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Retention of participants in medication-assisted programs in low- and middle-income countries: an international systematic review

Jonathan Feelemyer[1], **Don Des Jarlais**[1], **Kamyar Arasteh**[1], **Abu S. Abdul-Quader**[2], and **Holly Hagan**[3]

[1]The Baron Edmond de Rothschild Chemical Dependency Institute, Beth Israel Medical Center, New York, NY, USA

[2]Global AIDS Program, Centers for Disease Control and Prevention, Atlanta, GA, USA

[3]College of Nursing, New York University, New York, NY, USA

Abstract

Background and aims—Medication-assisted treatment (MAT) is a key component in overdose prevention, reducing illicit opiate use and risk of blood-borne virus infection. By retaining participants in MAT programs for longer periods of time, more noticeable and permanent changes in drug use, risk behavior and quality of life can be achieved. Many studies have documented retention in MAT programs in high-income countries, using a 50% average 12-month follow-up retention rate as a marker for a successful MAT program. This study contributes to a systematic understanding of how successful programs have been in retaining participants in low- and middle-income countries (LMIC) over time.

Methods—Using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a systematic literature search to identify MAT program studies that documented changes in retention over time for participants in buprenorphine and methadone programs in LMIC. Retention was measured for participants by length of follow-up, type of MAT and treatment dosage.

Results—There were 58 MAT program studies, with 27 047 participants eligible for inclusion in the review. Overall average retention after 12 months was 54.3% [95% confidence interval (CI) = 46.2, 63.7%]. Overall average retention was moderately good for both buprenorphine (48.3%, 95% CI = 22.1, 74.6%) and methadone (56.6%, 95% CI = 45.9%, 67.3%) after 12 months of treatment. Among programs using methadone there was no statistically significant difference in average retention by dosage level, and the 10 highest and lowest dosage programs obtained similar average retention levels after 12 months.

Correspondence to: Jonathan Feelemyer, Beth Israel Medical Center, The Baron Edmond de Rothschild Chemical Dependency Institute, 160 Water Street, FL 24, New York, NY 10038, USA. jfeelemyer@chpnet.org, jfeelemyer@gmail.com.

Declaration of interests

None

Conclusion—Medication-assisted treatment programs in low- and middle-income countries achieve an average 50% retention rate after 12 months, with wide variation across programs but little difference between those using buprenorphine versus methadone.

Keywords

Buprenorphine; developing countries; low- and middle-income countries; methadone; opiate abuse; opiate substitution programs

INTRODUCTION

Currently, there are an estimated 230 million users of illicit drugs globally [1], of whom 16 million are classified as opiate users [2]. The prevalence of illicit opiate use in the general population ranges from 0.2% in southeast Europe and Africa to as high as 1.6% in eastern Europe [2]. There are multiple complications that arise from illicit opiate use including overdose, blood-borne infections such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV), increased crime, reductions in legal employment and lower overall quality of life [3–8].

Medication-assisted treatment (MAT), also referred to as opiate substitution treatment (OST), is a key component in overdose prevention, reducing illicit opiate use and risk of blood-borne virus infection [9,10]. Multiple studies have highlighted the success of MAT treatment in high-income countries, documenting reductions in relapse, overdose and associated risky drug use behaviors [9,11–14].

Retention in MAT programs is important for a number of reasons. MAT program studies have shown that longer retention times are associated with better stabilization of participants and increased levels of social rehabilitation [15,16]. A study by Ward *et al.* concluded that retention levels in MAT programs should average at least 50% after 12 months, and several MAT program studies have shown that 12-month average retention is associated with significant reductions in heroin use and crime [10,17]. Additionally, the World Health Organization (WHO) has put into place specific guidelines for dosage levels of MAT programs, with recommendations that include a minimum of 60 mg of methadone or 2 mg of buprenorphine per day.

While there have been many successful MAT programs in high-income countries dating back to the early 1970s [18,19], expansion of these services in low- and middle-income countries (LMIC) has proved to be much more challenging [20,21].

There are many reasons why MAT treatment availability in LMIC has lagged behind high-income countries; MAT treatment is still illegal or highly restricted in some LMIC [22]; and many physicians are reluctant to prescribe MAT treatment to drug users even where laws and policies permit this [23]. There is a shortage of physicians and clinicians in LMIC who can adequately care for and treat opiate users with MAT treatments [24]. In many LMIC, there is a lack of practice guidelines governing the use of MAT; this can lead to very different prescribing patterns and dosing of MAT treatments to participants [24]. Finally, the cost of

MAT treatment, particularly buprenorphine, can be very expensive in LMIC, leading to shorter durations of MAT treatment along with lower doses [25,26].

