

# Common Opioids Involved in Drug Poisoning Presenting to the Emergency Department: A Cross-sectional Study

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## INTRODUCTION

One of the common causes of mortality is drug poisoning. Opium and opioids are the most important ones. Respiratory failure and noncardiogenic pulmonary edema are consequents of an opioid overdose. The opioid, its pharmacokinetic properties, and the mode of usage are important factors for clinical manifestations and treatment course. Awareness of poisoning and the right treatment can reduce the length of hospitalization and its mortality.<sup>[1-3]</sup>

Studies have shown that Iran has a high opiate abuse rate, and the most prevalently used is opium.<sup>[4,5]</sup> In addition to opium poisoning, tramadol and methadone's overdoses

## ABSTRACT

**Objective:** Opioids poisoning is of the most important cause of mortality. The objective of the study was to compare the demographic factors, clinical manifestations, and outcomes of the most common opioids involved in drug overdose presenting to the Emergency Department. **Methods:** This cross-sectional study was conducted from October 2016 to March 2017 in the Clinical Toxicology Department of the main referral center of the university. All poisoning cases with common opioids were included in the study. Demographic factors, clinical manifestations, and outcome were recorded in a check list. ANOVA, Chi-square or Fisher's exact test, and binary logistic regression analysis were used for outcome prediction. **Findings:** Two hundred and thirty six patients with opioids poisoning were evaluated during the study period. The most common opioids involved in poisoning were methadone (47.9%), tramadol (24.2%), and opium (21.6%). Patients with opium poisoning were older than others ( $P < 0.0001$ ). The rate of suicide was more in the tramadol group, while the past history of psychological problems was more observed in the methadone group ( $P < 0.0001$ ). Increasing age (odds ratio [OR], 1.05; 95% confidence interval [CI]: 1.02–1.09;  $P = 0.05$ ) and addiction ( $P = 0.01$ ; OR, 7; 95% CI: 1.55–31.52) was associated with an increased complications or death. Also patients with somatic disease had more chance of complications/death ( $P = 0.04$ ; OR, 3.71; 95% CI: 1.06–12.97). Kind of opioids was not a predictive factor in the outcome of the patients with acute poisoning. **Conclusion:** Age, addiction, and somatic disease should be considered as more important factors in outcome prediction with opioids poisoning, including opium, tramadol, and methadone.

**KEYWORDS:** Methadone, opioid, outcome, poisoning, Tramadol

are also growing due to alternative therapies in addiction treatment units and its recreational abuse.<sup>[6-8]</sup> Tramadol is one of the common causes of poisoning in adult males who have had a history of drug addiction or mental illness. International poisoning reports tramadol abuse as well.<sup>[9-12]</sup> The prevalence of methadone poisoning rose in people who have been on the “methadone maintenance treatment” and “methadone maintenance therapy” in a

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study performed in Wales, England.<sup>[13]</sup> Peltzer *et al.* also reported the epidemiology of illicit drug use in South Africa.<sup>[14]</sup>

In recent years, the pattern of poisoning has changed in our poisoning referral center. Besides opium, tramadol and methadone overdose are also observed, and the trend is rising.<sup>[15,16]</sup> Therefore we compared the demographic factors, clinical manifestations, and outcomes of the most common opioids involved in drug overdose presenting to the emergency department.

## METHODS

This cross-sectional study was conducted from October 2016 to March 2017 in the Clinical Toxicology Department of Noor Hospital, a leading referral center of Isfahan Province, Iran. Our center is facilitated, staffed, and designed exclusively to manage poisoned patients in our province. All patients with opioids poisoning (opium, tramadol, and methadone) were included in the study. Opioid poisoning was diagnosed by history, physical examination, complete or partial response to naloxone. Urine screening tests were also performed for patients. Patients who were discharged with his consent were excluded from the study. The Institutional Ethics Committee approved the project of Isfahan University of Medical Sciences with a Research Project 294148. Following the admission of the poisoned patients' to the emergency room and the necessary medical treatment, their clinical manifestations, and vital signs were examined and recorded. The variables including gender, age, history of somatic or psychiatric disease, addiction, co-ingesting, cause of poisoning (accidental, abuse, and suicidal), need for intubation and ventilation, length of hospitalization, and outcome (survived without complication, survived with complication or death) were recorded in a checklist. The Statistical Package for the Social Sciences version 13.0 (SPSS Inc, Chicago, IL, USA) was used for the analysis. Data were presented as mean  $\pm$  standard deviation or standard error (SE) or *n* (%) where appropriate. ANOVA and Chi-square or Fisher's exact tests were performed to compare the means of different variables and the frequency distribution among groups. Binary backward stepwise logistic regression analysis was used for outcome prediction in opioid poisoning. A  $P < 0.05$  was considered statistically significant.

