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Predictors of Treatment Retention in a Major Methadone Maintenance Treatment Program in Iran: a Survival Analysis

Tahereh Pashaei (PhD)^{ab}, Maryam Moeeni (PhD)^{cd}, Babak Roshanaei Moghdam (MD)^b, Hassan Heydari (PhD)^e, Nigel E Turner (PhD)^f, and Emran M Razaghi (MD)^{g*}

^aDepartment of Public Health, School of Health, Kurdistan University of Medical Sciences, Sanandaj, Iran

^bAddiction Research Center, Tehran University of Medical Sciences, Tehran, Iran

^cHealth Management and Economics Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

^dIranian Center of Excellence in Health Services Management, Tabriz University of Medical Sciences, Tabriz, Iran

^eAssistant professor, Faculty of Management and Economics, TarbiatModares University, Tehran, Iran

^fCentre for Addiction and Mental Health, Toronto, Canada

^gDepartment of Psychiatry, Tehran University of Medical Sciences, Tehran, Iran

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* Correspondence

Emran M Razaghi (MD)

Tel: +98912 1255458

Fax: +98 21 55419113

E-mail: razaghie@sina.tums.ac.ir

ABSTRACT

Background: To study correlates which are related to retention time of a cohort study of the opioid-dependent patients participating in the Methadone Maintenance Treatment (MMT) program offered by a major addiction treatment clinic in Tehran, Iran between April 2007 and March 2011.

Methods: Several parametric Survival models assuming Weibull, Log-normal and Log-logistic distributions were compared to search for association between covariates and risk of relapse and dropping out of treatment among 198 patient participants.

Results: According to Akaike Information Criterion (AIC), Log-normal model had the best fitting. Estimates of this model indicated that increase in average methadone dosage was associated with longer retention time. Correlates associated with shorter retention time were suffering from mental disorders, using stimulant drugs, being poly-substance dependents and having prior treatments.

Conclusions: Findings of this study provide support for giving more attention to patients who are poly-substance or stimulant-drug dependents, have non-substance psychiatric comorbidity and the ones with addiction treatment history. Independent of patient characteristics, retention improved as the dose of methadone increased.

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Introduction

According to the United Nations Office on Drugs and Crime (UNODC) World Drug Report 2011, Iran has the second highest prevalence rate of opiate use disorder in the world. The reported rate of substance-related death is 91 persons in one million of 15-64 years-old people; most of which results of opium use. Around 83% of Iranian opioid dependent individuals who sought treatment services in 2009 were addicted to opium¹. Methadone maintenance treatment (MMT) is one of the most accepted treatments for opioid dependence in Iran² and continues to be the most cost-effective treatment for opioid dependence around the globe³.

Retention time is not optimum in MMT programs⁴. In Iran, the average retention rate 76% for the first three months of treatment⁵. In other countries, the average retention rate for one year was from 30% to 60%⁶. A larger retention rate has been described as a remarkable achievement of treatment

programs⁷. To put the retention rates in a quantitative context, about 1400 MMT centers provide treatment services for more than 115000 participants in Iran⁸. These numbers underscore the significance of an even small increase in retention rate can benefit a large number of patients.

A high relapse rate means that a large number of patients drop out of the treatment and therefore the treatment is not effective⁹. Retention is usually associated with some main categories of predictors such as demographic and social factors¹⁰, poly-substance abuse¹¹, patients' psychological conditions⁶, and program characteristics including availability of maintenance programs such as MMT¹²⁻¹⁵.

Although, predictor variables of relapse in MMT program have been studied over the world, to our knowledge, determinants of relapse into drug among Iranian patient participating in MMT program has not sufficiently been

elaborated. Besides, none of limited number of studies focusing on this subject⁸ has applied survival models.

To narrow this gap in this study, we aimed to identify predictors associated with retention time in opioid-dependent patients participating in Iranian National Center for Addiction Studies (INCAS) MMT program in Tehran, Iran using survival models. This study might help us to recognize appropriate interventions and support systems in order to enhance efficacy of MMT programs in Iran.

