Addiction & Health

https://ahj.kmu.ac.ir
10.34172/ahj.2023.1277
Vol. 15, No. 3, 2023, 149-155

Original Article

Time Series Modeling and Forecasting of Drug-Related Deaths in Iran (2014-2016)

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Abstract
Background: Investigating the temporal variations and forecasting the trends in drug-related deaths can help prevent health problems and develop intervention programs. The recent policy in Iran is strongly focused on deterring drug use and replacing illicit drugs with legal ones. This study aimed to investigate drug-related deaths in Iran in 2014-2016 and forecast the death toll by 2019.
Methods: In this longitudinal study, Box-Jenkins time series analysis was used to forecast drug-related deaths. To this end, monthly counts of drug-related deaths were obtained from March 2014 to March 2017. After data processing, to obtain stationary time series and examine the stability assumption with the Dickey-Fuller test, the parameters of the Autoregressive Integrated Moving Averages (ARIMA) model were determined using autocorrelation function (ACF) and partial autocorrelation function (PACF) graphs. Based on Akaike statistics, ARIMA (0, 1, 1) was selected as the best-fit model. Moreover, the Dickey-Fuller test was used to confirm the stationarity of the time series of transformed observations. The forecasts were made for the next 36 months using the ARIMA (0,1,2) model and the same confidence intervals were applied to all months. The final extracted data were analyzed using R software, Minitab, and SPSS-23.
Findings: According to the Iranian Ministry of Health and the Legal Medicine Organization, there were 8883 drug-related deaths in Iran from March 2014 to March 2017. According to the time series findings, this count had an upward trend and did not show any seasonal pattern. It was forecasted that the mean drug-related mortality rate in Iran would be 245.8 cases per month until 2019.
Conclusion: This study showed a rising trend in drug-related mortality rates during the study period, and the modeling process for forecasting suggested this trend would continue until 2019 if proper interventions were not instituted.
Keywords: Drug abuse, Forecasting, Poisoning, Time series, Trend

Citation: Zarghami M, Kharazmi O, Alipour A, Babakhanian M, Khosravi A, Mirtorabi SD. Time series modeling and forecasting of drug-related deaths in Iran (2014-2016). *Addict Health*. 2023;15(3):149-155. doi:10.34172/ahj.2023.1277

Received: June 20, 2021, **Accepted**: September 8, 2021, **ePublished:** July 29, 2023

Introduction

Illicit drug use is a serious public health concern in Iran.[1] The prevalence of substance use in Iran and other Muslim countries, such as Afghanistan and Pakistan, is much higher than in Western societies.[2] Iran has a long history of substance use and borders Afghanistan, the largest producer of illicit drugs in the world, which provides easy access to drugs.[3] Alcohol and other substance use disorders make up about 2% of the burden of diseases in Iran, which is in line with global statistics, and places a heavy burden on the health system of Iran.[4] In Iran, a number of policies and programs have been implemented to reduce the harm caused by drug use. One such program is methadone maintenance treatment (MMT) for harm reduction developed in 2005. Iran's geographical placement in the region has important implications regarding drug transit from Afghanistan to Europe. As a result, border surveillance and very strict drug trafficking laws have been implemented to reduce the drug supply, demand, and harm.[5-8] Compared to the past decade, the age-adjusted rate for overdose and drug-related deaths has decreased and a diverse pattern of smoking as well

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as alcohol and other drug use has emerged among adolescents in Iran. Therefore, government officials should revise their policies on drug harm, supply, and demand reduction.[3,9]

In the long run, the mortality rate among drug users is 6 to 54 times higher than expected, and it is 8 times higher in patients recently treated for overdose compared to the general population.[8] History of severe psychiatric illness and accidental or intentional drug overdose are major mortality risk factors in this group.[8,9] In Iran, despite the presence of harm reduction programs, the rate of fatal drug poisoning is 152% higher than the corresponding rate two decades earlier.[10]

This is the first study that employs time series and forecasting for drug-related deaths in Iran. Accordingly, this study aimed to provide new and potentially more refined evidence on a unique dataset, which consists of monthly observations in Iran for nearly 3 years.