In many LMIC detoxification has been the conventional approach for drug users who wish to discontinue or reduce drug use [27]. However, in recent years there has been expansion and adoption of MAT treatment in LMIC in an effort to reduce drug withdrawal and relapse [20]. China, Indonesia and Iran are examples of countries that have expanded MAT treatment to drug users in the last 5–10 years [28–31].

The aim of this review is to measure retention among participants in MAT programs in LMIC by examining average retention longitudinally by type of opiate substitution drug (methadone versus buprenorphine) and by the mean dosage of the MAT given to participants. The goal is to establish if LMIC, given more limited resources, have achieved at least 50% average retention among MAT participants after 12 months of treatment.

METHODS

Search strategies

The literature search we conducted for this review utilized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28,32]. Studies of MAT programs were selected systematically from several sources, including PubMed, EMBASE, NLM Gateway and abstracts from International AIDS Society (IAS) 2000–2012 and International Harm Reduction Association (IHRA) 2000–2012 conferences. The search included all published studies from 1 January 2000 to 30 September 2012 and all conference abstracts published after 1 January 2000. We also searched references from review papers regarding drug-using populations for any country designated as an LMIC. Figure 1 presents the search terminology used to identify potentially eligible studies.

Study selection and eligibility criteria

In order for a MAT program study to be included in the review there had to be documentation of implementation or ongoing MAT treatment in a sample of drug users, with longitudinal measurements of average retention among MAT participants. We excluded any MAT program study that did not utilize buprenorphine or methadone for their MAT pharmacological treatment, or MAT program studies that only included participants or individuals from prison or institutionalized settings. Locations were restricted to countries that fitted the LMIC designation defined by the World Bank [33]; all high-income location MAT program studies were excluded unless they also included a separate analysis of an LMIC-located MAT program.

We included both MAT program studies with drug users who injected and those who did not inject. While we recognize that many drug users who use opiates inject, there are many locations where other routes of administration of opiates persist, such as smoking or snorting [34–36]. Thus, we chose to include all drug-user routes of administration, rather than restrict simply to people who inject drugs (PWID). This was especially important, as the participants in MAT programs were often not separated by or asked about their drug route of administration.

Data extraction

A standardized coding form was developed to abstract pertinent information for each MAT program study. Information collected included demographics of the drug-using population, study design characteristics of the MAT program, including location and services offered, and information related to average retention of participants over time. Each study was assigned a reference ID number after completion of coding. A sampling of all coding forms completed by the reviewer was checked for accuracy and quality by a second reviewer (H.H.) before finalization. Data were extracted from each coding form and entered into a database in order to obtain retention values for each of the included MAT program studies.

Assessment of risk of bias in studies

A quality check was performed to document the strengths and weaknesses of each of the studies; items in the quality checklist included recruitment method, comparability in loss to follow-up and retained participants and controlling for potential confounders that could affect the association between MAT treatments and retention in the MAT programs, such as antiretroviral treatment for HIV-positive individuals or needle exchange. This checklist was modified from quality checklists for primary studies put together by the Cochrane Collaboration of systematic reviews [37].

Data analysis

The individual average retention values for each MAT program study were pooled to derive weighted measures of results longitudinally by MAT type and by mean dosage. MAT type was divided into two categories of MAT pharmacological substance: methadone and buprenorphine.

Following MAT analysis, we then analyzed average retention by mean dosage level of MAT in each program. Dosage values were assigned a value of 1–4, where level 1 was designated as dosages inclusive of the 25th percentile and below, level 2 dosage was between the 26th inclusive of the 50th percentile, level 3 dosage was between the 51st percentile inclusive of the 75th percentile and level 4 was designated for any dosage above the 75th percentile up to the maximum dosage given in an individual MAT program study. Table 1 shows the cut-points for each of the different dosage levels. We weighed average retention values using random effects. I^2, a test traditionally used in meta-analysis and systematic reviews, was used to assess heterogeneity among the MAT program studies. Stata 12 was used for all data analysis using a random effects model based on the Der Simonian & Laird method [38].

To provide a check on the extreme dosage values for methadone, we examined retention for the 10 highest and 10 lowest methadone dose MAT program studies to determine if there was a statistically significant difference in average retention over time for those MAT program studies at the extreme high and low dosage levels. This examination was performed as we believed it was the most likely factor that would affect the retention of participants in the MAT programs.

RESULTS

Search results

Figure 2 shows the PRISMA diagram for the searching and screening that led to the final number of MAT program studies included in this review. The search included all published studies from 1 January 2000 to 30 September 2012 and all conference abstracts published after 1 January 2000. Searching identified 3090 paper titles. Two papers were published in languages other than English and could not be obtained, and a further 23 duplicate papers were excluded. We then screened 3065 abstracts against the inclusion criteria and retrieved 177 full text papers for further screening. Of the papers and reports retrieved, 58 met all criteria for inclusion and were coded for our review. These 58 MAT program studies described 85 different MAT samples, with 27 047 participants from 12 different countries. (Some MAT program studies presented data separately for two or more different samples in the same paper.)