Methods

Study design and data collection

All opioid-dependent patients were eligible to apply to MMT program if they were at least 17 years old. The exclusion criteria for the study were suicidal or homicidal ideation, frank delusions or overt aggressive and threatening behaviors. Over the four-year period from April 2007 to March 2011, 260 people started on MMT met the criteria for inclusion and exclusion criteria for the study and agreed to participate. Sixty-two patients discontinued their treatment at INCAS within one month from starting treatment program and transferred their care to other MMT centers for a variety of reasons including scheduling conflicts or finding another clinic closer to their home. They were excluded from the analysis because we did not have any information about their subsequent treatment. Thus, the sample size for the study was 198 patients (76% completion rate). A general practitioner trained in addictions medicine visited patients individually to provide them with an opportunity to get into the MMT program. Finally, the decision for recruitment was reached through doctor-patient discussion.

The participants were opioid-dependent patients participating in INCAS, MMT program in Tehran, Iran. INCAS was the first to provide MMT and pilot research for opioid dependence in Iran.

This research utilized a retrospective cohort study design. We used a checklist to collect the information that consists of basic demographic information, drug abuse and treatment history, risky behaviors and psychiatric and medical status. This checklist was completed based on INCAS Substance Abuse Profile (ISAP version1), filled at the time of enrollment into MMT program and recorded many of the patients' background information. At the time of enrollment, a written consent was obtained from each patient for using their de-identified information recorded at INCAS for research purposes.

The patients who had participated in the MMT program, provided by INCAS, between April 2007 and March 2011 were enrolled in this study. Each one needed to pay 700000 RLS per month (about \$2450) for treatment services, a reasonable cost somewhere between private and public sectors for MMT programs that are currently available in Iran.

Age of participants was entered according to official ID and the dose of methadone was recorded by the INCAS staff on a daily or weekly basis. During treatment, methadone dosage followed a flexible policy and changed frequently based on clinical wisdom. Patients' mental health condition measured according to reported physician diagnosis.

Statistical analysis

To examine the determinants of time to discontinuation of MMT, three groups of correlates were included in the study including socio-demographic and health variables, drug use variables, and methadone treatment variables. The socio-demographic and health characteristics were gender, age (at the time of enrollment), education, marital status, employment status, imprisonment history, and mental health condition. The drug use pattern variables consisted of addiction span, age at the time of becoming opioid-dependent, poly-substance abuse (i.e., using other substances such as, alcohol, cocaine, cannabis, tramadol, tranquilizer, etc. along with opioids), stimulant drug use, drug injection and treatment history. The third group of variables was related to the nature of the methadone maintenance treatment and included changes in methadone dosage taken by participants during the study period. Since, there were frequent methadone doses recording for each patient, the average dosage of methadone during treatment period for each patient was used as a potential correlate of relapse.

To analyze data, we applied survival models for right-censored time-to-event data that are more adequate than classical regression models in two ways. First, survival models are among the most appropriate statistical methods considering censored time-to-event data. Secondly, they include duration until an event along with occurrence of that event¹⁶. Several parametric Survival models assuming Weibull, Log-normal and Log-logistic distributions were compared to search for association between covariates and risk of relapse and dropping out of treatment among patient participants.

Selecting the best model was based on several relapse theories and statistical reasons:

First, Cox Proportional hazard regression as the most popular semi-parametric survival model is a robust and common choice for analyzing time-to-event data, but the validity of Cox model relies on the assumption of hazard proportionality. Weibull, Log-normal and Log-logistic distributions are the most popular parametric models utilized by researchers to depict hazard rate¹⁶.

Second, in many empirical studies, the baseline survival function is of great importance for researchers¹⁶. The relapse rate of patients addicted to different substances have a similar distribution i.e., the maximum risk of relapse is not immediately falling. Most patients relapse early and that the probability of relapse decreases then after¹⁷. Because of this reversed J-shaped baseline survival function of relapse, parametric survival models based on Log-logistic and Log-normal distributions can be thought of as the best options to evaluate the risk of relapse if statistical criteria can confirm them.