In this study, Autoregressive Integrated Moving Averages (ARIMA) was used to examine temporal changes, such as upward or downward trends, in fatal poisoning with drugs and alcohol in Iran in 2014-2016, and to forecast future trends. ARIMA is the most widely used model for short-term forecasting and investigating the stationarity and seasonality of a phenomenon, and it is a powerful analytical tool with simple interpretations; however, it is rarely used in public health programs.[11] This forecasting process can provide valuable information and credible evidence for policymaking. The ARIMA model can be a useful tool for predicting future drug related death cases and trend of drug death is important for the rational allocation of health resources. This study also aimed to examine the future to enable better decision-making and ultimately help ameliorate the situation of drug use in Iran.

Methods

The present time-series study follows another study by the same authors in 2019 entitled, "An estimation of drug-related deaths in Iran using the capture-recapture method"[12] with the ethics code IR.MAZUMS.REC.1398.445. Using the capture-recapture method, data on drug-related deaths, with applicable diagnostic codes in the International Classification of Diseases (ICD-10), for the years 2014-2016 were collected from the Iranian Ministry of Health and Medical Education and the Legal Medicine Organization. The recorded data from March 2014 to March 2017 were in the form of numbers of referrals by month with applicable ICD-10 codes.[13] The trend of deaths was evaluated over a period of 36 months.

After data processing, to obtain stationary time series and examine the stability assumption with the Dickey-Fuller test, ARIMA model parameters were determined using autocorrelation function (ACF) and partial autocorrelation function (PACF) graphs. Based on Akaike statistics, ARIMA (0,1,1) was selected as the best-fit model.

Modeling

In this study, time series analyses of Box-Jenkins and Box-Cox models were performed to forecast the number of drug-related deaths. Besides, the Kolmogorov-Smirnov and Bartlett's tests were used to assess the normality and equality of variances in data on drug-related deaths. To analyze the month-specific death toll from 2014 to 2016, ACF, PACF, dependency quantity, and time series structural decomposition graphs were utilized. According to these graphs, mean and variance were non-stationary. For a more detailed analysis, the Cox-Box transformation was also used. The estimated λ parameter in the Cox-Box transformation was 2.27. Then, a first-order differential operator was applied to the main observations. For further investigation, the Cox-Box transformation was reapplied to the transformed observations, which produced a value of one. As a result, there was no need to reapply the transformation to the observations. The λ parameter is estimated by the maximum likelihood method in Cox-Box transformation. Therefore, the non-stationarity of the variance was removed. Furthermore, the Dickey-Fuller test was used to confirm the stationarity of the time series of the transformed observations (Table 1).

Once these graphs were redrawn, it became clear that the minor trend in structural decomposition was not present anymore and stationarity in the mean and variance was restored. According to the ACF and PACF graphs, the proposed model in the ARIMA family is ARIMA (0,1,1) for the transformed observations. To enable evaluation and comparison with models close to ARIMA (0,1,1), the ARIMA (0,1,2) and ARIMA (1,1,1) models were also fitted to the initial time-series observations, and the AIC model selection criterion was used for the excellence of these models. According to the AIC criterion, a model with a lower AIC is better suited for this purpose. The results (Table 2) suggest the ARIMA (0,1,2) model provides a better fit. The final model of the observations was hence considered to be ARIMA (0,1,2) (Table 2).

