

# Methadone Related Poisoning on the Rise in Tehran, Iran

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## Abstract

**Background:** In Iran, methadone has been used for methadone maintenance treatment (MMT) as well as analgesic treatment in pain clinics. Recently, there are some reports regarding accidental and intentional methadone poisonings and deaths. The aim of this study was to evaluate the trend of methadone poisonings and deaths during a 10-year period in Tehran, Iran.

**Methods:** This was a retrospective cross-sectional study over 2000 to 2010. Patients with a documented methadone poisoning who were admitted in Loghman Hakim Hospital Poison Center in Tehran, Iran were identified and included in the study. The data including patients' age, gender, ingested dose, co-ingestants, intention of ingestion and outcome were extracted from the patients' medical records.

**Results:** During the study period, 1426 cases of methadone poisoning were recorded, of which, 1041 cases (73%) were men. Thirty-six cases (2.5%) died. Mean age of the patients was  $29.9 \pm 17$  years. In 476 cases, the intention of poisoning could not be determined, and in the remaining, the intention was misuse ( $n = 273$ , 28.7%), suicide ( $n = 254$ , 26.7%), accidental ( $n = 245$ , 25.8%) and abuse ( $n = 178$ , 18.8%). Mean of the ingested dose of methadone was  $120.6 \pm 306.8$  mg. The incidence of acute methadone poisoning per one million population of Tehran was 0.43 in 2000 that rose to 37.62 in 2010.

**Conclusion:** The results indicate that methadone poisoning and deaths have increased in Tehran. MMT clinics should be strictly run according to the national guideline to prevent methadone poisoning. With regard to high frequency of poly-drug use in methadone poisoning, it seems important to warn health care providers against prescription of other drugs with methadone.

**Keywords:** Death; Incidence; Iran; Methadone; Poisoning

**How to cite this article:** Soltaninejad K, Hassanian-Moghaddam H, Shadnia S. Methadone Related Poisoning on the Rise in Tehran, Iran. *Asia Pac J Med Toxicol* 2014;3:104-9.

## INTRODUCTION

Methadone is a synthetic opioid which was developed as an analgesic in the 1940s. It is the most widely used pharmacological treatment for opioid dependence and it has been used for methadone maintenance treatment (MMT) for more than 40 years worldwide (1).

Previous studies have shown that MMT reduces the risk of crime, illegal drug use, morbidity and mortality and improves social behaviors in patients compared to opioid abusers (2-6).

In Iran, methadone has been used for MMT program (from 2003) as well as analgesic treatments in pain clinics (7). Methadone had not been manufactured in Iranian pharmaceutical companies until 2002 and the importation had been the only source of the drug in the country. Between 2003 and 2010, the methadone production was reported to be 18,423 tons in the forms of tablet and syrup in Iran (7).

While there are positive aspects with regard to MMT program, recent studies showed that there are negative points with methadone use in some cases including accidental and intentional methadone poisoning and deaths (8-10).

Methadone poisoning results in clinical manifestations such as loss of consciousness, respiratory depression (bradypnea/apnea), cardiovascular disturbances (low blood pressure, cardiac dysrhythmia, QT interval prolongation), nausea, vomiting, seizure and miosis, which are the same as clinical features of poisoning with other opioids, though the duration of methadone poisoning is longer (11-14).

The purpose of this study was to evaluate the trend of methadone poisoning cases admitted to a referral hospital for poisonings in Tehran, Iran over a 10-year period from 2000 to 2010.

## METHODS

### Patients

Data for this study came from medical record system of Loghman Hakim Hospital Poison Center (LHHPC) which is the referral hospital for poisoned patients in Tehran, Iran. On average, more than 24,000 poisoned patients are admitted in this center annually with approximately over 14,000 inpatients, while the remainders are treated as outpatients (14).

This study is a retrospective cross-sectional study on methadone poisoning cases admitted to LHHPC between

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Received 5 June 2014; Accepted 17 September 2014

March 20th, 2000 and March 21st, 2010. Patients with a documented methadone poisoning were identified by application of the International Classification of Diseases (ICD10) computer diagnosis codes and included in the study. Methadone poisoning was diagnosed using a comprehensive history and clinical presentations. In addition, immuno-chromatography methods (Acon Laboratories Inc., CA, USA) on urine samples as the screening test and thin layer chromatography as the confirmatory test were applied. Cases without laboratory confirmation were excluded from the study.

