92% at 4-month, 3%−88% at 6-month, and 37%−91% at 12-month follow-ups in randomized controlled trials), and identified medication and behavioral therapy factors associated with retention. As expected, patients who received naltrexone or buprenorphine had better retention rates than patients who received placebo or no medication. Consistent with prior research, methadone was associated with better retention than buprenorphine/naloxone. And, heroin-assisted treatment was associated with better retention than methadone among treatment-refractory patients. Only a single study examined retention in MAT for longer than one year, and studies of behavioral therapies may have lacked statistical power; thus, studies with longer-term follow-ups and larger samples are needed. Contingency Management showed promise to increase retention, but other behavioral therapies to increase retention, such as supervision of medication consumption, or additional counseling, education, or support, failed to find differences between intervention and control conditions. Promising behavioral therapies to increase retention have yet to be identified.

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Keywords

opiate dependence; systematic review; treatment retention; behavioral therapies; medication-assisted treatment

Introduction

Opiate use and dependence are global problems.[1] The US has seen a significant increase in the illicit use of prescription opiates and stable levels of heroin use.[2,3] In 2007, there were approximately 1.2 million heroin users in the US, and 5.2 million people reporting inappropriate use of prescription opioids.[4] Among people who use heroin or prescription opiates, 50% and 11%, respectively, meet addiction criteria.[5] Opiate dependence in particular is viewed as a chronic, brain-based disorder with a high potential for relapse.[6,7]

The burden of opiate dependence is substantial, with high rates of morbidity and mortality, disease transmission, crime and law enforcement costs, family distress, lost productivity, and increased health care utilization.[8] In the US, opiates are second only to alcohol as the primary reason for addiction treatment admission. From 1999 to 2009, annual treatment admissions for opiate misuse increased from approximately 280,000 to 421,000 individuals.[9] A primary outcome in treating opiate dependence is retention in treatment because retention is associated with decreased drug use, improved social functioning and quality of life, and reduced mortality.[8,10] Because of the benefits of retention for other outcomes, this systematic review examined factors associated with retention in medication-assisted treatment for opiate dependence.

Medication-Assisted Treatment

Medications approved by the FDA for the treatment of opiate dependence are methadone, buprenorphine, and naltrexone. The safety of methadone is well established.[10] Methadone is used as a substitute for heroin or other opiates and, through mechanisms of tolerance and cross-tolerance, prevents opioid intoxication and withdrawal.[8] Methadone is administered orally in liquid, tablet, or dispersible tablet formulation and is used for maintenance and for assisting in withdrawal.[1,10] It is dispensed in specialized outpatient Methadone Maintenance clinics. Research has demonstrated methadone's efficacy in reducing heroin use, morbidity and mortality, and illegal activities.[11–14] Most patients require daily doses, and any "take-home" doses are strictly regulated to prevent diversion.[15]

Safety evaluations for buprenorphine are less developed than for methadone, but research suggests it is safe, with adverse effects equivalent to those of methadone and placebo.[10] Buprenorphine, a partial opioid agonist, is administered sublingually in tablet or film formulations. It is also used in opiate detoxification and maintenance treatment.[1] It is available both as a monotherapy and in combination with naloxone to reduce the harm associated with buprenorphine injection. Indeed, naloxone was combined with buprenorphine to decrease the potential for diversion and misuse of buprenorphine. Because buprenorphine is a partial agonist, associated physical dependence and withdrawal are less severe than with full agonists.[1] Another advantage is its availability as a prescription

medication outside of the highly regulated methadone clinic system; it can be taken once every two days, which makes it more appealing to many patients.[16] However, buprenorphine is relatively more expensive than methadone, making it more readily available to individuals with adequate resources.[1]

Naltrexone's safety is also well demonstrated, but evidence of its efficacy has not been strongly established.[8,10,17,18] Naltrexone is administered orally in tablet formulation or intramuscularly in an extended-release formulation.[10] Extended-release naltrexone is delivered by injection once per month. Subdermal implants for naltrexone are not currently FDA approved, although they are available at a limited number of treatment centers. Naltrexone completely blocks the effects of opioids and produces no euphoric effects.[1]

Present Study

The purpose of the present study is to identify factors associated with the outcome of retention in medication-assisted treatment (MAT) for opiate dependence; that is, treatment with methadone, buprenorphine, and naltrexone. We conducted a systematic review focused on comparisons of medications and behavioral therapies. Both sets of factors are modifiable and can be targeted for change to achieve better retention related to MAT. This review is intended to fill a critical gap in the literature in that identification of factors that promote higher rates of MAT retention will be useful to clinical providers and managers of addiction services seeking to achieve better outcomes among their opiate-dependent patients.

