

Associated Factors of Maintenance in Patients under Treatment with Methadone: A Comprehensive Systematic Review and Meta-Analysis

Farzaneh Farmani MSc¹, Hadi Farhadi PhD², Younes Mohammadi PhD³

Review Article

Abstract

Background: This comprehensive systematic review and meta-analysis were performed to assess the associated factors of maintenance in patients with methadone therapy in the world.

Methods: A systematic literature review was performed from several scientific databases; these include PubMed, Scopus, ISI Web of Science, and MEDLINE. We searched the following keywords: "Methadone", "Maintenance", "Retention", "Meta-analysis" and "Associated factors". Data were selected based on the inclusion and exclusion criteria. The purpose of this study was to assess the associated factors of maintenance in patients under treatment with methadone by an overall effect size, odds ratio (OR) [95% confidence interval (CI)] using meta-analysis.

Findings: We selected 24 researches out of 94413 for our study based on the inclusion and exclusion criteria for systematic review and meta-analysis. The pooled recognized five significant positive associations of age, marital status, employment status, gender, and length of treatment with methadone usage (OR age = 3.566, 95% CI = 3.296-3.836, $P < 0.001$; OR marital status = 1.101, 95% CI = 1.028-1.175, $P = 0.025$; OR employment = 1.157, 95% CI = 1.060-1.254, $P = 0.015$; OR gender = 4.686, 95% CI = 4.434-4.939, $P < 0.001$; OR duration of treatment = 1.543, 95% CI = 1.443-1.647, $P < 0.001$; respectively). However, education and injection status showed a non-significant positive association with methadone usage (OR education level = 1.279, 95% CI = 0.976-1.583, $P = 0.266$; OR injection status = 1.205, 95% CI = 0.725-1.658, $P = 0.442$).

Conclusion: This systematic-review and meta-analysis study displayed that factors such as age, marital and employment status, gender, and duration of treatment are effective on maintenance in patients under treatment of methadone.

Keywords: Methadone; Maintenance; Associated factors; Meta-analysis

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1- MSc Student, Department of Psychology, School of Educational Sciences and Psychology, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran

2- Assistant Professor, Department of Psychology, School of Educational Sciences and Psychology, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran

3- Assistant Professor, Modeling of Noncommunicable Diseases Research Center AND Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran

Correspondence to: Hadi Farhadi PhD, Email: farhadihadi@yahoo.com

Introduction

The illicit opioids use continues to present a problem both at the individual and societal levels.¹ Increased tolerance and continued use despite personal and social problems can be named as characteristics of opioid use disorder, as well as withdrawal and tolerance among other behavioral changes;² furthermore, increased human immunodeficiency virus (HIV) risk and susceptibility to other opportunistic infections such as hepatitis C and tuberculosis (TB) has been associated with opioid use,³ as well as infection,⁴ medical and psychiatric comorbidity,⁵ polysubstance consumption,⁵ criminal and illegal behavior,⁶ and a growth in opioid-related deaths.⁷

Methadone maintenance treatment (MMT), first synthesized in Germany as a substitute analgesic for morphine prior to world war II, is the most widely used harm-reduction approach to treating opioid.⁸ Americans discovered that it could be used to treat 1949 heroin withdrawal symptoms.⁹ Methadone is a safe, low-cost, and convenient generic drug for treatment of opioid dependence.¹⁰ Methadone is a synthetic analgesic with the ability to inhibit the euphoric effects of opioids and provide relief of withdrawal symptoms due to its longer duration of action.¹¹ Studies have shown that this treatment is effective in decreasing illicit opioid use, reducing criminal activity, and reducing mortality rates among patients.⁸

Studies have shown that many different factors are effective on the survival rate of patients in maintenance treatment. In general, they consist of three main categories: factors related to the patients, factors related to the treatment plan, and the characteristics of the community. Moreover, studies have shown that MMT attitude is one of the factors related to the treatment that is effective on the survival rate of patients in MMT.¹² Maintenance and commitment to treatment are two of the basic principles of MMT and often are known as criteria for its success and effectiveness.¹³

Based on the database review, the numerous studies are carried out on the epidemiological features and related factors of maintenance in patients under treatment with methadone in the world. An authentic measurement for these epidemiological and associated factors can be developed through a combination of the research

findings using meta-analysis. The present study aimed to comprehensively and systematically review the published data on the associated factors of maintenance in patients under treatment with methadone, using a meta-analysis.

