

Review Paper: Tramadol Poisoning: A Systematic Review of Studies in Iran



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ABSTRACT

Background: According to statistics, tramadol use is extremely prevalent in Iran. Besides, tramadol overdose is mostly observed in young individuals. Given the significance of this issue and the increasing prevalence of tramadol use in Iran, this study aimed to systematically review tramadol poisoning in Iran.

Methods: In this review, a search was conducted in Persian databases of IranMedex, SID, Medlib, Magiran, as well as Google Scholar using the keywords of “poisoning and tramadol” without a time limitation.

Results: Some of the main issues related to tramadol poisoning were as follows: the majority of cases consumed tramadol to commit suicide; most tramadol consumers were aged below 30 years; the majority of patients with tramadol poisoning were single and male; tramadol was mostly used orally; in most studies, patients were hospitalized for >24 hours; the majority of patients concomitantly took other medications with tramadol; in most studies, patients had a history of tramadol use; most studies reported a relationship between tramadol dose and seizures, and the most common cause of hospital referral was decreased consciousness level.

Conclusion: Tramadol misuse and poisoning could lead to seizures and often death. Besides, most cases with tramadol poisoning were aged below 30 and consumed tramadol to commit suicide. Thus, it is crucial to improve the youth’s awareness about tramadol use, develop methods to prevent suicides, and limit access to this drug, especially in young adults.

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1. Introduction

Poisoning is among the most common health problems in societies and a major cause of referrals to healthcare centers. Every year, several individuals with different ranges of poisoning symptoms (from minor illnesses to hospitalization in special hospital wards and mortality) refer to healthcare centers. Accordingly, these cases impose huge psycho-economic burdens on society, the individual, and the family [1]. Poisoning patterns and symptoms are often affected by socio-economic and cultural issues as well as common religious beliefs in societies. In general, poisoning cases occur either intentionally or accidentally. Deliberate poisoning results from the intentional use of pesticides to harm oneself or others [1, 2]. However, the most frequent drug intoxication is poisoning with an analgesic called tramadol. Moreover, most cases of tramadol poisoning occur deliberately due to high doses [3]. Tramadol is a synthetic 4-phenyl-piperidine analog of codeine, used for its potent analgesic activity with two different drug mechanisms [4, 5]. Tramadol poisoning severely damages the Central Nervous System (CNS); this condition can cause dizziness, nausea, vomiting, restlessness, facial numbness, ataxia, headache, seizures, decreased consciousness, and coma [6].

Tramadol was introduced to the Iranian pharmaceutical market as an alternative following the official announcement of the ban on prescribing diclofenac injection. The drug initially seemed to present a low dependency risk; however, its application was associated with some complications similar to morphine (e.g. nausea & vomiting). Besides, its long-term use increased the odds of drug dependence [7]. Therefore, the Commission on Narcotic Drugs of the World Health Organization (WHO) has classified tramadol as a drug under international control [8]. Initially, tramadol overdose was observed in individuals with substance dependence [9]. Currently, tramadol misuse has increased in society as an analgesic or aphrodisiac (due to misleading advertisements about its effects). Sometimes, some individuals, inadvertently or intentionally, consume high doses of the drug to commit suicide and become intoxicated [10]. The increased use of this drug in the current society and a higher number of referrals to healthcare and specialized poisoning centers have led to hospital overcrowding with the cases of tramadol overdose. Thus, this study aimed to identify the factors related to tramadol poisoning.

2. Materials and Methods

This study aimed to review tramadol poisoning cases.

Search strategy

In this review article, we searched studies online and there was no time limit for searching the internet. All published Persian articles were searched in the databases of IranMedex, SID, Medlib, Magiran, and Google Scholar using the keywords of “poisoning and tramadol”. The inclusion criteria of the study included the publication of articles in Persian, performing the studies in Iran, and tramadol-related poisoning cases present in the title of the articles. On the other hand, the exclusion criteria of the study were the lack of access to the full texts of the articles, animal studies, case report articles, short articles, and letters to the editor.

Articles were prepared by the researcher following the search of the mentioned keywords in databases. Then, the researcher assessed the articles which included the desired keywords in their titles and keywords. A total of 2615 articles were initially selected. Next, a more accurate assessment led to the selection and evaluation of 20 articles related to tramadol poisoning. In this regard, 8 articles were removed due to not being in Persian, unrelated titles, being performed outside Iran, conducted on animals, or duplication. Overall, 10 articles related to tramadol poisoning were entered into the present study. The article selection stages are shown in [Figure 1](#).

3. Results

In total, 10 articles related to tramadol poisoning were analyzed. Accordingly, the collected results suggested that most studies related to tramadol poisoning in Iran were performed from 2008 onward. [Table 1](#) presents the studies conducted on tramadol poisoning in Iran.

4. Discussion

Drug poisoning is the most common intoxication in Iran and the world. Besides, Such a condition causes numerous referrals to hospitals and healthcare centers in various countries, annually. While the diagnosis of acute poisoning based on clinical history can be clear, the diagnosis should also occur in patients with a low consciousness level or those who cannot give a medical history, or patients with a previous self-harm history [20]. One of the most prevalent drug intoxications is poisoning with analgesics, like tramadol.

