

# Methadone Poisoning in Children: A Systematic Review and Meta-Analysis in Iran

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## Abstract

**Context:** Symptoms of methadone poisoning, as one of the most dangerous types of poisoning, are very serious in children.

**Objectives:** The aim of this study was to describe causes and clinical symptoms of methadone poisoning in children admitted to hospitals in Iran.

**Data Sources:** Relevant studies published in national and international journals before January 29, 2016 were identified by studying the available databases, including PubMed, Web of Sciences, Google Scholar, Scopus, SID, Iranmedex, MagIran, and Irandoc.

**Study Selection:** After excluding duplicate, irrelevant, and low-quality articles, relevant papers were entered into the meta-analysis. The prevalence, mean, and standard deviation of methadone poisoning symptoms in children were statistically analyzed, using Stata version 11, and causes of methadone poisoning were presented in tables.

**Data Extraction:** Studies with unknown sample sizes, abstracts without access to full text, articles with quality assessment scores below 15.5, and studies carried out on non-Iranian populations were excluded from the meta-analysis.

**Results:** During the initial advanced search, 1594 articles were identified. After quality assessment, 12 papers were found eligible for the final systematic review and meta-analysis, based on the inclusion and exclusion criteria. The reported symptoms included drowsiness, vomiting, apnea, cyanosis, seizure, ataxia, and delirium. In the meta-analysis, prevalence of symptoms in referred patients was estimated at 44% (0.95% confidence interval, 0.288 to 0.609). The causes of poisoning in children included accidental feeding by parents, storage of drugs in inappropriate containers, parental addiction, and low educational level of parents.

**Conclusions:** It is important to keep methadone in a suitable container away from children. Also, it is essential to focus on educating parents on health issues of their children.

**Keywords:** Methadone, Poisoning, Children, Iran

## 1. Context

Illegal drug abuse is a worldwide problem. Today, many people who intend to quit drugs undergo methadone treatment to abandon their substance abuse; this has resulted in the access of other family members to this drug. Moreover, methadone seems attractive to children, considering its favorable taste (1).

Statistics show that poisoning is the second leading cause of child mortality, following accidents (2). According to reports, 22% of poisoned patients, admitted to emergency rooms in Iran, are adolescents; this rate seems quite significant compared to European countries (3). Opium poisoning is one of the most dangerous types of poisoning, accounting for around 10% of the total number of children

poisoned annually in Tehran, Iran (4). According to many studies in other regions of the country, various combinations of drugs account for up to 91% of cases of child poisoning (5).

Unsafe storage of methadone, particularly in form of syrup kept in soda bottles, glasses, and other medicine bottles, results in its confusion with other drugs (6). Therefore, unsafe use of empty methadone containers or use of insignificant amounts of the drug may cause serious complications in children (7). In every 1 mL of methadone syrup in Iran, there is 5 mg of methadone; it should be noted that a dosage of 1 mg/kg can cause apnea and death in children (8).

## 2. Objectives

The aim of this study was to raise awareness about the risks and clinical/epidemiological profile of methadone poisoning in children so that physicians educate patients about the risks involved before prescribing methadone.

## 3. Data Sources

In order to find relevant studies published electronically before January 29, 2016, national and international journals were searched in databases, including PubMed, Web of Sciences, Google Scholar, Scopus, SID, Iranmedex, MagIran, and Irandoc. The search was conducted, using the following keywords or their Persian equivalents, as well as Boolean operators (AND and OR): ("methadone maintenance program" OR "MMT" OR "methadone maintenance treatment" OR "opiate replacement therapy") AND ("tablet" OR "syrup" OR "tablet and syrup") AND ("methadone poisoning" OR "methadone poisoning in children" OR "Iranian pediatric toxicity").

A secondary search was conducted, which involved the reference sections of relevant review papers to find articles which were missed in the initial computerized search. The search was conducted by 2 independent researchers during April 10 - 30, 2016. A third researcher was assigned to manage any probable disagreements in the results between the researchers. In addition, all references of the articles, which were not electronically published, were reviewed. Researchers also consulted specialists and research centers involved in the meta-analysis subject.

## 4. Study Selection

### 4.1. Inclusion Criteria

Persian and English studies, which met the criteria and reported methadone poisoning in Iranian children, were included after quality assessment. Also, studies reporting the mean, standard deviation, and prevalence of clinical symptoms (according to Nelson essentials of pediatrics 7th edition, 2015) were entered into the meta-analysis.