Third, amongst parametric models, Log-normal distribution had the most appropriate fitting based on Akaike Information Criterion (AIC), which indicated that the relapse rate of participants had a maximum point and did not decrease immediately.

In this paper Weibull regression, log-logistic regression and log-normal regression were compared in terms of their AIC value. The AIC is a means of comparing statistical models based on the relative entropy and the number of parameters that helps identify an optimal model¹⁶. The

smaller than AIC, the better the fit of the model relative to the parameters included. Data analyses were performed with Stata 11 software.

Results

Tables 1 and 2 show descriptive statistics of the study sample. Of the total 198 individuals who participated in the treatment program, 91% were male. The median age at the time of recruitment was 34 years-old; about 28% of the study group were not high school graduates, 35% did not have full time job, and 50% were married. According to the patients' records, mainly based on reported physician diagnosis, only 17% of the study group was suffering from mental disorders, and around 23% had imprisonment history.

Relapse rate among patients was 43% (86 persons), and the median retention time was about six months. The median drug use span amongst participants was 10 years and the median age of starting drug use was 20 years-old. Concerning non-opioid substance abuse comorbidity, 57% of patients were poly-substance users and 33% were stimulant drug users. Methadone dosage followed a flexible policy and changed frequently based on clinical wisdom. Only 10% of participants reported injecting drugs. Approximately 77% of participants had been previously enrolled in treatment programs other than MMT. In addition, the average daily methadone dosage for each patient was 78.5 ±35 mg. While the minimum dose was 7.5 mg, the maximum reached to 195 mg per day (Table 1 & Table 2).

Table 1: Descriptive statistic of continuous variables

Variables	Mean	SD	Min	Max
Drug use span (yr)	12.64	10.35	1.00	50.00
Age of becoming opioid-dependent (year)	22.30	6.70	11.00	50.00
Age of including MMT program (year)	37.23	11.90	17.00	73.00
Methadone dosage (mg)	78.50	35.00	7.50	195.00
Retention (months)	7.00	5.99	1.00	48.00

Table 2: Descriptive statistic of dummy variables

Variables	Number	Percent
Gender		
Female	17	9.0
Male	181	91.0
Education		
Less than 12 years	141	71.0
At least 12 years	57	29.0
Unemployed		
Yes	69	35.0
No	129	65.0
Married		
Yes	99	50.0
No	99	50.0
Mental disorder		
Yes	33	17.0
No	165	83.0
Imprisonment history		
Yes	45	23.0
No	153	77.0
Treatment experience		
Yes	153	77.0
No	45	23.0
Poly substance use		
Yes	114	58.0
No	84	42.0
Using stimulant drugs		
Yes	65	33.0
No	133	67.0
Drug injection		
Yes	20	10.0
No	178	90.0

Figure 1 shows Kaplan-Meier estimate of relapse rate of all participants. The relapse rates at 4th, 10th and 26th month were 25%, 50% and 75% respectively.

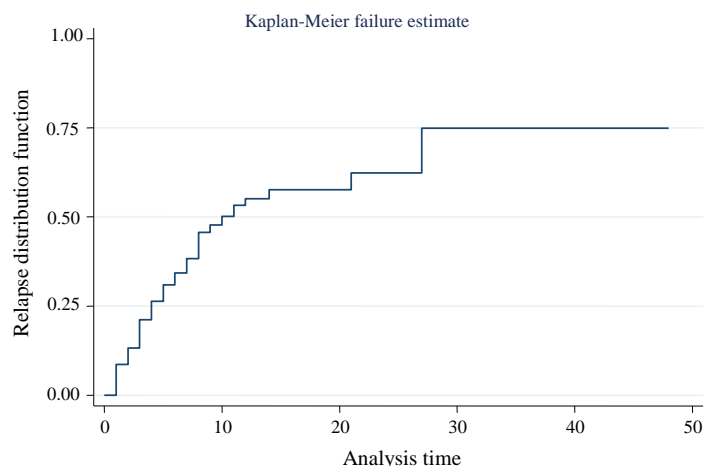


Figure 1: Kaplan-Meier estimate of relapse rate (1-St)

At the end of the data collection, 86 patients from all 198 participants reportedly experienced relapse into drugs, which led to dropping out of treatment. The remaining 112 patients who were actively following their treatment were considered as censored observation in survival analysis

Stepwise regressions (Backward elimination approach) were employed to fit the final models. Tables 3 and 4 explain results of different parametric models.