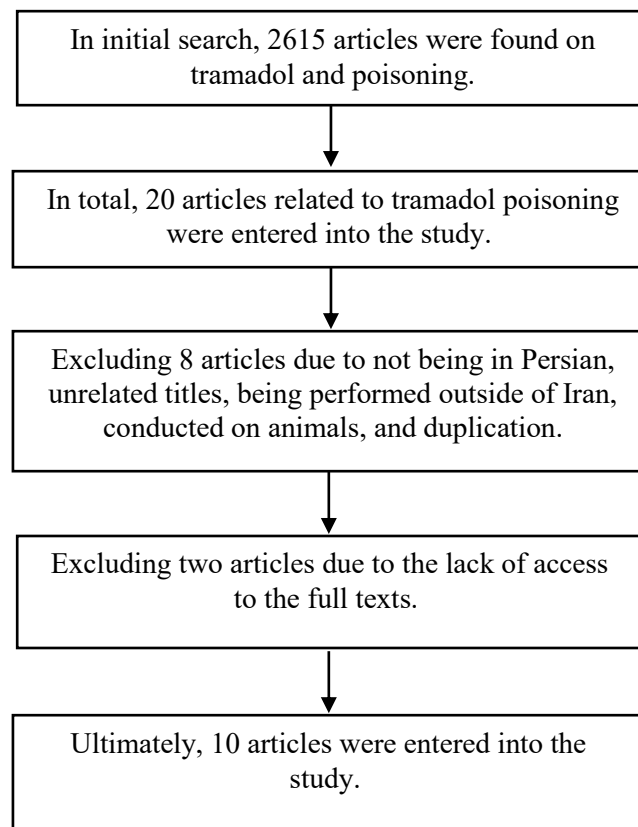


Figure 1. Flowchart of article review stages

Tramadol and age

Unfortunately, most poisoning cases caused by tramadol misuse occur in adolescents and adults. The most common age of tramadol poisoning is 18-32 years [21]. As per Ahmadi et al. [19], the majority of patients were in the age range of 21-30 years, and 43.4% of them were in the range of 12-20 years. Moreover, the Mean±SD age of the subjects was 22.5±6.25 years. According to the results, most cases of tramadol intoxication were aged 19 years (11.2%). However, no significant gender-wise difference was observed respecting age. According to Ezadi Mood et al. [17], the most prevalent age of poisoning was 18-27 years. Additionally, Aghakhani et al. [16] reported that the highest prevalence of poisoning was observed in patients aged 18-27 years, and the majority of poisoned patients were aged 21 years. In a research by Boushehri et al. [15], most patients with tramadol poisoning were aged 20-40 years, followed by <20 years, encompassing 94.8% of all cases of tramadol poisoning. Abbasi et al. marked that 50% of patients were below the age of 20, whereas 88% of them were aged <30 years [13].

In a study by Dalirrad et al. [14], the Mean±SD age of the participants was 23.29±7.04 years; the minimum

and maximum ages were 15 and 76 years, respectively. Moreover, 82.1% of individuals with tramadol poisoning were aged below 30 years, as reported by Shokrzadeh and associates [11]. In a study by Moradi et al., the Mean±SD age of the participants was 21.6±5.3 years; the minimum and maximum ages were 13 and 40 years, respectively. The highest frequency of poisoning was in the age range of 15-19 years [12]. In a research by Majidi et al., >50% of the patients were aged 21-30 years [10]. The prevalence of this issue is high among young individuals, indicating the abuse of tramadol at an early age. Due to their higher desire for high-risk behaviors, youth are more prone to abuse drugs, like tramadol. In Iran, tramadol abuse has increased due to availability, the lack of knowledge of tramadol complications, and suggestion by others to consume the drug as a normal analgesic [22]. Therefore, developing preventive programs for this age range is more critical, compared to other age groups.

Tramadol and gender

In a study by Ahmadi et al. [19], 75.6% of the 546 examined patients were male and 24.4% were female. Therefore, the level of tramadol use was higher in men, compared to women. In the research by Ezadi Mood et al., from 184