The primary reasons for exclusion of abstracts or full text papers included: the sample came from a prison or institutionalized setting; the MAT program was conducted in a high-income location; or there was no use of a MAT pharmacological treatment. Additionally, studies had to report retention over time; cross-sectional MAT program studies were excluded from this review. The majority of the MAT program studies were time–series cross-sectional, prospective cohorts or before and after studies.

Retention by MAT type

Overall average retention was 54.3% [95% confidence interval (CI) = 46.2%, 63.7%]. Programs with longer duration of follow-up (greater than 24 months) reported 74.5% average retention or greater among MAT participants regardless of the type of MAT used (however, a small number of studies measured follow-up for longer than 12 months).

Figures 3 and 4 show average retention rates over a 12-month follow-up period for buprenorphine and methadone MAT program participants, measuring average retention for participants at 3, 6 and 12 months of follow-up. Retention was measured at each time-point by the number of participants still in the program from the initial group of participants at the start of the retention measurement period. The overall weighted average retention in programs using buprenorphine was 74.5% at 3 months (95% CI = 67.2%, 81.9%), 69.2% at 6 months (95% CI = 62.5%, 75.9%) and 48.3% at 12 months (95% CI = 22.1%, 74.6%). For programs using methadone, average retention was 77.7% at 3 months (95% CI = 70.7%, 84.7%), 71.7% at 6 months (95% CI = 63.7%, 79.6%) and 56.6% at 12 months (95% CI = 45.9%, 67.3%).

There was high heterogeneity among studies; overall heterogeneity was 99.1% for 3-month average retention, 98.9% for 6-month average retention and 98.6% for 12-month average retention.

Retention analysis by dosage

There were 39 MAT program studies in the review that reported mean dosage. These 39 studies were divided into separate categories based on dosage of methadone or buprenorphine. Mean values were calculated for each MAT substance and then divided into percentiles: dosage 1 covered the 25th percentile, dosage 2 included the 26–50th percentiles inclusively, dosage 3 included the 51–75th percentiles inclusively and dosage 4 included dosages above the 75th percentile. The mean dosages for methadone and buprenorphine were 56.2 and 4.2 mg, respectively.

Table 1 gives average retention rates and dosage values for each percentile category. There was no statistically significant difference noted between dosage levels and pooled average retention values in MAT programs at 3, 6 or 12 months.

Among the 10 lowest methadone dosage MAT program studies the mean methadone dose was 42.5 mg, while among the 10 highest methadone dosage MAT program studies the mean methadone dose was 75.6 mg. In both high- and low-dose MAT program studies, average retention values were slightly higher for the low-dose MAT programs, but the difference between the two dosage levels did not reach statistical significance (see Table 2). The complete list of studies included in the calculation of these pooled retention values are given in Tables 3 and 4.

Risk of bias among included MAT program studies

There were eight MAT program studies that did not recruit or include a systematic sampling of participants from their MAT programs or did not include 100% of the MAT participants who visited the MAT program [39–46]. Thirty-one MAT program studies did not adequately compare demographics of follow-up participants to those who did not remain in the MAT programs [25,39–42,44–69]. Nineteen MAT program studies did not control adequately for confounders that could affect the retention levels seen in the individual MAT programs [15,47–53,56,60,62,65,67–73].

DISCUSSSION

There have been numerous systematic reviews and studies to assess average retention in MAT programs that focus primarily on high-income countries [9,74]; however, due to the relative recency of MAT programs in many LMIC, there has not been a systematic review to assess retention in those newer programs that have been developed in the last 10–15 years. We believe this review provides important data on retaining participants in MAT programs in LMIC.

With overall pooled 12-month average retention rates as high 54.3%, coupled with average retention rates of 57% among methadone programs and 48% among buprenorphine programs after 12 months, MAT programs in LMIC, as a whole, surpass the overall 50% average retention rate after 12 months. Our pooled average retention values are similar to studies evaluating MAT program retention in high-income locations such as Switzerland [75] and Germany [76], where average retention values among participants after 12 months ranged from 40 to 50%. While there has not been an extensive number of studies in LMIC

that measured retention for longer than 12 months, the studies that were included that examined retention at 24–48 months of follow-up reported similar average retention values to those seen in the first 12 months of follow-up. While more studies will be needed to verify retention over longer periods of time, these early studies show promising results among participants being retained in MAT in LMIC. We examined the studies with longer follow-up periods to determine if there were any factors unique to those studies, but we were unable to locate any systematic factor that could contribute to these retention values. As different programs documented retention values for the 24- and 48-month follow-up periods compared to studies that evaluated 12 months or less of follow-up time, there were no studies that saw a decrease in retention in the first 12 months and then an increase in retention following 12 months. All studies saw retention values decrease over time, regardless of the follow-up period.

