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Characteristics and risk factors of opioid poisoning in opioid-dependent individuals using their primary opioid of dependence: a registry-based study

Ahmad Nemati[1], Leila Etemad[2,3], Bita Dadpour[4,5], Anselm Wong[6,7], Mobin Gholami[1], Seyed Reza Mousavi[4,5], Anahita Alizadeh Ghomsari[4,5], Seyed Hadi Mousavi[4,5], Alireza Ghassemi Toussi[4,5], Khalil Kimiafar[8], Zahra Ataee[9], Maryam Vahabzadeh[4,5], Mohammad Amin Talebpour[10], Amir Mohammad Arasteh Nodeh[1], Fatemeh Abavisani[10] and Mohammad Moshiri[4,5*]

Abstract

Background Opioid addiction and poisoning are prevalent health issues in Iran, where various types of opioids are easily accessible. Despite being dependent on a specific type of opioid, some opioid-dependents abuse different types opioids which can prone them to some consequences. This study aimed to assess the characteristics and risk factors of opioid poisoning among opioid-dependent individuals poisoned by their own or opioid.

Methods This cross-sectional study analyzed data from the MTR-MUMS-Iran (May 2021-January 2022), including opioid-dependent adults poisoned by their regularly used opioid. Opioid dependency was categorized as synthetic opioid or opiate. Data extracted included demographics, opioid type, manner of poisoning, and clinical manifestations. Also, a comparison was conducted between poisoning prevalence with 2011 Iranian Mental Health Survey (IMHS) opioid dependency data.

Results Among 3064 registered cases, 116 patients with a mean age of 40.27 years were included, with a mortality rate of 1.7% ($n = 2$). The frequency of synthetic opioid and opiate overdose was similar (50.9% vs. 49.1%). Opium and methadone were the most common opioids involved. The most common clinical presentation was decreased level of consciousness (72.4%). Excessive use (50.9%), suicide (24.1%), were the main scenarios leading to poisoning. The manner of poisoning among elderly and opiate-dependent patients was excessive use, while younger synthetic opioid-dependent patients tended to attempt suicide. Furthermore, opiate-dependent individuals were more likely to co-ingest therapeutic medications and have underlying renal disease. The average hospital stay was 2.31 days, with age being a significant predictor of length of stay.

*Correspondence:
Mohammad Moshiri
Moshirim@mums.ac.ir; Moshirimo@gmail.com

Full list of author information is available at the end of the article

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Conclusion The findings of this study suggest some practical implications for physicians. Excessive use and suicide are the two main manners of opioid poisoning among opioid dependents. Women and methadone-dependent cases are at higher risk for opioid toxicity, and buprenorphine appears to be the safest opioid option.

Keywords Opioids, Substance related disorders, Poisoning, Iran, Public health

Introduction

It is estimated that 16–32 million individuals in the world are opioid dependent or have opioid use disorder (OUD) [1]. OUD imposes a serious burden of rehabilitation therapies, opioid poisoning, adulteration, or adverse drug reactions on the health system [2–4]. OUD is prevalent in Iran (with prevalence of more than 2%) and thus is a national health problem [5, 6]. Opioids are divided into 3 groups: opiates, semisynthetic opioids and synthetic opioids. Opium is a natural form of opioid extracted from the poppy plant. Opium belongs to the opiate group [7]. Semi-synthetic opioids include heroin and buprenorphine. Methadone, tramadol, fentanyl, and some other compounds also belong to the synthetic opioids [8]. Additionally, opioids can be administrated through a variety of routes, most notably by mouth, inhalation, and intravenous injection [9].

Opioid intoxication increases in line with the rising prevalence of opioid dependency, in developing and developed countries [10, 11]. Opioid poisoning can lead to impaired consciousness, respiratory failure, and even death. In a cohort study in England, drug intoxication has been identified as the leading cause of death among individuals who utilize illegal opioids [12]. In the USA, opioids were responsible for two-thirds of drug-related deaths in 2017 which has been increasing [11, 13].