Table 1. The studies conducted on tramadol poisoning in Iran

Authors	Title	Journal/ Index	Year of Study	Type of Study	Sample Size	Research Setting	Conclusion
Shokrza- deh et al. [11]	The characteris- tics of patients hospitalized due to tramadol poi- soning in Gorgan in 2008-2015	Journal of Mazandaran University of Medical Sciences/ Scopus	2008- 2015	Descriptive, analytical, and cross-sectional	1168	Fifth Azar Hospital in Gorgan	The obtained results indicated that suicide and abuse were the major causes of tramadol poisoning, oc- curring more in single men under the age of 30 y.
Moradi et al. [12]	Acute poisoning caused by tra- madol abuse and its causes in the patients referred to the poisoning ward of Farsh- chian Hospital in Hamadan	Hamedan Police Sci- ence Journal	2014	Descriptive, cross-sectional	92	Farshchian Hospital	Tramadol abuse is among the main causes of poisoning in young adults and adolescents, especially men, i.e., mainly intentional and suicidal.
Abbasi et al. [13]	Evaluating the time interval be- tween tramadol consumption and the occurrence of seizures and secondary at- tacks caused by drug use	Tehran Uni- versity Medi- cal Journal	2012- 2013	Futuristic and cross-sectional	150	Rasoul Akram & Loghman- e Hakim Hospitals in Tehran	The appropriate time to monitor patients is about 4 hours, after which patients can be discharged with warning signs.
Dalirrad et al. [14]	Evaluating the demographic characteristics and renal func- tion indices of patients with acute tramadol poisoning in Aya- tollah Taleghani Hospital in Urmia	The Journal of Urmia University of Medical Sciences	2012- 2013	Retrospective, descriptive	254	Taleghani Hospital in Urmia	Acute renal failure and hypercal- cemia were the complications of tramadol poisoning that should be considered in the diagnosis, treatment, and follow-up of these patients.
Majidi et al. [10]	Evaluating the demographic findings of tra- madol poisoning cases in women admitted to Aya- tollah Taleghani Hospital in Urmia	Nursing and Midwifery Journal	2012- 2013	Descriptive, cross-sectional	175	Ayatollah Taleghani Hospital	Tramadol is readily available in the community. According to the relevant results, young women with a low level of education are more prone to be the victims of tramadol abuse. Therefore, it is suggested that society's awareness of the adverse effects of tramadol abuse be increased and access to this drug be restricted to decrease the number of poisoning cases and adverse effects of tramadol.

Authors	Title	Journal/ Index	Year of Study	Type of Study	Sample Size	Research Setting	Conclusion
Boushehri et al. [15]	Evaluating the clinical findings and acute effects of tramadol poisoning	Iranian Journal of Anesthesiology and Critical Care	2012	Retrospective	233	Ayatollah Taleghani Hospital	Tramadol was most commonly used at the age of 20-40 years and was more common in men, compared to women. Besides, patients with a history of intermittent use accounted for the largest proportion of participants.
Aghakhani et al. [16]	The epidemiology of tramadol poisoning in Urmia	Nursing and Midwifery Journal	2011	Descriptive, cross-sectional	293	Ayatollah Taleghani Hospital	Given the high prevalence of tramadol poisoning in this study, compared to the misuse of other drugs, especially among young individuals, and its adverse effects on biopsychological health, it is recommended that the necessary measures be taken by the authorities to raise public awareness and train physicians and administrators, who are responsible for the provision of tramadol and health-care to patients with intoxication.
Izadi Mood et al. [17]	Clinical symptoms, the duration of hospitalization, and follow-up in tramadol poisoning	Journal of Isfahan Medical School/ Scopus	2010	Descriptive, cross-sectional	184	Noor and Ali Asghar Hospitals of Isfahan	Tramadol poisoning can cause central nervous and respiratory depression, tachycardia, seizures, and high blood pressure, which may be due to its two effects, namely its narcotic effect and the inhibitory impact on the resorption of monoamines.
Farzaneh et al. [18]	Comparing seizures in patients with tramadol poisoning in the groups with and without treatment with naloxone	Journal of Isfahan Medical School	2007-2010	Descriptive, cross-sectional	122	Emam Khomeyni Hospital	There was no relationship between tramadol-induced seizures and age, gender, drug dose, and a history of dependence on tramadol and other substances. Naloxone, in the treatment of tramadol poisoning, can increase the risk of seizures; although this is uncommon in therapeutic doses.
Ahmadi et al. [19]	The epidemiology of tramadol poisoning at Imam Khomeini Hospital in Kermanshah	Bimonthly Journal of Kermanshah University of Medical Sciences	2008	Descriptive-Analytical	546	Imam Khomeini Hospital in Kermanshah	Tramadol poisoning and misuse lead to fatal seizures. Most tramadol poisoning cases occur at the age of <30 years due to committing suicide. Therefore, the importance of raising youth's awareness about tramadol use and restricting the access and distribution of tramadol, especially at an early age, is undeniable.

patients with tramadol poisoning, 141(76.6%) individuals were male and the rest were female [17]. In another study by Aghakhani et al. [16], 92.02% of the subjects were male. In addition, Boushehri et al. reported that 82.4% of the subjects were male and 17.6% were female [15]. According to Abbasi et al., 94% of the subjects were male and the rest were female [13]. Dalirrad et al. mentioned that 119 subjects were men and 35 were women [14]. Shokrzadeh et al. marked that 75.6% of the participants were male [11]. Moreover, Farzaneh et al. reported that 89.5% of the patients were male and 10.5% were female [18]. According to Majidi et al., 83.3% of patients were male and 21.7% were female [10]. In addition, Moradi et al. mentioned that 89.1% of the participants were male [12].

According to two studies in the United States, the prevalence of tramadol poisoning was higher in female subjects, compared to male participants [23, 24]. Moreover, studies conducted in Iran provided contradictory data, which might be attributed to cultural differences and a higher tendency of American women to drug use. All studies conducted in Iran were indicative of a higher rate of tramadol poisoning in men, compared to women [13]. This may be because young men are more likely to abuse drugs, like tramadol, due to their greater tendency to engage in high-risk behaviors.