### 4.2. Exclusion Criteria

The exclusion criteria were as follow: 1) studies with an unknown sample size; 2) abstracts without access to full text; 3) studies with quality assessment scores below 15.5; and 4) studies carried out on non-Iranian populations. Full texts or abstracts of all papers, documents, and reports were extracted, based on the advanced search. First, duplicates were detected and excluded. Then, titles, abstracts, and full texts were reviewed, respectively, and irrelevant

papers were identified and removed. In order to prevent bias caused by reprint, the researchers carefully reviewed the results of studies to detect repeated findings.

### 4.3. Quality Assessment

After relevant studies were selected, their quality was assessed using the STROBE checklist (9), including 22 methodological questions on factors including sample size, sampling method, study design and objectives, data collection, definition of main variables, and statistical tests. Based on the quality assessment, studies were classified into 3 categories: low (< 15.5), moderate (15.5 - 29.5), and high (30 - 44) quality. Only moderate- and high-quality studies were entered into the final meta-analysis (9).

## 5. Data Extraction

Two independent researchers extracted the necessary information, including the author's name, date and location of the study, total sample size, prevalence of symptoms, and mean and standard deviation of methadone poisoning symptoms. The extracted results were entered into Excel spreadsheets. A third researcher managed disagreements in the results between the 2 researchers.

### 5.1. Analysis

Stata SE version 11 was used for data analysis. To evaluate heterogeneity of the results, Cochrane and I-squared indices were used. In order to estimate the prevalence of clinical symptoms caused by methadone poisoning in children in each study, the standard error of prevalence was calculated according to the binomial distribution formula. Since heterogeneity was significant, the random effect model was used to determine the prevalence of each symptom in Iranian children and measure the standardized mean difference of symptom scores.

The point estimates of the prevalence of methadone poisoning symptoms or the standardized difference of mean poisoning symptoms in Iranian children were illustrated by forest plots, including specific boxes (weight of studies) and crossed lines with 95% confidence intervals (CIs). The degree of publication bias was assessed, using Egger's test, and P value less than 0.1 was considered statistically significant.

## 6. Results

In the initial advanced search, 1594 relevant articles were found in national and international databases. After limiting the search strategy and excluding duplicates, 243 papers remained in the study. The title and abstract

screening revealed 192 irrelevant papers. The full texts of 51 remaining articles were reviewed, indicating 27 irrelevant studies. Then, through quality assessment of articles and based on the inclusion and exclusion criteria, 17 articles were excluded and 7 were entered into the meta-analysis procedure (Figure 1). The 8 articles which met the inclusion criteria are shown in Table 1.

In the meta-analysis, an estimate of 10% was calculated (0.95% CI, 0.42 to 0.28). Due to inconsistency among studies (I-squared index, 88%), CIs for each study and all studies were calculated, based on the random effects model (Figure 2). The middle dot in each segment is an estimation of the prevalence, and length of the segment represents 95% CI in each study. The diamond indicates the prevalence rate in the country of these studies.

In the meta-analysis estimations, the prevalence of symptoms in referred patients was 44% (0.95% CI, 0.288 to 0.609). Due to inconsistency among studies (I-squared index, 93%), CIs for each study and all studies were calculated, based on the random effects model (Table 2).

In 4 studies, a significant positive relationship was reported between methadone poisoning in children and family's level of income ( $P < 0.05$ ). However, no significant relationship was found between the year in which the data were collected and the increased rate of patient referral ( $P = 0.02$ ). Poisoning prevalence rates reported in Tehran were higher than other cities of the country in 4 consecutive years. Among the reasons for methadone poisoning, the highest prevalence was attributed to accidental use by children, while the lowest prevalence was related to intentional poisoning by an adult. The complete list of reasons for methadone poisoning is presented in Table 3.

## 7. Discussion

Methadone is a synthetic opioid with a long half-life. According to statistics, use of this drug has increased in recent years in the world. Since the substitution of addictive drugs with methadone from 2002 in Iran, this substance has begun to enter Iranian households and has become available to children.

