Factors Related to Relapse in Patients with Substance-related Disorders under Methadone Maintenance Therapy: Decision Tree Analysis

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ABSTRACT

Objectives: We sought to determine the main factors related to relapse in patients with substance-related disorders (SRDs) who received methadone maintenance therapy (MMT) using decision tree (DT) analysis. *Methods*: We conducted a cross-sectional study of 4175 patients referred to the 45 MMT centers in Kermanshah province, west of Iran. We included all patients who were under MMT for at least one year. All information was collected through an interview by a psychologist. Descriptive statistics and univariate and multiple regression models were used in statistical analysis. The Gini index was calculated to determine the cut-off point of nodes. We used the Classification and Regression Trees algorithm to create the DT. *Results:* The relapse rate was 76.6% for all participants, with no significant gender differences. The DT resulted in a five-level model of significant factors affecting substance abuse relapse. These included lower cost for buying substances, lower age at first substance use, history of quitting substances without medication, frequency of substances utilization per month, and frequency of methadone therapy. *Conclusions:* Knowing the main factors associated with substance abuse relapse could be important for health care providers to make better decisions for improving the treatment outcomes of SRDs.

S ubstance-related disorders (SRDs) are of two types: substance use disorders and substance-induced disorders.[1] SRDs are one of the most serious psychosocial problems in all societies,[2] and are a risk factor for suicide[3] and conditions such as AIDS.[4] Additionally, SRDs have negative economic and non-economic impacts on patients, their families, and society as a whole. It is considered one of the major public health problems in all countries regardless of their socioeconomic status.

Based on the Global Burden of Disease (GBD) study, substance abuse was responsible for 20 million disability-adjusted life years at the global level in 2010.[5] It has also been estimated that more than 2% of total burden of diseases at the global level are associated with SRDs.[6] Similar to other developing countries, the burden of substance abuse is high in Iran and has been identified as the third leading cause of disease burden among males.[7]

Iran, considering its geographic location, is a transit route to substances from countries such as Afghanistan and Pakistan to countries in Europe. Its location is one of the main contributors to the higher prevalence of substance abuse.[6,8] In addition, the higher prevalence of substance abuse and easier access to substances impact harm reduction outcomes among substance abuse patients. Over the past decades, several preventive programs have been launched to reduce the prevalence of SRDs in Iran. Harm reduction programs in 1994 and methadone maintenance therapy (MMT) in 1999 are two examples of such programs.[9] While the main goal of all these programs is harm reduction of substance abuse, there are some concerns regarding their success and continued abstinence. In previous studies, factors affecting the success of harm reduction included psychological, socioeconomic, and environmental factors, plus the quality of health care and family support.[10–13]

Although there are several reports regarding relapse among patients with substance abuse, none of them used the decision tree (DT). The DT is an easy to understand tool for both health policymakers and health care providers. Having useful information about the main determinants of harm reduction outcomes among SRDs patients is an important step toward a reduction in relapse rates, better patient management, and increased quality of life. Therefore, we sought to determine the related factors affecting the prevalence of relapse in a large sample of self-referred patients to MMT centers in Kermanshah, western of Iran, using the DT analysis and logistic regression model.

METHODS

This cross-sectional study was carried out in the Kermanshah province. Kermanshah is located in the western region of Iran and consists of 14 districts. The Kurdistan province borders it to the north, Hamadan and Lorestan provinces to the east, and Ilam province to the south. It is also bordered by Iraq to the west. The total population within the province was estimated to be approximately two million in 2015. The province has 95 MMT centers for the provision of services to patients with SRDs.

For this study, we included the available data in MMT centers in Kermanshah province in 2015. According to the guideline provided by the Ministry of Health and Medical Education, the same health care services are available for all patients in all MMT centers. We randomly selected 45 out of 95 of MMT centers and included all of their patients. All required information for registration of patients was collected through interviews with participants by full-time psychologists in the centers. Sociodemographic data such as age, sex, marital status (single, married, divorced), education level (illiterate or number of schooling years), and other relevant information including age at first substance use, money spent for buying substance per day, history of substance abuse (yes, no), type of substance (hallucinogen substance, stimulant substance, opium), frequency of substance use (every day, every other day, once a week), and frequency of methadone therapy in MMT centers (every day, every other day, once a week) were collected through interviews.

We included all patients who received methadone for at least one year. Those who refused to provide a urine opium test at specified times were excluded. It should be mentioned that in MMT centers, patients need to give urine samples monthly by request from a physician or psychologist. If the test result was positive, this was regarded as a relapse. Given that some persons may receive methadone by several centers, we used the four digits of clients' ID cards to identify and exclude duplicated cases.

