

Research Paper:

Evaluation of Methadone Consumption Rate Based on Post-mortem Toxicology Examinations in Cases of Drug-related Deaths in Iran: 2015-2017



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ABSTRACT

Background: Given the increasing prevalence of methadone overdose and the growing number of deaths in Iran, the present study was conducted to determine the mortality rate of methadone detected in the cadavers brought to the Forensic Medicine Organization between 2015 and 2017.

Methods: This cross-sectional study was performed on 7,486 cases of substance abuse deaths registered in the Forensic Medicine Organization during 2015-2017. In order to investigate the drug abuse, samples collected from the cadavers were initially examined for their drug contents, such as methadone, by standard screening methods and then confirmed by Thin Layer Chromatography (TLC). Using two checklists, the information collected about each cadaver consisted of the identity, autopsy and laboratory data. After data collection, they were entered into the Stata software version 14 MP.

Results: The cadavers' mean age was 36.6±12.6 years. Over the 3-year duration of the study, the standardized mortality rate increased from 35 to 39 cases per million per year. Of these cases, 6066 were randomly assigned to toxicology, 50.1% had used methadone one month before their death. Approximately 75% of the methadone abusers had taken another drug simultaneously, mostly morphine or methamphetamine.

Conclusion: Considering the relatively high prevalence of methadone detected post-mortem, monitoring for methadone entry into public market and identifying the death-related factors in the drug abusers are considered as significant measures to improve upon the current alarming situation in the Iranian society.

Keywords: Methadone, Drug abuse, Addiction, Toxicity, Mortality rates

Introduction

Drug abuse applies to the harmful, dangerous or excessive use of psychotropic, narcotic and non-medical substances [1].

This disorder is currently a major medical, social, economic, and cultural problem in the Iranian society [1, 2]. Drug abuse causes disorders of mood, behavior, and cognition. Also, it adversely affects the Iranian people socially, functionally and occupationally. Also, it increases

the incidence of disability and premature mortality of a relatively high proportion of the individuals [3-8].

The first therapeutic intervention to save drug addicts is detoxification [9]. In this context, one of the best methods of treating addiction is the use of methadone or Methadone Maintenance Therapy (MMT) [10]. This drug is clinically known to be effective, safe and cost-saving in the manage of addicts with known drug abuse [11]. In addition to preventing the recurrent drug abuse in most addicts, methadone improves the quality of mental and physical health [11]. Further, methadone is continued as a long-term maintenance treatment until the addict is successfully detoxified, which may take years [12]. A 15-year follow-up of addicts in New South Wales, Australia, has shown that MMT is associated with reduced risk of death in heroin abusers [13]. Decreasing the effect of methadone on mortality occurs when a person stays regularly on MMT program, suggesting that early withdrawal from this program will increase the risk of mortality. However, methadone use can be the cause of death in people with no drug addiction, such as children and adults who accidentally consume methadone prescribed for others. This may also apply to drug abusers who are going through the early weeks of quitting drugs that are getting adjusted for the methadone dosage [14].

The high prevalence of methadone overdose in Iran may occur while being enrolled on MMT, which has begun in recent years by increasing the access to methadone among young adults [15]. Despite the growing enrollments in MMT to treat drug addicts, we are witnessing increases in the number of deaths associated with methadone overdose. However, no systematic research has been conducted to investigate the status of methadone use among the deceased due to drug abuse. Therefore, the aim of the present study was to investigate the status of methadone based on post-mortem toxicological assessments of the cadavers autopsied at the Forensic Medicine Organization (FMO) in Tehran, Iran, between 2015 and 2017.

Materials and Methods

This was a cross-sectional study on drug-abuse deaths registered at the FMO in Tehran, Iran, between the years 2015 and 2017. Out of 9,078 drug abuse deaths over the 3-year period, 6,066 cases were randomly included. All of the data were extracted from the Iranian National FMO during the study period. The main variables for each death were name, age, sex, date of death, province of residence, and type of drug abused.

