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Original Article

Mortality in methadone poisoning: a decade-long analysis of clinical predictors in an Iranian cohort

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Abstract: Objective: This study aimed to evaluate the relationships between demographic characteristics, clinical features, treatment modalities, and outcomes in patients with acute methadone intoxication in Yazd. Methods: This retrospective, hospital-based cohort study analyzed the clinical data of 1,400 patients diagnosed with methadone intoxication. Demographic data, clinical symptoms, laboratory tests, treatment methods, and outcomes were obtained from patients' medical records and the hospital information system. Results: The majority of patients (68.4%) were male, and most intoxication incidents occurred in the 15-30-year age group (37.4%). The most common clinical manifestations were decreased level of consciousness (97.5%), respiratory depression (84.9%), and miosis (82.0%). The most frequent complications were elevated creatine phosphokinase (CPK) (19.6%), aspiration pneumonia (10.4%), seizures (6.0%), and acute respiratory distress syndrome (ARDS) (0.9%). Endotracheal intubation was required in 12.9% of cases. The overall mortality rate was 1.4%. Logistic regression analysis identified elevated CPK (OR = 2.06, 95% CI: 1.16-3.66, P = 0.014), ARDS (OR = 27.86, 95% CI: 4.55-170.74, P < 0.001), and the need for endotracheal intubation (OR = 31.64, 95% CI: 8.37-119.60, P < 0.001) as independent predictors of mortality. Conclusions: Acute methadone intoxication in this region predominantly affects young males and presents with significant central nervous system and respiratory depression. Although the mortality rate is relatively low, the development of ARDS, rhabdomyolysis (indicated by elevated CPK), and the requirement for endotracheal intubation are important risk factors associated with a significantly higher likelihood of death.

Keywords: Methadone, poisoning, mortality, risk factors

Introduction

Methadone is a long-acting synthetic opioid receptor agonist. It is used for its analgesic properties in managing chronic pain and as a first-line agent in opioid agonist therapy, known as methadone maintenance treatment (MMT), for individuals with opioid use disorder (OUD). Its unique pharmacokinetic profile, with rapid and sustained oral bioavailability and a mean half-life of 24-36 hours, allows for daily dosing, which results in stabilization of these patients by alleviating withdrawal symptoms and cravings for illicit opioids [1]. The expansion of MMT has been a key strategy in harm reduction, but it has also increased the risk of diversion and poisoning [2]. The benefits of long-term MMT programs include improved health status, clos-

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er family relationships, and enhanced social functioning for participants [3]. However, methadone-related poisoning has become a growing problem in a number of countries.

Since 2003, MMT programs have been expanded in Iran to combat high rates of opiate addiction [4]. The rise in poisonings is multifactorial, including accidental ingestion, self-poisoning, and therapeutic error. An important factor is the general public's lack of awareness regarding the potency of methadone and its slow onset of action, which can lead to unintended overdose when individuals take additional doses, erroneously believing that the previous dose had no effect. Establishing an exact toxic or lethal dose of methadone is complicated by considerable inter-individual differences and the tolerance created by regular use [5]. Significant respiratory depression has been observed in opioid-naïve persons at doses as low as ~1 mg/kg. However, no consensus is reached on a universally lethal dose as the presence of tolerance, concomitant use of other central nervous system depressants, and individual metabolic variations contribute to the aberrant toxicity [6]. The risk is particularly high in opioid-naïve individuals who may use diverted methadone recreationally [7]. Moreover, accidental poisoning in children has become a tragic and frequent occurrence, frequently as a direct result of improper storage of methadone syrup, which has a consistency similar to other liquids, in homes where a family member is in MMT [8, 9]. This is a leading cause of pediatric opioid poisoning and is preventable with better storage practices and public education [10].

In addition to these circumstances, methadone poisoning can lead to a variety of serious complications. Cardiovascular effects may include bradycardia, hypotension, and especially prolongation of the QTc interval on the electrocardiogram, which may result in life-threatening arrhythmias such as torsades de pointes. This is a known risk associated with methadone compared to other opioids [11]. Neurological complications may include seizures, which are generally due to severe hypoxia. Other severe complications include non-cardiogenic pulmonary edema (also known as acute respiratory distress syndrome, ARDS), aspiration pneumonia due to unconsciousness and loss of airway reflexes, and rhabdomyolysis. The pathophysiology of rhabdomyolysis is multifactorial, involving prolonged immobility, muscle compression, and tissue hypoxia [12].