We defined substance abuse using the criteria provided by the World Health Organization.[14,15] Accordingly, substance abuse is the state of periodic or chronic intoxication detrimental to the individual and society, produced by the repeated consumption of a substance (natural or synthetic).[15,16] Substance dependence was measured by using the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-V).

DT analysis was used to explore data to select the best independent determinants with the best cut-off point. Compared to regression models, DT analysis can automatically take into account interactions between variables. The Gini index was calculated to determine the cut-off point of nodes. Also, the Classification and Regression Trees algorithm was used to create the DT. This algorithm creates two branches in which the branches have maximum homogeneity within each node and maximum heterogeneity between them. To avoid an over-fitted tree, the minimum sample size for the parent node was 100 patients. Furthermore, the final model was pruned and complexity parameters were plotted against the number of terminal nodes.

We used the Gini index to split the root node. For the confidence, the relapse rate (76.6%) was used to create the DT. The data was divided into two parts, training sample (80.0%) and test sample (20.0%). Firstly, using the training sample, the conceptual model was created; then using test sample, the final model created. Finally, model accuracy was calculated using specificity and sensitivity. Nearly 1.0% of data was missing, which was excluded from analyses. Also, the determinants of relapse rate were examined by univariate and multiple logit regression models. All analyses were performed using SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) with a significance level set at 0.05. The study was conducted according to the Helsinki Declaration

Table 1: Factors related to relapse in self-referred addicts to methadone maintenance therapy centers by univariate and multiple regression models.

Variables	Relapse, n/total (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex			
Male	3091/4037 (76.6)	1	-
Female	104/138 (75.4)	0.92 (0.62–1.37)	-
Marital status			
Single	652/870 (74.9)	1	-
Married	2346/3056 (76.8)	1.14 (0.62–1.37)	-
Divorced	181/245 (73.9)	0.94 (0.62–1.37)	-
Education, years			
Illiterate	167/206 (81.1)	1	-
≤ 5	635/759 (83.7)	1.19 (0.80–1.78)	-
6–9	937/1184 (79.1)	0.88 (0.60–1.28)	-
10–12	1149/1559 (73.7)	0.65 (0.45–0.94)	-
≥ 13	310/463 (66.9)	0.47 (0.31–0.71)	-
Age at first drug use, years			
< 15	222/311 (71.4)	1	1
15–19	1090/1467 (74.3)	1.24 (0.93–1.65)	1.13 (0.85–1.51)
20–24	738/951 (77.6)	1.65 (1.23–2.24)	1.38 (1.01–1.87)
25–29	542/670 (80.9)	1.79 (1.30–2.46)	1.76 (1.27–2.45)
30–39	397/526 (75.5)	1.41 (1.01–1.97)	1.31 (0.94–1.82)
≥ 40	211/250 (84.4)	2.45 (1.52–3.90)	2.32 (1.49–3.59)
Total budget buying substance per day, US$			
< 2	962/1337 (72.0)	1	1
2–4.9	571/812 (70.3)	0.92 (0.76–1.11)	0.92 (0.75–1.12)
5–9.9	361/465 (77.6)	1.35 (1.05–1.73)	1.38 (1.06–1.79)
10–14.9	565/699 (80.8)	1.64 (1.31–2.05)	1.63 (1.30–2.07)
≥ 15	741/862 (86.0)	2.38 (190–2.99)	1.41 (1.91–3.07)
Frequency of methadone therapy in MMT centers			
Each day	1420/1988 (71.4)	1	-
Every other day	501/590 (84.9)	2.25 (1.76–2.88)	-
Once a week	1279/1597 (80.1)	1.68 (1.37–1.88)	-
History for quitting without treatment			
No	261/656 (39.8)	1	1
Yes	2939/3300 (89.1)	3.27 (2.43–4.40)	2.14 (1.69–2.71)
Frequency of substance use before abstinence			
Every day	1014/1293 (78.4)	1	1
Every other day	299/342 (87.4)	1.91 (1.35–2.70)	1.90 (1.30–2.78)
Once a week	1887/2540 (74.2)	0.79 (0.67–0.93)	0.76 (0.64–0.91)
Types of substance			
More than one drugs	309/362 (85.4)	1	-
Hallucinogen	329/450 (73.1)	0.46 (0.32–0.66)	-
Stimulant drugs	255/331 (77.0)	0.57 (0.39–0.84)	-
Opium related drugs	2090/2731 (76.5)	0.55 (0.41–0.75)	-
Substance use disorder			
No	230/347 (66.3)	1	-
Yes	2807/3648 (76.9)	1.69 (1.34–2.14)	-