Tramadol and marital status

In a research by Ahmadi, 80.8% of the subjects were single and only 19.2% of them were married [19]. According to the results, a significant gender-wise relationship was observed between the participants. However, the prevalence of tramadol poisoning was higher in married women, compared to men. In the study by Izadi Mood et al., 112 out of 184 patients with tramadol poisoning were single [17]. Furthermore, Aghakhani et al. reported that 65.5% of the participants were single. However, the prevalence of tramadol poisoning was higher in married women, compared to married men [16]. Moreover, Boushehri et al. indicated that 75.5% of the patients were single. The obtained results indicated that marital status provided no effect on the decrease of poisoning among women; the frequency of intoxication cases in single women was equal to married women. Moreover, there was a higher rate of married women with tramadol poisoning, compared to married men [15]. Shokrzadeh et al. also reported that 64.3% of the participants were single. Furthermore, women (90.2) further used tramadol to commit suicide, compared to men (61.4) [11]. In the studies by Farzaneh et al. [18] and Majidi et al. [10], 50% and 52.6% of the subjects were single, respectively.

A cause of enhanced tramadol use among single individuals might be increased marriage age. Thus, being married decreases the odds of tramadol poisoning. The lower prevalence of poisoning among married individuals may be due to their higher attention to health because of their responsibility toward family. In addition, studies revealed that married women had a higher prevalence of tramadol poisoning, compared to married men, which might be due to drug abuse in Iran. Furthermore, adults (especially women) use this drug to commit suicide [14].

The most common causes of tramadol poisoning:

In the research by Ahmadi et al. [19], the most frequent cause of poisoning by tramadol was suicide (98.7%). Similarly, Mood et al. [17] reported that most patients used tramadol to commit suicide. In the research by Abbasi et al. [13], the most common reason for poisoning was suicide. Furthermore, Dalirrad et al. [14] reported that 45.3% of poisoning cases were due to suicide. In the research by Shokrzadeh et al. [11], the most common cause of tramadol use was deliberately and to commit suicide (65.5%). In the study by Majidi et al., 78.9% of tramadol poisoning cases were due to suicide [10]. Moreover, Moradi et al. marked that the most frequent cause of poisoning by tramadol was suicide (58.7%) [12]. The ease of access and the great desire to commit suicide are important aspects in this regard that should be considered [25, 26].

Tramadol and poisoning (the most common route of tramadol poisoning)

In the research by Ahmadi et al., 99.4% of patients were intoxicated through oral consumption; only 6% of poisoning was caused intravenously [19]. Furthermore, all poisoning cases occurred by the oral consumption of tramadol in studies by Aghakhani et al., Boushehri et al., Abbasi et al., Shokrzadeh et al., as well as Majidi and colleagues [10, 11, 13, 15, 16]. This might be due to easy access to the oral form of tramadol in pharmacies and the market [19].

Frequency (mean) of tramadol dose used in patients

As per Ahmadi et al., most patients with tramadol poisoning consumed less than 1000 mg of the drug [19]. Additionally, no significant gender-wise difference was observed among subjects concerning the distribution of the amount of tramadol consumed. In the study by Izadi Mood et al., the Mean±SD dose of consumed tramadol was 2006±7466 mg with a minimum and maximum dose of 100 and 10000 mg, respectively [17]. In the study by

Aghakhani et al., most patients were intoxicated with <1000 mg of tramadol [16]. In the research by Boushehri et al., 18(7.7%) subjects consumed <200 mg of tramadol, whereas 3(31.3%) and 122(52.3%) individuals used 200-800 and >800 mg of the drug, respectively. Moreover, 20(8.7%) individuals consumed an uncertain amount of the drug [15]. In the study by Abbasi et al., all patients took <400 mg of tramadol [13]. Furthermore, the lowest and highest doses of tramadol consumed were respectively 200 and 12000 mg, reported by Dalirrad and associates [14]. In the study by Majidi et al., 50% of the explored patients consumed <400 mg of tramadol, while the other 50% used tramadol doses above 400 mg [10]. The low dose of tramadol could be because most patients had limited experience in taking tramadol.

Tramadol and hospitalization duration

Tramadol poisoning severely damages the nervous system and leads to dizziness, nausea, numbness, ataxia, headache, seizures, and decreased consciousness level; all of which result in hospitalization [27]. Spieller et al. reported that the complications of tramadol poisoning (dizziness, nausea, vomiting, numbness, decreased consciousness, seizures, & coma) led to the long-term hospitalization of approximately 10% of intoxicated patients in the ICU [6]. In the research by Ahmadi et al., the longest hospitalization duration of patients with tramadol poisoning was 48 hours (37.8%). Moreover, there was a significant relationship between tramadol dose and hospitalization duration [19]. However, Izadi Mood et al. found no significant association between tramadol dose and hospitalization duration. Moreover, the Mean±SD duration of hospitalization was 14±9.2 hours with a minimum and maximum duration of 15 minutes and 52 hours, respectively [17]. In the research by Aghakhani et al., 61.9%, 31.1%, and 7% of the patients were hospitalized for less than 2 days, 2-4 days, and more than 4 days, respectively [16]. Boushehri et al. argued that 8.71% of the patients were hospitalized for >24 hours while 49.7% of them remained in the hospital for >48 hours [15]. Shokhrzadeh et al. reported that 36.1% of the studied patients were hospitalized in the ICU [11]. In most studies, patients were hospitalized for >24 hours, which could be due to the high doses of tramadol.