Methadone is a dangerous drug for children, as very small amounts of it can cause various disorders including: 1) central nervous system symptoms including loss of consciousness, miosis, delirium, and convulsion; 2) respiratory symptoms such as apnea; 3) skin symptoms; dermatologic signs and symptoms including hair loss; 4) cyanosis; 5) cardiovascular difficulties including bradycardia, bradyarrhythmia, hypotension, cardiac arrest, filiform pulse, peripheral circulation failure, prolonged corrected QT interval, and risk of torsades de pointes; 7) metabolic complications including respiratory and metabolic acidosis; 8)

hypercapnia, hyponatremia, hypoxia, hypoxemia, and hypoglycemia; and 9) death (10-12).

Substance abuse by parents is not a new phenomenon, and it is unquestionably causing serious damage to children. Neglecting children's health may even lead to their death. Methadone poisoning often occurs in families with methadone-using parents (13). This has a direct connection with neglecting children and abusing them physically or emotionally. Since children living under such conditions are exposed to many physical and psychological threats compared to normal children, it is necessary to develop crisis intervention methods in order to rectify environmental defects.

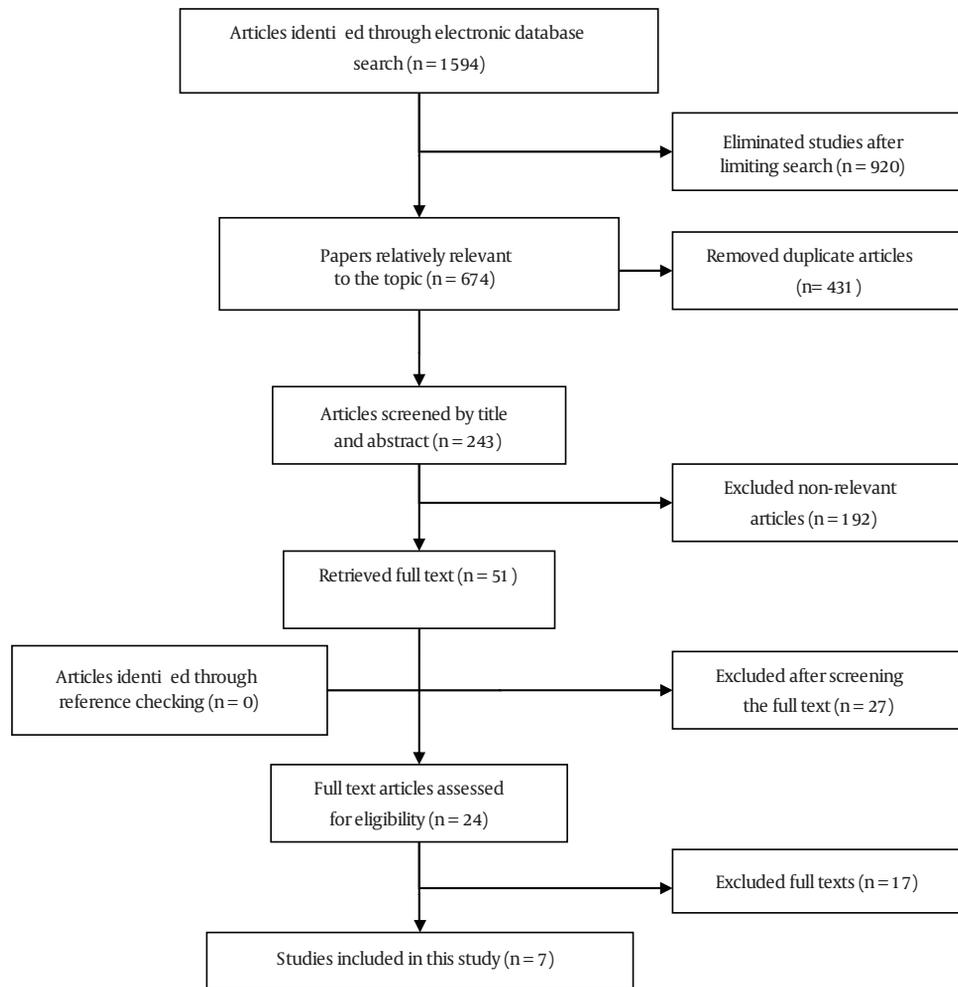
Medical staff including pediatric specialists, caregivers, and healthcare workers should be prepared and well trained for these interventions. The responsibility of a social worker is to manage and coordinate connections between hospital centers and home environment. It is also necessary for different institutions to concentrate more on physical and behavioral effects of parents' addiction on children so that children can be protected and provided with developmental opportunities in healthy families.