Method

To begin the systematic review, we entered the following search string in PubMed: ("opiate substitution treatment"[Mesh] OR "Opioid-Related Disorders/drug therapy"[Mesh] OR "Opioid-Related Disorders/rehabilitation"[Mesh]) AND ("naltrexone"[Mesh] OR "buprenorphine"[Mesh] OR "methadone"[Mesh]). The search (conducted on January 15, 2015) was limited to studies of humans reported in English language journal articles and published after December 31, 2009. This time frame was chosen to ensure that findings are relevant to current treatment programs, and also to constrain the studies to a manageable number for review. Excluded were case studies, abstracts, reviews, and commentaries. We also entered the same search string, publication date limits, and other constraints in CINAHL, using the option to exclude articles identified in MEDLINE (which is accessed within PubMed). From PubMed, a total of 289 unique citations were screened for inclusion. From CINAHL, only one additional citation was identified and screened, for a total of 290 unique citations.

Each citation (abstract) was reviewed by two authors; a full article review was conducted if one or both authors considered it to be indicated (the two authors agreed initially on the status of 285 of the 290 abstracts [98%]). Studies were eliminated at this stage of abstract review mainly because they focused on adults who were not opiate-dependent, on infants born to women maintained on opioid agonist medication, on short-term detoxification rather than medication-assisted treatment, or on biochemical effects of medications (e.g., hepatic safety). With this approach, 69 articles were retained for full text review because they possibly examined factors associated with retention in MAT for opiate dependence (Figure

1). Two authors conducted data extraction on each of the final 55 articles (elimination of 14 articles was also agreed upon by two authors' reviews). Data collected from each study included study design, conditions, total number of participants (and percent male), type of medication, measure of retention, and retention rate. All articles retained reported studies of individuals with opiate dependence. When studies provided retention rates at more than one follow-up point, we coded the rate for the longest follow-up.

Regarding study design, the US Preventive Services Task Force's quality rating criteria for individual studies rates randomized controlled trials (RCTs) the highest.[19] Therefore, we separated RCTs from studies with other designs. In non-RCT designs, quasi-experimental studies are rated higher than cohort designs or case-control studies.[19] More fine-grained criteria rate prospective cohort higher than retrospective cohort studies, and rate cohort studies higher than case-control studies.[20]

Results

MAT Retention Rates

The RCTs listed in Table 1 found a wide range of retention in MAT at follow-ups of 1 month (72.0%; N=1 RCT), 3 months (19.0% to 94.1%; N=9 RCTs), 4 months (45.9% to 91.9%; N=4 RCTs), 6 months (3.0% to 88.0%; N=13 RCTs), and 12 months (37.0% to 90.7%; N=6 RCTs). Studies with a design other than RCT, listed on Table 2, also found a wide range of retention in MAT at follow-ups of 3 (68.0% to 87.0%, N=1 study), 6 (21.4% to 78.1%; N=6 studies), or 12 (26.0% to 85.0%, N=6 studies) months.

RCTs with a Medication Focus

Significant findings.—We focus first on RCTs that compared medication delivery conditions. (See Table 1, in which rates in the last column are significantly different within a given study unless otherwise noted in the table. Also, summaries of studies in this narrative follow the same order of studies in the table.) Patients receiving a 4-week rather than a briefer buprenorphine taper prior to naltrexone had higher MAT retention rates (50.0%) at 3-month follow-up.[21] Receipt of a naltrexone implant rather than placebo was associated with a higher 3-month retention rate (52.0% vs 28.0%).[22] Receipt of naltrexone rather than placebo was also associated with higher 6-month retention rates (≥20%), and a longer duration of MAT, but the additional receipt of guanfacine (used for ADHD and hypertension) did not increase retention rates.[23,24] Receipt of buprenorphine rather than placebo was associated with a higher 6-month retention rate (65.7% vs 30.9%).[25] When all patients received counseling, receipt of buprenorphine rather than placebo or naltrexone was again associated with a higher 6-month retention rate.[26] Among patients who were HIV+, those receiving buprenorphine within the HIV clinic rather than a referral to an opioid treatment program were more likely to be in MAT at 12 months.[27] Thus, as expected, receipt of naltrexone or buprenorphine was associated with better retention in MAT than placebo or no medication.

Three studies found that receipt of methadone rather than buprenorphine/naloxone was associated with higher retention in MAT at 4 months (73.9% vs. 45.9%) and at 6 months

(74.0% vs 46.0%; 57.6% overall).[28–30] Methadone receipt, compared to buprenorphine receipt, was also associated with higher end-of-pregnancy MAT retention rates among women receiving comprehensive pre-natal care and contingency management.[31] However, among patients receiving oral methadone but still injecting heroin, 6-month retention rates were higher when patients were given injectable heroin (88.0%) or methadone (81.5%) than retained on oral methadone (69.0%); similar findings held at 12-month follow-up in another treatment-refractory sample.[32,33] Similarly, among treatment-refractory patients, heroin-assisted treatment was associated with a higher 12-month retention rate than was methadone.[34,35]

Non-significant findings.—Contrary to the studies cited above that found an advantage for methadone relative to buprenorphine,[28–31] one study found that patients had high 3-month retention rates (85.0%) whether they received methadone or buprenorphine/naloxone, perhaps because the latter group also received a dose taper and referral to treatment, i.e., weekly individual drug counseling and group therapy.[36] Six-month MAT retention rates were also comparable (48%) for patients with chronic non-malignant pain who received either methadone or buprenorphine/naloxone.[37] High 12-month retention rates (88%) were found among treatment-refractory patients treated with either diacetylmorphine (the active ingredient of heroin) or hydromorphone (a semisynthetic opioid analgesic).[38] In another study, patients' 1-month retention in MAT did not differ according to whether they received direct or indirect induction of buprenorphine/naloxone.[39]