The residuals corresponding to this model were also evaluated for their dependence and normality. The ACF,

Table 1. The Dickey-Fuller test results for the transformed data

Dickey-Fuller statistic	*P* value
-7.4398	0.01

Table 2. A comparison of the goodness of fit of the models

Model	AIC
ARIMA (0,1,2)	368.08
ARIMA (0,1,1)	372.20
ARIMA (1,1,1)	368.82

PACF, and QQ-Plot graphs for the residuals showed uncorrelated normal observations. The Ljung-Box test was used to confirm the residuals in this section were not correlated. In the final section, forecasts were made for the next 36 months using the ARIMA (0,1,2) model, and the same confidence intervals were applied to all months, except for the first month and the correlate graph until 2019 was presented using ARIMA (0,1,1). Time Series and Forecast Package in R software was used for model fitting and forecasting the intended time series data. Additionally, some of the analyses were performed using Minitab software. The final data were analyzed using R 3.4.3 (Time Series and Forecast Package) software,[14] Minitab, and SPSS-23.

Inclusion criteria

The present study was conducted based on the ICD-10 codes for drug-related deaths due to poisoning. The leading cause of drug-related deaths was drug overdose, including acute alcohol intoxication (both ethyl and methyl variants) and opioid, tranquilizer (barbiturates and benzodiazepines), and stimulant (cocaine and amphetamines) overdose.[13]

Results

According to the Ministry of Health and the Legal Medicine Organization, there were a total of 8883 drug-related deaths in Iran in 2014-2016 with 2840, 2810, and 3233 deaths in 2014, 2015, and 2016, respectively. Figure 1 shows the mean of the series is almost stationary. There is also a slight trend in the time series but there is no seasonal or periodic trend. To more precisely examine the time series components, including trend, seasonal effect, and random component, the time series is broken down using the moving average method. The structural time series breakdown shows a slight upward trend in the time series. An upward trend may affect the stationarity of the mean of the time series (Figure 1).

ACF and PACF graphs were used to determine moving average and autoregressive degrees. Figure 2 present the ACF and PACF graphs of the transformed data, respectively. Inspecting the ACF and PACF, it appears that the ACF is cutting off at lag 1 and the PACF is tailing off. This would suggest that the drug-related death rate follows an MA (1) process or drug-related deaths follow an ARIMA (0,1,1) model. Instead of focusing on one model, ARIMA (0,1,2) and ARIMA (1,1,1) models are suggested for fit to the data. As a preliminary analysis, we will fit these models (Figure 2).

After applying a Box-Cox transformation, the variance was clearly stabilized and no trend can be overtly observed. Figure 3 presents the time series of drug-related deaths between 2014 and 2016 after the Box-Cox transformation ($\lambda = 1$).

Figure 4 shows the structural time series breakdown of the transformed data under Cox-Box and the first-order differential operator. The Cox-Box transformation and first-order differential operator eliminated and then, the