Understanding the reasons behind opioid intoxication in Iranian patients regularly using these substances is critical due to the high prevalence of opioid dependence in Iran, with opioid overdose being a major cause of morbidity and mortality. Moreover, between 2014 and 2016 in Iran, opioid poisoning was the reason for 87% of drug-related deaths [14]. A significant portion of these overdoses involve individuals who are already opioid-dependent. Iran's geographical proximity to Afghanistan, a major opium producer, has historically contributed to widespread opium use, deeply ingrained in some traditional practices [15]. While opium remains prevalent, tramadol abuse, especially among younger individuals seeking euphoric effects, analgesic effects, or addressing premature ejaculation, is on the rise [16, 17]. Heroin, common in many developing nations like Iran, is also present, particularly among vulnerable populations [5]. Over the past two decades, methadone and buprenorphine have become increasingly prevalent in Iran, primarily due to the implementation of Methadone Maintenance Treatment (MMT) and Buprenorphine Maintenance Treatment (BMT) programs [18, 19]. While intended to reduce harm, a proportion of these medications have been diverted or sold illegally, leading to increased rates of methadone and buprenorphine-related intoxications [19]. This surge in intoxications underscores the importance of this study in understanding the specific factors contributing to opioid intoxication among Iranian opioid-dependent patients within the unique context of Iran's opioid landscape.

While various mechanisms can lead to opioid poisoning – including accidental overdose, suicide attempts, iatrogenic causes, and altered drug metabolism [1, 3, 20],– a particularly relevant scenario in settings like Iran involves individuals dependent on opioids experiencing intoxication from the very substances they habitually use [21]. But this phenomenon, where a patient becomes poisoned with their own opioid of dependence, warrants specific attention. This group is distinct because factors like tolerance, altered metabolism, and the potential for unintentional dosage errors or fluctuations in opioid purity can lead to unexpected and severe toxicity even when using a familiar substance [22, 23].

Therefore, this study aims to address the gap in knowledge regarding the specific characteristics of opioid intoxication caused by the same opioid on which the individual is dependent. We conducted a cross-sectional study on data from the Medical Toxicology Registry of the Mashhad University of Medical Sciences (MTR-MUMS) in Iran to evaluate the reasons behind poisoning, patient characteristics, clinical presentations, the specific opioids involved, and the outcomes of these cases. By elucidating these aspects of "own opioid" poisoning in opioid-dependent individuals, we intend to provide valuable insights that can inform clinical practice and guide healthcare policymakers in developing targeted strategies to mitigate the risk of opioid poisoning within this vulnerable population.

Method

This is a cross-sectional study conducted on data from MTR-MUMS- Iran from May 2021 to January 2022. MTR-MUMS registers adult poisoned patients admitted to the clinical toxicology department of Imam Reza Hospital of MUMS (CTD-IRH-MUMS) [24]. Incomplete data were excluded. MTR-MUMS is approved by the ethical committee of MUMS, IR.MUMS.REC.1394.726. and all registered cases have signed consent forms. Date used in the current research was extracted without any personal informational characteristics of registered cases,

such as name, national code, etc. The data was also converted to codes to conceal the identities.

The study included all registered cases of opioid poisoning in MTR-MUMS involving patients who were opioid-dependent and had ingested opioids they regularly used. Opioid dependency was determined based on self-reports from patients or their relatives, as well as adherence to the DSM-V criteria. Specifically, patients were considered opioid-dependent if they met at least three of the eleven DSM-V criteria for opioid use disorder, as documented in their medical records by the attending physicians. Patients who reported using multiple types of opioids or whose urine toxicology tests indicated the presence of more than one opioid compound were excluded from the study. Sex, age, manifestation (sign and symptom), specific type of opioid dependency, the most probable manner of poisoning, and their outcomes were extracted from the MTR-MUMS data-bank. These extractions were performed by trained research assistants, who were blind to the study's hypotheses to reduce information bias.

Poisoned patients were categorized into two groups according to their specific type of opioid dependency including synthetic opioids and opiates. In this research the term opiate refers to opium and semisynthetic opioids. Synthetic opioids included methadone and tramadol.