Several studies failed to find significant effects on MAT retention for medications provided in addition to a primary opiate medication. In one, 3-month retention among patients receiving oral naltrexone did not differ according to whether they received varying doses of Memantine (a dementia drug) or a placebo (retention rates of ≥19%).[40] And, 3-month retention among patients receiving buprenorphine did not differ according to whether they received escitalopram or placebo for depression.[41] Finally, among cocaine-dependent patients maintained on methadone for dual opioid dependence, those receiving disulfiram instead of placebo did not have a significantly different likelihood of MAT retention at a 4-month follow-up.[42]

RCTs with a Behavioral Therapy Focus

Significant findings.—Among non-treatment-seeking hospitalized patients, a comparison of detoxification to facilitated linkage to buprenorphine treatment found higher rates of MAT retention among patients in the facilitated linkage condition; nevertheless, only 16.7% of linked patients were retained at 6 months.[43] Compared to methadone-only patients, patients receiving methadone with contingency management were more likely to be retained at 3 months (67.5% vs 81.7%; 67.0% vs 81.0%).[44,45] Similarly, compared to naltrexone-only patients, patients receiving naltrexone and contingency management were more likely to be retained at 6 months (16.0% vs 54.0%).[46]

Non-significant findings.—Several studies have examined MAT retention rates associated with different behavioral therapies among patients receiving methadone. Daily supervision of consumption was associated with a lower, but not significantly lower, 12-

month retention rate (72.7%) compared to twice-weekly (85.7%) or no (94.1%) supervision.[47] Adding counseling to receipt of daily methadone did not increase 6-month MAT retention rates, which were 76% or higher.[48] The provision of pharmacist-delivered motivational interviewing did not improve 6-month retention rates compared to usual care (rates of ≥ 81%).[49] Patients whose methadone was accompanied by web-based education but reduced (fewer sessions of) counseling had a comparable rate of MAT retention as patients receiving methadone plus more counseling (and no education); results suggest that less counselor staffing does not interfere with retention, but the overall retention rate at 12 months was only 38.7%.[50] Varying counseling provision by whether it was routine or emergency only, in the context of different counselor caseloads and amounts of patient supervision, was not significantly associated with 4-month (89% to 92%) or 12-month (37% to 61%) retention rates.[51,52]

Another set of studies examined MAT retention rates associated with different behavioral therapies among patients receiving buprenorphine. The provision of cognitive behavioral treatment, contingency management, or both, did not significantly improve 4-month retention rates compared to no additional treatment (rates ≥ 65%).[53] Similarly, the provision of intensive rather than standard outpatient counseling did not improve 6-month retention rates (≥ 57%).[54] Furthermore, the provision of telephone support did not benefit 12-month retention rates (55.0%) above usual care (55.0%), although patients with at least three completed telephone support calls had higher retention rates than patients in usual care.[55]

The lack of significant findings related to behavioral therapies and MAT retention holds among samples of more complex opioid-dependent patients. Among patients diagnosed with HIV receiving buprenorphine/naloxone, patients provided with physician management only had an 80% 3-month retention rate compared to 59.0% with enhanced medical management (drug and medication adherence counseling) added on to physician management; this difference was not significant.[56] Among partners of opioid-dependent pregnant women, participation in a support group, or receiving more comprehensive therapy, education, and case management, was not associated with number of days in MAT with methadone.[57] Among individuals who were under judicial supervision, adding psychosocial counseling to naltrexone treatment was not associated with MAT retention rates at 6-month follow-up.[58]

Studies with non-RCT Designs with a Medication Focus

Significant findings.—Studies with a cohort design found methadone compared to buprenorphine was associated with better retention rates at 6 and 12 months, and compared to Jitai tablets (a traditional Chinese medicine used to treat neuropsychiatric disorders) at 12 months.[59–63] Higher doses of buprenorphine, especially early in treatment, were associated with better retention in MAT at a 6-month follow-up.[64]

Non-significant findings.—In contrast to studies finding an advantage for methadone, a large study of public outpatient programs in Italy found high rates of MAT retention at 12 months for both methadone (93%) and buprenorphine/naloxone (89%).[59,61,62,65]

Studies with non-RCT Designs with a Behavioral Therapy Focus

Significant findings.—Among patients receiving buprenorphine/naloxone, a psychosocial program with group cognitive behavioral therapy yielded a higher MAT retention rate at 6 months (55%) than did brief counseling in primary care (33%) or individual counseling in opioid treatment (21%).[66] Patients on methadone maintenance had a higher 12-month retention rate in a contingency management take-home condition (74%) than in a daily supervision (58%) or non-contingent take-home condition (50%).[67] In a retrospective cohort study of patients receiving buprenorphine, MAT retention at 12-month follow-up was associated with the receipt of substance abuse counseling and psychiatric medication.[68]