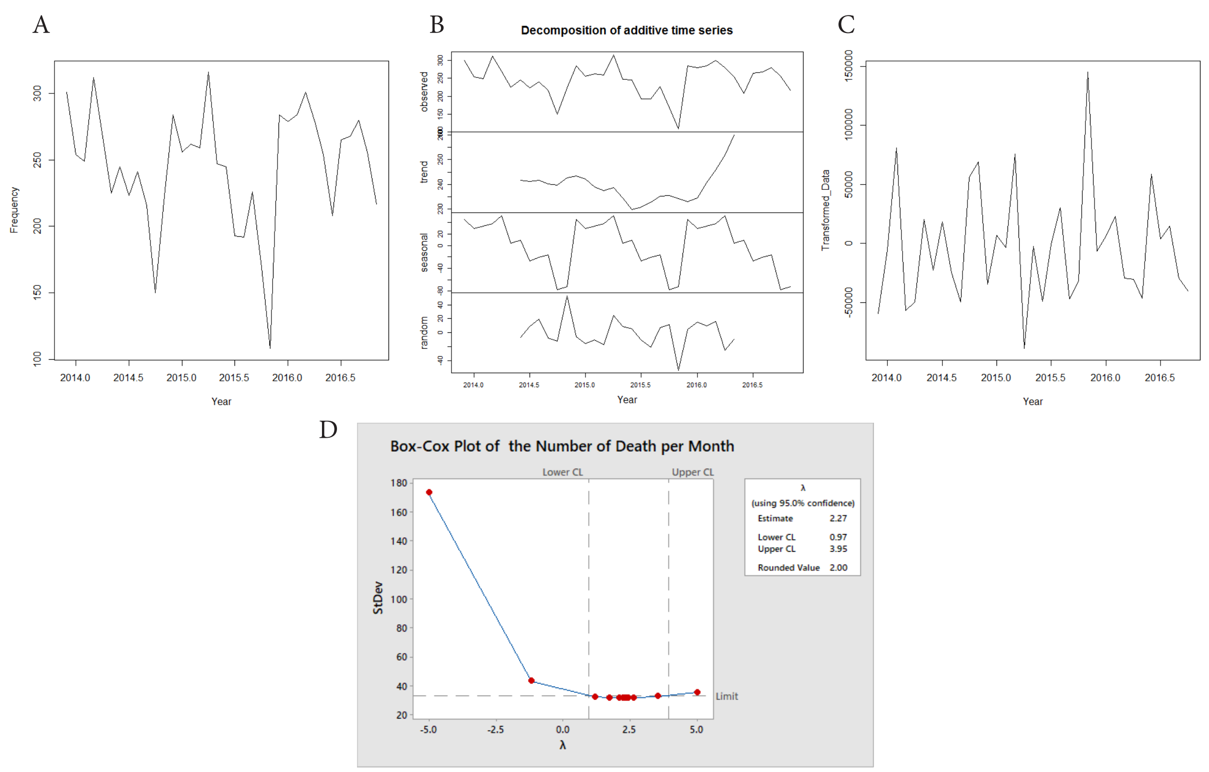

Figure 1. **(A)** Time series graph of total drug-related deaths in Iran in 2014-2016, **(B)** Structural time series decomposition, **(C)** Time series graph of transformed observations from 2014 to 2016, **(D)** Structural time series decomposition after transformations