To investigate the cases of drug abuse at the forensic toxicology laboratories, urine, liver, gastric tissues, gallbladder and vitreous specimens were first screened, using immune-chromatography method to determine the presence of such drugs as methadone, methamphetamine, morphine, tramadol, benzodiazepine, diphenoxylate, alcohol, and other substances. The detected drugs were subsequently investigated to differentiate the false from the true positive incidence, using confirmatory methods, as Thin Layer Chromatography (TLC), High Performance Liquid Chromatography (HPLC), and Gas Chromatography or Spectrometry (GC/MS).

The Iranian FMO laboratories routinely use two checklists to collect the identity of the cadavers, and the autopsy and laboratory data. For the current study, the completion of the checklists was performed by an anatomist at each provincial FMO center. This individual collected the demographic and epidemiological data and forwarded them monthly to the FMO center in Tehran. The deaths from drug abuse were assessed based on the International Classification of Diseases (ICD-10), using T40, T43, F10-F19, X42, X62 and Y12 codes.

The cadavers' ages were categorized into subsets of 10 to 79 years, and 80 years and older. This grouping was observed based on the WHO classification to calculate years of life lost due to premature death. In cases where the cadavers' ages had not been registered initially, the individuals were assigned to various groups, and the median age in each subgroup was assigned to the individuals in groups.

In the distribution of the age variable, we paid attention to such factors as the level of education, and marital and employment status so that the age grouping of individuals was most accurate. Upon data extraction, the data were initially inspected for quality control, and the duplicates and indeterminable items were eliminated. The missing or outlier data, if any, were eliminated or modified during the statistical analyses.

Statistical analyses: The collected data were entered into Stata software, version 14 MP. The relative frequency and percentage, and the mortality rate were used to describe the data. The [Formula 1](#) was used to calculate the mortality rate:

1. Annual mortality rate=

$$\frac{\text{Number of methadone deaths/year}}{\text{Population in midyear}} \times 100,000$$

To calculate mortality rates by marital status, educational level, and province of residence of the subgroups, we also used data on file from the official Iranian Census conducted during 2015-2017. The census in Iran is performed once every five years. To estimate the population growth between 2011 and 2016, the [Formula 2](#) was used. We multiplied the numerical values by the population of the previous year to arrive at the growth rate for a given period:

$$2. \text{ Growth rate} = \frac{\text{Population of variable based on census 2016}^{\frac{1}{5}}}{\text{Population of variable based on census 2011}}$$

Using the above formula, the estimated population was calculated from the denominator of the fraction.

Results

In total, 9,361 cases of drug abuse deaths occurred between 2015 and 2017. The mean age of the cadavers was 36.6±12.6 years. The mean age for the male and female cadavers were 37.0±12.3 and 32.7±14.6, respectively. The annual number of deaths due to drug abuse for 2015, 2016 and 2017 were 3003, 3269 and 3089, respectively. The crude mortality rate increased from 51.3 cases to 59.4 cases per million, and the standardized mortality rates increased from 35 to 39 cases per million of the population ([Table 1](#)).

Of all the deaths, 6,066 were assigned to drug toxicity, with 3,038 (50.1%) of them having used methadone a month prior to their death. Specifically, 12.3% of these subjects had only used methadone while the other 37.4% had used methadone and other drugs simultaneously. Among the methadone abusers, 75.4% had used both methadone and other drugs simultaneously, and only 24.6% had used methadone alone ([Table 2](#)).

The highest proportion of methadone abuse in drug-related deaths was observed in the age group of less than 10 years old followed by the age group of 10-19 years old. Specifically, 72.4% of the death cases occurred in the age group below 10 years old and 58.4% of those aged 10-

19 years old had consumed methadone ([Table 3](#)). [Table 4](#) shows the frequency of methadone consumed with other drugs. As seen in [Table 4](#), methadone had the highest likelihood of being abused simultaneously with morphine (18.7%) and methamphetamine (17%), respectively.