Treatment of methadone poisoning is based on markers of immediate supportive care, stressing mainly the need for the maintenance of the patient's airway and for adequate ventilation. The specific antagonist of the opioid, naloxone, lies at the basis of pharmacological treatment, but since methadone has a longer duration of action than naloxone and its half-life is only 30-90 minutes, the patient will frequently need repeated boluses of naloxone or a continuous intravenous infusion of it in order to avoid respiratory depression Guidelines recommend a continuous naloxone infusion for methadone overdoses, rather than the management of short-acting opioid poisonings Therefore, patients need to be monitored for a prolonged period of time, as in the hospital for at least 24 hours. In severe respiratory failure, intubation and mechanical ventilation must be employed to prevent fatal hypoxia.

Treatment of methadone poisoning is based on principles of immediate supportive care, with emphasis on maintaining the patient's airway and ensuring adequate ventilation. The specific opioid antagonist, naloxone, is the mainstay of pharmacological treatment. However, because methadone has a longer duration of action (half-life 24-36 hours) than naloxone (half-life 30-90 minutes), patients frequently require repeated boluses of naloxone or a continuous intravenous infusion to avoid recurrent respiratory depression [13]. Guidelines recommend a continuous naloxone infusion for methadone overdose, rather than the intermittent boluses used for short-acting opioid poisonings [12]. Therefore, patients need to be monitored for a prolonged period, typically in the hospital for at least 24 hours. In cases of severe respiratory failure, intubation and mechanical ventilation must be employed to prevent fatal hypoxia.

While the overall clinical picture of methadone intoxication is generally well documented, there is broad variation between patients in terms of demographic characteristics, incidence of complications, and outcomes depending on the geographical region and healthcare setting. Local data are necessary to formulate clinical guidelines, allocate health resources, and determine appropriate public health inter-

ventions. In Iran, although several studies have been conducted on methadone toxicity, a comprehensive investigation of the clinical picture and determinants of mortality in the city of Yazd has been lacking. This gap presents a challenge for local healthcare providers who manage these poisonings and for policymakers tasked with developing regional prevention strategies.

This study was therefore undertaken to address this lack of information. It aims to characterize the demographic profile, clinical features, treatment modalities, and outcomes in patients presenting with acute methadone poisoning to two major referral hospitals in Yazd over a ten-year period. The specific objectives were to describe the demographic and clinical characteristics of the patient cohort, to ascertain the frequency of major complications such as ARDS, seizures, and rhabdomyolysis, and to identify the key clinical and therapeutic factors that serve as independent predictors of mortality. The elucidation of these factors is expected to provide important, relevant, evidence-based information that can be used to improve the medical management of methadone poisoning and to advance public health programs aimed at reducing the impact of this problem on the community.

Methods

Study design and setting

A retrospective, cohort study was designed to examine the records of patients admitted for acute methadone poisoning. The study was carried out in two large hospitals containing medical facilities in Yazd province in Iran, the Shah Vali Hospital in Yazd and the Shahid Beheshti Hospital in Taft. These institutions serve as the area's referral centers for toxicologic and poisoning cases, thus representing the area's background sample of such occurrences. The information was obtained for all patients qualified for selection that were admitted during a decade, which covered the period from March 21, 2014, to March 20, 2023 (Iranian calendar years 1393-1402). The study was approved by the Institutional Review Board and by the Ethical Committee at Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The information available on patients was completely anonymized to maintain confidentiality while the research was being conducted.

Participants

The population for the study focused on the patients diagnosed with acute methadone poisoning within the study timeline. The inclusion criteria comprise: (1) history of methadone ingestion documented by the patient, family, or witnesses, (whether by accidental ingestion, a suicide attempt, or by methadone misuse/abuse); (2) documented clinical evidence of an opioid toxidrome which caused a decrease in the level of consciousness, and respiratory depression (bradypnea or apnea) and miosis; (3) diagnosis made by the physician in attendance or clinical toxicology physician; and (4) in the event of a case, clinical response to naloxone was documented, and on the contrary, the exclusion criteria comprise: (1) other opioid or central nervous system (CNS) depressants such as opium syrup, tramadol, or heroin for which co-ingestion was confirmed or suspected strongly; (2) other neurological or respiratory conditions pre-existing which were sufficient to explain the presenting problems; and (3) medical records which were incomplete and lacked the necessary clinical or outcome data.

