Evaluation of Drug Abuse Relapse Event Rate Over Time in Frailty Model

Somaye Hosseini a, Abbas Moghimbeigi b,*, Ghodratollah Roshanaei b, Farzaneh Momeniarbat c

aDepartment of Biostatistics and Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran.
bModeling of Noncommunicable Disease Research Center, Department of Biostatistics and Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran.
cDepartment of Psychology, Science and Research Branch, Islamic Azad University, Hamadan, Iran.

Abstract

Objectives: Drug dependence as a chronic disorder is reversible over time and has a cost burden for individuals, families, and society. An individual who has stopped taking drugs for a long time may start taking drugs again. The variables affecting the reuse of drugs are not well known. Therefore a study of the factors that increase the length of time away from drugs is essential.

Methods: This study used data collected by the Bushehr addiction treatment centers (Tolloe and Pasargadae) from 100 men with drug addiction from March 2006 to September 2010. The shared frailty model was used to study the influence of variables on the duration of time away from drug use. The most common method for entering intra-class (personal) correlation is the survival frailty model, which uses parametric survival data for the evaluation of recurrent events. A Weibull distribution for time to event with gamma shared frailty was used.

Results: The mean (standard deviation) age and age at onset of opium use of the sample were 33.85 (8.11) and 20.65 (6.87), respectively. About 30% of the men studied had chronic disease and 36% had a mental illness. The mean (frequency mean) of the amount of opium used were 4.73 (3.8) g and 2.54 (1.14) times per day. The desire to end drug use was 97% and 3% for the men with drug addiction and their families, respectively, at the time when the men stopped using opium. The age at onset of opium use [p = 0.046, hazards ratio (HR) = 1.30], history of chronic disease (p = 0.005, HR = 249.635), and marital status (p = 0.06, HR = 0.027) are important in the reuse of opium.

Conclusion: We found that opium addiction is related to other chronic diseases and to the age at onset of opium use. A prospective study following up individuals with drug addiction who try to stop drug use in addiction treatment centers could help to determine the risk factors of resuming drug use.

*Corresponding author.
E-mail: moghimb@yahoo.com

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1. Introduction

Drug dependence is a known social disorder and has become a major problem in some communities in recent years. Drug dependence causes long-term and recurrent suffering for individuals, families, and communities and a cure has not yet been found. Although an individual may stop using drugs for a long time, he or she may begin to use drugs again. Demographic and social factors and familial influence affect the start of drug use, continuing drug use, and return to drug use after time away from drugs [1]. During the addiction review process there is a fundamental problem in that individuals often have several unsuccessful attempts to stop drug use prior to when they are successful in finally stopping taking drugs [2]. It is therefore necessary to determine the factors which can prolong the period away from drugs.

The addiction process can thus be seen as a recurrent event. Recurrent events data have often been analyzed using standard survival analysis methods with an adjustment for events occurring for each person that leads to a marginal model or a frailty model [3].

As a result of the increasing use of survival analysis in medical research, there is now a need for a more flexible and efficient model for survival data. Standard methods of survival analysis in clinical research are based on the assumption that the sample is a homogeneous group. Thus survival models assume that the survival of individual patients is independent of each other and the patients’ survival time distributions are the same. However, in many instances the study group cannot be assumed to be homogeneous and individual group members have different risk factors [4–6]. In many instances the importance of some factors associated with the disease are still unknown, e.g., economic factors. It is very difficult or impossible to measure all the effective and appropriate factors related to an event [7]. Ignoring unknown shared risk factors may lead to dependency between survival times and bias estimation of parameters. In these situations, we use frailty models to solve these problems. Frailty models are the most common methods for entering the intra-class (personal) correlation in survival analysis. These models formulate the variation of survival times as two sources. The first source is the natural variation explained by hazard function and the second source is the shared variation between individuals in a group (individual) expressed by the shared frailty variable [5,8,9].