## RESULTS

Two hundred fifty patients had inclusion criteria during the study period. Fourteen patients were excluded because they were discharged with their consent. The most common opioids involved in opioid poisoning were methadone, tramadol, and opium. Of the 236 patients,

51 (21.6%) were opium poisoning, 57 (24.2%) tramadol poisoning, 113 (47.9%) methadone poisoning, and 15 (6.4%) had ingested mixed opioids. Poisoning was more common in men. The mean age of the patients among different groups was significantly different so that patients with opium poisoning were older, and tramadol cases were observed mostly at a younger age. There were significant differences among groups in the frequency distribution of suicide rates and a history of addiction. The suicide rate in patients with tramadol was higher (35.1%). In contrast, most tramadol poisoning cases (73.7%) did not have an addiction to history. One hundred and ninety six (83.05%) patients had ingested only opioids, and 40 (16.95%) opioid poisoning cases had co-ingestion, which was not significant among different groups.

There was no significant difference in the comparison of vital admission signs among groups. In the tramadol group, 24.6% had a seizure, compared with no attacks in the other groups, and patients were more conscious of admission than other groups. About 6.4% of patients had nausea and vomiting, all taking methadone. Comparing different variables, including gender, age, clinical manifestations on admission in the four study groups (opium, tramadol, methadone, and mixed opioids poisoning), are shown in Tables 1 and 2.

The admission venous blood gas analysis showed a significant difference in pH, PCO<sub>2</sub>, and HCO<sub>3</sub> levels among different groups. The pH value was higher in the tramadol group ( $7.35 \pm 0.63$ ) than the mixed opioids poisoning group ( $7.30 \pm 0.07$ ), which was the least. The PCO<sub>2</sub> value and HCO<sub>3</sub> concentration in the tramadol group were lower ( $43.58 \pm 9.43$  and  $24.24 \pm 4.34$ , respectively).

Seventeen patients were intubated and connected to the ventilator, thirteen of whom (76.5%) were poisoned with methadone. The maximum duration of hospitalization (mean  $\pm$  SE) was in patients with methadone poisoning ( $93.37 \pm 4.28$  h), and the lowest was related to tramadol poisoning ( $64.2 \pm 20.24$  h) ( $P = 0.02$ ). Most patients survived without complications. Sixteen patients found complications. No complication was observed in the tramadol group [Table 2]. A binary backward stepwise logistic regression analysis was performed to ascertain the effects of different variables on outcome. Results indicated that among all studied variables, age, history of addiction, and somatic disease were essential factors in outcome prediction. Increasing age was associated with increased complications or death. The chance of complications or death was higher for patients with a history of addiction. Furthermore, patients who had a history of somatic disease had the worst

**Table 1: Comparison of age and admission clinical manifestations in patients with common opioids poisoning**

Variables	Opioids				P
	Methadone (n=113)	Tramadol (n=57)	Opium (n=51)	Mixed opioid ingestion (n=15)	
Age (years)	36.44±16.32	28.03±7.88	45.38±15.57	37.60±12.76	0.00
Respiratory rate (/min.)	18.20±8.54	17.31±3 0.13	20.25±12.99	20.13±12.92	0.33
Systolic blood pressure (mmHg)	125.45±18.81	129.84±17.46	129.13±21.68	117.06±15.69	0.08
Heart rate (/min)	90.02±22.46	88.85±17.46	85.98±20.86	87.86±12.55	0.70
Temperature (°C)	40.04±32.01	36.94±0.18	37.05±0.40	37.03±0.29	0.77
Central nervous system					
Alert	41 (37.3)	27 (47.4)	19 (37.3)	2 (13.3)	0.00
Lethargic/obtundation	50 (45.5)	14 (24.6)	30 (58.8)	12 (80)	
Stupor	6 (5.5)	0 (0)	0 (0)	0 (0)	
Coma	0 (0)	0 (0)	1 (2)	1 (6.7)	
Agitation	6 (5.5)	2 (3.5)	1 (2)	0 (0)	
Seizure	0 (0)	14 (24.6)	0 (0)	0 (0)	