Data extraction and assessment

Data extraction from the patients' medical records was performed in a thorough and systematic manner using paper records and the electronic Hospital Information System (HIS). A data extraction form was designed specifically for this purpose. The form was designed in detail to collect patient demographic data, clinical presentation, laboratory values, treatment, and outcomes. To ensure the uniformity and adequacy of the extracted data, three researchers were assigned to this task. The following data were collected:

Demographic and medical history: Age, sex, marital status, and the patient's level of education were recorded. The circumstances of poisoning were documented and classified as accidental, suicidal, or abuse/misuse (non-prescribed use for recreational purposes or self-medication). The presence of pre-existing opioid addiction was recorded.

Clinical and laboratory measures: Clinical data obtained upon the patient's admission to the hospital will be documented, including neurological status (presence of seizures, miosis, or decreased level of consciousness) and respiratory status (presence of bradypnea, apnea, or signs of respiratory distress).

The initial neurological assessment used recorded clinical examinations. If the medical records had GCS documentation, that was used. Seizures, abnormal pupils (including miosis), neurological deficits (focal), and atypical motor response were noted. For suspected neurological issues, the documentation included neurology consultation notes and any completed imaging studies.

The primary laboratory values that were obtained serum electrolytes (Natrium, kalium), tests of renal function (blood urea nitrogen, creatinine), hepatic enzymes (aspartate to aminotransferase [14], alanine aminotransferase [7]), tests of complete blood (total white cells count, hemoglobin), and random blood glucose. The data of blood gas examinations (ABG), including pH, partial pressure of carbon dioxide (pCO2), and bicarbonate (HCO3) were taken from this sample.

Complications and interventions

The development of significant inpatient complications was noted, such as: pneumonia due to aspiration, acute respiratory distress syndrome (ARDS) and rhabdomyolysis. According to similar studies in the toxicologic literature [15], the term rhabdomyolysis was specifically defined as a CPK (creatine phosphokinase) serum level > 975 IU/L. Key therapeutic interventions were also recorded, particularly the use of the narcotic antagonist naloxone or the need for advanced airway management using endotracheal intubation.

Outcome variables

The primary outcome variable was in-hospital mortality which was defined as death from any cause during the hospital stay. In the context of a retrospective design and limitations in documentation, cause-specific mortality (e.g., respiratory failure, cardiac arrhythmia or sepsis) was not possible. Thus, mortality was examined as all-cause in-hospital death.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were measured and expressed as mean ± standard deviation (SD) and normality was assessed using the Kolmogorov-Smirnov test. Frequencies and percentages were used to summarize categorical variables. The Chi-square test or Fisher's exact test were used when expected cell counts were < 5 to determine the association between categorical predictors and in-hospital mortality. Multivariable binary logistic regression with the enter method was used to determine independent predictors of mortality. Clinically relevant variables or variables with significance in bivariate analysis were included in the model. Odds Ratios (OR) with 95% confidence intervals (CIs) were used to express the results. All tests were two-tailed and significance was determined at $P < 0.05$.

Results

Demographics and baseline characteristics of the cohort

A total of 1400 patients with acute methadone poisoning were included in the analysis. The cohort was predominantly male (n = 958, 68.4%). The distribution of age groups showed that the largest proportion of patients were in the 15-30-year group (n = 524, 37.4%), followed by the 31-45-year age group (n = 391, 27.9%). There was also a significant number of cases under 15 years of age (n = 233, 16.6%) (**Table 1**).

Clinical presentation, hospital course, and outcomes

The most common clinical manifestations were related to central nervous system and respiratory depression. The majority of patients (n = 1365, 97.5%) presented with a decreased level of consciousness. Respiratory depression was noted in 84.9% (n = 1188) of cases (bradypnea or apnea), and miosis was seen in 82.0% (n = 1148).

A considerable number of complications were noted during hospitalization. Seizures occurred in 6.0% (n = 84) of patients. Pulmonary complications were also frequently observed, with

Table 1. Demographic and baseline characteristics of patients with methadone poisoning

Characteristic	Category	n (%)
Gender	Male	958 (68.4)
	Female	442 (31.6)
Age Group (years)	< 15	233 (16.6)
	15-30	524 (37.4)
	31-45	391 (27.9)
	46-60	181 (12.9)
	> 60	71 (5.1)
Marital Status	Single	699 (49.9)
	Married	659 (47.1)
	Divorced	42 (3.0)
History of Addiction	Yes	1012 (72.3)
	No	388 (27.7)
Motive for Ingestion	Misuse/Abuse	887 (63.4)
	Suicide Attempt	419 (29.9)
	Accidental	94 (6.7)