There have been many studies on cigarette smoking and its prevalence in Iran [10,11], but few studies about ending drug and cigarette addiction. Li et al [12] used a cure fraction frailty model to study smoking cessation. Multiple regression using proportional hazards frailty models was applied to identify independent predictors and correlates of the duration of repeated abstinence episodes [13]. It is important to know the risk factors affecting the recurrence times of drug addicts who attempt to end their use of drugs. In this study we used the frailty model to determine these risk factors. We used a gamma distribution with finite mean because the risk function is always positive for the frailty. We also used the frailty model to consider the heterogeneity in individuals with drug addiction and we considered the mean of the frailty variable to be equal to one [8,9].

2. Materials and methods

This study used data collected from 100 patients admitted to two addiction treatment centers in Bushehr (Tolloee and Pasargad). The data were recorded from March 2006 to September 2010. The available covariates, demographic information, and drug use data were collected. The time frame of this study was divided into 3 month intervals. Smoking status was defined by questions about the use or non-use of drugs at 3 month intervals.

Participants were allowed to indicate that during the previous 3 months: (1) they had not used drugs at all; (2) they had used drugs, but had stopped at some time during the interval; or (3) they had used drugs continuously. For the individuals who indicated (2), the time of stopping drug use and the duration of cessation were unknown. It is difficult to distinguish between groups (2) and (3) and we considered them as “users since last visit.” Individuals who answered (1) positively were treated as non-users since their last visit.

In this study we only considered use of opium and non-use of opium; use of other drugs was not considered. In addition to demographic questions and questions about employment status, three questions were asked about the age of onset of the use of opium, the history of chronic disease, and mental and psychiatric illnesses. The following questions were also asked at each 3 month time interval: (1) amount of opium used and frequency of opium use per day; (2) the use or non-use of other drugs (including heroin, crack cocaine) at least once a week; (3) whether the decision to stop drug use was made by the individual or with their family; and (4) whether alcohol was consumed at least once a week.

We used a parametric shared frailty analysis for recurrent events. This included proportional hazards, a Weibull distribution for time events, and gamma shared frailty frequency dependence on time. We defined a model based on the hazard of the $k^{th}$ individual in the $j^{th}$ event and the $a_k$ frailty for this individual. Frailty is the multiplicative risk effect of the hazard function $h(t|x_k)$. This assumed a gamma distribution with a mean of 1 and variance $\theta$. Also, we assumed that $h(t|x_k)$ had a Weibull distribution. Therefore:
where $x$ is the dependent variable of interest.

The frailty is included in the model to account for unobserved participant-specific factors that are unaccounted for by the other predictors in the model. These unobserved participant-specific factors can be a source of within-participant correlation. We used the shared frailty term to indicate that observations of each individual are clustered and correlated $[13]$. To fit the model, we considered recurrence in each 3-month interval so that the first interval of interest for every individual was the first non-smoking interval. The continuously and repeated non-use intervals were assumed to be a without recurrent interval and the interval after these intervals in which the individual reused narcotic drugs was assumed to be a recurrent interval. Individuals who had made no attempt to stop drug use were therefore left out of the study.

The opium consumption rate, consumption frequency, employment status, and use of other drugs in each interval were also recorded. For example, Figure 1 clearly shows the narcotic-using status at each interval of one individual. The letters U and N denote opium use and non-use intervals, respectively. An attempt to stop using opium is defined as the opium non-use interval immediately after a use interval (e.g., the first and fourth non-use intervals in Figure 1). Similarly, a relapse to use is defined as the opium use interval immediately after a non-use interval (e.g., the second interval in Figure 1). For example, if an individual follows an opium use pattern like that in Figure 1, at the second period she or he has reused opium and after two periods has attempted to stop opium use and then relapsed to opium use in the sixth period. After 6 months again he or she has another attempt to stop drug use and remains a non-user until the end of the study. The variables in the model were selected using a forward strategy with entry and removal of the 0.05 and 0.1 levels.