Table 3: Results of Weibull & Log-logistic models for retention time

Variable	Weibull regression		Log-logistic regression	
	Time Ratio	P value	Time ratio	P value
Methadone dosage	1.025	0.001	1.025	0.001
Treatment experience	0.514	0.012	0.518	0.010
Mental disorders	0.548	0.001	0.543	0.001
Poly substance use	0.318	0.016	0.315	0.001
Stimulant drugs use	0.648	0.151	0.650	0.050

Table 4: Results of Log-normal model for retention time

Variable	Coefficient	SE	Time ratio		
			SE	P value	
Methadone dosage	0.026	0.003	1.027	0.003	0.001
Treatment experience	-0.587	0.229	0.556	0.127	0.048
Mental disorders	-0.574	0.167	0.564	0.094	0.001
Poly substance use	-1.080	0.200	0.340	0.068	0.001
Stimulant drugs use	-0.409	0.164	0.664	0.109	0.048
Wald chi ² (5)	155.810	-	-	-	-
Log pseudolikelihood	-140.440	-	-	-	-
Akaike Information Criterion	296.880	-	-	-	-

Fitting of the models were compared by the means of AIC. To assess the relative merits of the models we compared the AIC. The Weibull regression model produced an AIC of 301.52, the Log-Logistic regression and AIC of 298.37 and the Log-normal produced an AIC of 296.88. As noted above the lower the AIC the better the fit. The lowest AIC score belonged to Log-normal regression (AIC=296.89). As the consequence, in this sample, Log-normal distribution modeled relapse more accurately.

Accelerated failure time (ATF) form of parametric models were measured to find covariates related to retention time and at the same time the risk of relapse. Subsequently, in all models, effect of each covariate was calculated as time ratio (TR) instead of hazard ratio. According to the results obtained from Log-normal regression, the time ratio and the coefficient of the average methadone dosage were 1.03

($P < 0.001$) and .026 ($P < 0.001$) respectively, which meant that on average, each 1-mg incremental rise in methadone dose increased predicted retention time by 0.027 month. On the other hand, estimated time ratio and coefficient for mental disorders were respectively 0.564 ($P < 0.001$) and -0.587 ($P < 0.001$), which implied that on average, predicted retention time for participants suffering from mental disorders was approximately 56% shorter as compared to the retention time for others. In addition, participants who were poly-substance dependents had about 34% shorter retention time in contrast with the ones who were solely opioid-users (TR=0.34, coefficient=-1.08, $P < 0.001$). Moreover, predicted treatment retention among patients using stimulant drugs was on average 66% shorter as compared to the retention time for other patients (TR=0.664, coefficient=-0.409, $P = 0.048$). Finally, having treatment history shortened predicted retention time by 56% on average (TR=0.556, coefficient=-0.587, $P = 0.048$). Being unemployed was negatively related to retention time but was not significant and then removed from model through stepwise regression ($P = 0.093$). Not all other covariates that were examined were significant.

Discussion

In this study of retention treatment in an MMT program in Iran, we found both individual and provider level factors as independent predictors of patient dropout. Individual factors that were associated with shorter retention in treatment included suffering from mental disorders, poly-substance or stimulant-drug abuse, and presence of prior treatment. The only provider-level factor that was positively associated with treatment stay was average methadone dosage.

Median retention time among patients was six months. Relapse rate was 25% at 4th month, 50% at the 10th month and 75% at 26th month. These findings are similar to other studies. For instance, in Indonesia, relapse rates were calculated as 25.8% in the 3rd month and 38.7% at 6th month¹⁸. Three-month relapse rate was found to be 24% in an Iranian patient population⁵.