In some cases, the main manner of poisoning could not exactly be defined therefore more than one manner was considered. The main clinical presentation and the most probable manner of toxicity were recorded according to the attending physician's opinion. All patients were evaluated by at least two physicians independently, who re-evaluated the history, clinical, and laboratory findings of recorded cases, excluding those with incomplete medical records or uncertain intoxication diagnoses. In instances of disagreement between the attending physician and the second physician, a third physician reviewed the documents and medical history to reach a consensus. Additionally, we recognized the potential influence of physician subjectivity in diagnosis and addressed this concern by implementing standardized criteria for coding in the dataset of MTR-MUMS and involving multiple reviewers to ensure consistency and accuracy in data classification. Given the nature of this cross-sectional study on the existing registry data, formal sample size calculations were not performed. Instead, we aimed to include all eligible cases registered during the study period to maximize the robustness of our findings (Fig. 1).

Statistical analysis

The extracted data was imported into the SPSS software version 11.5. Frequency of gender, manifestations, specific type of opioid dependency, and most probable manner of poisoning are shown as numbers and/or percentages. Fisher's exact test, chi-squared test, and logistic regression were used to investigate the relationship between qualitative variables. As the distribution of age of cases in different groups (sex, opioid type, etc.) were not normal (P value of Kolmogorov-Smirnov test < 0.05) Mann–Whitney U or Kruskal–Wallis tests were applied. Furthermore, we compared our poisoning prevalence with national opioid dependency data from the 2011 Iranian Mental Health Survey (IMHS) to contextualize our findings. Direct estimation and Fisher's exact test were used to compare these data [5]. The level of significance was accepted at a p-value < 0.05.

Results

The findings of the study, as illustrated in Fig. 1, indicate that among 3,064 registered cases in the MTR-MUMS, 116 opioid-dependent patients who experienced poisoning from their own opioids were eligible for inclusion. The majority of these patients were male (94 cases, 81%), with an average age of 40.27 ± 17.76 years (range = 17–91 years). Most patients fell within the 20 to 39 age group ($n = 61$, 52.6%) (Table 1). Of the cases, 57 (49.1%) were dependent on opiates and experienced poisoning due to them, while 59 (50.9%) were dependent on synthetic opioids. Notably, those dependent on opiates were older than those dependent on synthetic opioids (P.Value (PV) < 0.001). Moreover, opium dependency and poisoning were more prevalent among older individuals compared to those dependent on methadone (PV < 0.0001) and heroin (PV = 0.02) (Fig. 2). In contrast, tramadol-dependent patients were the youngest group (PV < 0.0001).

The most frequently observed clinical presentation was decreased level of consciousness ($n = 84$, 72.4%). Younger patients were more likely to experience vomiting, weakness, and seizures (PV < 0.001) (Table 2). Besides, Seizures were only observed in patients who were intoxicated with tramadol. There was no significant difference in clinical manifestations between the opiate and synthetic opioid groups.

Misuse or abuse was the predominant mode of poisoning in both opioid-dependent groups (Table 3). Suicide attempts were more prevalent among synthetic opioid-dependent individuals compared to those dependent on opiates (PV = 0.003). The average age of patients who attempted suicide was lower than that of those who overdosed (27.57 ± 9.61 vs. 44.02 ± 18.83 years, PV < 0.0001). Opiate-dependent patients were more likely to experience co-ingestion of medications at therapeutic doses (excluding benzodiazepines) and underlying renal disease than their synthetic opioid-dependent counterparts (PV = 0.02 and PV = 0.045, respectively).