Retention over time in a MAT program is an integral part of harm reduction. Through the continued interaction between clients and staff, supervision of medication regimens and the monitoring of overall health status of participants, MAT programs can reduce drug use and risky behaviors significantly [15,16]. In addition, retention in MAT programs has been associated with higher rates of antiretroviral treatment (ART) initiation for HIV-positive drug users, better ART adherence and higher levels of virological response [77,78]. Finally, with prolonged MAT, overdose and relapse are reduced significantly and, over time, many drug users are able to discontinue illicit drug use permanently [17].

Working collaboratively with government and policy officials is paramount to ensuring the success of MAT programs in LMIC. Although MAT programs have gained wide acceptance in many high-income countries, there still exists political as well as considerable cultural opposition to treatment with pharmacological substances for people with substance use disorders in LMIC [22]. However, as we were able to document 58 studies in this review evaluating MAT programs in LMIC, there is growing evidence of acceptance of these treatment methods, especially in locations that have large numbers of opiate users, such as China, the Republic of Georgia, India, Indonesia, Iran, Malaysia, Thailand, Ukraine and Vietnam [79]. This is especially important given that WHO has recognized the lack of MAT programs in LMIC and the need for these programs to be implemented in the developing world [80].

Many of the countries represented here did not implement MAT into their harm reduction programs until the early 2000s, and many locations have implemented MAT treatment only in the last 5 years. It is likely that the success of MAT programs in LMIC have built upon the knowledge gained from the decades of treatment in many high-income countries. By adapting successful strategies that work from established programs, new MAT programs have the potential to be more successful than earlier programs that did not have the benefit of the knowledge from previous established programs.

Limitations

Our study has several limitations that should be noted. There was variation in the MAT program study designs; some studies utilized time–series cross-sectional, prospective cohorts and before-and-after studies. While a prospective cohort design would be ideal for

this type of descriptive analysis, we were unable to convert the data from the other study designs into prospective cohorts. Not all programs that used methadone or buprenorphine used the same dosage of MAT treatment. While the majority of MAT program studies used WHO guidance for minimum dosing of MAT treatment [81], there was variation in treatments above and below that minimum level. Indeed, while WHO recommends a minimum of 60 mg of methadone and 2 mg of buprenorphine, treatment dosages ranged from 27.7 to 104.3 mg for methadone and 1 to 9.3 mg for buprenorphine in the studies included in this review. Among buprenorphine program studies that recorded the dosage used among participants, 70% used a therapeutic level, while 67% of methadone program studies that recorded the dosages used a therapeutic level. However, even with lower than optimal dosage of MAT treatments, pooled average retention in programs remained above 50% after 12 months. Because a 50% average retention minimum has been established as necessary for a successful MAT program [17], most LMIC have been able to achieve success in average retention over time among MAT participants.

There was great heterogeneity in the average retention rates among the programs in this review, and caution must be used in interpreting the summary average retention rates. Mean medication dosage did not explain any of the heterogeneity. There are many additional factors, such as eligibility criteria, staff training, services offered in addition to medication, frequency of required clinic attendance and program discharge policies that might explain some of the heterogeneity, but we were not able to examine these. We also attempted to examine if there was any relationship to country and heterogeneity, but did not find any trends based on study location. Finally, while we would like to have examined the studies in relationship to the time-period of study, given the narrow nature of the study years (MAT treatment has only recently been introduced in many LMIC), there was not enough variation to warrant a separate analysis of this factor.

The studies included in the review come from a diverse set of locations within each country that was examined. As many of the studies took place at the province or the city level, they may not be representative of the coverage of MAT services in the country as a whole. It will be important in future, as expansion of MAT services continue in LMIC, to monitor coverage and identify gaps in locations where there are high numbers of opiate users in need of treatment.

In many countries, there are local social conventions and other factors that could potentially affect the rates of retention of MAT participants over time, in addition to alternative services to treat opiate use, including acupuncture [82] and herbal medications that have been used extensively in Asia [83,84]. As many treatment programs offer additional services beyond medically assisted treatment, these services could have certainly contributed to some of the higher retention values seen in some of the studies. However, as the majority of studies did not factor these additional services into the retention values documented, we were not able to examine the additional services as a factor of the retention values seen as part of this meta-analysis. Additional research will be needed to explain more clearly the heterogeneity in retention rates.