Methods

Our research question was based on population/intervention (or predictor in observational study)/comparison/outcome (PICO) principle which is as follows:

Population = methadone treated patients

Predictors = age, gender, employment, education, marital status, duration of treatment

Outcome = maintenance

Search strategy: A number of international databases (including ISI Web of Science, PubMed, Scopus, and MEDLINE) were searched for relevant articles (up to June 2017); the target keywords included "Substance-Related Disorder", "Drug Dependence", "Drug Addiction", "Drug Habituation", "Substance Use Disorder", "Substance Abuse", "Substance Dependence", "Substance Addiction", "Drug Abuse", "Drug Use Disorder", "Opioid-Related Disorder", "Opiate Dependence", "Opiate Addiction", "Narcotic Abuse", "Narcotic Dependence", "Narcotic Addiction", "Addiction", "Methadone", "Maintenance", "Retention", "Recurrence", "Relapse", "Marital Status", "Educational Status", "Gender", "Sex", "Injections", "Employment", "Employment Status", "Occupational Status", "Treatment Outcome", "Clinical Effectiveness", "Treatment Effectiveness", "Patient Relevant Outcome", "Clinical Efficacy", "Patient Relevant Outcome", "Rehabilitation Outcome", "Opiate Substitution Treatment", "Opioid Substitution Treatment", "Opioid Substitution Therapy", "Opiate Replacement Therapy", "Opioid Replacement Therapy" with combination "OR", "AND" and "NOT" Boolean Operators in the title, abstract and keywords field (Table 1). No limitation was set while searching databases. Reference lists of all related studies were also reviewed for other related publications. The search results were evaluated randomly by a group of researchers, and it was reported that no relevant study was ignored. We also tried to identify any gray literature in the ProQuest database.

Table 1. Search strategy

("Substance-Related Disorders" [MeSH Terms]) OR ("Drug Dependence" [Text Word]) OR ("Drug Addiction" [Text Word]) OR ("Drug Habituation" [Text Word]) OR ("Substance Use Disorder" [Text Word]) OR ("Substance Abuse" [Text Word]) OR ("Substance Dependence" [Text Word]) OR ("Substance Addiction" [Text Word]) OR ("Drug Abuse" [Text Word]) OR ("Drug Use Disorder" [Text Word]) OR ("Opioid-Related Disorders" [MeSH Terms]) OR ("Opiate Dependence" [Text Word]) OR ("Opiate Addiction" [Text Word]) OR ("Narcotic Abuse" [Text Word]) OR ("Narcotic Dependence" [Text Word]) OR ("Narcotic Addiction" [Text Word]) OR ("Addiction" [Text Word]) AND ("Methadone" [MeSH Terms]) AND ("Maintenance" [MeSH Terms]) OR ("Retention" [Text Word]) NOT ("Recurrence" [MeSH Terms]) OR ("Relapse" [Text Word]) AND ("marital status" [MeSH Terms]) AND ("Educational Status" [MeSH Terms]) AND ("Gender" [Text Word]) OR ("sex" [MeSH Terms]) AND ("Injections" [MeSH Terms]) AND ("Employment" [MeSH Terms]) OR ("Employment Status" [Text Word]) OR ("Occupational Status" [Text Word]) AND ("Treatment Outcome" [MeSH Terms]) OR ("Clinical Effectiveness" [Text Word]) OR ("Treatment Effectiveness" [Text Word]) OR ("Patient Relevant Outcome" [Text Word]) OR ("Clinical Efficacy" [Text Word]) OR ("Patient Relevant Outcome" [Text Word]) OR ("Rehabilitation Outcome" [Text Word]) AND ("Opiate Substitution Treatment" [MeSH Terms]) OR ("Opioid Substitution Treatment" [Text Word]) OR ("Opioid Substitution Therapy" [Text Word]) OR ("Opiate Replacement Therapy" [Text Word]) OR ("Opioid Replacement Therapy" [Text Word]) AND (Filters: Publication date up to June 2017) AND (Filters: English Language)

The search was limited to original articles and abstracts which were published in English language that stated related features and predictive factors of maintenance treatment in patients under treatment with methadone in different regions of the world. All of these steps were taken by two authors (Farmani and Farhadi) and any disagreements with article selection were resolved through discussion, and a third author was available to resolve the disagreement. Additionally, as an agreement on effect size, Kappa coefficient was reported between two authors.