In some societies, when parents temporarily lose the custody of their child, they are given a list of treatment centers where they can be admitted to quit their addiction. If they successfully quit, they can regain their child's custody, and if not, the child will be adopted by another family permanently by governmental planning systems. In any case, since the root causes of the problem are not addressed, problems may reoccur, as another child may be born with similar drug exposure (14).

In the present study, about 9.7% of the reported cases were due to deliberate poisoning of children by their parents. In a study conducted in Australia from 1991 to 2005 on reasons for child homicide, immediate diagnosis and treatment of mental disorders in parents, specifically mothers, were highlighted; moreover, it was proposed that changes must occur in parents' methadone use patterns (13). However, in older children, methadone poisoning was found to be mainly a suicidal act, related to a history of psychiatric disorders in children or their families (15). Similarly, in a study by Masoudpour et al., child addiction was accountable for their poisoning (16).

However, in many reported cases, the cause of methadone poisoning was accidental drug intake by children, which was a consequence of their access to methadone and similarity of methadone containers to other drink containers. As recommended by many researchers in different countries, these drugs should be maintained in child-resistant containers and be inaccessible to children (17).

Despite the proposed solutions, methadone poisoning



**Figure 1.** Literature Search and Review Flowchart for the Selection of Primary Studies

in children is still a major unresolved problem (18). For instance, in Canada, despite the packaging of methadone in child-resistant containers, attachment of warning labels to containers, and informing parents (by physicians and pharmacists) about the importance of preventing children's access to the drug, still some cases of methadone poisoning have been reported in children (19). Since such measures are not taken in Iran, the risk is more serious and there is evidence of frequent referrals of pediatric patients with acute methadone poisoning in Iran, compared to other countries (20).

Some addicted parents obtain excessive amounts of methadone from clinics since they do not have enough time to visit clinics or clinics are closed; therefore, they are sometimes forced to use their children's bottles to keep the medicine (21). Symptoms such as sleepiness and decreased

level of consciousness, which are among the silent symptoms, do not trigger enough attention in parents to take care of their poisoned child, which may lead to late admission of the child to hospital and increase the risk of poisoning (17).

In the present study, boys were found to be more at risk, compared to girls. According to statistics by the world health organization (WHO), the rate of fatal accidents in boys under 15 years of age is up to 24% higher than that of girls. Different reasons have been suggested for sex differences in the rate of accidents, including boys' greater tendency towards risky behaviors and physical activity, which can lead to impulsive behaviors. In addition, boys tend to be more curious than girls, which can be troublesome for the parents (22).

The results of the present study showed that the mean

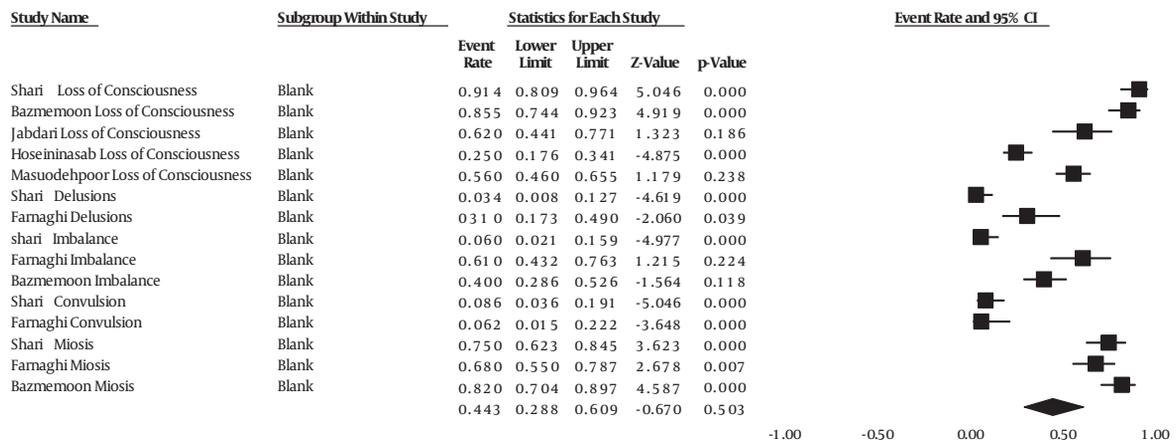
**Table 1.** Common Clinical Symptoms Reported in Methadone-Poisoned Children