CONCLUSIONS

This study has documented levels of average retention after 12 months among MAT program participants in LMIC that are comparable to average retention rates seen among MAT participants in high-income countries [78,85]. These average retention values are very promising, given that MAT programs have been implemented only recently or have been in operation for short periods of time in many LMIC, with some countries implementing programs only in the last 10 years. Moving forward, the knowledge gained in these pilot and early implementation programs in LMIC should only help to increase average retention while decreasing drug use and risky behaviors over time in future programs.

It remains crucial that lawmakers, policymakers and researchers work collaboratively with law enforcement and other authorities to ensure that these programs can exist with minimal interference, and that proper funding from government and non-governmental organizations can be obtained. Finally, it is important that locations with high levels of heroin and opium use are staffed with clinicians and physicians trained to work with and prescribe MAT treatment, as the lack of trained clinicians remains one of the biggest obstacles to implementing programs in many locations.

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("Medication Adherence" OR "Medication Adherence/ethnology" OR "Medication Adherence/psychology" OR "Medication Adherence/statistics and numerical data" OR “Adherence” OR “Retention” OR "Viral Load" OR "Treatment Failure" OR "Patient Compliance/drug effects" OR "Patient Compliance/statistics and numerical data" OR "Directly Observed Therapy" OR "Drug Combinations" OR "Drug Therapy, Combination" OR "Treatment Outcome" OR “Compliance” OR "Self Administration" OR "Medication Therapy Management" OR “QOL” OR “QALY” OR “Relapse” OR “Overdose” OR “Methadone compliance”)
AND
("Buprenorphine/administration and dosage" OR "Buprenorphine/adverse effects" OR "Buprenorphine/analogs and derivatives" OR "Buprenorphine/antagonists and inhibitors" OR "Buprenorphine/contraindications" OR "Buprenorphine/diagnostic use" OR "Buprenorphine/immunology" OR "Buprenorphine/supply and distribution" OR "Buprenorphine/therapeutic use" OR "Buprenorphine/toxicity" OR "Buprenorphine/urine" OR "Methadone/administration and dosage" OR "Methadone/adverse effects" OR "Methadone/analogs and derivatives" OR "Methadone/analysis" OR "Methadone/antagonists and inhibitors" OR "Methadone/contraindications" OR "Methadone/diagnostic use" OR "Methadone/metabolism" OR "Methadone/supply and distribution" OR "Methadone/therapeutic use" OR "Methadone/therapy" OR "Methadone/toxicity" OR "Methadone/urine" OR "Opiate Substitution Treatment" OR “Methadone” or “Buprenorphine” OR ”Subutex” OR “Suboxone” OR “Drug Therapy" OR "HIV Infections/drug therapy" OR “Symoron” OR “Dolophine” OR “Amidone” OR “Methadose” OR “Physeptone” OR “Heptadon” OR “Temgesic” OR “Buprenex” OR “Buprenex”)
AND
("Substance-Related Disorders" OR "Substance Abuse, Intravenous" OR "Substance Abuse Detection")
NOT
("United States" OR "Canada" OR "London" OR "Great Britain" OR "Scotland" OR "Australia" OR "Germany" OR "Japan" OR "France" OR "Greece" OR "Italy" OR "Spain" OR "Poland" OR "Austria" OR "Netherlands" OR "Ireland" OR "Northern Ireland" OR "Belgium" OR "Switzerland" OR "Portugal" OR "Denmark" OR "United States" OR "Canada" OR "London" OR "Great Britain" OR "Scotland" OR "Australia" OR "Germany" OR "Japan" OR "France" OR "Greece" OR "Italy" OR "Spain" OR "Poland" OR "Austria" OR "Netherlands" OR “Ireland" OR "Northern Ireland" OR "Belgium" OR "Switzerland" OR "Portugal" OR "Denmark")

Figure 1.
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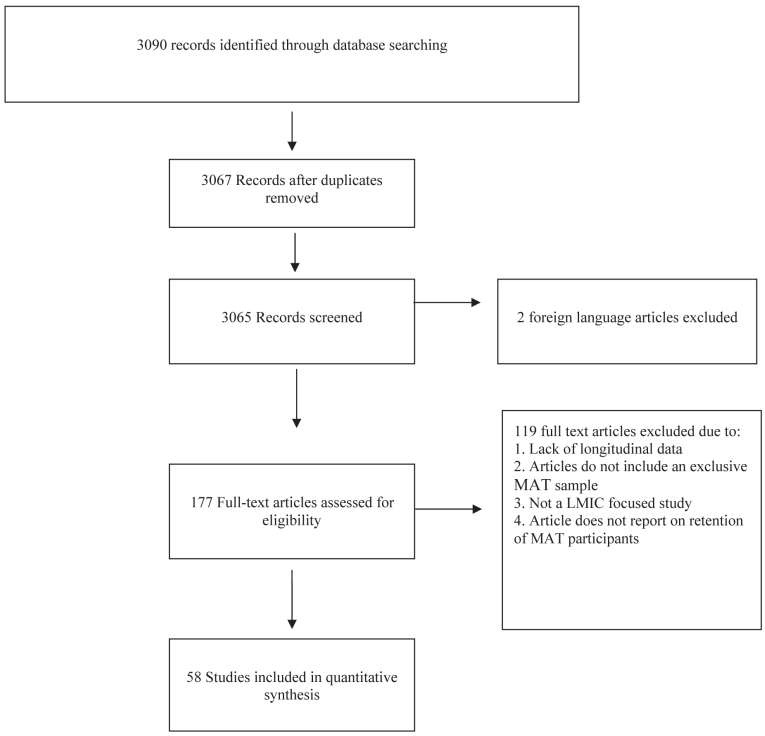