Inclusion and exclusion criteria: Inclusion criteria were: 1) studies published between 2008-2017; 2) studies on associated features and predictive factors of maintenance treatment in patients under treatment with methadone in different countries of the world; and 3) case-control and cohort studies.

The exclusion criteria were as follows: 1) case reports, review articles, and congress abstracts; 2) studies published in languages other than English; 3) studies without extractable data; 4) meta-analysis, systematic reviews, and duplicate publication of a study (or a study published both in English and another language) with the exception of duplicate and matching studies for which the most sample sizes and complete detailed results were provided.

Data extraction: From all of the previous studies, the author's name, publication date, study setting and country, sample size, journal, and risk factors were extracted (Table 2). These data were reviewed and confirmed by three researchers, independently. Furthermore, when

data were unclear, before recording an entry in the dataset, the other authors were consulted and consensus was achieved.

Quality assessment and risk of bias: As a basis for reporting systematic reviews of other types of research, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and The Newcastle-Ottawa Scale (NOS) can be used. In addition, NOS could be used to assess the methodological quality of any outcome. For the primary research, a score was assigned to each item related to study type, sample size, research objectives, population, and inclusion/exclusion criteria; In addition, the method of analysis and appropriate presentation of results were determined as follows: studies assigned 0-3, 4-6, or 7-9 were considered as low, moderate, or high-quality studies, respectively.^{12,13} Based on a NOS checklist, articles with scores less than 5 were excluded from the current study. The average score for all articles in this study was 7.1.

In order to evaluate the strength of the associated factors of maintenance in patients under treatment with methadone, pooled odds ratio (OR) and its corresponding 95% confidence interval (CI) were used. In the present study, Cochran's Q test and I-squared (I^2) were used to assess the heterogeneity and the variation in the pooled estimations; the significance was considered at $P < 0.1$ level.¹⁴ When heterogeneity existed between the individual studies, the pooled ORs were derived from a random effect model; otherwise, the pooled effect sizes were derived by a fixed effect one. Meanwhile, for sensitivity analysis, a particular study or group of studies (if

Table 2. Characteristics of studies included in the systematic review and meta-analysis

First author	Magazine	Country	Number of participants
Horyniak et al. ¹⁶	International journal of drug policy	Australia	145
Johnson and Richert ¹⁷	International journal of drug policy	Sweden	277
Bachireddy et al. ¹⁸	Drug and Alcohol Dependence	Malaysia	460
Roux et al. ¹⁹	Clinical Infectious Diseases	France	113
Burns et al. ²⁰	Addiction	Australia	15600
Roux et al. ²¹	Addiction	France	1558
Hosztafi and Furst ²²	Neuropsychopharmacol Hung	Greece	3320
Wei et al. ²³	Journal of Addiction Medicine	China	5849
Kimber et al. ²⁴	Lancet Psychiatry	Australia	32033
Van Nguyen et al. ²⁵	Harm Reduction Journal	Northern Vietnam	241
Socias et al. ²⁶	Drug and Alcohol Dependence	Canada	397
Zhou et al. ²⁷	Journal of Addiction Medicine	China	10398
Ledberg ²⁸	Journal of Substance Abuse Treatment	Sweden	441
Ratcliffe et al. ²⁹	Heroin Addiction and Related Clinical Problem	UK	511
Keegan et al. ³⁰	Heroin Addiction and Related Clinical Problem	Ireland	228
Peles et al. ³¹	The American journal of drug and alcohol abuse	USA	1269
Holland et al. ³²	Addiction (Abingdon, England)	UK	293
Jiao et al. ³³	AIDS care	China	288
Mitchell et al. ³⁴	Journal of psychoactive drugs	USA	351
Peles et al. ³¹	Drug and Alcohol Dependence	Israel	758
Comiskey and Snel ³⁵	Substance use and misuse	Canada	106
Lee et al. ³⁶	Scientific reports	Taiwan	180
Zhang et al. ³⁷	AIDS care	China	648
Darker et al. ³⁸	Irish Journal of Medical Science	Ireland	189