First Author	Type of Study	Publication Year	Location	Sample Size	Results (Symptoms)	Limitations	Strengths
<b>Sharif</b>	Cross sectional	2015	Isfahan (Kashan)	58	Drowsiness, vomiting, nonapneic breathing, cyanosis, convulsions, ataxia, delirium, miosis, hypotension, loss of consciousness, and recurrence of symptoms after naloxone injection	Lack of information on the exact cause of poisoning in children	Description of the clinical symptoms/signs and laboratory findings of methadone poisoning in children under 12 years
<b>Shadnia</b>	Cross sectional	2013	Tehran	292	Naloxone relationship with apnea	Retrospective design of the study, limited amount of information on each case in the hospital records, selection bias (as ICD10 criteria were used to choose code T40.3 for methadone toxicity, which may not be used uniformly by database operators in hospitals)	Description of clinical symptoms and signs and their prevalence
<b>Farnaghi</b>	Cross sectional	2012	Tehran	31	Drowsiness, vomiting, apnea, cyanosis, convulsions, ataxia, delirium, miosis, lethargy, and respiratory infection during hospitalization	Lack of information on addiction, parental education, child abuse, birth, economic status, and location of patients	Information on demographics, poisoning, and clinical symptoms, laboratory findings, and clinical course of the disease
<b>Bazmemc</b>	Cross sectional	2014	Hamadan	62	Drowsiness, vomiting, nonapneic breathing, cyanosis, convulsions, imbalance, miosis, hypotension, loss of consciousness, and respiratory infection during hospitalization	Lack of information on the exact cause of poisoning in children	Description of the prevalence of symptoms after poisoning
<b>Gharib</b>	Case report	2014	Tehran	1	Hypotension and apnea	Possibility of misinterpretation of clinical manifestations and behavioral changes in developmental disorders	Complete explanation of the clinical course and treatment
<b>Jabbehda</b>	Descriptive and cross sectional	2013	Tehran	31	Drowsiness, vomiting, nonapneic breathing, seizures, decreased glucose level, respiratory infection during hospitalization, and loss of consciousness	Lack of information on the exact cause of poisoning in children	Report of the prevalence of symptoms
<b>Hoseini Nasab</b>	Cross sectional	2016	Tehran	105	Vomiting, apnea, cyanosis, convulsions, and loss of consciousness	Lack of information on the prevalence of symptoms	Information on the exact cause of poisoning in children, educational level of parents, hospital costs, and length of hospital stay
<b>Masoudp</b>	Cross sectional	2015	Kerman	97	Loss of consciousness, apnea, meiotic pupils, and drowsiness	No interpretation of the significant relationships between different variables	Description of important factors such as seasonal and maternal conditions, addiction, order of birth, economic status, and location among methadone-poisoned children

length of hospital stay was 2.2 days, which is longer than that reported by LoVecchio and et al. in the USA (23). Since the average half-life of methadone in children can exceed 25 hours and in overdose conditions, it can reach above 50-59 hours (24), the mean hospital stay of 2.2 days seems reasonable, considering the risks and symptoms of poisoning, as well as risks of complications (eg, aspiration pneumonia and gastrointestinal symptoms).

In most relevant studies, the mean age of patients was

under 6 years, whereas, for instance, in a similar study in the USA (23), the average age of patients was 18 years. Since in the present study, the average age of patients was less than those in the other studies, attention should be paid to the possible difference of metabolism in children of different ages. In addition, since most children in the study were neglected by their parents, risk of delayed visit, lack of access, malnutrition, pulmonary complications (eg, aspiration pneumonia), and other problems during hospitaliza-



#### Meta Analysis

**Figure 2.** The Prevalence of Symptoms in Referred Patients Based on the Random Effects Model

**Table 2.** Pooled Estimates of Methadone Poisoning Symptoms in Iran

Symptoms	Study	N	Prevalence (Meta-Analysis Estimate)	Event Rate (%95 CI)
Hypertension	2	151	10%	0.045 - 0.237
Loss of consciousness	3	151	80%	0.612 - 0.928
Meiotic pupils	3	151	76%	0.690 - 0.827
Delirium	2	89	3%	0.012 - 0.084
Ataxia	3	151	5%	0.029 - 0.108
Convulsion	3	151	12%	0.045 - 0.285
Cyanosis	3	151	25%	0.117 - 0.460
Apnea	2	89	48%	0.383 - 0.589
Nonapneic breathing	3	151	41%	0.223 - 0.634
Vomiting	3	151	56%	0.357 - 0.754
Drowsiness	3	151	72%	0.323 - 0.934

tion were more frequent.