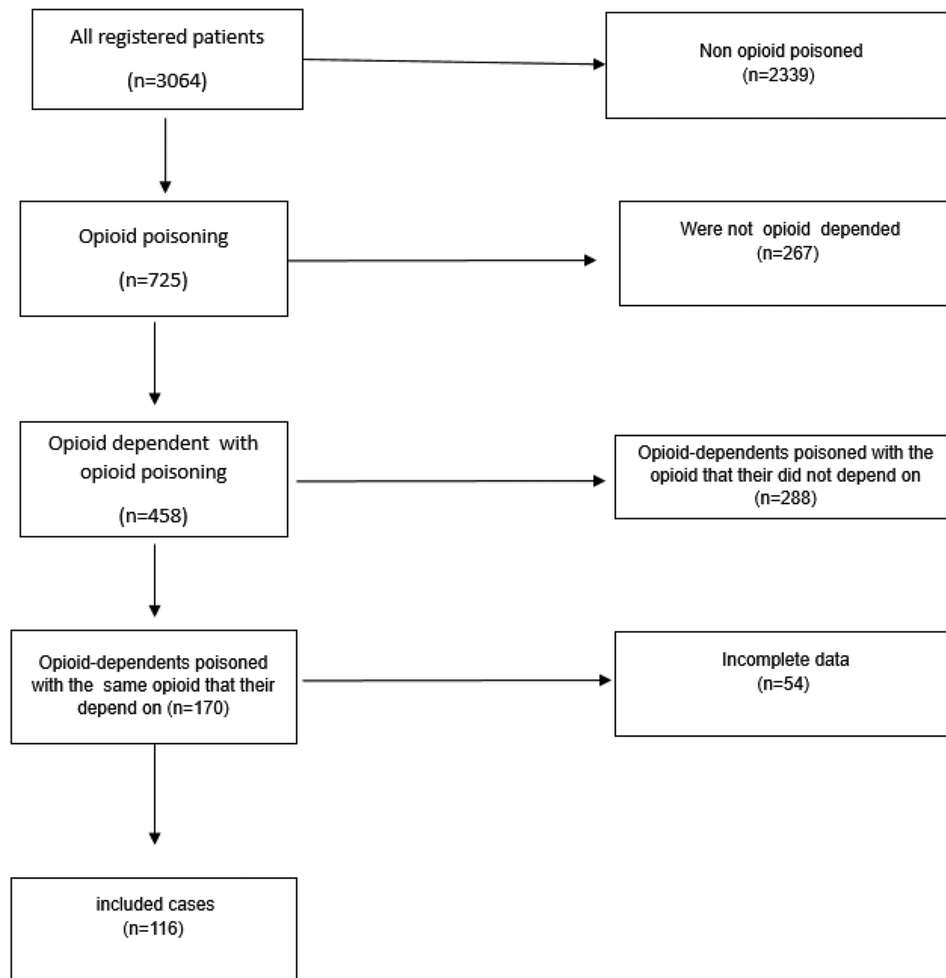

Fig. 1 Flowchart of extraction data of opioid-dependent patients poisoned with their own opioids, extracted from Medical toxicology registry of Mashhad university of medical science, Iran (MTR-MUMS) data –bank

Table 1 Type of opioid, sex, and age distribution in opioid-dependent opioid-poisoned cases, registered in medical toxicology registry of Mashhad university of medical science, Iran (MTR-MUMS)

		Opiate					Synthetic opioids				PV##
		Opium	Heroin	Buprenorphine	Total	P value	Methadone	Tramadol	Total	P value	
Sex	male	37	6	2	45	0.662	39	10	49	0.669	0.639
	female	11	1	0	12		9	1	10		
	total	48	7	2	57		48	11	59		
Age (years)	Mean ± SD (Median)	50.06 ± 20.13 (50.5)	32.29 ± 4.03 (33.0)	40.0 ± 14.14 (40.0)	47.8 ± 19.65 (40.0)	0.066	35.6 ± 12.68 (33.5)	25.45 ± 9.16 (22.0)	40.28 ± 17.76 (34.5)	0.015**	< 0.0001**
Age groups (years)	< 20	0	0	0	0	0.0546$	5	2	7	0.312$	< 0.0001$
	20–39	20	7	1	28		25	8	33		
	40–59	14	0	1	15		16	1	17		
	≥ 60	14	0	0	14		2	0	2		

* Mann-Whitney U test, ** Kruskal Wallis Test, $ Chi-Square PV##= between two main opioid groups

Comparing the frequency of various types of opioid poisoning and dependency of current research and data from the IMHS, revealed that methadone dependency is a risk factor for opioid poisoning, while opium and heroin showed the opposite trend (Table 4) [5, 25]. The IMHS reported a male-to-female ratio of 13:1; however, a direct comparison indicated that being female is a risk factor for opioid poisoning among opioid-dependent individuals (Odds Ratio (OR) = 3.16, Confidence Intervals (CI) 95%[1.36,7.01], PV = 0.01) [5].