UK: United Kingdom; USA: United States of America; AIDS: Acquired immune deficiency syndrome

any) with the highest impact on the heterogeneity test were removed successively. A funnel plot was established for checking the existence of publication bias. The funnel plot asymmetry was measured by Egger's linear regression test and Begg's test ($P < 0.05$ level was considered statistically significant publication bias).¹⁵ All statistical analyses were conducted using STATA software (version 11.0; Stata Corporation, College Station, TX).

Results

Eligible studies: Figure 1 shows the process of including or excluding potential studies. In the first screening process, 94413 papers were excluded due to duplication, and not including the searched terms in their keywords or titles. For abstract assessment, 4101 articles were retained. In the secondary screening process based on abstract evaluation, 4024 of publications were excluded; this resulted in retaining 77 articles for detailed full-text evaluation. After full-text evaluation, 24 articles describing associated factors of maintenance treatment were retained.

Main results, meta regression and sensitivity

analysis: A summary of pooled results, heterogeneity, and publication bias test of the association between risk factors of maintenance and methadone usage is shown in table 3. Meta-analysis results recognized five significant positive associations of age, marital status, employment status, gender, and duration of treatment with methadone usage (OR age = 3.566, 95% CI = 3.296-3.836, $P < 0.001$; OR marital status = 1.101, 95% CI = 1.028-1.175, $P = 0.025$; OR employment = 1.157, 95% CI = 1.060-1.254, $P = 0.015$; OR gender = 4.686, 95% CI = 4.434-4.939, $P < 0.001$; OR duration of treatment = 1.543, 95% CI = 1.443-1.647, $P < 0.001$; respectively) (Figure 2). However, education and injection status showed a non-significant positive association with methadone usage (OR education level = 1.279, 95% CI = 0.976-1.583, $P = 0.26$; OR injection status = 1.205, 95% CI = 0.725-1.658, $P = 0.44$). The results of meta regression analysis showed that year of publication and location of study (country) have not statistically significant effect on the association between risk factors of maintenance and methadone usage.