The medical files of all inpatients with methadone poisoning were reviewed. Trained personnel used a purpose-made questionnaire, which was designed by toxicology experts, and extracted data including patients' age, gender, ingested dose, co-ingestants, intention of ingestion and outcome from the patients' medical records.

Ethical committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved the project. The confidentiality of patients' information was maintained.

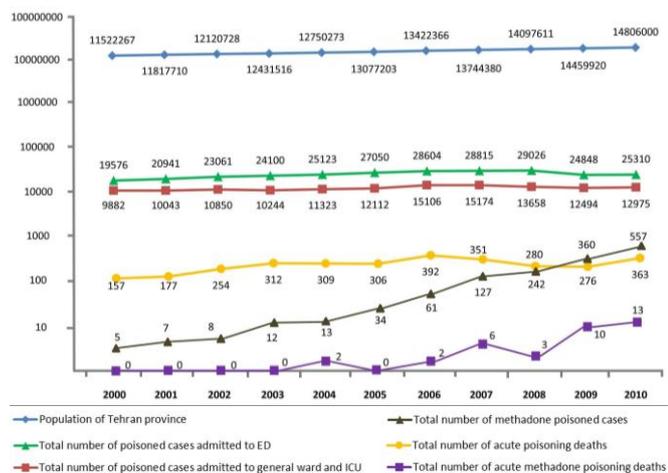
#### Statistical analysis

The data are shown with frequency and percentage (%) for categorical variables, and with mean  $\pm$  standard deviation (SD) and median (range) for continuous variables. Using Kolmogorov-Smirnov test, Mann-Whitney U test, and Chi-square test, the data were analyzed. All statistical analysis was performed with SPSS software (version 13.0, SPSS Inc., Chicago, IL). P values of less than 0.05 were considered to be statistically significant.

## RESULTS

### Epidemiologic profile of all types of acute poisoning

During the study period, 276,454 poisoned patients with different substances were admitted to the emergency department of LHHPC, from which 137,429 patients were admitted to general ward and intensive care unit. Among these, 3177 patients (2.31%) died (Figure 1). The incidence rate of acute poisoning per one million population of Tehran was 1699 and 1709 in years 2000 and 2010, respectively (Figure 2).



**Figure 1.** Trend of acute methadone poisoning, and total admission due to acute poisoning to Loghman Hakim Hospital Poison Center from March 20th, 2000 and March 21st, 2010

### Epidemiologic profile of acute methadone poisoning

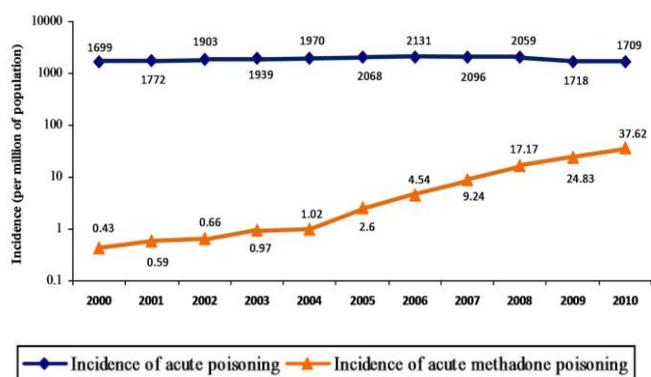
During this ten-year period, 1426 cases of methadone poisoning were recorded; of which, 385 cases (27%) were women and 1041 (73%) were men. Thirty-six cases (2.5%) died which most of them were men (77.8%) (Figure 1 and Table 1). The incidence rate of acute methadone poisoning was 0.43 per one million population of Tehran in the year 2000 that rose to 37.62 in 2010 (Figure 2).

Mean age of the patients was  $29.9 \pm 17$  years (median = 28 years, range 1-87 years). When age plotted against gender, mean age of men was significantly higher than women ( $31.6 \pm 16.7$  vs.  $25 \pm 16.8$  years,  $P < 0.001$ ).

The most common intention of poisoning was misuse (28.7%) followed by suicide (26.7%), accidental (25.8%), and abuse (18.8%). The intention of poisoning could not be determined in 476 cases (Table 1). Figure 3 shows the distribution of cases according to intention of poisoning and gender. The difference between men and women regarding the intention of poisoning was found to be significant ( $P < 0.001$ ). In this respect, the intention of poisoning in men were more likely to be due to abuse or misuse, while suicidal ingestion of methadone was relatively equal between men and women.