Non-significant findings.—A study of primary care patients receiving buprenorphine/naloxone found physician management with weekly dispensing to be marginally significantly associated with better retention (87% at 3 months) than physician management with dispensing 3 times per week plus cognitive behavioral therapy (68%).[69] Pregnant women who received vouchers for both MAT (methadone or buprenorphine) attendance and providing drug-free biological samples had a comparable retention rate at 1-month post-delivery to that of pregnant women who received vouchers for MAT attendance only.[70]

Discussion

This systematic review, summarizing 55 articles published during the past five years (from 2010 through 2014), found wide variability in the rates at which opiate-dependent patients are retained in medication-assisted treatment. As expected, retention rates are likely to decrease as the duration of follow-up lengthens.[51,52] Retention in treatment represents the accomplishment of system and program goals that are important for patients' attaining and sustaining substance-free and productive lives.[71,72] This review identified medication factors and behavioral therapies associated with MAT retention to help clinical providers and managers of addiction services implement procedures linked to patients' achieving better outcomes.

Notably, only a single study examined retention for longer than one year, even though the National Institute on Drug Abuse (NIDA) recommends a minimum of one year in methadone maintenance treatment for best outcomes.[73] Indeed, despite extensive and prolonged use of methadone to treat heroin addiction since the mid-1960s, little is known about its effects over the long-term. The FDA issued in 2006 a physician safety alert regarding increased cardiac arrhythmias and deaths among methadone patients.[74] More recent Norwegian animal studies suggest that methadone may negatively affect cognitive functioning, such as learning and memory.[75] However, long-term studies of the effectiveness and consequences of MAT for opiate-dependence have yet to be conducted.

Medications and Retention

With regard to medications, this review found, as expected, that patients in RCTs who received naltrexone or buprenorphine had better 3-, 6-, or 12-month retention rates than patients who received placebo or no medication. RCTs and cohort studies also found that

patients who received methadone rather than buprenorphine/naloxone were more likely to be retained in MAT at 4- and 6-month follow-ups and at the end of pregnancy. As reviewed by Whelan and Remski (2012), there is significant evidence that better MAT outcomes for opioid dependence are associated with high activity at the mμ receptor, for example, "the narcotic blockade" achieved with high doses of methadone; therefore, buprenorphine's weaker mμ activity may account for its poorer performance compared to methadone in clinical trials.[76] In addition, buprenorphine retains fewer people when doses are delivered flexibly or at low fixed doses, compared to fixed medium or high doses; however, fixed doses are rarely used in clinical practice.[16] This is consistent with the finding cited here that higher doses of buprenorphine, especially early in treatment, were associated with better retention.[64]

The studies in this review finding benefits to retention of heroin-assisted treatment relative to methadone among treatment-refractory patients agree with earlier evidence in support of treatment with fully supervised, self-administered injectable heroin, when compared with oral methadone, for individuals with long-term refractory heroin dependence.[77–81] However, heroin prescription is a controversial approach to treatment because of the question of whether giving users the drug they are addicted to constitutes treatment at all. Nevertheless, in the short term, heroin prescription may be considered as an effective way to retain users in treatment who have a history of failing in other treatment settings, with consequent benefits in terms of reduced drug use, HIV-risk behavior, and crime, and better social reintegration.[82–84]

Behavioral Therapies and Retention

In the RCTs reviewed, only the behavioral therapy of Contingency Management (CM) showed promise as an intervention to increase retention in MAT for opiate dependence. Similarly, Gerra et al.'s quasi-experimental study (2011) found a higher retention rate in a CM condition.[67] In one of the RCTs, in China, participants in the CM condition drew for prizes on an escalating scale for having ingested methadone on each of the previous three days or having submitted a drug-free urine specimen; prizes ranged from very small to small monetary incentives (1 Yuan or 15 cents US, to 20 Yuan or $2.94 US).[45] In another RCT conducted in China, in the CM intervention, participants drew for prizes for seven consecutive days of taking methadone, on an escalating scale; prizes were vouchers that could be redeemed only to pay for treatment.[44] In the US, Dunn et al. (2012) found support for employment-based reinforcement of naltrexone adherence in terms of retention in MAT; in the CM condition, participants were required to ingest oral naltrexone under staff observation to gain access to a workplace where they could work and earn monetary vouchers.[46]

The efficacy of CM in terms of better retention and other treatment outcomes has also been established in studies of individuals dependent on stimulants or nicotine, with the benefits most apparent early in treatment.[85–88] Indeed, CM has relatively strong empirical support in the treatment of addictions, but even so, CM has had weak and uneven adoption in clinical practice.[89] The main barriers to use of CM are cost and ideology, such as beliefs by clinicians that CM does not address the underlying causes of addiction, or undermines a

patient's internal motivation for abstinence. These barriers have been addressed through the development of lower-cost adaptations as well as clinician trainings to address ideological concerns and make CM more community friendly.[89]

Other than Contingency Management, RCTs of behavioral therapies to increase retention failed to find differences between conditions. However, some of these studies may have been inadequately powered.[47,56] Nevertheless, the lack of efficacy for behavioral therapies tested provides consistency with the body of studies that failed to find additional medications for psychological conditions, such as depression, to be efficacious in increasing MAT retention for opiate dependence.