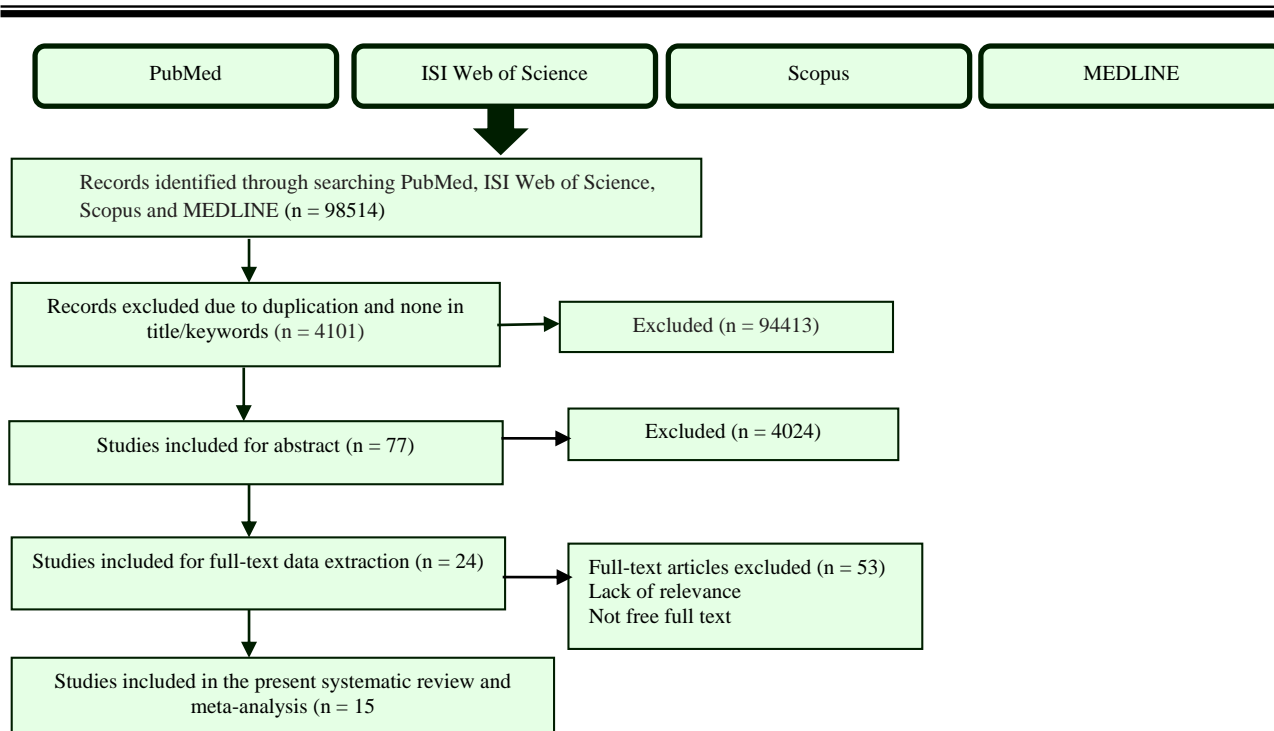


Figure 1. Flowchart for literature search and study selection

We did sensitivity analysis by sequential omission of individual studies. For each of the risk factors of maintenance, after omission, there was no alternation in the pooled OR of methadone usage; this indicates our statistically robust results in all of the risk factors of maintenance.

Heterogeneity and publication bias: The heterogeneity analysis was conducted by I^2 test, and P heterogeneity < 0.10 and $I^2 > 50\%$ was considered as significant heterogeneity among the studies. The heterogeneity between studies were observed in all of the risk factors of maintenance except marital status; age ($I^2 = 100\%$; $P < 0.001$), education level ($I^2 = 84.5\%$; $P < 0.001$), injection

status ($I^2 = 99.8\%$; $P < 0.001$), employment status ($I^2 = 90.1\%$; $P < 0.001$), gender ($I^2 = 100\%$; $P < 0.001$), and duration of treatment ($I^2 = 100\%$; $P < 0.001$). Accordingly, the fixed effects model and random effects model were applied to pool the results. In order to evaluate the publication bias, we used the funnel plot and also the Egger's and Begg's tests. No publication bias was found in all analyses (Figure 2).

Discussion

Drug addiction can be considered as a chronic relapsing disease.³⁹ There are numerous pathways to addiction and in the real world, poly-drug use is common.³⁹

Table 3. Meta-analysis of the pooled association between associated factors of maintenance and methadone usage

Associated factors of maintenance	No. of studies	P	Pooled OR (95% CI)	Heterogeneity test (I^2 , P)	Publication bias		Effect model
					Begg's test's P	Egger's test's P	
Age	15	< 0.001	3.566 (3.296-3.836)	(100, < 0.001)	0.920	0.550	Random
Education	4	0.260	1.279 (0.976-1.583)	(84.5, < 0.001)	0.730	0.360	Random
Marital status	4	0.025	1.101 (1.028-1.175)	(44.4, 0.145)	0.990	0.820	Fixed
Injection	5	0.440	1.205 (0.725-1.658)	(99.8, < 0.001)	0.990	0.270	Random
Employment	7	0.015	1.157 (1.060-1.254)	(90.1, < 0.001)	0.760	0.340	Random
Gender (female as reference level)	12	< 0.001	4.686 (4.434-4.939)	(100, < 0.001)	0.050	0.780	Random
Duration of the treatment	3	< 0.001	1.543 (1.443-1.647)	(100, < 0.001)	0.990	0.290	Random