Figure 4 shows the distribution of cases according to the intention of poisoning in different age groups. There was also a significant difference between different age groups according to intention of poisoning ( $P < 0.001$ ). In this respect, accidental ingestion was more common in lower ages especially among patients under 12 years of age, while suicidal ingestion, abuse and misuse were more common in older ages especially among adult patients (19 to 45 years of age).

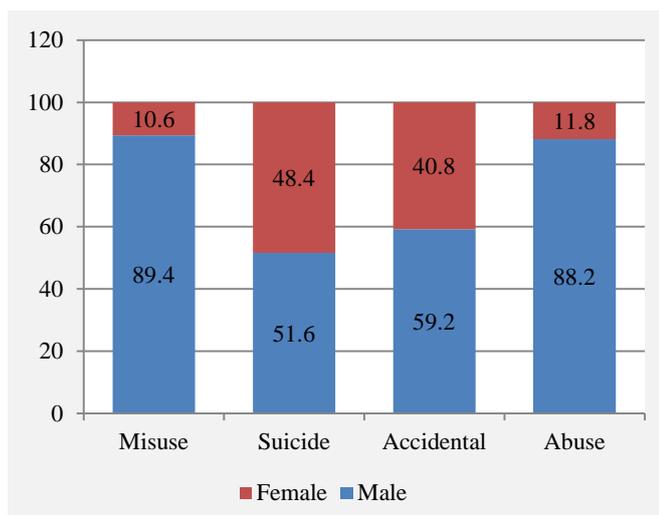
Mean of the ingested dose in all patients was  $120.6 \pm 306.8$  mg (median = 40 mg, range 5-3600 mg). Mean of the ingested dose in men and women was  $126 \pm 327.2$  mg (median = 40 mg, range 5-3600 mg) and  $108 \pm 253.5$  mg (median = 36 mg, range 5-2500 mg), respectively, which their difference was not statistically significant ( $P = 0.56$ ).



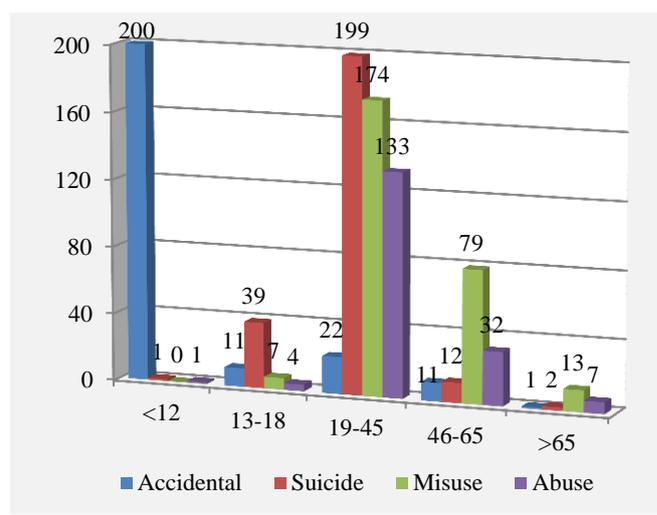
**Figure 2.** Trend of incidence of acute methadone poisoning and acute poisoning cases admitted to Loghman Hakim Hospital Poison Center per million of Tehran population during March 20th, 2000 and March 21st, 2010