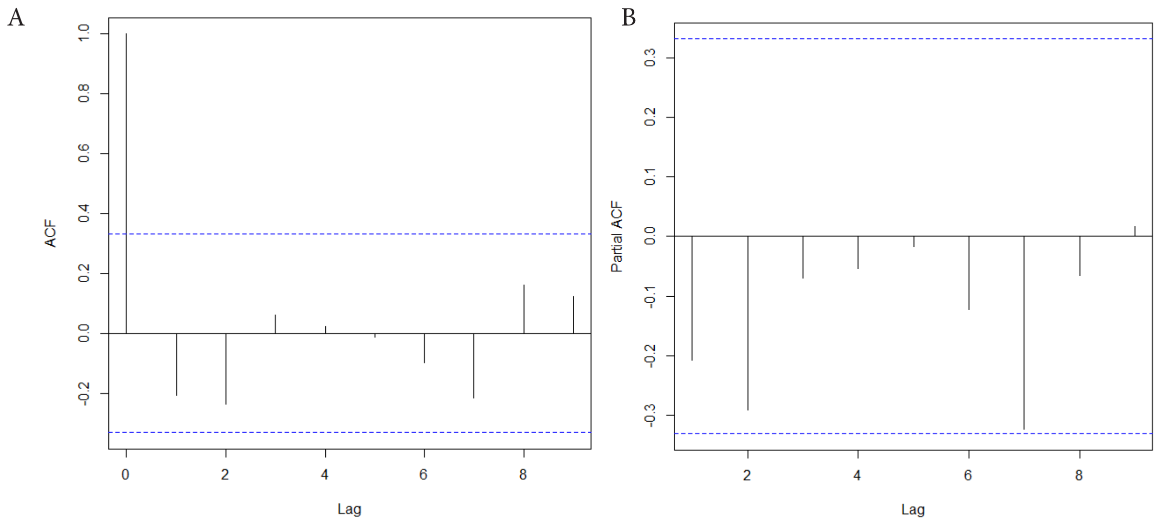

Figure 2. (A) ACF graph of transformed data, (B) PACF graph of transformed data

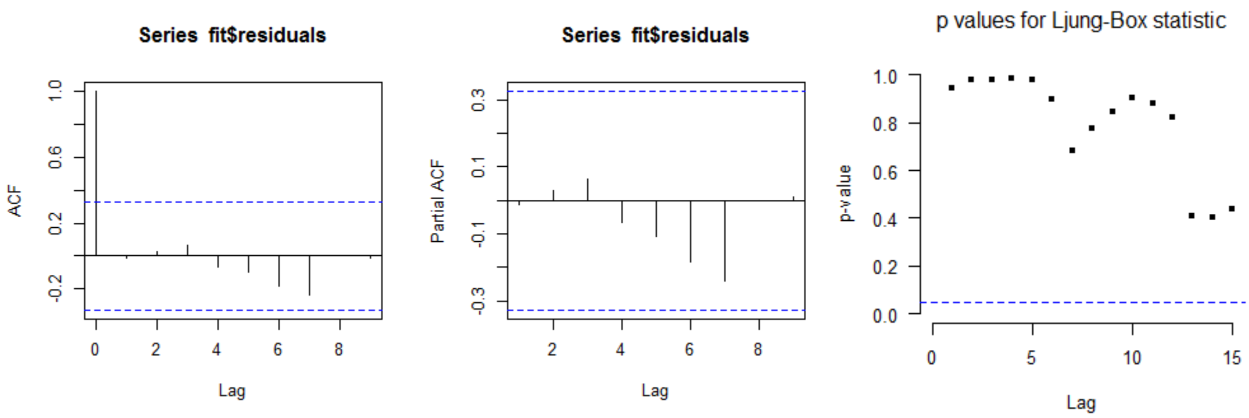

Figure 3. Residual analysis plots for transformed data

data trend and the time series of the transformed data became stationary. The Dickey-Fuller test was used to further investigate the stationarity of the transformed time series data. The Dickey-Fuller test produced a *P* value of 0.01, confirming the stationarity of the transformed data (Table 1).

Model selection

According to the results presented, the ARIMA (0,1,1), ARIMA (0,1,2), and ARIMA (1,1,1) models appear suitable for fit to the data. The AICs were compared to select the best model. The AICs of ARIMA (0,1,1), ARIMA (0,1,2), and ARIMA (1,1,1) models were 372.2, 368.08, and 368.82, respectively. A comparison of the AICs of the proposed models for fit to the data shows the ARIMA (0,1,2) model has the lowest AIC and is the best model for fit to the data.

The model parameters were estimated using the maximum likelihood method. To test the goodness of fit of the proposed model, the residuals were analyzed intuitively using the Ljung-Box test (Figure 3).

The ACF of the standardized residuals shows no apparent departure from the model assumptions, and the Q-statistic is never significant at the lags shown. The normal QQ plot of the residuals suggests that the assumption of normality is appropriate. The PACF graph confirms the correlation is zero for all delays. The proposed fitted model is hence valid for checking the residuals (Figure 4)

Forecasting

Using the forecasting model, we forecasted the drug related deaths cases in each month from 2017 to 2019 would be 245.85 with 95% confidence interval (152.4652 -339.2351) (Figure 5 and Table 3).