It is noteworthy that the existing methadone syrups in Iran contain 5 mg/mL of active ingredient, while the tablets are 5, 20, and 40 mg (25). However, in European countries and America, methadone syrups contain 1 mg/mL of methadone (26); therefore, more severe cases of poisoning are reported in Iranian children. Also, poverty and self-treatment at home, fear of social stigma, intentional child poisoning by mentally ill parents, child addiction, parental addiction, residence in rural areas, neglect by

working mother, and inaccessibility to health care are the main reasons for delayed visits and longer periods of treatment at hospital. The reasons for the higher number of poisoned patients in Tehran in comparison with other cities (27) could be the greater population density, higher rates of social disorders, and inadequate attention of working parents to their children in Tehran.

**Table 3.** The Most Important Reasons for Methadone Poisoning in Children Referred to Hospitals

Reasons for Methadone Poisoning	Author's Name	Year	Sample Size	Prevalence Percentage (%)
Storage in inappropriate containers (mineral water and soft drink bottles and diphenhydramine and cough syrup glasses)	Ayoubi	2016	424	62.91
	Ghorbani	2015		
	Sharif	2015		
	Farnaghi	2012		
	Gharib	2014		
	Masoudpour	2015		
Accidental use by children	Sharif	2015	120	69.7
	Bazmemoon	2014		
Parents' mistake in feeding the drug to their children	Sharif	2015	413	60.67
	Shadnia	2013		
	Bazmemoon	2014		
	Gharib	2014		
Intentional poisoning by parents or a family member	Ghorbani	2015	616	9.7
	Hoseini Nasab	2016		
	Manoochehrifar	2016		
History of child poisoning	Ayoubi	2016	245	29.1
	Hoseini Nasab	2016		
Parents' psychological disorders	Ayoubi	2016	280	21
	Mansouri	2013		
Parents' low level of education	Ayoubi	2016	342	38
	Hoseini Nasab	2016		
	Masoudpour	2015		
Parents' addiction	Masoudpour	2015	482	50.21
	Ayoubi	2016		
	Hoseini Nasab	2016		
	Mansouri	2013		

## 8. Conclusion

Methadone therapy is a health policy which can have major impacts on target groups in the society if implemented according to the health ministry's protocols. Physicians, who are involved in methadone maintenance treatment program, with their extensive knowledge about the risks and side effects of methadone, can educate patients on how to keep and consume this drug, and help to smoothly implement the program.

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## Footnotes

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## References

1. Taheri F, Yaraghi A, Sabzghabae AM, Moudi M, Eizadi-Mood N, Gheshlaghi F, et al. Methadone toxicity in a poisoning referral center. *J Res Pharm Pract.* 2013;2(3):130-4. doi: [10.4103/2279-042X.122387](https://doi.org/10.4103/2279-042X.122387). [PubMed: [24991620](https://pubmed.ncbi.nlm.nih.gov/24991620/)].
2. Mohammadi N, Karbakhsh M, Pajoumand A. Epidemiologic aspects of deliberate self-poisoning in adolescents: a hospital-based study in Tehran. *Tehran Uni Med J.* 2007;65(4):59-64.
3. Sarjami S, Pajoumand A. One year epidemiological study of acute adult and adolescent poisoning admitted to Loghman hospital, Tehran 2004-2005. *Sci J Forensic Med.* 2008;13(48):235-40.