**Table 1.** Characteristics of methadone poisoned patients

Parameter	Year											Total
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	
Total number of cases	5	7	8	12	13	34	61	127	242	360	557	1426
Sex												
Female	3	2	3	1	5	7	19	38	68	107	132	358
Male	2	5	5	11	8	27	42	89	174	253	425	1068
Age (Year), Mean $\pm$ SD	27 $\pm$ 3.7	29.6 $\pm$ 16.5	36 $\pm$ 11.6	34.6 $\pm$ 17.2	29.7 $\pm$ 14.9	33.2 $\pm$ 15.4	29.3 $\pm$ 11.6	28.5 $\pm$ 14.5	25.7 $\pm$ 17.7	30.6 $\pm$ 17.1	31.2 $\pm$ 17.7	---
Median (Range)	28 (22-32)	26 (4-58)	31.5 (24-58)	35 (3-60)	28 (1-69)	30 (5-78)	27.5 (2-54)	28 (1-65)	26 (1-87)	28 (1-84)	29 (1-86)	---
Misuse	0	0	2	1	2	8	4	32	37	68	119	273
Abuse	0	0	2	1	0	3	4	21	28	67	52	178
Suicide	2	2	1	1	0	5	14	22	34	69	104	254
Accidental	0	1	0	1	0	1	5	16	57	69	95	245
Not determined	3	4	3	8	11	17	34	36	86	87	187	476
Ingested dose (mg)												
Mean $\pm$ SD (Median) (Range)	-----	-----	18.7 $\pm$ 6.3 20 (10-25)	30 $\pm$ 32.5 15 (10-100)	27.5 $\pm$ 10.6 27.5 (20-35)	62.1 $\pm$ 60.5 45 (5-250)	90.1 $\pm$ 197.3 50 (5-1250)	72.1 $\pm$ 62.6 50 (5-250)	130.3 $\pm$ 238 50 (5-1500)	84.4 $\pm$ 178 30 (5-1250)	165 $\pm$ 423.6 40 (5-3600)	---
Outcome												
Survived												
Female	3	2	3	1	4	7	19	36	67	105	130	377
Male	2	5	5	11	7	27	40	85	172	245	414	1013
Death												
Female	0	0	0	0	1	0	0	2	1	2	2	8
Male					1	0	2	4	2	8	11	28



**Figure 3.** Distribution of methadone poisoned patients according to intention of poisoning and gender



**Figure 4.** Distribution of methadone poisoned patients according to intention of poisoning and age group

**Table 2.** Distribution of methadone poisoned patients according to past history of drug/substance abuse, gender and age range

Type of drug/substance	Number of the patients							
	Total	Men	Women	Age range (Year)				
				<12	13-18	19-45	46-65	>65
Methamphetamine	33	25	8	0	0	32	1	0
Ecstasy	1	0	1	0	0	1	0	0
Opium	266	249	17	5	2	164	83	12
Iranian crack*	136	125	11	0	5	120	9	2
Heroin	16	15	1	0	1	9	6	0
Shireh**	5	5	0	1	0	1	3	0
Buprenorphine	2	1	1	0	1	1	0	0
Cannabis	4	4	0	1	0	3	0	0
Ethanol	3	2	1	0	0	2	1	0
Tramadol	7	5	2	0	1	5	1	0
Poly drug/substance***	387	307	80	4	14	286	68	15
Patients with past drug/substance abuse history	860	738	122	11	24	624	172	29
Patients without past drug/substance abuse history	535	278	257	216	63	209	39	8

\* White and high purity heroin

\*\* Refined opium extract

\*\*\* Abuse of more than one type of drug/substance

Mean of time elapsed from methadone ingestion to admission to hospital was  $8.7 \pm 8.8$  hours (median = 6 h, range 1-72 h) in men, and  $6.4 \pm 6.3$  hours (median = 4 h, range 1-48 h) in women, which were significantly different from each other ( $P < 0.001$ ).

Past drug/substance use history (PDH) for 535 cases (38.4%) was negative and for 860 cases (61.6%) was positive (Table 2). For 31 cases, PDH could not be obtained. Considering the gender, there was a significant difference between men and women according to PDH (738 vs. 122,  $P < 0.001$ ). There was also a significant difference between

age groups according to PDH ( $P < 0.001$ ). In this respect, most of the patients with positive PDH were within the age range of 19 to 45 years ( $n = 624$ , 72.5%) followed by patients within age range of 46 to 65 years ( $n = 172$ , 20%).

Co-ingestion of methadone with other substances could not be established in 28 cases (2%). In the remaining 1398 cases (98%), co-ingestion was negative in 732 cases (52.4%). Among those who co-ingested methadone with other substances, most cases ( $n = 305$ , 21.8%) had multi drug/substance co-ingestion, followed by co-ingestion with benzodiazepines ( $n = 159$ , 11.4%) (Table 3).