Limitations

The major limitation of this study is that we relied on only two databases, PubMed and CINAHL, for the search of the literature, and did not review gray literature (e.g., technical reports, conference proceedings) or unpublished studies of retention in MAT, which may be more likely to show no effect for interventions intended to improve retention. However, PubMed, a service of the US National Library of Medicine, provides access to MEDLINE, the NLM database of indexed citations and abstracts to medical, nursing, dental, health care, and preclinical sciences journal articles, and includes additional life sciences journals not in MEDLINE. We also selected only English-language articles, although there may be publications relevant to this review that are not in English. We used study design to indicate the methodological rigor of the studies reviewed, but did not report attrition rates by condition, or effect sizes pertaining to the strength of interventions. Future systematic reviews are needed to address the additional limitation that this study focused on medication and behavioral therapy factors related to retention in MAT for opiate addiction, to the exclusion of other factors such as patient determinants, and other outcomes such as abstinence and psychosocial functioning.

Conclusion

This systematic review covering the past five years of research on MAT retention by opiate-dependent individuals suggests a continued advantage for methadone over buprenorphine, although the implementation of buprenorphine at higher doses may overcome this difference. In addition, offering MAT with contingency management may be associated with higher retention rates. The methodological quality of the body of research on retention is good given the large number of investigations using RCT designs. However, it is critical to address longer-term associations between medications and behavioral therapies and outcomes of MAT such as retention.[90,91] Together, studies in this systematic review suggest that practices can be managed to increase the retention of opiate-dependent patients in medication-assisted treatments and ultimately improve their quality of life.

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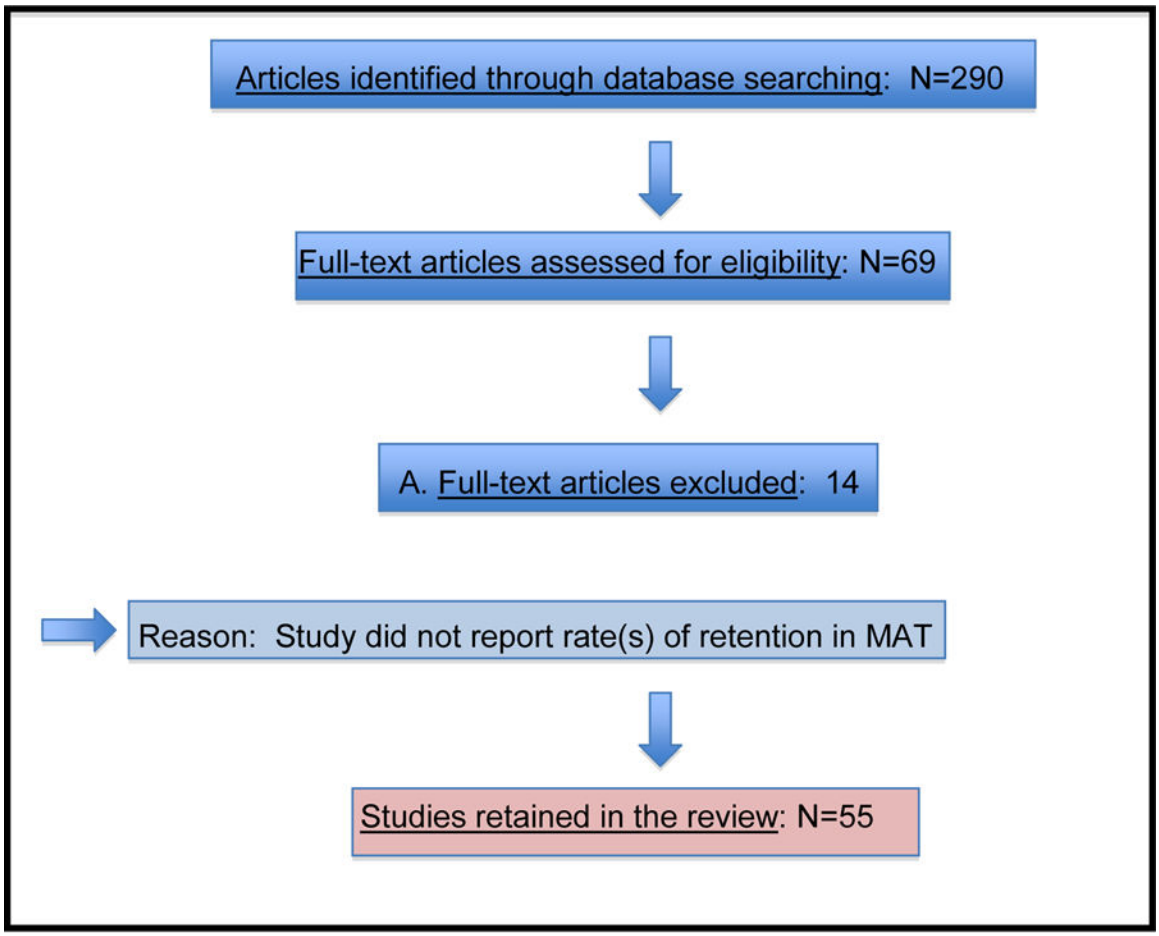

Figure 1.
Article selection process for retention in medication-assisted treatment for opioid dependence. (Adapted from "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement")

Table 1.