Tramadol and the time of use

In the research by Ahmadi et al., 46.1% of the patients consumed the drug at night, whereas 41.7% and 12.2% of them used the drug in the evening and morning, respectively. In this regard, no significant gender-wise difference was observed in patients [19]. Aghakhani et al.

reported that the drug was mostly consumed in the evening and night [16]. According to the results, tramadol was mostly used at night or evening, which are leisure times of individuals [19].

Tramadol and concomitant medications

Most cases of tramadol poisoning are deliberate poisonings induced by high doses. Increased tramadol dose alone is not a life-threatening condition; most tramadol-generated deaths are due to the adjunct use of several other drugs [3]. In the research by Ahmadi et al., 26% of patients had taken other medications along with tramadol, with benzodiazepines (49.3%) as the most commonly used agents [19]. Izadi Mood et al. reported that 100 patients used only tramadol and the rest consumed other drugs in addition to tramadol. In this regard, the most commonly used drugs in these patients were clonazepam and acetaminophen [17]. According to Aghakhani et al., 17.5% of patients took other medications plus tramadol, with benzodiazepines being taken more than other drugs [16]. In the research by Dalirrad et al., 15% of patients reported the concomitant use of another drug [14]. Shokhrzadeh et al. marked that 51 patients used other drugs along with tramadol; in this respect, benzodiazepines and narcotics were used by 20 and 17 cases, respectively, and two other cases consumed other drugs [11]. In the research by Majidi et al., 15.8% of patients used codeine, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and benzodiazepines adjunct to tramadol [10]. Given the consumption of drugs to commit suicide, other drugs might have been concomitantly used with tramadol accidentally. Notably, some medications, like acetaminophen, are over-the-counter medications [17]. In addition, using benzodiazepines with tramadol increases the risk of poisoning, especially at low doses of tramadol. Given the high prevalence of tramadol and benzodiazepine among the young society members, the authorities should focus on this area. In addition, the prevention and proper treatment of poisoning; the provision of required education to medical students and assistants and general practitioners working in emergency wards; and equipping healthcare centers with tools to take toxicology tests must be prioritized by the ministry of health [17, 28, 29].

Tramadol and seizure

Recognized under the alkaloid class, tramadol has central analgesic properties, i.e., industrially based on the molecular structure of the drug. It is a sedative and its analgesic effects are similar to narcotics. Most tramadol poisonings occur deliberately and in high doses. In this regard, fatal seizures are among the most common effects of

tramadol poisoning [30]. According to Ahmadi et al., 40% of patients manifested symptoms of seizure. Additionally, there was a significant relationship between male and female participants respecting the occurrence of seizures. In this respect, seizures were more frequent in male patients, compared to female individuals [19]. Furthermore, seizures were reported as 24.4%, 18.1%, 33.5%, 69.3%, 41.3%, and 35.1% in the studies by Izadi Mood et al., Aghakhani et al., Boushehri et al., Abbasi et al., Dalirrad et al., and Shokrzadeh et al., respectively [11, 13-17]. The amount of tramadol used is effective in causing seizures; it can be because low doses of tramadol in individuals with a low history increase the risk of seizures.

Tramadol dose and seizures

Ahmadi et al. identified a significant relationship between the dose of tramadol and seizures [19]. Moreover, a significant correlation was observed between tramadol dose and seizure in the study by Izadi Mood and colleagues. In the mentioned research, the minimum and maximum doses were 100 and 10000 mg, respectively [17]. Aghakhani et al. stated that tramadol dose affected seizures [16]. In the research by Dalirrad et al., the lowest and highest doses related to seizures were 100 and 8000 mg, respectively [14]. According to Farzaneh et al., the lowest dose-related to seizures was 1000 mg. However, no significant relationship was observed between tramadol dose and seizures [18]. Low doses of tramadol can increase the risk of seizures in subjects who used the drug only a few times [16]. The elevated dose of tramadol increases the risk of ataxia and seizures in patients. According to studies, tramadol poisoning causes severe poisoning of the nervous system; it makes it quite reasonable for neurological symptoms, like seizures to increase with elevated doses of tramadol. This difference in seizure-related dose may also be attributed to the non-dose-dependent seizures in patients with tramadol poisoning.

Previous use of tramadol

In the study by Izadi Mood et al., 34% of patients reported a history of tramadol use [17]. Moreover, 56.6% of the subjects presented a history of intermittent consumption; however, 21.9% of the cases had a history of continuous consumption in the research by Boushehri and associates. The history of intermittent and continuous consumption was reported at 56.6% and 21.9%, 58.7%, 76.4%, 66.4%, and 26.3% in the studies by Boushehri et al., Abbasi et al., Dalirrad et al., Farzaneh et al., and Majidi et al., respectively [10, 13-15, 18]. The reason for the history of tramadol can be attributed to the high dependence of these patients on tramadol.