Table 2. Clinical characteristics, interventions, and outcomes

Characteristic	n (%)
Primary Clinical Findings	
Decreased Level of Consciousness	1365 (97.5)
Respiratory Depression	1188 (84.9)
Miosis	1148 (82.0)
Complications	
Elevated CPK (> 975 IU/L)	275 (19.6)
Aspiration Pneumonia	145 (10.4)
Seizures	84 (6.0)
ARDS	12 (0.9)
Interventions & Hospital Course	
Naloxone Administration	1252 (89.4)
Endotracheal Intubation	181 (12.9)
ICU Admission	889 (63.5)
Outcome	
In-Hospital Mortality	20 (1.4)

10.4% (n = 145) developing aspiration pneumonia and 0.9% (n = 12) developing the more serious acute respiratory distress syndrome (ARDS). Rhabdomyolysis, defined as a creatine phosphokinase (CPK) level > 975 IU/L, occurred in 19.6% (n = 275) of the cohort.

In terms of clinical management, 89.4% (n = 1252) received naloxone, and 12.9% (n = 181) received advanced airway management with endotracheal intubation. The mean length of hospitalization was 1.98 days (SD = 2.00). The majority of patients (n = 889, 63.5%) required admission to an intensive care unit (ICU) for advanced monitoring and treatment.

In total, 20 patients (1.4%) died during hospitalization. To further characterize this non-survivor subgroup, their descriptive data were analyzed. The mean age of the deceased patients was 30.25 years, and 15 (75.0%) were male. Among this group, 14 (70.0%) had a history of addiction, and the most common motive for ingestion was reported as misuse/abuse (55.0%) (**Table 2**).

Factors associated with in-hospital mortality

Bivariate analysis was performed to assess the relationship between a variety of clinical factors and in-hospital mortality. Four variables were found to have a significant relationship with an increased risk of mortality. The death rate was significantly higher for patients who developed ARDS (41.7%) compared to those who did not (1.1%), χ^2 (1, N = 1400) = 138.96, P < .001. Also, patients requiring endotracheal intubation had a significantly higher death rate (9.9%) than non-intubated patients (0.2%), χ^2 (1, N = 1400) = 104.19, P < .001.

The presence of rhabdomyolysis (elevated CPK) was also significantly associated with mortality: 5.5% of those with elevated CPK died, compared with 0.4% of those with normal CPK, χ^2 (1, N = 1398) = 39.31, P < .001. Patients who had seizures had a significantly increased mortality (4.8%) compared to those who did not (1.2%), χ^2 (1, N = 1400) = 7.03, P = .008. These associations are shown in **Table 3**.

Independent predictors of in-hospital mortality

A multivariable logistic regression analysis was performed to determine independent predictors of in-hospital mortality while controlling for covariates. The model included ARDS, endotracheal intubation, elevated CPK, seizures, and aspiration pneumonia as predictor variables. The model was statistically significant, χ^2 (5) = 87.46, P < .001, and explained approximately 43.6% of the variance in mortality (Nagelkerke R^2 = .436). The model had great predictive accuracy, with correct classification of 98.8% of cases.

After adjustment for other variables in the model, three significant independent predic-

Table 3. Bivariate analysis of factors associated with in-hospital mortality

Factor	Died, n (%)	Survived, n (%)	Total, n	*p*-value
ARDS				< .001
Present	5 (41.7)	7 (58.3)	12	
Absent	15 (1.1)	1373 (98.9)	1388	
Endotracheal Intubation				< .001
Yes	18 (9.9)	163 (90.1)	181	
No	2 (0.2)	1217 (99.8)	1219	
Elevated CPK				< .001
Yes (> 975 IU/L)	15 (5.5)	260 (94.5)	275	
No (Normal)	5 (0.4)	1118 (99.6)	1123	
Seizures				0.008
Yes	4 (4.8)	80 (95.2)	84	
No	16 (1.2)	1300 (98.8)	1316	

Note: N varies slightly due to missing data for CPK analysis (N = 1398).

tors of mortality were revealed. The most powerful was the necessity for endotracheal intubation, which increased the odds of death by over 31 times (OR = 31.64, 95% CI [8.37, 119.60], P < .001). The development of ARDS was likewise a powerful predictor, increasing the odds of mortality by nearly 28 times (OR = 27.86, 95% CI [4.55, 170.74], P < .001). In addition, elevated CPK resulted in a doubling of the odds of death (OR = 2.06, 95% CI [1.16, 3.66], P = .014).