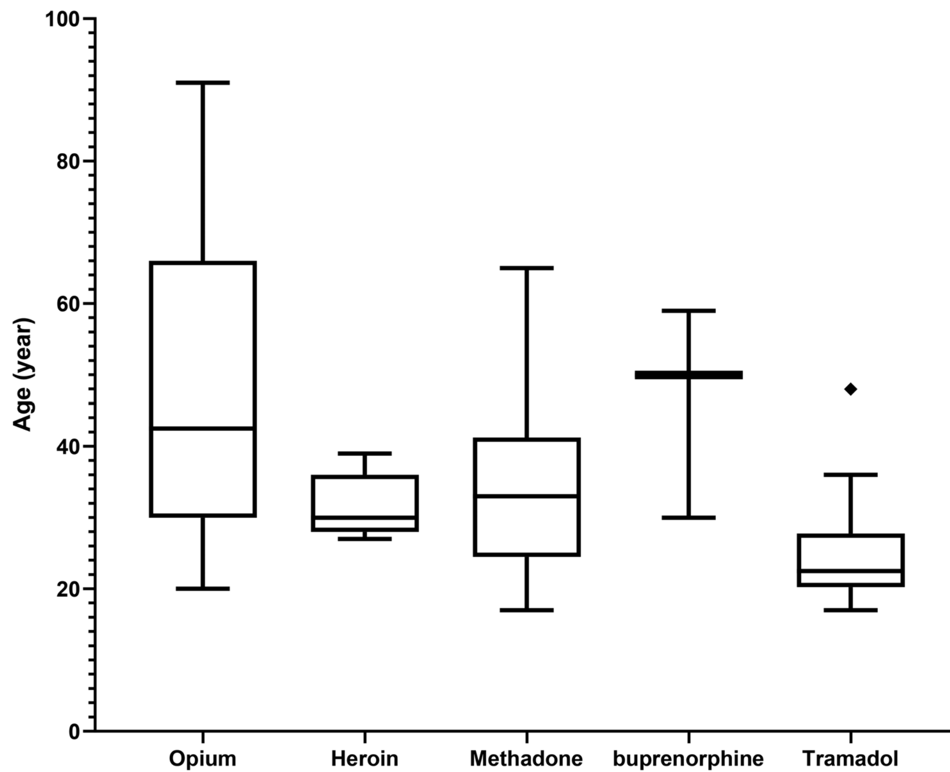

Fig. 2 The age distribution in opiate and opioid-poisoned cases with their own medications

Table 2 The main presentation of opioid-poisoned cases with their own opioids, registered in medical toxicology registry of Mashhad university of medical science, Iran (MTR-MUMS) by type of opioid, sex, and age

			Loss of consciousness (LOC)	Vomiting	Weakness	Seizure	Respiratory failure
Frequency (%)			84(72.4)	20(17.2)	7 (6.0)	2(1.7)	16 (12.1)
sex		male	67	16	6	2	12
		female	17	4	1	0	4
Age(years) Mean ± SD (Median)		With symptoms	41.29 ± 18.52 (36.0)	30.85 ± 12.08(30.0)**	31.86 ± 6.44 (33.0)**	24.50 ± 2.12 (24.5)**	46.43 ± 25.0 (43.0)
		Without symptoms	37.62 ± 15.57 (32.5)	42.24 ± 18.12 (38.5)	40.82 ± 18.13 (35.0)	40.22 ± 17.80 (35.0)	39.43 ± 16.52 (34.5)
Opioid types	Opiate	Opium	35	7	1	0	7
		Heroin	4	2	2	0	2
		Buprenorphine	2	0	0	0	0
		Total	41	9	3	0	9
	Synthetic opioids						
		Methadone	36	9	3	0	5
		Tramadol	7	2	1	2	2
		Total	43	11	4	2	7

**=PV < 0.01 Non-parametric, LOC = Loss of consciousness

There were two fatalities recorded: men aged 38 and 68 who were dependent on and poisoned by opium. They presented with loss of consciousness and died within a day of being admitted to the hospital. The average length of hospital stay was 2.31 ± 1.52 days (median = 2.00, range = 1.0–8.0 days). An analysis using regression modeling to assess the relationship between hospital stay duration and various factors—including age, sex, method of poisoning, type of opioid, and primary presentation—showed that only age remained significant (R^2 =0.235, b = 0.038, CI = 0.022–0.055, PV < 0.0001). Specifically, for every increase of ten years in age, the length of hospital stay increased by 0.3 to 0.5 days.