Summary of published randomized controlled trials on medication and behavioral therapies potentially associated with retention in medication-assisted treatment for opiate dependence (N=38 studies)

First author, year, country	Conditions	Sample N (% Male)	Medication	Retention outcome	Retention rate
Sigmon[21], 2013, USA	1 vs 2 vs 4 week taper; all received individual behavioral therapy (Community Reinforcement Approach)	Community, illicitly using prescription opioids; 70 (69.0)	BUP taper, then NTX	In MAT at 3 months	50.0% 4-week taper 21.0% 2-week taper 21.0% 1-week taper
Tiihonen[22], 2012 Russia	NTX implant vs placebo (P) implant	Polydrug dependent; 100 (not provided)	NTX	In MAT at 2.5 months	52.0% NTX, 28.0% P
Krupitsky[23], 2011, Russia	NTX vs P; all received counseling	<30 days of detox + abstinent at least 7 days; 250 (88.0)	NTX	Number of days in MAT up to 180	Med=168 NTX Med=96 P
Krupitsky[24], 2013, Russia	NTX+Guanfacine (G) vs NTX +GP vs NTXP+G vs NTXP+GP; all received counseling	Medically hospitalized; 301 (82.4)	NTX, G	In MAT at 6 months	26.7% NTX+G 19.7% NTX+GP 10.7% NTXP+G 6.7% NTXP+G NTX+G, NTX +GP> NTXP+G, NTXP+GP
Ling[25], 2010, USA	BUP vs P; all received counseling; 18 sites	In addiction treatment; 163 (68.7)	BUP	In MAT at 6 months	65.7% BUP 30.9% P
Ruger[26], 2012, Malaysia	P vs NTX vs BUP; all received counseling	Not provided; 126 (not provided)	BUP, NTX	In MAT at 6 months	15.4% P 20.9% NTX 40.9% BUP BUP>P,NTX
Lucas[27], 2010, USA	HIV clinical-based BUP vs case management plus referral to opioid treatment program	HIV+; 93 (72.0)	BUP, MET	In MAT at 12 Months	Rates not provided: BUP>referral
Saxon[28], 2013, USA	BUP vs MET; 8 sites	MAT seekers; 1,269 (not provided)	BUP, MET	In MAT at 4 months	Significance not reported: 45.9% BUP 73.9% MET
Woody[29], 2014, USA	MET vs BUP/NLX; 9 sites	MAT patients; 1,269 (67.8)	MET, BUP/NLX	In MAT at 6 months	74.0% MET 46.0% BUP
Potter[30], 2013, USA	MET vs BUP/NLX; 9 sites	MAT patients; 1,269 (67.8)	MET, BUP/NLX	In MAT at 6 months	Rates not provided: 57.6% overall; BUP<MET
Jones[31], 2010, USA, Austria, Canada	BUP vs MET: all received comprehensive care and contingency management; 7 sites	Pregnant women; 187 (0.0)	BUP, MET	In MAT at end of pregnancy	82.0% MET 67.0% BUP
Strang[32], 2010, England	Supervised injectable (inj) MET vs supervised inj heroin vs optimized oral MET; all patients had a case worker	Receiving oral MET but still injecting heroin; 127 (73.0)	MET, heroin	In MAT at 6.5 months	Significance not reported: 81.5% inj MET 88.0% inj heroin 69.0% oral MET