Tramadol and mortality

Overall, 5, 2, one, and one case expired due to tramadol poisoning in the research by Ahmadi et al., Izadi Mood et al., Abbasi et al., and Dalirrad et al., respectively. However, no mortality cases were reported in the studies by Aghakhani et al., Boushehri et al., Shokrzadeh et al., as well as Majidi and associates [10, 11, 13-17, 19].

Tramadol and addiction

In the study by Izadi Mood et al., the majority of intoxicated patients indicated a history of substance dependence; the most frequently used drugs were opium and heroin [17]. Furthermore, the drug abuse rate was reported as 44.9% in the study by Dalirrad and colleagues [14]. Moreover, Farzaneh et al. documented that 45.9% of the patients had a history of narcotics use [18]. Opium is the most widely used drug, because of the shared border of Iran with Afghanistan. Additionally, the tendency of individuals with substance dependence to tramadol use supports the drug's narcotic effects. Therefore, the medical community is required to create special restrictions on narcotics in the case of tramadol [17].

Tramadol and respiratory pattern:

In the research by Boushehri et al., among 226 patients, 7 individuals required intubation, one encountered a cardiac arrest, and 25 manifested tachypnea [15].

Tramadol and gastrointestinal status

In the research by Boushehri et al., 2, 3, and 16 subjects presented nausea, vomiting, gastrointestinal bleeding, and epigastric pain, respectively [15].

Tramadol and a history of diseases

In the study by Izadi Mood et al., 15% of patients had a history of diseases; most of which were renal disease and subsequent seizures [17]. In addition, Farzaneh et al. reported that 7(5.7%) subjects had central nervous system problems [18]. Moreover, Majidi et al. declared that 29.5% of patients presented a history of depression [10].

Tramadol and time distribution (season)

In the study by Shokrzadeh et al., patients with tramadol poisoning were evaluated for 7 years; the obtained results demonstrated that most intoxication cases occurred in Fall and Summer [11].

The most common causes of hospital referral

In the research by Izadi Mood et al., Boushehri et al., Abbasi et al., Farzaneh et al., Shokrzadeh et al., and Moradi et al., the most common cause of hospital referral was a decreased level of consciousness. However, Aghakhani et al. reported the most common cause to be seizures [11-13, 15-18]. Tramadol might cause severe nervous system poisoning. This complication might be due to the inhibitory effects of tramadol on the reabsorption of monoamines. It also causes mild poisoning of the cardiovascular system [31].

Treatment

In the research by Izadi Mood et al., 89% of patients were treated with active charcoal. In addition, gastric lavage was performed on 81% of the patients, and 25% and 11% of them received naloxone and anticonvulsants, respectively. Moreover, 5% of patients had tracheal intubation and mechanical respiration while 3% of the individuals were only monitored without performing any of the mentioned procedures [17]. In the study by Aghakhani et al., most treatment procedures were performed with the concomitant use of charcoal, naloxone, and gastric lavage [16]. While Boushehri et al. used naloxone (43.35%) and diazepam (22.32%), Dalirrad et al. and Farzaneh et al. applied naloxone for 80.3% and 49.12% of the cases, respectively. In the study by Shokrzadeh et al., 92, 69, 32, and 24 patients were treated with charcoal, lavage, naloxone, and anticonvulsants [11, 14, 15, 18]. In a study performed by Tashakori et al. on 158 patients referred with tramadol poisoning to the healthcare center affiliated with the University of Mashhad, naloxone was reported ineffective in treating tramadol-induced seizures [32]. Saeedi et al. performed a research in Tehran to evaluate the effect of naloxone on tramadol-induced seizures in 59 patients with this condition. Accordingly, they concluded that while the mentioned drug improved the complications caused by tramadol poisoning, it also created abnormal brain waves after injection [33].

In a study by Manson et al., difficulty breathing, drowsiness, seizures, and cardiac arrest were reported as the symptoms of tramadol poisoning. Naloxone is generally the antidote used to eliminate the complications of tramadol poisoning. However, this medication increases the risk of seizures despite eliminating the symptoms of tramadol poisoning to some extent [18]. Furthermore, most studies have used naloxone to treat patients with tramadol poisoning. However, it has been mostly reported that the therapeutic effect of tramadol might cause seizures,

especially one day after the onset of the treatment. Tramadol-Related seizures do not respond to naloxone but are inhibited by benzodiazepines. Therefore, naloxone should be used with caution in tramadol poisoning [18].

5. Conclusion

According to the present study results, the most frequent cause of poisoning by tramadol was suicide. Tramadol misuse and poisoning leads to seizures and often death. Besides, tramadol poisoning mostly occurs in individuals below the age of 30 years due to suicide. Thus, the awareness of the youth about tramadol use must be improved. Additionally, methods should be developed to prevent suicide and limit the access of individuals to this drug, especially at young ages. Raising public awareness, as well as skill-based training, is essential for physicians and practitioners who are responsible for the provision of tramadol and care to patients intoxicated with the drug.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

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Author's contributions

Conceptualization, data collection, and investigation: Reza Akhavan and Mahdi Foroughian; Writing – original draft, writing – review & editing, and supervision: All authors.