OR: odds ratio; CI: confidence interval.
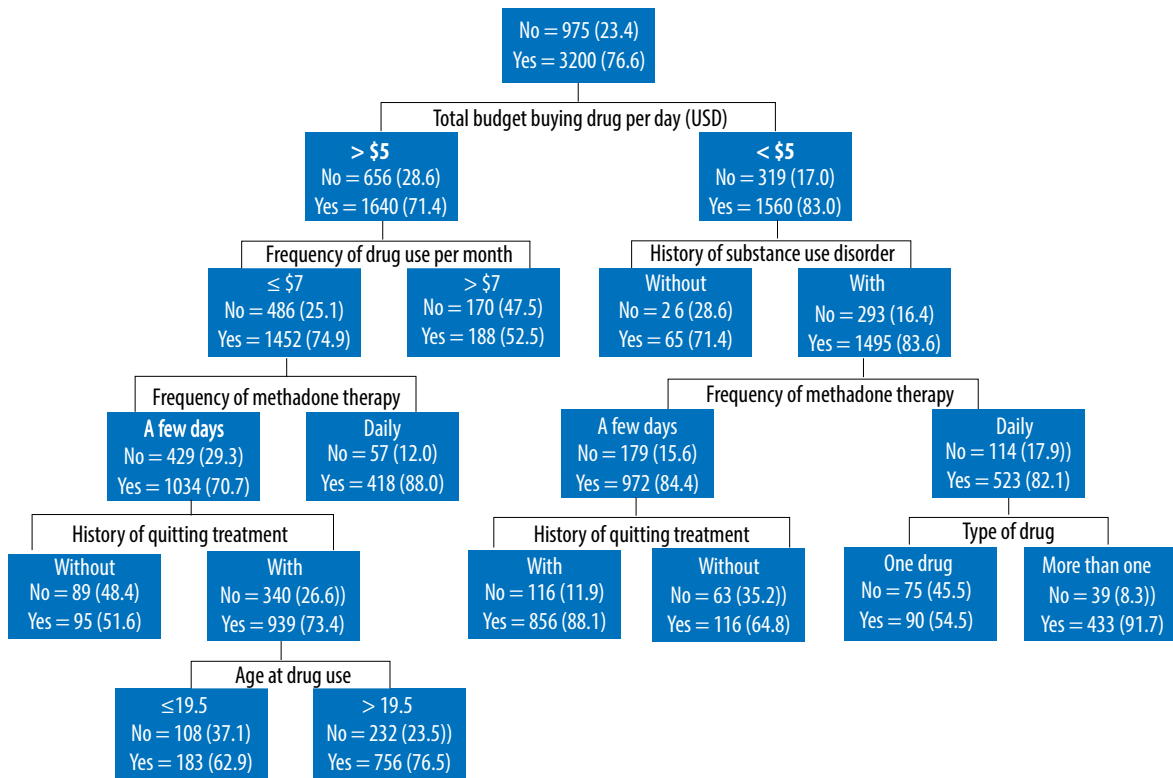
Figure 1: Decision tree analysis of factors related to relapse in patients with substance-related disorders receiving methadone maintenance therapy.

and was approved by the Ethical Committee of Kermanshah University of Medical Sciences.

RESULTS

A total of 4175 self-referred patients to MMT centers participated in the study of which 96.7% (4037) were male. The average of age of males and females were 40.0±11.3 and 40.0±12.6 years, respectively ($p = 0.690$). The mean of age at first substance use was 24.1±8.2 years in males and 29.7±10.5 years in females ($p > 0.001$). The overall relapse rate was 76.6% with no significant differences between men and women (76.6% vs. 75.4%, respectively).

Univariate and multiple regression models revealed that sex, marital status, and years of schooling were not significantly associated with the relapse rate ($p > 0.050$) [Table 1]. While in the univariate model, the type of substance use and frequency of substance use before methadone therapy were associated with relapse, but there was no significant association between these variables and relapse in the multiple regression model. In addition, age at first substance use, the total budget for buying substance per day (US$), history for quitting without methadone

therapy, and frequency of substance use before quitting were associated with relapse in the multiple regression model ($p > 0.050$).

All explanatory variables [Table 1] were used as quantitative variables to create the DT and the Gini index to calculate all cut-off points. The DT resulted in a five-level model. The sensitivity of training and testing groups were 74.0% and 72.0%, respectively. Also, the specificity of these groups were 66.0% and 65.0%, respectively. The accuracy rate of training and testing models were 70.0% and 68.0%, respectively.