Results of Log-normal regression showed that increase in average methadone dosage was significantly associated with longer treatment retention time. This finding confirmed that MMT plays an effective role in longer abstinence as evidenced elsewhere^{3,12-15,19-20}. On average, predicted retention time increased by about .027 months as methadone dose rose by 1-mg. This result is supported by the belief that taking continuous high methadone dosage obstructs the opiate receptor system and helps with opiate-drug use treatment²¹. As it was mentioned earlier, the average dose of methadone in this study was about 78.5 mg. According to earlier studies and the NIH expert panel, methadone dosage above 60 mg is most effective in retaining patients with opiate dependency²². Next great significant predictor in Log-normal model was history of mental distress. As results indicated, participants who were not mentally healthy had significantly higher risk to drop out. This foreseeable result is consistent with some previous studies considering the direct relationship between mental distress and time to relapse²³. Besides, MMT participant with psychiatric disorder have shorter retention^{4,31}. One study suggested more staff and better services should be provided for patients with mental distress in order to increase retention time despite the associated higher costs⁴. In addition, opioid-dependent patients who have comorbid psychiatric disorders are

stabilized on higher doses of methadone²⁴.

Poly-substance abuse was the third robust predictor of retention time. Patients who were poly-substance dependents were at much higher risk of relapse. Those patients who were mixed drug users were more likely to quit treatment program²⁵. Previous dependence on substances such as alcohol and cocaine could lead to shorter retention time in opioid-dependent patients⁶. Simultaneous injection of heroin and alcohol was also shown to increase the risk of relapse¹³.

A striking result emerging from our data was the significant impact of stimulant- drug abuse on retention time. Participants using stimulant drugs had a shorter retention time as compared to the non-users. This association is also reported by others²⁶. One evident reason for treatment failure in stimulant drug co-users is that these substances create strong craving²⁷.

The last significant finding of this study was that prior treatments predicted shortened treatment retention. There is inconsistent evidence in literature concerning this correlation. While one earlier study has demonstrated negative association between history of treatment and retention time²⁸, there is another study that has shown the reverse²⁹. Patients with unsuccessful treatment history might have lessened self-efficacy, which can make them more vulnerable to treatment failure. Returning to treatment can also cause frustration and hopelessness in patients, their social support networks and their clinicians; all of which can negatively affect treatment outcome. Patients with a history of treatment usually have more unfavorable treatment outcomes because their drug problem is shown to be more severe³⁰.

None of the socio-demographic correlates (including age, education, marital status, employment status etc.) was significant in this study. This finding is in contrast with a former study that shows individual differences in socio-demographic factors can predict treatment retention¹³. One reason that our study failed to find such association might be due to small sample size and the fact that patients recruited were all receiving treatment from one clinic that is geographically located in the southern part of Tehran where people mostly belong to middle to lower socioeconomic status.

This study had several limitations. We could not analyze the impact of social and family support on relapse rate due to lack of any information about these important factors recorded at the time of recruitment. The results of this study should be interpreted with caution because of the small sample size and not readily generalized because of the rather homogeneous patient population in our study.

Our study also had several strengths. One of the strongest merits of this study was that we applied parametric survival models. In Iran, none of the studies in this field has ever used survival models and in other countries, only few studies have used this model to study relapse and retention in patients with addiction. The presence of a follow-up program and calling patients' family members to find out why some patients dropped out of INCAS were both other strengths of this study.

Conclusions

MMT is an effective treatment for the opioid-dependent individuals. In order to help patients remain in retention longer, this study advocates serious focus on poly-substance

and stimulant-drug dependents, patients with non-substance psychiatric comorbidity as well as the treatment-experienced ones. We suggest higher methadone dosage and provision of more accessible psychiatric services to these subgroups of patients in order to achieve more successful treatments in MMT programs.

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Conflict of interest statement

Authors did not receive financial support from any organization. This journal is allowed to review all data if requested.

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