First author, year, country	Conditions	Sample N (% Male)	Medication	Retention outcome	Retention rate
Oviedo- Joekes[33], 2010, Canada	Inj diacetylmorphine or inj hydromorphine vs oral MET	Treatment refractory; 192 (61.4)	Inj diacetelyl- morphine, inj hydromorphine, MET	In MAT at 12 months	Aboriginals: 84.4% Inj 57.1% MET Non-Aboriginals 90.7% Inj 50.9% MET
Nosyk[34], 2010, Canada	Heroin-assisted treatment (HAT) vs MET	Treatment refractory; 251 (61.4)	HAT, MET	In MAT at 12 months	Rates not provided; Better in HAT vs MET
Eiroia- Orosa[35], 2010, Germany	HAT vs MET; all received psychosocial services	Treatment refractory or treatment dropouts; 1,015 (73.3)	Heroin, MET	In MAT at 12 months	Significance not reported: 67.2% HAT 40.0% MET
Otiashvili[36], 2013, Republic Of Georgia	MET vs BUP/NLX +dose taper+referral to treatment; all were offered individual and group counseling	Treatment settings; 80 (95.0)	MET, BUP/NLX	In MAT at 3 months	No difference: 85.0% overall
Neumann[37], 2013, USA	MET vs BUP/NLX	Chronic non-malignant pain patients; 54 (53.7)	MET, BUP/NLX	In MAT at 6 months	48.1% overall 46.4% MET 50.0% BUP/NLX
Oviedo-Joekes[38], 2010, Canada	Diacetylmorphine vs hydromorphone	Treatment-refractory; 140 (not provided)	Diacetylmorphine, hydromorphine	In MAT at 12 months	No difference: 87.8% Diacetyl 88.0% Hydromor
Amass[39], 2011, 10 European countries	Direct induction (DI) vs indirect induction (II)	In MAT; 187 (80.2)	BUP/NLX	In MAT at 1 month	No difference: 81.8% DI 80.8% II
Bisaga[40], 2011, USA	Memantine (M) 60 mg/day vs M 30 mg/day vs P; all received therapy	New to MAT; 81 (81.5)	NTX	In MAT at 3 months	No difference: 22.0% M-60 19.0% M-30 26.0% P
Stein[41], 2010, USA	Escitalopram (for depression) vs P; all received physician management	Depression symptoms; 147 (76.0)	BUP	In MAT at 3 months	No difference: 66.7% Escit 44.0% P
Oliveto[42], 2011, USA	Disulfiram vs P; all received cognitive behavioral therapy (CBT)	Cocaine dependent; 161 (55.9)	MET	In MAT at 3.5 months	No difference: Rates not provided; 64.8% overall
Liebschutz[43], 2014, USA	Detoxification (detox) vs facilitated linkage to treatment	Medically hospitalized, not seeking addiction treatment; 145 (71.2)	BUP/NLX	In MAT at 6 months	3.0% Detox 16.7% Linkage
Chen[44], 2013, China	MET+contingency management (CM) vs MET only	New to MAT; 246 (92.3)	MET	In MAT at 3 months	81.7% MET+CM 67.5% MET
Hser[45], 2011, China	CM vs usual care (UC)	MAT patients; 319 (76.2)	MET	In MAT at 3 months	81.0% CM 67.0% UC
Dunn[46], 2013, USA	CM vs prescription (take-home MAT)	Unemployed, in detox or on street; 67 (61.2)	NTX	In MAT at 6 months	54.0% CM 16.0% Prescrip
Holland[47], 2012, Scotland	Supervision: None vs 2 times per week vs daily	In MAT for 3 months at baseline; 60 (70.0)	MET	In MAT at 3 months	No difference: 94.1% None

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First author, year, country	Conditions	Sample N (% Male)	Medication	Retention outcome	Retention rate
					85.7% 2x wk 72.7% Daily
Chawarski[48], 2011, China	Daily medication (DM) vs DM plus weekly drug and HIV counseling (DM plus)	Heroin-dependent; 37 (81.0)	MET	In MAT at 6 months	No difference: 83.3% DM plus 76.2% DM
Jaffray[49], 2014, Scotland	Pharmacies randomized to intervention (pharmacists received motivational Interviewing [MI] training & resources) vs UC	Mainly unemployed; 76 pharmacies; 542 patients (63.6)	MET	In MAT at 6 months	No difference: 88% MI 81% UC
Marsch[50], 2013, USA	MAT+counseling vs MAT+reduced counseling+ web-based education	New to MAT; 160 (75.0)	MET	In MAT at 12 months	No difference: 38.7% overall
Schwartz[51], 2011, USA	Interim (daily administration +emergency counseling; counseling; I) vs standard (take-home administration +regular counseling; S) vs restored (S+counselor reduced caseload; R); 2 sites	New to MAT; 230 (70.0)	MET	In MAT at 4 months	No difference: 91.9% I 80.8% S 88.9% R
Schwartz[52], 2011, USA	I vs S vs R	On MAT program wait list; 230 (70.0)	MET	In MAT at 12 months	No difference: 60.6% I 54.8% S 37.0% R
Ling[53], 2013, USA	CBT vs CM vs CBT+CM vs no behavioral treatment	Community and treatment settings; 202 (69.3)	BUP	In behavioral treatment at 4 months	No difference: 71.7% CBT 69.4% CM 73.5% CBT +CM 64.7% None
Mitchell[54], 2013, USA	Outpatient (OP) counseling vs intensive outpatient (IOP) counseling	African-Americans starting MAT; 300 (62.3)	BUP	In MAT at 6 months	No difference: 58.7% OP 56.6% IOP
Ruetsch[55], 2012, USA	Telephone support (TS) vs vs UC (324 provider sites)	New to MAT; 1426 (59.0)	BUP	In MAT at 12 months	No difference: 55.0% TS 56.1% UC
Tetrault[56], 2012, USA	Physician management (PM) vs PM +enhanced medical management (EMM)	HIV+; 47 (83.0)	BUP/NLX	In MAT at 3 months	No difference: 80.0% PM 59% PI +EMM
Jones[57], 2011, USA	Helping (motivational enhancement therapy, education, case and contingency management) vs control (support group)	Non-treatment seeking partners of opioid-dependent pregnant women; 62 (100)	Detox plus aftercare or MET	Days of treatment (most commonly MAT), past month, up to 30	No difference: H; M=15.2 (SD=2.0) C; M=14.9 (SD=6.4)
Coviello[58], 2010, USA	NTX plus psychosocial treatment only; all were under judicial supervision	Offenders; 111 (82.0)	NTX	In treatment (MAT or psychosocial) at 6 months	No difference: 32.0% NTX 29.0% psychosoc

Note: Reported retention rates within studies are significantly different unless otherwise noted. BUP = buprenorphine, NTX = naltrexone, MET = methadone, NLX = naloxone; P = placebo, Med = median, inj = injectable, HAT = heroin-assisted treatment, CBT = cognitive behavioral therapy, I = interim, S= standard, R = restored, M = mean, SD = standard deviation

Table 2.