Discussion

Based on the study findings, the standardized mortality rate in men was more than seven times that of women. The results of other studies in this area are in line with our findings [[7](#), [16](#), [17](#)]. The high mortality rate by substance abuse in men can be attributed to their social freedom in the Iranian society, whereas the low rate in women may be linked to the fact that their social relationships are controlled by their families [[18](#)]. However, the importance of this issue in women should not be overlooked, and it is recommended that rehabilitation centers for addicted women be provided for treatment and access to more accurate information [[19](#)]. During the three-year study period, there was an increasing trend in methadone use in drug-related deaths. Consistent with the results of the present study, the findings of Soltaninejad, et al. showed that during the 10-year study, there was a significant surge in methadone-related deaths, while the total number of overdose cases and total deaths remained constant [[20](#)].

The results of studies in other countries showed the same pattern in terms of increased rates of methadone overdose and mortality [[21-23](#)]. The cause of this upward trend in Iran may be an increased tendency to MMT, arbitrary use for self-medication, or methadone abuse. On the other hand, unnecessary and unregulated methadone supply has made it easily available to everyone. Previous studies have also emphasized the need for monitoring controlling methadone distribution into the public market [[20](#)]. The highest proportion of methadone overdose in drug-related deaths was observed in the age group of less than 10 years and then in 10-19 years old. Due to the fact that poisoning in these age groups is often due to accidental or mistaken use, preventive mea-

Table 1. Crude and standardized mortality rates due to drug abuse in Iran between 2015 and 2017

Year	No. (%) Deaths	(In One Million People)					
		Crude Death Rate			Standardized Age Mortality Rate		
2015	3003 (32.1)	51.3	6.5	38	61	5	35
2016	3269 (34.9)	60.6	7.5	40.9	66	8	38
2017	3089 (33.0)	59.4	6.7	38.2	59	8	39

Table 2. Frequency distribution of methadone consumption in cases of drug-related death between 2015 and 2017

Toxicology Test Result for Methadone	No. (%)									Grand Total
	2015			2016			2017			
	Male	Female	Total	Male	Female	Total	Male	Female	Total	
Negative	862 (55.2)	111 (55.2)	973 (55.2)	969 (50.6)	112 (45.9)	1081 (50)	861 (45.7)	96 (41.7)	957 (45.3)	3011 (49.9)
Methadone	169 (10.8)	13 (6.5)	182 (10.3)	234 (12.2)	27 (11.1)	261 (12.1)	276 (14.7)	26 (11.3)	302 (14.3)	745 (12.3)
Methadone & Other drugs	530 (34)	77 (38.3)	607 (34.5)	714 (37.2)	105 (43)	819 (37.9)	746 (39.6)	108 (47)	854 (40.4)	2280 (37.8)

asures are needed to reduce the risk of such accidents. In addition, the risk of death from accidental overdose of methadone is higher in young people with a history of substance abuse [24]. The mean age of methadone users in this study was 36.6 ± 12.6 years and the male to female ratio was 12:1. In a recent study by Akhgari, et al. on methadone deaths in Tehran between 2009 and 2015, the mean age of the cases of death was 34 years and the male to female ratio was 9:1 [16]. The toxicity results showed that 12% had used methadone alone with 38% had used methadone simultaneously with other drugs. In relative agreement with our findings, previous studies have reported approximately between 6% to 15% of the poisoning deaths were associated with methadone [25-27].

In the study by Peltzer et al., the highest percentage (28%) of drug-related toxicity was also reported in methadone users [28]. The relatively high abuse of methadone together with opioids may be due to the increased rate of self-treatment with methadone, contributing to an increased death rate due to drug abuse. Since the blood levels of the substances examined were not available in cases where several drugs had been detected on post-mortem examinations, it was not possible to judge the main substance responsible for the mortality. However, this association may be compared to those reported in studies conducted among the survivors of MMT and methadone overdose.