Conflict of interest

The authors declared no conflicts of interest.

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References

- [1] Masoumi GH, Eizadi-Mood N, Akabri M, Sohrabi A, Khalili Y. [Pattern of poisoning in Isfahan (Persian)]. *J Isfahan Med School*. 2012; 29(163):2003-10. <http://jims.mui.ac.ir/index.php/jims/article/view/1434>
- [2] Islambulchilar M, Islambulchilar Z, Kargar-Maher MH. Acute adult poisoning cases admitted to a university hospital in Tabriz, Iran. *Hum Exp toxicol*. 2009; 28(4):185-90 [DOI:10.1177/0960327108099679] [PMID]
- [3] Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet*. 2004; 43(13):879-923. [DOI:10.2165/00003088-200443130-00004] [PMID]
- [4] Odonkor CA, Chhatre A. What's tramadol got to do with it? A case report of rebound hypoglycemia, a reappraisal and review of potential mechanisms. *Pain Physician*. 2016; 19(8):E1215-20. [DOI:10.36076/ppj/2016.19.E1215]
- [5] Barann M, Stamer UM, Lyutenska M, Stüber F, Bönisch H, Urban B. Effects of opioids on human serotonin transporters. *Naunyn Schmiedebergs Arch Pharmacol*. 2015; 388(1):43-9. [DOI:10.1007/s00210-014-1056-3] [PMID]
- [6] Spiller HA, Gorman SE, Villalobos D, Benson BE, Ruskosky DR, Stancavage MM, et al. Prospective multicenter evaluation of tramadol exposure. *J Toxicol Clin Toxicol*. 1997; 35(4): 361-4. [DOI:10.3109/15563659709043367] [PMID]
- [7] Shamsi Meimandi M, Nakhaei N, Shojaei Baghini M, Mazhari Sh, Sharifi S, Sharifi F. [Knowledge of Kerman general practitioners about tramadol (Persian)]. *J Kerman Univ Med Sci*. 2005; 12(3):202-8. <https://www.sid.ir/en/journal/ViewPaper.aspx?id=69434>
- [8] Lewis KS, Han NH. Tramadol: A new centrally acting analgesic. *Am J Health Syst Pharm*. 1997; 54(6):643-52. [DOI:10.1093/ajhp/54.6.643] [PMID]
- [9] Afshari R, Ghooshkhanee H. Tramadol overdose induced seizure, dramatic rise of CPK and acute renal failure. *J Pak Med Assoc*. 2009; 59(3):178. [PMID]
- [10] Majidi M, Nekouei S, Delirrad M. [Demographic findings of tramadol poisoned women admitted to Ayatollah Taleghani hospital, Urmia, Iran from Jan 2012 to Jan 2013 (Persian)]. *Nurs Midwifery J*. 2014; 12(8):761-6. <http://unmf.umsu.ac.ir/article-1-1467-en.html>
- [11] Shokrzadeh M, Hajimohammadi A, Delaram A, Shayeste Y. [Characteristics of Patients Hospitalized with Tramadol Intoxication in Gorgan, Iran, 2008-2015 (Persian)]. *J Mazandaran Univ Med Sci*. 2017; 26(146):185-90. <http://jmums.mazums.ac.ir/article-1-9646-fa.html>
- [12] Moradi A, Taheri SK, Erfani N, Sebatiani M. [Acute poisoning due to tramadol abuse and its causes in patients referred to poisoning ward of Farshchian Hospital of Hamadan (Persian)]. *J Hamedan Police Sci*. 2017; 4(3):81-94. <https://www.magiran.com/paper/2230088>
- [13] Abbasi B, Hafezimoghadam P, Ansari Nejad N, Sarvari M, Ramim T. [Assessment of time interval between tramadol intake and seizure and second drug-induced attack (Persian)]. *Tehran Univ Med J*. 2015; 73(8):592-9. <http://tunj.tums.ac.ir/article-1-6966-fa.html>
- [14] Delirrad M, Ebrahimi E, Majidi M. [Evaluation of demographic characteristics and renal function indices in acute tramadol intoxicated patients in Ayatollah Taleghani hospital, Urmia, Iran (Persian)]. *Stud Med Sci*. 2015; 25(12):1060-6. <https://www.sid.ir/en/journal/ViewPaper.aspx?ID=440375>
- [15] Boushehri B, Dalir Raad M, Valizad Hasanlouee MA, Jaaberi M. [Evaluation of clinical findings and acute complications in patient's admitted to Urmia Taleghani Hospital with tramadol intoxication at 2012- 2013 (Persian)]. *Iran J Assoc Anesthesiol Crit Care*. 2014; 36(1):41-9. <https://www.magiran.com/paper/1285576>
- [16] Agakhani N, Nikoonejad A. [Epidemiology of tramadol poisoning in Urmia (Persian)]. *Nurs Midwifery J*. 2015; 12(12):1081-7. <http://unmf.umsu.ac.ir/article-1-1892-fa.html>
- [17] Ezadi N, Sabzghabae AM, Safdari A, Yaraghi A. [Clinical signs, hospitalization duration and outcome of tramadol intoxication (Persian)]. *J Isfahan Med Sch*. 2011; 28(117):1187-93. <https://www.sid.ir/fa/Journal/ViewPaper.aspx?ID=145927>
- [18] Farzaneh E, Samadzadeh M, Shahbazzadegan B, Sayadrezai I, Mostafazadeh B, Sarbandi Farahani A, et al. [Comparing the frequency of seizure in patients intoxicated with tramadol treated with or without naloxone (Persian)]. *J Isfahan Med Sch*. 2012; 30(197):1012-8. <http://jims.mui.ac.ir/index.php/jims/article/view/1861>
- [19] Ahmadi H, Hosseini J, Rezaei M. [Epidemiology of tramadol overdose in Imam Khomeini hospital, Kermanshah, Iran (2008) (Persian)]. *J Kermanshah Univ Med Sci*. 2011; 15(1):e79395. <https://sites.kowsarpub.com/jkums/articles/79395.html>
- [20] Riordan M, Rylance G, Berry K. Poisoning in children 1: General management. *Arch Dis Child*. 2002; 87(5):392-6. [DOI:10.1136/adc.87.5.392] [PMID] [PMCID]
- [21] Rahmani AH, Jamshidi F, Bayat N. Tramadol poisoning and prevalence of common side effect. *Int J Pharma Res Health Sci*. 2016; 4(5):1429-32. [DOI:10.21276/ijprhs.2016.05.17]
- [22] Goodarzi F, Mehrpour O, Eizadi-Mood N. A study to evaluate factors associated with seizure in tramadol poisoning in Iran. *Indian J Forensic Med Toxicol*. 2011; 5(2):66-9. <https://www.semanticscholar.org/paper/A-study-to-evaluate-factors-associated-with-seizure-Goodarzi-Mehrpour/19cbea576bc17bc75bcdca9b0c795471a3cd2293>
- [23] Marquardt KA, Alsop JA, Albertson TE. Tramadol exposures reported to statewide poison control system. *Ann Pharmacother*. 2005; 39(6):1039-44. [DOI:10.1345/aph.1E577] [PMID]
- [24] Clarot F, Gouille JP, Vaz E, Proust B. Fatal overdoses of tramadol: Is benzodiazepine a risk factor of lethality? *Forensic Sci Int*. 2003; 134(1):57-61. [DOI:10.1016/S0379-0738(03)00100-2]
- [25] Gardner JS, Blough D, Drinkard CR, Shatin D, Anderson G, Graham D, et al. Tramadol and seizures: A surveillance study in a managed care population. *Pharmacotherapy*. 2000; 20(12):1423-31. [DOI:10.1592/phco.20.19.1423.34854] [PMID]
- [26] Petramfar P, Borhani Haghighi A. Tramadol induced seizure: Report of 106 patients. *Iran. Red Crescent Med J*. 2010; 12(1):49-51. <https://www.sid.ir/en/journal/ViewPaper.aspx?ID=165753>