OR: Odds ratio; CI: Confidence interval

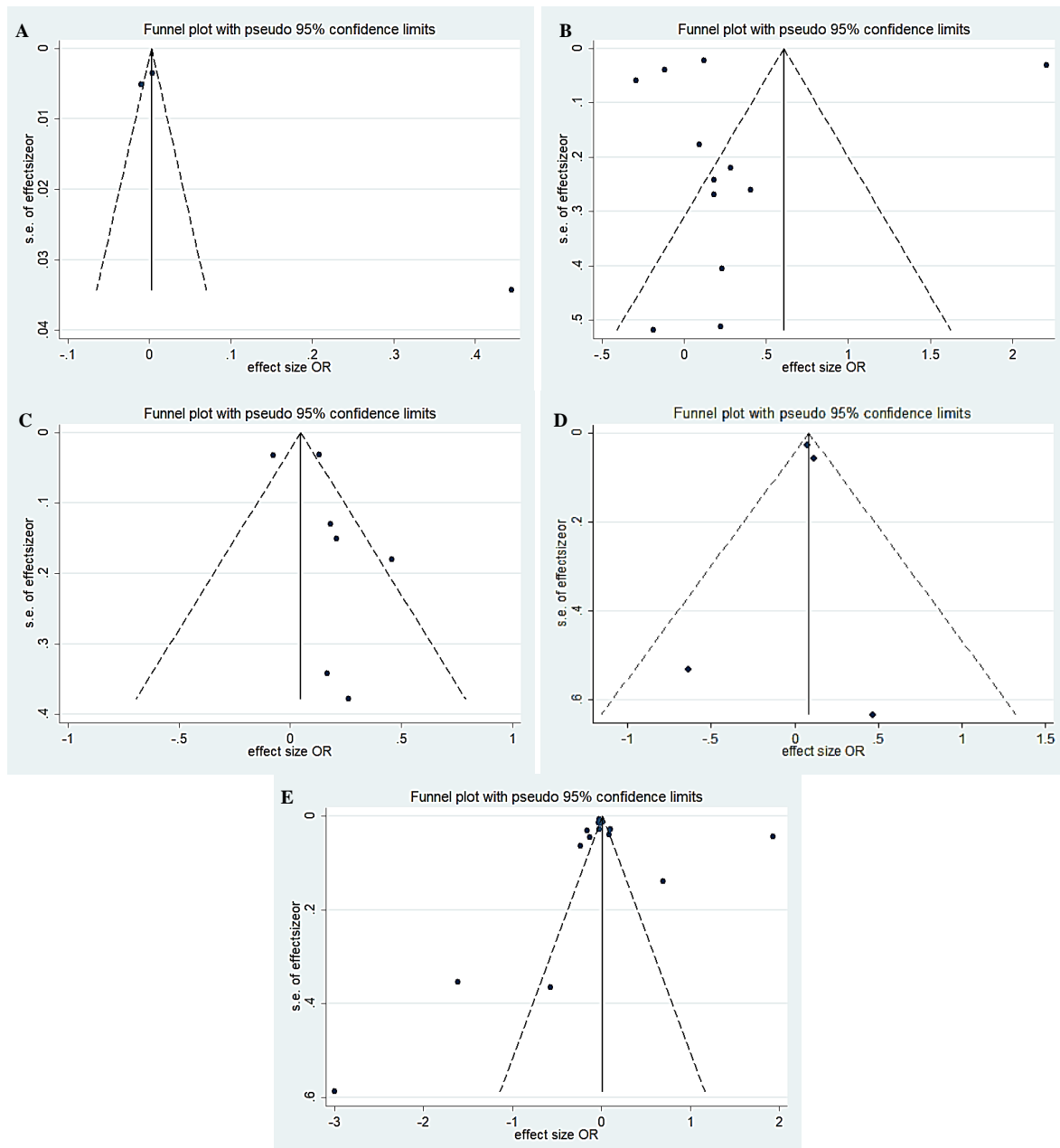


Figure 2. (A) Forest plot of meta-analysis for duration of treatment, (B) Forest plot of meta-analysis for gender, (C) Forest plot of meta-analysis for employment status, (D) Forest plot of meta-analysis for married status, (E) Forest plot of meta-analysis for age