In the current study, methadone was the most commonly used drug together with morphine followed by

Table 3. Frequency distributions of methadone consumption in cases of drug-related death in Iran by age group

Age Group	No. (%)							
	2015		2016		2017		Total	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
10>	15 (60)	10 (40)	26 (78.8)	7 (21.2)	22 (75.9)	7 (24.1)	63 (72.4)	24 (27.6)
10-19	51 (53.7)	44 (46.3)	66 (55)	54 (45)	74 (66)	38(34)	191 (58.4)	136 (41.6)
20-29	233 (47.4)	259 (52.6)	286 (53.7)	247 (46.3)	292 (57)	217(43)	811 (52.9)	723 (47.1)
30-39	271 (46.5)	312 (53.5)	364 (49.4)	372 (50.6)	356 (56.6)	273(43.4)	991 (50.9)	957 (49.1)
40-49	134 (39.9)	202 (60.1)	179 (46.5)	206 (53.5)	243 (53.1)	214(46.9)	556 (47.2)	622 (52.8)
50-59	56 (38.1)	91 (61.9)	99 (46.9)	112 (53.1)	102 (48.3)	109 (51.7)	257 (45.2)	312 (54.8)
60-69	10 (23.2)	33 (76.8)	35 (44.3)	44 (55.7)	33 (43.4)	43 (56.6)	78 (39.4)	120 (60.6)
70-79	1 (11)	8 (89)	6 (33.3)	12 (66.7)	6 (33.3)	12 (66.7)	13 (28.9)	32 (71.1)
80<	1 (20)	4 (80)	1 (14.3)	6 (85.7)	2 (28.6)	5 (71.4)	4 (21)	15 (79)
Uncertain	21 (60)	14 (40)	23 (43.4)	30 (56.6)	30 (41)	43 (59)	74 (46)	87 (54)
Total	793 (44.8)	977 (55.2)	1085 (49.9)	1090 (50.1)	1160 (54.7)	961 (45.3)	3038 (50.1)	3028 (49.9)

Table 4. Frequency distribution of methadone co-consumed with other drugs

Drug Type		Methadone No. (%)							
		2015		2016		2017		Total	
		Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Morphine	Positive	169 (22.3)	471 (50.4)	169 (15.6)	516 (47.7)	228 (19.7)	456 (47.6)	566 (18.7)	1443 (47.9)
	Negative	620 (77.7)	502 (49.6)	911 (84.4)	565 (52.3)	928 (80.3)	501 (52.4)	2459 (81.3)	1568 (52.1)
Amphet-amine	Positive	114 (14.4)	132 (13.6)	112 (10.4)	175 (16.2)	114 (9.9)	1042 (57.3)	340 (11.2)	1349 (34.8)
	Negative	675 (85.6)	841 (86.4)	968 (89.6)	906 (83.8)	1042 (90.1)	778 (42.7)	2685 (88.8)	2525 (65.2)
Metham-phetamine	Positive	170 (21.4)	143 (14.7)	179 (16.6)	231 (21.4)	166 (14.4)	223 (23.3)	515 (17)	597 (19.8)
	Negative	619 (78.6)	830 (85.3)	901 (83.4)	850 (78.6)	990 (85.6)	734 (76.7)	2510 (83)	2414 (80.2)
Codeine	Positive	60 (7.6)	110 (11.3)	88 (8.1)	179 (16.6)	97 (27.7)	136 (14.4)	245 (11)	425 (14.2)
	Negative	729 (92.4)	863 (88.7)	992 (91.9)	902 (83.4)	258 (72.3)	809 (85.6)	1979 (89)	2574 (85.8)
Tramadol	Positive	96 (12.2)	180 (18.5)	125 (11.6)	210 (19.4)	141 (12.2)	189 (19.8)	362 (12)	579 (19.2)
	Negative	693 (87.8)	793 (81.5)	955 (88.4)	871 (80.6)	1015 (87.8)	768 (80.2)	2663 (88)	2432 (80.8)
Benzodiaz-epine	Positive	52 (6.6)	32 (3.3)	55 (5.1)	36 (3.3)	53 (4.6)	28 (2.9)	160 (5.3)	96 (3.2)
	Negative	737 (93.4)	737 (93.4)	941 (96.7)	1025 (94.9)	1103 (95.4)	929 (97.1)	2865 (94.7)	2916 (96.8)
Diphenox-ylate	Positive	0 (0)	0 (0)	1 (0.1)	1 (0.1)	3 (0.3)	0 (0)	4 (0.1)	2 (0.1)
	Negative	789 (99.9)	789 (99.9)	972 (100)	1079 (99.9)	1153 (99.7)	957 (100)	3021 (99.9)	3009 (99.9)
Alcohol	Positive	18 (3.1)	18 (3.1)	32 (4.1)	19 (3.4)	25 (2.2)	34 (7.2)	62 (3.7)	121 (6.6)
	Negative	566 (96.9)	566 (96.9)	748 (95.9)	535 (96.6)	504 (95.3)	441 (92.8)	1605 (96.3)	1717 (93.4)
Other Drugs	Positive	165 (15.6)	165 (15.6)	152 (15.6)	198 (18.3)	123 (10.6)	115 (12)	486 (16)	447 (14.9)
	Negative	624 (84.4)	624 (84.4)	821 (84.4)	882 (81.7)	1033 (89.4)	842 (88)	2539 (84)	2554 (85.1)