**Table 3.** Distribution of methadone poisoned patients according to history of co-ingestion and gender

Type of drug/substance	Number of the patients		
	Total	Men	Women
Opium	51	48	31
Shireh*	7	6	1
Heroin	3	3	0
Iranian crack**	42	35	7
Buprenorphine	1	1	0
Tramadol	24	17	7
Ethanol	6	4	2
Barbiturates	1	1	0
Benzodiazepines	159	114	45
Cannabis	2	2	0
Methamphetamine	32	30	2
Tricyclic antidepressants	14	10	4
Analgesics	19	12	7
Poly drug/substance	305	237	68

\* Refined opium extract  
\*\* White and high purity heroin

## DISCUSSION

The results of this study demonstrate that during a 10-year period between 2000 and 2010, the rate of acute methadone poisoning increased in Tehran province. The methadone poisoned patients aged 30 years on average and were most commonly men. A clear rise in the number of methadone related deaths was also observed during the study period; nevertheless, the total number of all types of poisoning and the total number of deaths was stable meanwhile. Although studies in other countries showed the same pattern with regard to gender and increase in methadone overdose and mortality (11,15,16), the patients in our study were younger, which could be attributed to factors such as difference between population characteristics and prevalence of opioid dependence in Iran with that of western countries (17,18). Moreover, the age onset for opioid abuse is lower in Iran (17,18)

In this study, a marked growth in methadone poisoning was observed from the year 2005. The rate of methadone poisoning in Tehran province in the years of 2005 and 2010 which were 2.60 and 37.62 per 1,000,000 population, respectively, were almost six and 87.5 times higher than its rate in 2000. One reason for the escalation of methadone poisoning could be the growing rate of methadone misuse, as ascertained in other studies (17-20). The other possible reason is drug diversion from MMT and pain clinics and improper implementation of the policy of the MMT clinics with regard to dosing, taking the drug to home and /or patient follow up (19-21).

In this study, the main cause of poisoning in men was misuse and abuse of methadone. On the other hand, the main

cause of poisoning in women was suicide and accidental poisoning. This result could be explained by the fact that most of the patients with positive PDH for opioids were men. In addition, most of the misuses, abuses and suicides were observed in the age range of 19-45 years old, and most of the accidental ingestions were observed in the patients aged less than 12 years old. Furthermore, mean age of all patients was 30 years. These results are similar to a study in France by Glaizal et al. which showed 80% of cases with suicidal methadone poisonings were men at the third decade of their life (11).

During the study period, the mean ingested dose has increased. One of the explanations could be availability of the methadone in Iranian drug market due to production and distribution of the pharmaceutical forms of methadone in the country since 2003. Another explanation is production of more potent formulations of methadone since 2006 In Iran (7). Nowadays, there are two formulations of methadone available in Iran: syrup (5 mg/mL, 120 and 250 mL) and tablets (5, 20, and 40 mg) (22).

The most common co-ingested drug/substance with methadone was benzodiazepines and other opioids in this study. This result resembles the findings of previous studies in the United States, the United Kingdom and Iran (15,23,24).

Increase of methadone poisoning related deaths over 2000 to 2010 was found in the present study. In this way, some studies suggested that MMT programs could be a contributor to the significant increase of the methadone related deaths (15,20). In a recent study, Mostafazadeh and Farzaneh showed the great risk for choosing methadone for suicide among opioid addicts under MMT who had no history of previous suicidal attempt (25). These facts raise the necessity to maintain intensive surveillance on MMT program and the clinics that offers this service. In this study, the mortality rate was higher in men than women. One of the reasons could be the referral delay to the hospital in male patients. Another explanation is the higher frequency of co-ingestion in men than women in our study.

## LIMITATIONS

Because this was a retrospective study, the most notable limitation was unavailability of some patients' details in medical records. As the ingested dose of methadone was determined by taking history from the patients, some patients may have not declared the exact dose.

## CONCLUSION

The results of this study indicate that parallel with increase in production and availability of methadone in Iran, poisoning with this drug has been increased. As MMT program is vital for harm reduction in addicts, especially for intravenous drug users, it seems that the MMT clinics should be strictly run according to the national guideline of the MMT clinics to prevent methadone poisoning. In addition, with regard to high frequency of poly-drug use in methadone poisoning, especially co-ingestion of benzodiazepines, it seems important to warn health care providers against prescription of other drugs with methadone.

## ACKNOWLEDGMENT

The authors would like to thank Dr. M. Eslampanah for her valuable help in data collection.

**Conflict of interest:** None to be declared

**Funding and support:** This work was supported by the grants from Toxicological Research Center of Shahid Beheshti University of Medical Sciences.

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