Figure 2.
lowchart of literature search review for review

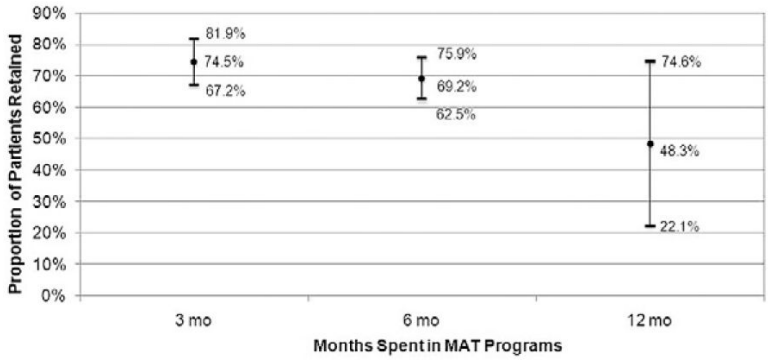

Figure 3.

Pooled buprenorphine retention (with 95% confidence interval) over 12 months for low- and middle-income countries (LMIC) medication-assisted treatment (MAT) participants

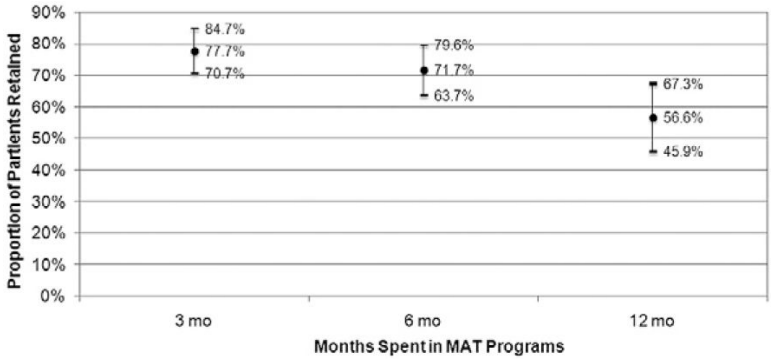

Figure 4.

Pooled methadone retention (with 95% confidence interval) over 12 months for low- and middle-income countries (LMIC) medication-assisted treatment (MAT) participants

Table 1

Pooled retention by dosage of medication-assisted treatment (MAT) and length of follow-up period.

		Retention (%)	Lower 95% CI	Upper 95% CI
Dose 1				
3 months	Methadone:	88.2	78.5	98.0
6 months	27.7–45.5 mg	69.5	49.8	89.1
12 months	Buprenorphine: 1.0–2.0 mg	56.3	54.4	58.2
Dose 2				
3 months	Methadone:	74.8	55.3	94.2
6 months	45.6–52.2 mg	67.9	59.5	76.4
12 months	Buprenorphine: 2.1–4.0 mg	*a*	*a*	*a*
Dose 3				
3 months	Methadone:	77.5	66.2	88.9
6 months	52.3–62.5 mg	71.2	56.9	85.6
12 months	Buprenorphine: 4.1–5.2 mg	44.4	16.2	72.7
Dose 4				
3 months	Methadone:	81.3	69.0	93.6
6 months	≤62.6 mg	69.1	51.1	87.1
12 months	Buprenorphine: ≤5.3 mg	64.0	41.6	86.3

[a]Insufficient primary data available for pooled analysis at this dosage 12-month follow-up for dose 2. CI = confidence interval.

Table 2

Pooled retention values for 10 highest and lowest methadone dosage medication-assisted treatment (MAT) programme studies.