methamphetamine. Studies have shown that after opiates, methamphetamine is the most commonly used substance in Iran [29]. A high prevalence of methamphetamine abuse has also been reported in earlier studies on Iranian opiate users [30, 31].

The co-consumption of drugs may be due to the fact that MMT is a common treatment for drug abusers in Iran. The Iranian methadone abusers assume that using methamphetamine can help reduce the side effects of methadone, such as sexual disorders and depression, while increasing their energy, attention span, and concentration, and improving their social relationships [32]. Cardiac disorders and arrhythmias play important roles in deaths from methadone abuse [33]. This drug alters cardiac muscle conductance, characterized by increased

QT intervals, and can lead to sudden death. Similarly, methamphetamine can also have toxic effects on the heart, leading to acute myocardial infarction, cardiac hypertrophy, and peripheral vascular fibrosis [34]. Therefore, the concurrent consumption of the two drugs may increase the risk of death.

Conclusions

In drug-related deaths, the rate of methadone-associated deaths was higher in the age of less than 10 years old than those at older ages. It is highly likely that methadone toxicity in this age group is often accidental. To reduce such accidents in this age group, clear and serious training should be given to people who need to use this drug and are on methadone maintenance. Considering

the relatively high prevalence of methadone overdose in cases of drug-related deaths, monitoring the methadone entry into the free market and identifying the causes of death among methadone users may be one of the critical measures to improve the current crisis of drug related deaths in Iran. The easy access to methadone in the public market has helped addicts to use the drug together with other drugs concurrently. Co-consumption of multiple drugs in addition to the high risk of mortality is also one of the major causes of people getting addicted to methadone in the first place.

Limitations and recommendation: Overall, due to limitations in the forensic data, it was not clear whether the deceased had used methadone as a maintenance treatment to quit their addiction or methadone was the main manner of their drug abuse. Overall and based on the findings from previous research, MMT has been associated with reduced risk of HIV-AIDS, viral hepatitis and blood borne infections. The reason is that MMT reduces the tendency of intravenous drug abusers to inject drugs and the shared use of infected syringes. Further, MMT is considered a cost-effective strategy in the management of addiction, thus its efficacy to date has been established by numerous studies. Therefore, we recommend that the effectiveness of these measures be assessed in future studies on various Iranian populations.

Ethical Considerations

Compliance with ethical guidelines

All ethical guidelines and institutional instructions were followed in this study as set by the School of Public Health & Neuroscience Research Center, Shahid Beheshti University of Medical Sciences. The University's Ethics Committee approved this study (registration Code: IR.SBMU.PHNS.REC.1397.136).

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Author's contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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