4. Farnaghi F, Jafari N, Mehregan FF. Methadone poisoning among children referred to Loghman-Hakim hospital in 2009. *Pejouhandeh*. 2012;**16**(6):299-303.
5. Moghadamnia AA, Abdollahi M. An epidemiological study of poisoning in northern Islamic Republic of Iran. *East Mediterr Health J*. 2002;**8**(1):88-94. [PubMed: 15330564].
6. Goldfrank L, Flomenbaum N, Lewin N. Toxicologic emergencies. 7th ed. McGraw-Hill; 2002. pp. 590-607.
7. Dupuy G, Cavalcanti L, Bourgogne E, Brichant-Petitjean C, Gomberoff L, Bloch V, et al. Are empty methadone bottles empty? An analytic study. *Harm Reduct J*. 2014;**11**:20. doi: 10.1186/1477-7517-11-20. [PubMed: 24990630].
8. Haddad M, Shannon W, Winchester F. Clinical management of poisoning and drug overdose. 3rd ed. Philadelphia: WB saunders; 2007. pp. 640-7.
9. Ghorbani F, Salimkhani N, Pakdel S. Methadone poisoning in children and some factors affecting it: a cross-sectional study in Tabriz, North-west of Iran. *Inter J Pediatric*. 2015;**3**(4):725-31.
10. Sharif MR, Nouri S. Clinical Signs and Symptoms and Laboratory Findings of Methadone Poisoning in Children. *Iran J Pediatr*. 2015;**25**(1):e176. doi: 10.5812/ijp.176. [PubMed: 26199683].
11. Gharib B, Farshadmoghadam H, Hosseini F, Yaghmaie B. Be careful of lies: a six-year-old boy with respiratory distress and decreased level of consciousness. *Acta Med Iran*. 2014;**52**(6):481-3. [PubMed: 25130158].
12. Hosseininasab A, Vahidi A, Bagheri-Charouk F. Predisposing Factors for Methadone Poisoning in Children Hospitalized at Kerman Afzalipour Hospital, Iran. *Addict Health*. 2016;**8**(1):61-6. [PubMed: 27274794].
13. Nielsens OB, Large MM, Westmore BD, Lackersteen SM. Child homicide in New South Wales from 1991 to 2005. *Med J Aust*. 2009;**190**(1):7-11. [PubMed: 19120000].
14. McAlpine C, Marshall CC, Doran NH. Combining child welfare and substance abuse services: a blended model of intervention. *Child Welfare*. 2001;**80**(2):129-49. [PubMed: 11291898].
15. Manouchehrifar M, Derakhshandeh N, Shojaee M, Sabzghabaei A, Farnaghi F. An Epidemiologic Study of Pediatric Poisoning; a Six-month Cross-sectional Study. *Emerg (Tehran)*. 2016;**4**(1):21-4. [PubMed: 26862545].
16. Masoudpour N, Zare-Bidaki M, Sedighi E, Bakhtar M. Frequency and related factors of methadone poisoning in children aged under 15 years attending children emergency center of Rafsanjan Ali-Ebne-Abitaleb hospital In 2013. *J Rafsanjan Univ Med Sci*. 2015;**14**(7):561-74.
17. Palmiere C, Staub C, La Harpe R, Mangin P. Parental substance abuse and accidental death in children. *J Forensic Sci*. 2010;**55**(3):819-21. doi: 10.1111/j.1556-4029.2010.01349.x. [PubMed: 20345788].
18. Li L, Levine B, Smialek JE. Fatal methadone poisoning in children: Maryland 1992-1996. *Subst Use Misuse*. 2000;**35**(9):1141-8. [PubMed: 11349679].
19. Gibson JC, Vulliamy A. Accidental methadone poisoning in children: a call for Canadian research action. *Child Abuse Negl*. 2010;**34**(8):553-4. doi: 10.1016/j.chiabu.2010.02.002. [PubMed: 20605632].
20. Alotaibi N, Sammons H, Choonara I. Methadone toxicity in children. *Arch Dis Child*. 2012;**97**(5).
21. Shadnia S, Rahimi M, Hassanian-Moghaddam H, Soltaninejad K, Noroozi A. Methadone toxicity: comparing tablet and syrup formulations during a decade in an academic poison center of Iran. *Clin Toxicol (Phila)*. 2013;**51**(8):777-82. doi: 10.3109/15563650.2013.830732. [PubMed: 23972442].
22. Peden M, Oyegbite K, Ozanne-Smith J, Hyder AA, Branche C, Rahman AKMF. World Report on Child Injury Prevention. Geneva: World Health Organization; 2008.
23. LoVecchio F, Pizon A, Riley B, Sami A, D'Incognito C. Onset of symptoms after methadone overdose. *Am J Emerg Med*. 2007;**25**(1):57-9. doi: 10.1016/j.ajem.2006.07.006. [PubMed: 17157684].
24. Kliegman RM, Stanton B, Geme J, Schor N. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier Inc; 2015. p. 459.
25. Fda. Available from: <http://www.Fda.gov/item/463>.
26. British Pharmacopoeia. Medicines and healthcare products regulatory agency (MHRA). *Med Pharmaceut Substanc*. **1 and 2**.
27. behzistitehran. Available from: <http://www.behzistitehran.org.ir/>.