In the multivariable model, seizures (P = .166) and aspiration pneumonia (P = .142) were not statistically significant independent predictors of mortality. The complete results of the logistic regression analysis are presented in **Table 4**.

Discussion

This extensive retrospective study provides useful insight into the demographic features, clinical characteristics, and prognostic factors in a large cohort of 1400 patients with acute methadone poisoning in Yazd, Iran. Data indicate that the overall mortality rate for the cohort is low, but the group manifests a strikingly different demographic profile and a series of serious, life-threatening complications that predict fatal outcomes. The main findings demonstrate that methadone poisoning predominantly affects young males and generally occurs in association with misuse, and that the development of ARDS, the need for intubation, and the occurrence of rhabdomyolysis were found to be the most important prognostic variables for survival.

Demographic profile and context of poisoning

A key finding of this study is the demographic group affected. The preponderance of males (68.4%) is consistent with many national and international reports on addiction and poisoning, which highlights the differential sex incidence of risk-taking and addiction. This gender disparity has been noted globally [16]. This consistently demonstrate higher rates of opioid misuse and risk-taking behaviors among men. This pattern likely reflects sociocultural and behavioral factors that predispose males to substance use and high-risk consumption practices.

More remarkable, however, is the youth of our cohort, with the highest incidence (37.4%) in the 15-30-year age group. This contrasts markedly with experiences from some Western countries, where methadone-related deaths often occur in older individuals.

Within these contexts, fatalities are typically linked to therapeutic accumulation, comorbid conditions, or polypharmacy in patients treated chronically. On the contrary, our results indicate that in this region, methadone poisoning is more related to the non-medical use of methadone by younger individuals [16]. This is evidenced by the fact that misuse or abuse accounted for 63.4% of the cases, combined with the high prevalence of prior addiction (72.3%). This suggests diversion, recreational use, or improper dosing, such as dose stacking or co-use with other depressant agents. Prior studies from Iran indicate the ease of obtaining methadone through unofficial routes as a key factor for the misuse of methadone among youth [4]. When compared to Western systems of more stringent maintenance therapy, the results from our study suggest opioid use and misuse among individuals who are opioid naïve, as well as poor public awareness of the risks associated with long-acting opioids, less regu-

Table 4. Multivariable logistic regression analysis of predictors for in-hospital mortality

Predictor Variable	B	SE	Wald	*p*-value	Odds Ratio (OR)	95% CI for OR
ARDS	3.327	0.925	12.94	< .001	27.86	4.55, 170.74
Endotracheal Intubation	3.455	0.678	25.93	< .001	31.64	8.37, 119.60
Elevated CPK	0.722	0.293	6.06	0.014	2.06	1.16, 3.66
Seizures	0.956	0.69	1.92	0.166	2.6	0.67, 10.06
Aspiration Pneumonia	-1.042	0.71	2.16	0.142	0.35	0.09, 1.42
Constant	-7.48	0.843	78.69	< .001	0.001	

Note: B = regression coefficient; SE = standard error; CI = confidence interval. Model statistics: χ^2 (5) = 87.46, P < .001; Nagelkerke R^2 = .436.

latory control and oversight, and more availability of long-acting opioids.

Clinical presentation and major complications

The clinical features of patients in our cohort are consistent with the classic opioid toxidrome, characterized by nearly universal decreased level of consciousness (97.5%) and high rates of respiratory depression (84.9%) and miosis (82.0%). The findings are consistent with existing descriptions of opioid toxicity and reaffirm methadone's strong central nervous system depressant effects [17]. This is underscored by the fact that 63.5% of patients required ICU admission. Considering the typical general opioid poisoning reports [17, 18], the need for intensive care in almost two-thirds of patients indicates that methadone poisoning is likely to result in a longer and/or more severe respiratory depression, attributable to its long half-life and delayed peak effects [19]. This places a greater need for monitoring in such patients, especially in environments where critical respiratory depression could occur after the patient had initially been stabilized.

Rhabdomyolysis as a prognostic factor

Rhabdomyolysis (CPK levels exceeding 975 IU/L) is found in 19.6% of patients. The condition can lead to myoglobin induced acute renal failure and life threatening electrolyte imbalances which occur from prolonged immobilization, muscle compression, and hypoxia. This is of particular concern considering the contributing factors to overall morbidity and mortality [20]. The incidence found is significantly greater than the rate of 4.6% documented in Aghabikloei et al. report in another Iranian cohort [15]. This could be due to differences in diagnostic criteria, the timing of CPK collection, the length of immobilization prior to hospital arrival, or overall poisoning severity in our cohort. CPK levels were associated with more than a twofold increase in mortality (OR = 2.06). This demonstrates that rhabdomyolysis is a significant prognostic indicator in this cohort. Symptoms of rhabdomyolysis have also been documented in other forms of poisoning [14]. These results support the need for further studies and the implementation of measures in order to reduce the incidence of rhabdomyolysis, acute renal failure and electrolyte imbalances.