Discussion

The results of this study revealed the death rate increased slightly among illicit drug users in Iran in 2014-2016. According to the World Health Organization (WHO), in the same period, the number of drug-related deaths in the US and UK also increased, which could be attributed to increased access to drugs and the inefficiency of harm reduction approaches. After the Islamic Revolution, the

Table 3. Interval estimation for the death toll by 2019

Year	Month	95% Confidence interval	
		Lower bound	Upper bound
2017	April	149.7580	316.8699
	May	152.4652	339.2351
	June	152.4652	339.2351
	July	152.4652	339.2351
	August	152.4652	339.2351
	September	152.4652	339.2351
	October	152.4652	339.2351
	November	152.4652	339.2351
	December	152.4652	339.2351
	January	152.4652	339.2351
	February	152.4652	339.2351
	March	152.4652	339.2351
2018	April	152.4652	339.2351
	May	152.4652	339.2351
	June	152.4652	339.2351
	July	152.4652	339.2351
	August	152.4652	339.2351
	September	152.4652	339.2351
	October	152.4652	339.2351
	November	152.4652	339.2351
	December	152.4652	339.2351
	January	152.4652	339.2351
	February	152.4652	339.2351
	March	152.4652	339.2351

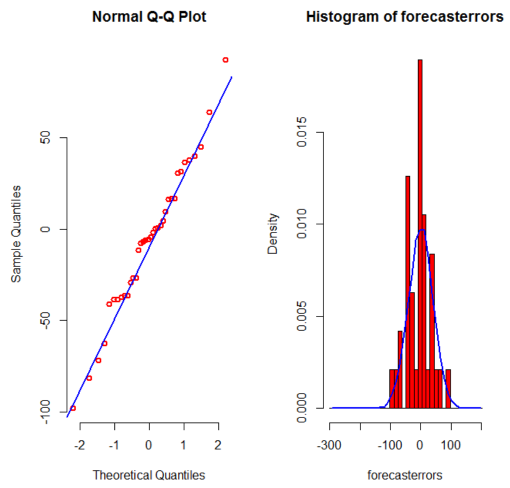

Figure 4. Normal QQ plot of the residuals

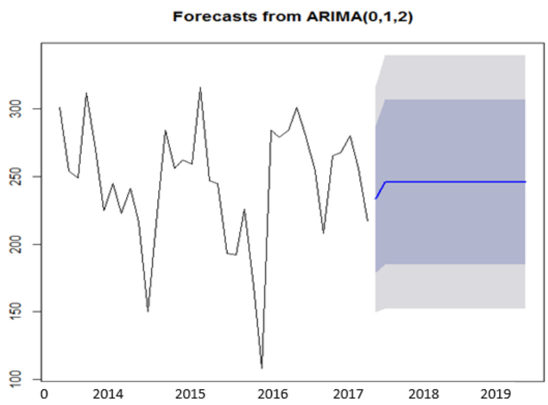

Figure 5. Forecasts of time-series data by 2019 using the ARIMA (0,1,2) model

criminal justice system of Iran has taken many steps to combat drug use but none of them has managed to reduce this phenomenon.[15] In 2005, the National Association of Medical Examiners passed a bill requiring all drug- and alcohol-related deaths to be autopsied by a forensic pathologist, leading to the uncovering of a large number of drug-related deaths.[16]

To minimize the harm to the users, and to the society at large, the Iranian government has focused on harm reduction approaches in recent years. MMT, an effective harm reduction method, is a viable alternative for heroin users. Iran, with the most proliferative harm reduction infrastructure in the Middle East, has provided good access to MMT.[17] However, surveys show many clients of these centers continue to use other illicit drugs, such as methamphetamine. The major reasons for this tendency include compulsory drug treatment programs, social stigma, police confrontation, and difficulty in obtaining government-issued identification, which socially marginalizes those attending harm reduction centers.[17]

ARIMA time-series analysis is a great model for searching for the effect of programme and policy interventions on drug-related problems in countries, but it is rarely used in studies of public health programmes.[11] We included all drug poisonings (regardless of intent), for example, accidental, assault, intentional, and undetermined poisonings, in our analysis. The rising rates of drug poisoning mortality have largely driven this epidemic, which is geographically wide in Iran[18] and around the world because drug availability, prescribing patterns, and resources to combat overdose vary by region.