Considering the harmful physical, psychological, and social effects of opiate drugs, it is necessary to pay attention to this disease and its treatment. Due to the high incidence of relapse and the increased risk of lethal poisoning after detoxification, maintenance treatment for the agonist is considered as the first phase of treatment sessions. Methadone is a long-acting agonist with a half-life of about 24 to 36 hours. In scientific literature, methadone maintenance has

been consistently shown to effectively decrease drug use and improve social functioning. Patients receiving methadone maintenance have much greater treatment retention than those receiving other treatments;⁴⁰ therefore, methadone can be considered as the first phase of opioid substitution therapy.²⁴

The long-term maintenance of patients in treatment is very important and other positive MMT outcomes, such as reducing the risk of

recurrence of drug use, have been shown to be positively associated with the length of time when patients are treated.⁴¹ Shelf life is one of the most important indicators in MMT.⁴² In a national and prospective study in which a group of methadone clinics participated, the maintenance rate was reported to be 81% in the first month and 52% after six months. In another study, examining 492 patients in a MMT clinic, the maintenance rate for treatment after one year was reported to be 74.4%.⁴³ Studies in New York, Italy, and Eastern Europe have reported maintenance rates for treatment of 23 months, 7 months, and 2.5 months, respectively.⁴⁴

Various factors are effective in maintenance therapy with methadone.⁴⁵ The results of maintenance analysis show that factors predicting the maintenance rate on treatment, including age, marital status, housing status, type of substance use, and family history, have a positive and significant relationship with maintenance rates on treatment.^{46,47} We reviewed 24 articles published until 2017. These studies were conducted in various countries like France, Malaysia, China, etc. In the current investigation, variables like age, education, gender, etc. were considered in the study. The findings revealed that age, gender, and marital status had statistically significant relationships with maintenance in methadone treatment. However, it was found that there is not any statistically significant relationship between variables like education and injection in maintenance treatment with methadone; therefore, the retention rate is one of the best indicators of MMT efficiency.^{48,49}

As treatment through methadone maintenance has numerous advantages such as decreasing the use of illegal substance, stabilizing the patient's life, reducing the arbitrary use of drugs, reducing unlawful actions, reducing dangerous behaviors [common injection which may lead to transfer of illnesses resulting from blood pathogens like acquired immune deficiency syndrome (AIDS) and hepatitis]. Hence, treatment through methadone maintenance and shelf life in this treatment is effective both for the individual and for the society.

This research had some limitations like lack of access to the full text of some papers which prevented us from including their results into the current study. Furthermore, in this investigation, there was a linguistic limitation as only studies

written in English were reviewed and studies in other languages were not included.

Age, as one of the factors, was considered as an important factor in this study. In earlier years, because of hysteria and sexual issues, risk of tendency to substance and as a result, failure in treatment is higher. As a result, paying attention to younger's morale and mood in this treatment method is of great significance; moreover, being married and having family, both as permanent supporting factors and as motivators, can help the patient under treatment with methadone. Single and divorced individuals are in the exposure to the relapsing use because of lack of common marriage sense, lack of commitment and attachment.

One of the other factors which is important for these patients is job. Having job is effective in reducing failure of treatment because of making an appropriate mental environment, providing social status, and increasing self-confidence.

With regard to various factors, education was more challenging. With increase in literacy level, maintenance in treatment did not improve. As shown, the degree of relapse in individuals in higher education was reported to be more than illiterate individuals. The reason is that individuals with higher educational degrees thought that they can control the issue and it seems that they are reluctant to receive information regarding prevention of relapsing from treatment center employees. This point should be considered in MMT for individuals who have higher educational degrees. Hence, paying more attention to them and selecting appropriate techniques for communicating with them are necessary.

It seems that using other treatment methods like group treatment, family treatment, and consulting with individual can be effective besides methadone treatment. However, effectiveness or lack of it and the degree of effectiveness of these methods need further research.

Conclusion

Since addiction treatment is an important issue, it is important to pay attention to the factors that lead to maintenance in the treatment of patients undergoing methadone treatment. In this study, various factors were investigated. The factors such as age, marital status, employment status, gender, and duration of treatment were effective in treating, but education

and injection did not make any significant difference in this study. Therefore, it is necessary to do more research and studies on their effectiveness and how effective they are.