The first level of the DT was defined by the average daily budget for buying substances. The relapse rate for those who spent more than US$5 per day buying substance with SRDs for more than one substance was 91.7% compared to 54.5% in those addicted to only one substance. In addition, no history of methadone treatment in those who received methadone once or twice a week decreased the risk of subsequent relapse (64.8% vs. 88.1%). Among those who spent less than US$5 per day buying substances and those who more frequently consumed substances (seven times or more per month), being on daily methadone therapy increased the risk of relapse (88.0% vs. 70.7%). If the age of

first substance use was less than 19.5 years old, the rate of relapse reach was 76.5% versus 62.9% in those who started to use substances at 19.5 years of age or older [Figure 1].

DISCUSSION

This is the first attempt to evaluate the factors affecting the relapse rate in people with SRDs using DT analysis and the logistic regression model. Given the different characteristics and frequency of effective factors on harm reduction and treatment among people referred to MMT clinics, developing a prognostic model is a cornerstone to help physicians to make better treatment choices and then to improve treatment outcomes. We found no similar study for comparing the results and validation of the model. It is necessary to examine the validation of the model in future similar studies.

The results of our study revealed that the overall relapse rate is 76.6%, which is different from both national and international studies. For example, studies conducted in different parts of Iran reported relapse rates of 30.4%[17] and 72%.[18] In the US, about one-third of people relapsed in the first year, and two-thirds relapsed over 10 years after quitting.[19] A relapse rate of 91% has also been reported in Dublin, Ireland.[20] Another study from San Diego showed that about two-thirds (67%) of adults used substances when they were at a social event.[21] Nevertheless, a high relapse rate in the region, a downward trend in the age-adjusted rates of fatal substance overdose in both genders has been reported in Kermanshah province. In fact, harm reduction or treatment for substance addiction has a complex nature, which is associated with social, cultural, environmental, and personal factors. All these factors may lead to differences in relapse after harm reduction and treatment.

Several studies have shown that education level is a predictor of treatment outcome.[22–24] In this study, however, education level did not remain in the DT and multiple logistic regression models. We expected to have education as one of the main determinants of relapse in the final model and DT. Educated people have more self-efficacy with better psychosocial and personality characteristics that indirectly affect both the onset of substance use and experiencing successful abstinence.

Patients who expend more than US$5 per day for buying substances had a better treatment outcome.

In this group, about half of those patients who used substances less than seven days per month had successful treatment. In our opinion, the higher expenditures for buying substances may reflect the economic status of the patients. In this regard, a survey[25] conducted among 111 adolescents to identify the relationship between compulsive buying and risky behaviors reported a significant correlation between uncontrolled buying in college students and substance abuse.

The DT also indicated that among patients who used substances more than seven days per month, having occasional MMT (not daily) has a positive impact on the treatment outcome. In addition, within the group of these subjects, those who had a history of quitting substance without medication had 48.4% success rate compared to 26.6% of those without the history of quitting. In line with our results, a study conducted to determine factors associated with illicit opioid use showed that daily MMT dosages were associated with illicit opioid use.[26] Although we did not have any information about the depression status of our patients, the treatment of depressive symptoms may be an important issue to improve treatment outcomes in substance abuse patients.[27]

Patients aged > 19.5 years at first substance use with no history of substance withdrawal had better treatment success. Similarly, the previous epidemiological studies indicated that a younger age at first substance use was associated with an increased risk of substance abuse disorders and the rate of relapse.[28–30] One reason may be the interaction between genetic and other environmental factors, although this causal mechanism is not well known yet.[31]

The results from another arm of the DT showed that the treatment success rate depends on the variable stratified. For example, patients who spent less than US$5 per day buying substances and had no other SRDs had better treatment outcomes (83.0% vs. 71.4% relapse rate). A positive treatment outcome was observed in individuals with a comorbidity and SRDs (83.6% vs. 71.4%) with daily MMT (82.1% vs. 84.4%) and with single substance use (54.5% vs. 91.7%).

This study has several limitations. We conducted a cross-sectional study design, and the associations should be interpreted cautiously. On the other hand, data from medical records were used and some variables were also collected based on self-reported data, which raises the issue of

information bias. In addition, we had no access to the cohort's psychological functioning, social and family support system, and socioeconomic status. Despite the mentioned limitations, our results can be important and provides additional information for physicians to make better decisions for improving treatment outcomes.

CONCLUSION

Variables such as substantial expenditures, age at first substance use, history of quitting substance without medication, frequency of substance utilization per month, and frequency of methadone therapy effect on the substance abuse relapse. In addition, the DT based approach revealed a useful approach to show the effect of these factors on the treatment result at different levels.

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