Table 3 The mode of poisoning in opioid-poisoned cases with their own opioids, registered in medical toxicology registry of Mashhad university of medical science, Iran (MTR-MUMS) by type of opioid

Manner of poisoning	Frequency (%)	opiate				Synthetic opioids		
		opium	Heroin	Buprenorphine	Total	Methadone	Tramadol	Total
Misuse and abuse of opioids more than before	60(50.9)	26	4	2	32	23	5	30
Suicide	28(24.1)	8	0	0	8*	14	6	20*
Body packing	7 (5.1)	3	2	0	5	2	0	2
Co-ingestion of benzodiazepine	22(19.0)	7	2	0	9	11	2	13
Taking another drug	10 (8.6)	8	0	0	8*	2	0	2*
Underlined renal disorders	9 (8.7)	9	0	0	9*	0	0	0*
Unknown	18 (16.4)	8	1	0	9	9	0	9

*=PV < 0.05 comparing total opiate with total Synthetic opioids

Table 4 Evaluation the risk of poisoning by their own opioid in opioid dependent cases with different opioids. The results of the current research with the Iranian mental health survey (IMHS) [5] were compared by a direct Estimation method and fisher's exact test

Opioid type	Current research	IMSH	OR (95%CI)	PV
Opium	41.4%	82%	0.156 (0.084–0.287)	< 0.0001
Heroin	6.03%	16%	0.324 (0.125–0.763)	0.0128
Buprenorphine	1.2%	2.5%	0.661 (0.116–3.29)	> 0.999
Methadone	41.4%	16%	3.56 (1.95–64.8)	< 0.0001
Tramadol	9.5%	N/A	N/A	-

OR = Odds ratio, 95%CI = 95% confidence interval

Discussion

Our study aimed to evaluate the reasons behind opioid intoxication in patients already dependent on specific opioid types, utilizing data from MTR-MUMS. We found that opium and methadone were the leading causes of intoxication in this population. Interestingly, opium intoxication was more prevalent among older adults, while methadone and tramadol intoxication were more common in younger individuals. Decreased level of consciousness was the most frequent presenting symptom at the emergency room The primary modes of intoxication included misuse, abuse, and tragically, suicide attempts. Methadone was particularly associated with suicide attempts, especially amongst younger patients. When compared to existing literature regarding opioid dependence prevalence in Iran, our data and comparison with our data registry suggests that methadone poses a particularly high risk for intoxication, and that females may be at increased risk of opioid poisoning overall [5].

This study on opioid intoxication at MTR-MUMS showed a higher proportion of males than females, consistent with other Iranian studies on opioid poisoning [26, 27], though the male-to-female ratio was lower than that seen in opioid dependency overall in Iran (4.1 vs. 13.1) [5]. This suggests women might be more susceptible to opioid toxicity, potentially due to hormonal factors or fat body composition, aligning with findings from other research [22]. The majority of intoxication cases in this study involved individuals aged 20–39, mirroring trends seen in Iran and internationally [28, 29]. Unlike this study, acute opiate poisoned patients with age 14 to 25 years were more common than other age groups in southwestern Iran [30]. A significant portion (16%) of the patients in our study were elderly, highlighting opioid addiction as a considerable concern within this population, supported by prior research from the same medical center by our research team [31]. In that we found that more than half of elderly patients were dependent on opioids, so it seems that opioid addiction among opioid intoxicated elderlies.

Based on previous research, altered mental status and loss of alertness are the most common symptoms of

opioid intoxication, whereas respiratory failure has been recognized as the most common presentation leading to death subsequent to opioid intoxication [32] (similar to our study). Out of 11 patients, only 2 cases of tramadol overdose exhibited seizures, which contrasts with studies indicating that seizures are the most frequent manifestation of tramadol poisoning [16, 33–36]. This small dataset should be interpreted with cautious; it may be explained by findings from Taghaddosi Nejad et al. [17], who determined that addiction does not correlate with the occurrence of seizures following tramadol ingestion due to reduction of sensitivity to adverse events such as seizures.