Pooled methadone retention for MAT participants by length of follow-up				
		Retention (%)	**Lower 95% CI**	**Upper 95% CI**
Low dose				
3 months (*n* = 257)	Methadone	80.3	64.9	95.7
6 months (*n* = 939)	(average dose):	79.6	64.6	94.5
12 months (*n* = 2665)	42.5 mg	49.6	36.3	63.0
High dose				
3 months (*n* = 100)	Methadone	79.2	61.5	96.9
6 months (*n* = 127)	(average dose):	62.1	36.7	87.4
12 months (*n* = 243)	75.6 mg	47.0	25.5	68.5

CI = confidence interval

Table 3

Cohort studies including buprenorphine medication-assisted treatment (MAT) treatment in low- and middle-income countries (LMIC).

Study	Location	Study year	Length of follow-up (months)	Recruitment type	Sample size (n)	Dosage	Retention
Ahmadi 2002 [52]	Shiraz City, Iran	2001	6	Systematic	513	1.0 mg	33.9%
						3.0 mg	64.3%
						8.0 mg	80.1%
Ahmadi 2002 [47]	Shiraz City, Iran	2001	4	Systematic	180	1.0 mg	29.3 %
						2.0 mg	46.2%
						4.0 mg	68.3%
Ahmadi 2002 [49]	Shiraz City, Iran	2001	4	Systematic	330	1.0 mg	47.3 %
						2.0 mg	58.2%
						4.0 mg	70.9%
Ahmadi 2002 [86] [49]	Shiraz City, Iran	2001	4	Systematic	420	1.0 mg	45.7 %
						2.0 mg	55.7%
						4.0 mg	62.8%
Ahmadi 2003 [50]	Shiraz City, Iran	2001	3	Systematic	123	1.0 mg	29.3%
						3.0 mg	46.3%
						8.0 mg	68.3%
Ahmadi 2003 [53]	Shiraz City, Iran	2002	3	Systematic	36	4.0 mg	58.3%
Amstrong 2010 [39]	Manipu and Nagaland India	2006–2007	12	Systematic	2569	*	50.8%
Bruce 2007 [25]	Multicenter, Ukraine	2005–2006	6	Convenience	207	9.3 mg	75.0%
Chawarski 2008 [87]	Muar, Malaysia	2006	3	Convenience	24	8.0 mg	92.0%
Dorabjee 1998 [56]	New Delhi, India	1995–1998	36	Convenience	1611	4.0 mg	61.8%
Dvoriak 2008 [58]	Kherson and Kiev, Ukraine	2004–2004	6	Convenience	1129	6.3 mg	66.0%
Kermode 2011 [59]	Manipur and Nagaland India	2006–2007	18	Convenience	1744	*	65.0%
Lawrinson 2008 [15]	Multicenter, Ukraine	2005	6	Convenience	72	8.4 mg	74.0%
Schaub 2009 [88]	Multicenter, Ukraine	2008–2009	6	Convenience	151	5.0 mg	79.5%
Schaub 2010 [89]	Multicenter, Ukraine	2008	6	Convenience	140	5.0 mg	84.0%
Schottenfeld 2008 [73]	Muar, Malaysia	2005–2006	12	Convenience	44	5.0 mg	14.0%
Yadav 2012 [46]	Multicenter, India	2011	6	Convenience	458	5.2 mg	45.0%

* Dosage of pharmacological treatment was not available

Table 4

Cohort studies including methadone medication-assisted treatment (MAT) treatment in low- and middle-income countries (LMIC).