ARDS and mortality risk

Only 0.9% of the patients developed ARDS; however, this condition proved significant in a predictive sense. Those who developed ARDS had almost 28 times the odds for death, making ARDS the strongest predictor in the study. This aligns with earlier Iranian studies, with an incidence of around 1.5% [15]. Despite the rarity, ARDS is extremely lethal. ARDS is hypothesized to be the result of non-cardiogenic pulmonary edema due to the hypoxic damage to the alveolar membrane and the strong activation of the sympathetic response when there is severe central nervous system depression [21]. Though uncommon, when ARDS does present, there is severe respiratory compromise. Given the stark mortality of ARDS [22], complex critical care is needed to manage the condition; hence, the extreme death that was seen and noted in our cohort requires recognition and the provision of advanced respiratory support at the onset of pulmonary edema. In comparison to myriad respiratory depression alone, ARDS relatively and critically represents a shift in the clinical continuum.

Management interventions as markers of severity

Therapeutic interventions provided in our cohort detail the severity of methadone toxicity. 89.4% of patients received naloxone which correlates with the frequent occurrence of a clinically significant opioid toxidrome, as well as marked CNS depression. Endotracheal intubation was the strongest predictor of mortality, increasing the odds of dying over 31 times. This association is not causal, as the need for mechanical ventilation is indicative of severe respiratory failure, significant CNS depression, severe ARDS, or protective airway collapse. Therefore, intubation should be seen as a marker for severe clinical conditions instead of contributing to death [20, 23]. Our intubation rate is similar to the 11.7% Lee et al. found in a U.S. cohort [24], while higher than other Iranian studies [25]. These factors may show differences in the severity of patients upon presentation, co-ingestion patterns, or the institutional criteria for airway management.

Limitations and strengths

This study's primary strengths are its large sample size and ten-year duration, that offers a long-term perspective on methadone poisoning in the region. However, it has some limitations. First, considering the study's retrospective design, the dose of methadone ingested could not be estimated accurately. The ingestions were of uncertain number, and patients were likely to be unreliable reporters because of altered mental status or possible retrograde amnesia. Furthermore, most patients had a history of opioid addiction, and this may have had a direct impact on the clinical severity. Second, toxicology results were not available, and the considered co-ingestion of other substances could not be entirely excluded, even with the strict exclusion criteria. Third, the mortality of the study participants could only be evaluated considering all causes of in-hospital deaths, and the cause-specific mortality was not ascertainable from the available records. Also, the research was conducted in Iran, and consequently, its findings may not be genera lizable to other countries where policies and drug use patterns differ.

Implications and future directions

This study's findings have important implications for both clinical practice and public health. Clinicians should be especially aware of the possibility of rhabdomyolysis and ARDS in patients with severe methadone poisoning. This includes monitoring CPK levels, watching for respiratory distress, and instituting early, expert airway management when needed.

Efforts to prevent abuse should be directed at young people. This can be achieved through public campaigns educating young people about the dangers of using illicitly obtained methadone and through stricter regulations to prevent its diversion. A key harm-reduction measure is to ensure that all methadone syrup is dispensed only in child-resistant, clearly labeled containers to prevent accidental poisoning in children.

Future investigations should be prospective, include multiple centers, and employ standardized data collection and routine toxicology analyses. Future research should also include studies into genetic factors, such as variations in CYP450 enzymes, that may explain the variance in toxicity exposure among patients. Specifically, polymorphisms in the CYP2B6 gene have been linked to methadone clearance and risk of toxicity [26].

Conclusion

Acute methadone poisoning is a significant public health challenge that predominantly affects young men through misuse in Yazd, Iran. Most of these patients survive, but the poisoning can be severe, causing CNS depression and respiratory depression. Severe outcomes are strongly predicted by three key complications: the development of ARDS, the presence of rhabdomyolysis, and the need for endotracheal intubation.

These findings highlight the need for clinicians to be aware of these high-risk signs. They also underscore that targeted prevention programs are necessary to reduce the non-prescribed use of methadone, especially among young people.

Disclosure of conflict of interest

None.

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