Data are presented as mean±SD or n (%) where applicable. SD=Standard deviation

**Table 2: Comparison of different variables in patients with opioids poisoning**

Variables	Opioids				P
	Methadone (n=113)	Tramadol (n=57)	Opium (n=51)	Mixed opioid ingestion (n=15)	
Gender					
Male	86 (76.10)	35 (61.4)	38 (74.5)	13 (86.7)	0.09
Female	27 (23.90)	22 (38.6)	13 (25.5)	2 (13.3)	
Route of poisoning					
Injection	0	0	1 (1.97)	0	0 0.00
Ingestion	113 (100)	57 (100)	31 (60.78)	15 (100)	
Inhalation	0	0	19 (37.25)	0	
Type of exposure					
Drug abuse	1 (0.9)	0	0	0	0.00
Accidental	15 (13.3)	0	0	0	
Suicide	19 (16.8)	20 (35.1)	3 (5.9)	2 (13.33)	
Unknown	78 (69)	37 (64.9)	48 (94.1)	13 (86.67)	
Addiction history					
Yes	67 (59.30)	15 (26.3)	27 (52.9)	14 (93.3)	0.00
No	45 (39.82)	42 (73.7)	24 (47.1)	1 (6.7)	
Unknown	1 (0.88)	0	0	0	
History of suicide					
Yes	10 (8.85)	7 (12.28)	0	3 (20)	0.03
No	88 (77.88)	48 (84.22)	45 (100)	11 (73.33)	
Unknown	15 (13.27)	2 (3.50)	6 (0)	1 (6.67)	
History of psychological disease					
Yes	16 (14.16)	6 (10.52)	3 (5.89)	5 (33.3)	0.05
No	91 (80.54)	50 (87.72)	47 (92.15)	10 (66.7)	
Unknown	6 (5.30)	1 (1.76)	1 (1.96)	0	
History of somatic disease					
Yes	28 (24.78)	7 (12.28)	15 (29.41)	4 (26.67)	0.08
No	74 (65.48)	48 (84.22)	33 (64.71)	9 (60)	
Unknown	11 (9.74)	2 (3.50)	3 (5.88)	2 (13.33)	
Co-ingestion					
Sedatives and antipsychotic	11 (39.28)	7 (25)	4 (14.28)	6 (21.42)	0.17
Stimulants	5 (83.33)	1 (16.67)	0	0	
Analgesics	1 (16.67)	3 (50)	1 (16.67)	1 (16.67)	
Outcomes					
Survived without complication	97 (85.84)	56 (98.25)	44 (86.3)	14 (93.3)	0.006
Survived with complications or death	16 (14.14)	1 (1.75)	7 (13.7)	1 (6.7)	

Data are presented as n (%)

outcome [Table 3]. Type of opioids (tramadol, opium, or methadone) was not a predictive factor for the outcome.

## DISCUSSION

This study's general purpose was to determine and compare the clinical characteristics of the patients poisoned with common opioids, including methadone, tramadol, opium, and mixed opioids. Most cases were methadone poisoned (47.9%). Based on patients' history, the most critical factor in poisoning with methadone was its easiness in community pharmacies, MMT facilities, or street markets. About 13.3% of the patients ingested methadone accidentally. Some pharmaceutical companies prepare methadone as a solution with a sweet fruit taste, and this may attract young children or ingest accidentally by the elderly. However, 16.8% attempted suicide with methadone. Tendencies to commit suicide have been reported in methadone poisoning patients in other studies.<sup>[17,18]</sup> This comorbidity may necessitate the educational programs to prevent suicidal attempts in nonaddict patients with psychiatric disorders and patients on methadone maintenance treatment.<sup>[19]</sup> Finally, access limitation to methadone can be considered an appropriate approach to prevent and reduce methadone poisoning.