Conflict of Interests

The Authors have no conflict of interest.

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عوامل مرتبط با ماندگاری در درمان بیماران تحت درمان با متادون:

یک مرور سیستماتیک و فراتحلیل

فرزانه فرمانی^۱، دکتر هادی فرهادی^۲، دکتر یونس محمدی^۳

مقاله مروری

چکیده

مقدمه: مطالعه حاضر به صورت سیستماتیک و فراتحلیل و با هدف ارزیابی عوامل مرتبط با ماندگاری در درمان بیماران تحت درمان با متادون در جهان انجام شد.

روش‌ها: در این پژوهش، مقالاتی از پایگاه‌های اطلاعاتی PubMed، ISI Web of Science، Scopus و MEDLINE به صورت سیستماتیک مرور گردید. کلید واژه‌های «متادون، نگهداری، فراتحلیل و عوامل مرتبط» مورد جستجو قرار گرفت و داده‌ها با توجه به معیارهای ورود و خروج انتخاب گردید. هدف از انجام این تحقیق، ارزیابی عوامل مرتبط با نگهداری در بیماران تحت درمان با متادون با نسبت شانس (Odds ratio) یا OR) و فاصله اطمینان (Confidence interval یا CI) ۹۵ درصد به کمک فراتحلیل بود.

یافته‌ها: ۲۴ مطالعه از ۹۴۴۱۳ مورد بر اساس معیارهای ورود و خروج جهت مرور سیستماتیک و فراتحلیل انتخاب شد. در این مطالعه تلفیقی، پنج عامل مرتبط مثبت معنی‌دار شناخته شد که شامل سن ($P = ۰/۰۲۵$ ، $OR = ۱/۱۷۵$ ، $CI = ۱/۰۲۸-۱/۱۷۵$)، اشتغال ($P = ۰/۰۱۵$ ، $OR = ۱/۱۷۵$ ، $CI = ۱/۰۶۰-۱/۲۵۴$)، وضعیت زناشویی ($P = ۰/۰۰۱$ ، $OR = ۳/۵۶۶$ ، $CI = ۳/۳-۲۹۶/۸۳۶$)، وضعیت زناشویی ($P = ۰/۰۰۱$ ، $OR = ۴/۶۸۶$ ، $CI = ۴/۴۳۴-۴/۹۳۹$)، مدت درمان ($P = ۰/۰۰۱$ ، $OR = ۱/۵۴۳$ ، $CI = ۱/۴۴۳-۱/۶۴۷$)، سطح تحصیلات ($P = ۰/۲۶۶$ ، $OR = ۱/۲۷۹$ ، $CI = ۰/۹۷۶-۱/۵۸۳$) و تزریق ($P = ۰/۲۰۵$ ، $OR = ۱/۲۰۵$ ، $CI = ۰/۷۲۵-۱/۶۵۸$)، $P = ۰/۴۴۲$) ارتباط مثبت غیر معنی‌داری را نشان داد.

نتیجه‌گیری: نتایج مطالعه نشان داد که عواملی همچون سن، وضعیت تأهل، وضعیت اشتغال، جنسیت و مدت زمان درمان، در ماندگاری درمان بیماران تحت درمان با متادون مؤثر می‌باشند.

واژگان کلیدی: متادون، نگهداری، عوامل مرتبط، فراتحلیل

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۱- دانشجوی کارشناسی ارشد، گروه روان‌شناسی، دانشکده علوم تربیتی و روان‌شناسی، واحد اصفهان (خوراسگان)، دانشگاه آزاد اسلامی، اصفهان، ایران
 ۲- استادیار، گروه روان‌شناسی، دانشکده علوم تربیتی و روان‌شناسی، واحد اصفهان (خوراسگان)، دانشگاه آزاد اسلامی، اصفهان، ایران
 ۳- استادیار، مرکز تحقیقات مدل‌سازی بیماری‌های غیر واگیر و گروه اپیدمیولوژی، دانشکده بهداشت، دانشگاه علوم پزشکی همدان، همدان، ایران

Email: farhadihadi@yahoo.com

نویسنده مسؤول: دکتر هادی فرهادی