Excessive use was the most common form of toxicity, similar to previous studies [26, 37]. White et al. suggested that opioids dependent individuals developed a faster tolerance to the euphoric effects than some adverse effects of opioids such as respiratory depression. Thus, they take too much opioid for the induction of euphoric effects, which can end up to intoxication [38]. In the current study, the opioid toxicity scenario was unknown in eighteen patients; it might be due to purchasing drugs from a new drug dealer or the same drug dealer with different purity percentages or chemical compositions [37]. According to estimates, suicide attempts are made by approximately 8–17% of opioids dependent patients and the risk is more than genera population [39]. Near one-third of drug overdose suicides in the United States in 2017 were attributed to opioids [11]. Also, nearly one-third (37.4%) of suicidal attempts in Toronto (1998–2015) had been attributed to opioids [20]. In Iran, opioids were the reason for around half of all suicides due to acute poisoning in the elderly [40]. In Iran, additionally, 26% of poisonings related to methadone were caused by individuals who committed suicide [41]. Similarly, suicide was the second scenario of intoxication and occurred more with synthetic opioid; which is consistent with a study in Canada [42].

In the current study, opium and methadone caused intoxication more than other opioids. Previous studies revealed that the pattern of intoxication with type of opioids is different in various regions of Iran. In Ardabil, a city in northwest Iran, tramadol was the most common type of opioid which caused intoxication [28]. In Esfahan, a city in the central part of Iran, heroin was the main cause of intoxication [26]. While, In Khorramabad and Hamedan, opium was the most common type of intoxication [27, 43]. This regional variation in opioid use patterns likely reflects differences in drug availability, local drug markets, and cultural preferences.

The observation that Methadone is a less safe opioid, is supported by comparing the frequency of various types of opioid poisoning and dependency of current research with the results of the Iranian mental health survey [5]. Previous studies have also documented a rising prevalence of methadone poisoning across all age groups [44, 45]. But this trend appears particularly pronounced among young people. Notably, in our study, individuals intoxicated with methadone were, on average, 15 years younger than those dependent on or poisoned by opium [41]. This suggests that methadone may be more accessible or appealing to younger populations, potentially due to misperceptions about its safety or its lower cost compared to other opioids.

Conversely, buprenorphine appears to be the least dangerous opioid in this study. This finding aligns with a systematic review by Ansari et al. [25] which concluded that buprenorphine use presents a low risk in addiction treatment. However, this conclusion should be interpreted cautiously due to the small sample size (n = 2) in the current study. other explanations might be as, Iranian patients' lower willingness to initiate opioid substitution therapy (OST) [18]; buprenorphine's limited availability to drug dealers [46]; the higher cost of buprenorphine [18]; and its reduced euphoric effects compared to other opioids.

In a cohort study in England, the mean patient length of stay for opioid-related hospitalizations was 2.8 days [47]; which is slightly longer than the 2.31 days observed in our study. A study focusing specifically on heroin overdose patients in England reported a length of stay of 4.39 days [48]. Interestingly, our study did not find any association between the type of opioid and hospital stay length. However, we did observe that older patients stayed in the hospital longer than younger patients, which may be due to their increased health complications and age-related physiological changes requiring more extensive treatment [49].

Clinical and public health implications

Enhancing routine screening for opioid dependency and co-occurring mental health conditions among patients attending opioid harm reduction clinics and primary healthcare centers is crucial [50]. Counseling patients and their families on safe opioid use, encouraging opioid cessation, or facilitating enrollment in opioid substitution therapy programs like MMT and BMT are vital interventions [18, 51].

Furthermore, government health policymakers and the Ministry of Health should implement stricter regulations and oversight of MMT and BMT clinics to prevent diversion of methadone and buprenorphine to unintended recipients [52]. Healthcare providers, physicians, and psychologists at these centers should receive specialized training in screening for suicidal ideation, behavioral issues, and mental health disorders, and provide face-to-face education on safe medication use [51]. Finally, public health initiatives should include widespread advertising

campaigns to raise awareness, and consideration should be given to providing patients and their families with naltrexone kits and education on their use to reverse opioid overdose symptoms, potentially reducing morbidity and mortality [53].