- [27] Loram LC, Mitchell D, Skosana M, Fick LG. Tramadol is more effective than morphine and Amitriptyline against ischaemic pain but not thermal pain in rats. *Pharmacol Res.* 2007; 56(1):80-5. [DOI:10.1016/j.phrs.2007.04.003] [PMID]
- [28] Bruyndonckx RB, Meulemans AI, Sabbe MB, Kumar AA, Delooz HH. Fatal intentional Poisoning cases admitted to the university hospitals of Leuven, Belgium from 1993 to 1996. *Eur J Emerg Med.* 2002; 9(3):238-43. [DOI:10.1097/00063110-200209000-00006] [PMID]
- [29] Islam MN, Islam N. Retrospective study of 273 deaths due to poisoning at sir Salimullah Medical college from 1988 to 1997. *Leg Med.* 2003; 5(S1):129-31. [DOI:10.1016/s1344-6223(02)00128-1]
- [30] Ghazimirsaeid SA, Khakzad M, Dinpanah H, Amani N, Rahimi M, Manuchehri AA. Tramadol, seizure caused by an overdose and acute renal failure: A case report. *World Appl Sci J.* 2014; 32(7):1204-8. [DOI:10.5829/idosi.wasj.2014.32.07.1252]
- [31] Clarot F, Gouille JP, Vaz E, Proust B. Fatal overdoses of tramadol: Is benzodiazepine a risk factor of lethality? *Forensic Sci Int.* 2003; 134(1):57-61. [DOI:10.1016/S0379-0738(03)00100-2]
- [32] Tashakori A, Afshari R. Tramadol overdose as a cause of serotonin syndrome: A case series. *Clin Toxicol (Phila).* 2010; 48(4):337-41. [DOI:10.3109/15563651003709427] [PMID]
- [33] Saidi H, Ghadiri M, Abbasi S, Ahmadi SF. Efficacy and safety of naloxone in the Management of postseizure complaints of tramadol intoxicated patients: A self-controlled study. *Emerg Med J.* 2010; 27(12):928-30. [DOI:10.1111/j.1463-1326.2010.01249.x]