Shiels et al stated in their study that Rapid increase in drug poisoning mortality have occurred in communities and not limited to a certain race or area. Rapid interventions in public health are needed for this public health emergency.[19]

Forensic Toxicology Center of Iran has identified methadone as a major cause of death.[20] In recent years, harm reduction approaches, including MMT, have not been effective enough in reducing the death toll due to substance use. This fact, again, puts emphasis on the superiority of preventive programs.[15]

As explained, harm reduction programs, including

MMT, have not been successful enough in reducing deaths due to overdose; therefore, three suggestions are made for updating harm reduction policies:

1. Implementing the naloxone program in the target population, namely families and physicians: This program includes recognizing opioid overdose and temporarily reversing it. The program has been successfully implemented in some countries and training families, emergency personnel, and police is part of this program in Iran.[21]
2. Implementing harm reduction policies for adolescents at schools, training their parents with the related skills, and involving the parents in primary drug use prevention programs at schools.[21-23]

Reviewing Iran's criminal code demonstrates that the criminalization of drug offenses accelerated after the Islamic Revolution but it did not have much effect on reducing drug use.[15] Iran executed 509 drug traffickers in 2011, triggering a human rights outcry. As a result, Iran ended its cooperation with the EU on reducing drug use.[24] According to the UN, drug dependence is a complex multidimensional health problem.[25] Decriminalizing drug dependence or delaying criminal punishments until the affected individuals receive appropriate healthcare and social support, will facilitate these individuals' access to therapists and harm reduction programs.[15,26] Portugal was the first country to decriminalize all drugs in 2001, and subsequently achieved the second lowest rate of drug-related deaths among EU countries, compared to the world average.[27] Many Asian countries have successfully implemented similar programs and have attained lower rates of HIV transmission among drug users.[25,26] Nevertheless, these countries are now faced with a wave of novel illicit drugs, such as amphetamine-type stimulants.[25] There is no substitute treatment for these novel drugs yet and only long-term psychological interventions can reduce their harm.[25] Clinicians and patients should discuss the pragmatic aspects of treatment delivery beforehand, because psychosocial interventions may vary in terms of intensity, duration, modality, and media (e.g., face-to-face in most psychotherapies, very limited contact, online, or telephone consultation). The long recovery process could undermine public opinion about drug policies.[28]

Limitations

This study had two limitations:

Although a time series model requires short intervals for analysis,[29] the overall number of years surveyed in this study was small, and the number of points required for ARIMA analysis was decreased.

This study was the first to examine the trend of drug-related deaths (i.e., by opioids, stimulants, and alcohol) in Iran from 2014 to 2016 and forecast the death toll until 2019. Since there is no dedicated national record for registering drug-related deaths or drug overdoses in Iran, and as different organizations and sources report different statistics, there may be undercounts. To address this problem, the present study used statistics from two major death registries in Iran to correct the error caused by undercounts. The Forensic Medicine Organization's lack of cooperation in providing accurate statistics on the types of drugs involved was a major limitation of the present study. Understanding the pattern and type of drug use in each region of the country can help design suicide prevention strategies and reduce the risk of accidental poisoning.

Conclusion

The time series modeling and forecasting of drug-related deaths in Iran showed an upward trend from 2014 to 2016 and this trend would continue until 2019. Public health measures should be formulated to focus on high-risk age groups and identified regions. Thus, ARIMA models can help government to manage the huge pressure that drug related deaths is exerting on Iranian healthcare system.

Acknowledgments

The authors would like to thank Iranian Ministry of Health and Medical Education (MOHME) and the Iranian Legal Medicine Organization (LMO) for Giving data.

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Writing–review & editing: Masoudeh Babakhanian, Mehran Zarghami.

Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving in accordance with the ethical standards of the institutional and/or national research committee of Iran (Research ethics code: IR.MAZUMS.REC.1398.445; 2019).

Funding

This work was supported by Psychiatry and Behavioral Sciences Research Center, Addiction Institute, Mazandaran University of Medical Sciences.

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