Study	Location	Study year(s)	Length of follow-up (months)	Recruitment type	Sample size (n)	Dosage	Retention
Ahmadi 2003 [50]	Shiraz City, Iran	2001	4	Convenience	41	30.0 mg	61.0%
Ahmadi 2003 [51]	Shiraz City, Iran	2001	3	Convenience	204	50.0 mg	23.5%
Ahmadi 2003 [53]	Shiraz City, Iran	2002–2002	3	Convenience	36	40.0 mg	83.3%
Cao 2012 [70]	Multicenter, China	2004–2010	72	Convenience	72	60.0 mg	64.3%
Chawarski 2011 [90]	Wuhan, China	2006	3	Systematic	17	45.0 mg	80.0%
Che 2010 [91]	Yunnan Province, China	2008–2009	6	Systematic	218	50.0 mg	57.0%
Chen 2011 [92]	Multicenter, Taiwan	2007–2008	18	Systematic	1533	70.0 mg	28.6%
Chen 2012 [93]	Multicenter, Taiwan	2009	3	Systematic	334	*a*	38.0%
Chen 20127 [94]	Quangdong Province, China	2010–2011	3	Systematic	74	54.5 mg	70.3%
Diah 2005 [54]	Bali and Jakarta, Indonesia	2003–2004	3	Convenience	100	*a*	100%
Dolan 2011 [55]	Tehran, Iran	2007–2008	12	Convenience	97	67.0 mg	41.2%
Duo 2011 [57]	Yunnan, China	2008–2009	6	Convenience	1129	*a*	79.0%
Dvoriak 2012 [40]	Multicenter, Ukraine	2011–2011	24	Convenience	300	*a*	88.5%
Ganjgahi 2010 [41]	Tehran, Iran	2010	3	Convenience	266	*a*	30.0%
Gu 2012 [71]	Guzngzhou, China	2010	6	Convenience	158	*a*	51.3%
He 2011 [95]	Gunagdong China	2009	6	Convenience	516	44.4 mg	55.2%
Hser 2011 [96]	Shanghai, China	2009–2010	6	Systematic	160	51.0 mg	60.3%
Hser 2012 [97]	Shanghai China	2009–2010	3	Systematic	100	51.0 mg	94.0%
Khodabandeh 2012 [60]	Multicenter, Iran	2010–2011	24	Convenience	300	80.0 mg	74.0%
Lambdin 2012 [61]	Dar el Salaam, Tanzania	2010–2011	12	Convenience	289	*a*	78.0%
Lawrinson 2008 [15]	Multicenter, China	2005	6	Convenience	102	44.5 mg	88.0%
	Multicenter, Iran	2005	6	Convenience	101	46.1 mg	85.0%
	Multicenter, Indonesia	2005	6	Convenience	127	65.8 mg	69.0%
	Multicenter, Lithuania	2005	6	Convenience	102	52.4 mg	74.0%
	Multicenter, Thailand	2005	6	Convenience	118	27.7 mg	85.0%
Li 2011 [98]	Yunnan, China	2008–2009	6	Convenience	168	60.6 mg	100%
Li 2012 [99]	Sichuan, China	2009–2011	24	Convenience	89	59.6 mg	91.0%
		2009–2011	9	Convenience	89	60.0 mg	92.1%
Liu 2009 [42]	Guizhou, China	2007–2008	14	Convenience	1003	38.0 mg	57.4%
Liu 2012 [100]	Ruili, China	2005–2009	48	Convenience	1878	*a*	70.0%
Lua 2012 [62]	Terengganu, Malaysia	2009–2010	12	Convenience	75	64.7 mg	76.0%
Mohamad 2010 [72]	Kelantan, Malaysia	2007	6	Convenience	64	57.2 mg	54.7%
Mokri 2004 [63]	Tehran, Iran	2002	3	Convenience	100	93.0 mg	80.0%
Moszynski 2011 [64]	Multicenter, Afghanistan	2010–2011	12	Convenience	71	90.0 mg	74.5%
Musa 2011 [65]	Pahang, Malaysia	2007–2009	24	Convenience	107	*a*	62.6%
Ngmansun 2010 [66]	Quatre Bornes, Maruitas	2006–1010	48	Convenience	2000	*a*	91.0%
Padaiga 2007 [101]	Multicenter, Lithuania	2004	6	Convenience	102	52.0 mg	69.6%

Study	Location	Study year(s)	Length of follow-up (months)	Recruitment type	Sample size (n)	Dosage	Retention
Pang 2007 [102]	Multicenter, China	2004–2005	12	Convenience	1662	44.9 mg	55.6%
Ruan 2007 [103]	Southeastern China	2002–2005	36	Convenience	333	*a*	70.2%
Sarasvita 2005 [68]	Jakarta, Indonesia	2003–2004	18	Convenience	209	*a*	57.0%
Sarasvita 2012 [67]	Jakarta, Indonesia	2006–2008	18	Convenience	178	76.9 mg	61.3%
Shabadal 2012 [43]	Kabul, Afghanistan	2010–2011	18	Convenience	200	*a*	25.5%
Shi 2007 [44]	Beijing, China	2006	6	Convenience	102	44.7 mg	85.0%
Subata 1999 [45]	Multicenter, Krygystan	2002–2005	48	Convenience	152	63.0 mg	60.0%
Todadze 2011 [104]	Tbilisi, Georgia	2005–2007	18	Convenience	30	*a*	100%
Tran 2012 [105]	Hai Pohng & Ho Chi Minh, Vietnam	2008–2010	24	Convenience	965	*a*	70.0%
Tran 2012 [2] [69]	Hai Pohng & Ho Chi Minh, Vietnam	2009–2009	9	Convenience	370	104.3 mg	98.1%
Vanichseni 1991 [106]	Bagkok Thailand	1990	1	Convenience	120	47.0 mg	75.8%
Verachai 1998 [107]	Thanyarak, Thailand	1990–1996	72	Convenience	195	61.9 mg	17.0%
Wang 2012 [108]	Southern Vietnam	2007–2008	18	Convenience	368	*a*	20.1%
Xiao 2010 [109]	Xi’an, China	2006	3	Convenience	172	*a*	82.6%

[a]Dosage of pharmacological treatment was not available.