Summary of non-RCT published studies on treatment factors associated with retention in medication-assisted treatment for opiate dependence (N=17)

First author, year, country	Design	Sample N (% Male)	Medication	Retention outcome	Retention rate
Gryczynski[59], 2013, USA	Prospective cohort, MET vs BUP; secondary analysis of two RCTs	African-Americans entering MAT; 478 (65.2)	MET, BUP	In MAT at 6 months	78.1% MET 57.7% BUP
Pinto[60], 2010, England	Prospective cohort, MET vs BUP; all received care coordination	Requesting MAT; 361 (75.0)	MET, BUP	In MAT at 6 months	69.6% MET 42.5% BUP
Bounes[61], 2013, France	Prospective cohort	Treatment settings; 151 (74.0)	MET, BUP	In MAT at 12 months	78.0% MET 26.0% BUP
Serpelloni[62], 2013, Italy	Retrospective cohort (65 publicly-funded addiction treatment sites)	Patients in MAT in 2010; 8,145 (84.2)	MET, BUP	Days of stay during 2010	MET: M=246.2 (SD=110.1) BUP: M=240.5 (SD=111.7)
Hao[63], 2013, China	Prospective cohort, MET vs Jitai tablets; all received psychosocial counseling	Completed detox; 386 (84.4)	MET, Jitai tablets	In MAT at 12 months	85.0% MET 74.3% Jitai
Gryczynski[64], 2014, USA	Prospective cohort; secondary analysis of RCT studying counseling	African-Americans entering MAT; 297 (61.9)	BUP	In MAT at 6 months	57.9% overall; retention associated with higher BUP dose, especially early in treatment
Curcio[65], 2011, Italy	Quasi-experimental: MET vs BUP/NLX; 10 sites	Public outpatients; 3,812 (89.8)	MET, BUP/NLX	In MAT at 12 months	No difference: 92.5% MET 89.4% BUP/NLX
Miotto[66], 2012, USA	Quasi-experimental: opioid treatment program (OTP), individual counseling vs primary care (PC), brief counseling vs psychosocial program (PP) with group CBT	Community sample; 94 (58.0)	BUP/NLX	In MAT at 6 months	21.4% OTP 33.3% PC 54.5% PP
Gerra[67], 2011, Italy	Quasi- experimental: supervised daily (SD) vs CM vs non-contingent take-home (NT); all received psychosocial treatment; 3 sites	Heroin dependent; 300 (82.0)	MET	In MAT at 12 months	58.0% SD 74.0% CM 50.0% NT CM>SD, NT
Haddad[68], 2012, USA	Retrospective cohort; 2 health care sites	Patients in MAT in 2007–08; 266 (69.2)	BUP	In MAT at 12 months	61.6% overall; retention associated with during-MAT receipt of psychiatric medication and substance abuse counseling
Moore[69], 2012, USA	Quasi-experimental: PM+weekly dispensing vs PM+3 times per week dispensing+CBT	Primary care patients; 58 (74.1)	BUP/NLX	In MAT at 3 months	Marginal difference: 68.0% PM+CBT 87.0% PM
Winklbaur- Hausknost[70], 2012, Austria	Quasi-experimental: vouchers for attendance vs vouchers for attendance +drug free biological samples	Pregnant women in multidisciplinary care; 59 (0.0)	MET, BUP	In MAT at 1 month post-delivery	No difference: 22% attendance 10% attendance + samples
Coviello[92], 2012, USA	Prospective cohort; 5 sites	Offenders; 61 (92.0)	Extended release injectable NTX	In MAT at 6 months	40.0%
Fox[93], 2012, USA	Prospective cohort	HIV+82 (72.0)	BUP	In MAT at 6 months	56.0%

First author, year, country	Design	Sample N (% Male)	Medication	Retention outcome	Retention rate
Fiellin[94], 2011, USA	Prospective cohort	HIV+303 (67.7)	BUP/NLX	In MAT at 12 months	49.0%
Apelt[95], 2013, Germany	Prospective cohort	Patients who had received MAT then began BUP-NLX; 337 (76.6)	BUP/NLX	In MAT at 12 months	57.1% overall
Blanken[73], 2010, Netherlands	Prospective cohort; all received psychosocial, medical support	Positive responders to HAT; 149 (83.2)	MET plus heroin	In MAT at 4 years	55.7%

Note: Reported retention rates within studies are significantly different unless otherwise noted. BUP = buprenorphine, MET = methadone, NLX = naloxone,

NTX = naltrexone, HAT = heroin-assisted treatment