Limitations

We did not investigate the route of opioid administration, which is crucial as it can significantly influence toxicity levels; for instance, intravenous heroin use may result in higher toxicity compared to oral ingestion [54]. Additionally, we did not collect data on important socioeconomic and psychosocial variables, such as education, employment status, and the presence of comorbid psychiatric disorders. Previous research has highlighted the relevance of these factors in relation to opioid toxicity [55]. Furthermore, the categorization of the manner of poisoning relied solely on self-reports from patients or their relatives, which may introduce bias in physician judgment and affect the accuracy of our findings. Also, we did not specify whether any of the cases involved substance use under the supervision of rehabilitation centers [18].

In addition, our sample size of 116 patients raises questions about statistical power and generalizability. While this number was determined based on available cases from the MTR-MUMS during the specified period, we acknowledge that a larger sample size would enhance the robustness of our findings. The limited sample size may restrict the ability to detect subtle associations and reduce the external validity of our results. One significant limitation is the exclusion of polysubstance users from our analysis, which could introduce selection bias. By focusing solely on individuals who were poisoned by their own opioid, we may have overlooked important interactions and risk factors associated with concurrent substance use.

Conclusion

Although opioid addiction is a global health problem, the prevalence of reasons behind opioid poisoning with their own drugs among opioid dependents patients is unclear up to now. The most common types of opioids responsible for opioid intoxication were opium and methadone, and the least common was buprenorphine. In addition, opioid excessive use and suicide were the most prevalent manner of intoxication among opioid-dependent patients with their own substances. Regarding the prevalence of opioid dependency between males and females, women dependent on opioids are at a higher risk of drug intoxication, significantly precipitating suicidal behavior. It seems that methadone is a less safe opioid in dependent cases and buprenorphine is the safest. Methadone poisoning is higher among young people. Further research, should be undertaken to explore the reason for opioid poisoning among opioid dependents. This information can be used to develop targeted interventions aimed at opioid dependents to reduce opioid poisoning. Moreover, there are some concerns about generalizability of our study, since this data is collected in a referral poisoning center and some patients with less sever signs may not be transferred to this hospital. Therefore, caution should be exercised when extrapolating these results to broader populations. Future multi-center studies are warranted to validate our findings and explore regional variations in opioid poisoning patterns.

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Author contributions
A.N. cooperated in collecting data, drafting the manuscript, data analysis . B.D. and L.E. contributed in conceptualization and supervision the study protocol, K.K. and A.W. cooperated in drafting the manuscript. MA.T ., F.A and AM.AN. collaborated in gathering data. M.G . contributed in data analysis. SR.M. , SH.M., Z.A., A.AG , M.GT . and M.V. were physicians that visited the patients, cooperated in data collection, recruited study participants., M.M. designed study, drafting the manuscript, conceptualization, supervision study, data analysis and will amend the manuscript according to the editor's comments.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval
The study was approved by the ethics committee of the Research Department of Mashhad University of Medical Sciences protocol number: IR.MUMS.REC.1394.726, also is in compliance with the ethical guidelines outlined in the 1964 Declaration of Helsinki.

Informed consent
Informed consent was obtained from all subjects and their legal guardians or parents. Moreover, for illiterate patients, informed consent was obtained by their legal guardian or their parents. The data was anonymized through coding to protect the identities of the individuals involved.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Pharmaceutical Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[3]International UNESCO Center for Health-Related Basic Sciences and Human Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Medical Toxicology Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

[5]Department of Clinical Toxicology and Poisoning, Imam Reza (p) Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[6]Department of Medicine, School of Clinical Sciences at Monash Heath, Monash University, Victoria, Australia
[7]Department of Critical Care, University of Melbourne, Victoria, Australia
[8]Department of Health Information Technology, School of Paramedical and Rehabilitation Sciences, Mashhad University of Medical Sciences, Mashhad, Iran
[9]Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[10]Student Research Committee, Faculty of Medicine, Islamic Azad University, Mashhad Branches, Mashhad, Iran

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