Our results showed that patients in the opium poppy group were older, and tramadol users were younger. Perhaps because opium has long been known as a medication in traditional society and more senior people still use opium as a pain reliever, tramadol is used in young people as analgesics or more abuse. Age also had a predictive value for the outcome, which was similar to other studies on methadone acute poisoning.<sup>[7,20]</sup> In each group, the percentage of men was higher than that of women, which could be due to the more liberal social relationships of men in society and easier access to drugs. This has been reported in previous studies.<sup>[7,8,20]</sup> Ingestion was the most commonly used methods in all groups, but in an earlier study in Iran, the most frequently used way was inhalation,<sup>[21]</sup> which was mostly due to the consumption of most opium on that study as an inhaler, while in this study most patients have ingested methadone alone or in combination with other opioids.

Our results showed sedatives and antipsychotics were the most common substances reported in conjunction

with opioids. While in a study in Ohio from 2002 to 2014 using Poison Control Center data, benzodiazepines and ethanol were the most common substances reported in conjunction with opioids.<sup>[22]</sup>

The suicide rate was higher in patients with tramadol poisoning (35.1%) compare to other groups. Patients with tramadol poisoning also had a history of previous suicide (12.28%) and a history of psychological problems (10.52%), which could be the reason for more suicide attempted. The rate of suicide was less in the opium group compare with others. None of the patients in this group had a history of previous suicide, but 5.89% of the patients with opium poisoning had a history of psychological problems. Abuse of opium is a health care problem in the Middle East region, which has rooted in many socioeconomic factors.<sup>[23]</sup>

Addiction history was most in methadone poisoning cases. This may be due to many addicted patients under methadone maintenance therapy (MMT) protocol.<sup>[24,25]</sup> Our logistic regression analysis showed patients who had addiction history and somatic disease had more chances of complication/death, which may be due to the insufficiency of organs responsible for drug metabolism and elimination and the reduced function of the respiratory system in addicted patients. Although there was no significant difference among groups concerning the history of the somatic disease, it was less in the tramadol group, which is compatible with the younger age of patients in the tramadol group.

The seizure was observed only in the tramadol group, similar to other studies on tramadol poisoning.<sup>[26-29]</sup> Rates of complications were significantly different among patients with methadone, tramadol, opium, or mixed opioid poisoning. It was more in the methadone group (14.14%) compare to others. 24.78% of the patients in the methadone group had a history of the somatic disease. History of somatic disease was also predictive for more complications or death. Pulmonary edema among the deceased cases with acute methadone poisoning has been reported previously.<sup>[30,31]</sup> A case series of methadone complications amongst opioid-dependent patients have been reported in Malaysia.<sup>[32]</sup> Therefore, although methadone is useful in maintenance therapy,

**Table 3: Outcome prediction in patients with opioids poisoning**

Variables	Nonadjusted OR			Adjusted OR		
	$\beta$	P	OR (95% CI)	$\beta$	P	OR (95% CI)
Age	0.05	0.001	1.05 (1.022-1.092)	-	-	-
Addiction	1.94	0.01	7 (1.55-31.52)	-	-	-
History of somatic disease	1.71	0.004	5.53 (1.72-17.72)	1.31	0.04	3.71 (1.06-12.97)

OR=Odds ratio, CI=Confidence interval



its clinical concerns can impact its safety.<sup>[20]</sup> In a study by Faul *et al.*, from 2007 to 2014, a massive decline in methadone-related overdose deaths have been observed. They concluded that preferred drug list policies requiring prior authorization might help reducing methadone overdoses.<sup>[33]</sup>

In conclusion, Methadone poisoning was more common than tramadol and opium poisoning. Tramadol poisoning cases were younger than others. The suicide rate was more in the tramadol poisoning group, while the history of psychological problems was more observed in the methadone group. Age, past history of addiction, and somatic disease should be considered as more important factors in outcome prediction with opioids poisoning. Type of opioids (tramadol, opium, or methadone) was not predictive factors in the outcome.

### AUTHORS' CONTRIBUTION

Nastaran Eizadi-Mood, Elham Haghshenas, Ahmad Yaraghi and Ali Mohammad Sabzghabae were involved in concept and design of the study. Elham Haghshenas did acquisition of data. Ziba Farajzadegan and Nastaran Eizadi-Mood analyzed and interpreted the data. All authors contribute in drafting the article or revising it critically. Final version of the articles was approved for publishing by all authors. The manuscript has been read and approved by all the authors.

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### Conflicts of interest

There are no conflicts of interest.

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