3. Results

All of the 100 individuals with a drug addiction in this study were men. The mean (standard deviation) age and age at onset of drug use of the sample were 33.85 (8.11) and 20.65 (6.87), respectively. A total of 9.1% of the sample group were unemployed. About 30% of the sample had chronic disease and 36% had a mental illness. Heroin and crack cocaine were used by 25% of the sample. The mean amount of opium used and its frequency mean were 4.73 (3.8) g and 2.54 (1.14) per day. A total of 10% of the sample drank alcohol at least once a day. The decision to stop drug use was made by the drug users in 97% of the sample and by their family in 3% of the sample in the intervals in which the individuals stopped using opium.

Table 1 gives the results of the model with the shared frailty component. For $0 = 0$, the likelihood ratio test was statistically significant ($p < 0.001$) and suggested within-participant correlation so the frailty component must be in the model. The estimated Weibull shape parameter $p$ is 4.89 and indicates an increased hazard over time ($\hat{p} > 1$). However, the Wald test shows $\ln(p) = 0$ ($p = 1$) is significant ($p < 0.001$). This means the time to recurrence risk increases. The table also shows that the age at the onset of addiction [$p = 0.046$, hazard ratio (HR) = 1.30], history of chronic disease ($p = 0.005$, HR = 249.635), and marital status ($p = 0.06$, HR = 0.027) have a significant role in the relapse time to using opium again.

4. Discussion

To address the factors affecting the cessation of drug use in the field of treatment for drug addiction, this study followed up behavioral outcomes at various time intervals. The parameters measured were analyzed in a traditional frailty model to determine the factors which affect the reuse of opium $[3-5]$. We recommend collecting these measures during the course of treatment; however, in this work we used historical data registered with addiction treatment centers.

In a previous study, factors such as inappropriate friends, unemployment, poverty, family problems, improper behavior of family, and improper behavior of spouses were found to be related to a return to drug abuse $[14]$. In study conducted by Seraji et al $[15]$, the factors affecting a relapse to drug use were found to be unemployment and changes in income. However, in this study we found that the age at onset of drug use and a history of chronic disease were both significant in the time interval to a return to drug use. Marital status was also significant to relapse time at the 0.1 level.

![Figure 1](image-url)  
Figure 1. Time plot of an individual’s pattern of using opium.
Some workers have considered addiction as a chronic illness \cite{16,17}. We found historically that having at least one chronic disease affected the relapse time. In other words, the addiction is related to other chronic diseases such as mental disorders.

The potential limitations of this study include the reliance on self-reported data. As the time elapsed since the event of first opium use will be longer for those who started at a younger age, the shift in age of first opium use would probably be even more obvious. As we relied on the self-reporting of interval times for opium use, these times may not be completely true and may be biased.

In conclusion, we found the addiction is related to other chronic diseases and to the age at which drug abuse began. Developing a prospective study to follow up individuals with addiction who try to stop drug use in addiction treatment centers could help to determine the risk factors for resuming drug use.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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Table 1. Parametric model with frailty component

| Parameter                        | Coefficient | SE  | p       | 95% Confidence interval |
|----------------------------------|-------------|-----|---------|-------------------------|
| Age at onset of addiction (y)   | 0.26        | 0.13| 0.047   | 0.003 0.52              |
| Marital status (yes = 1, no = 0)| −3.62       | 1.97| 0.060   | −7.47 0.23              |
| History of chronic disease (yes = 0, no = 1)| 5.52| 1.99| 0.005   | 1.63 9.42              |
| Intercept                       | −9.2        | 3.64| 0.011   | −16.3 2.07              |
| Ln(p)                           | 1.59        | 0.3 | 0.000   | 1.00 2.19              |
| Ln(q)                           | 0.61        | 0.37| 0.090   | −0.11 1.33              |
| P (Weibul shape parameter)      | 4.93        | 1.49| 0.011   | 2.72 8.92              |
| 1/p                             | 0.2         | 0.06| 0.011   | 0.11 0.37              |
| θ (frailty variance)            | 1.84        | 0.67| 0.095   | 0.89 3.78              |

*Likelihood ratio test for θ = 0: x² = 23.09 and p < 0.001. SE = standard error.