

# Research Paper: Investigating the Characteristics of Tramadol-induced Seizures: A Cross-sectional Study



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## ABSTRACT

**Background:** According to statistics, tramadol intoxication is one of the most common drug poisoning cases in Iran. Because seizure is one of the severe and dangerous side effects of tramadol, the present study aimed to investigate the characteristics of tramadol-induced seizures.

**Methods:** In this cross-sectional descriptive study, all patients who referred to the emergency departments due to the tramadol-induced seizures were examined by the census method. The patients' data were collected with a checklist. Then, the data were analyzed with descriptive and inferential statistical tests in SPSS v. 23 and at a significant level of  $P < 0.05$ .

**Results:** In this study, 350 patients (52.9% male, and 47.1% female) were examined. The Mean±SD dose consumed was 1171.4±802.77 mg. The minimum dose that caused the seizure was 200 mg, and the average dose consumed of tramadol was different in patients who had one, two, or three seizures outside the hospital ( $P=0.002$ ). The consumed average dose of tramadol was 1144.5 mg, 2017.7 mg, and 511.1 mg for patients who had one, two, or three seizure(s), respectively. There was a significant relationship between dose consumed and the number of seizures ( $P=0.001$ ). The study showed that patients who had a one-time seizure, have experienced this condition outside the hospital. There was a significant relationship between the number of seizures and the location of the seizure (outside or inside the hospital) ( $P=0.001$ ).

**Conclusion:** The results showed no significant relationship between consumed dose and location of the seizure. The number of seizures is not dependent on the consumed dose. It means that increasing the consumed dose, the number of seizures does not increase, and there is no significant relationship between the amount of dose consumed and the number of seizures.

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## 1. Introduction

**T**ramadol is a synthetic and codeine-derived drug (4-phenylpiperidine codeine analog) that has an analgesic application with two different mechanisms [1, 2]. Tramadol has been widely accepted as a drug with a weak  $\mu$ -receptor agonist activity that blocks the pain pathways and inhibits the reabsorption of biogenic amines, especially serotonin and norepinephrine in the central nervous system. It also increases the pain threshold [3]. Although it appears to be a safe and effective analgesic, the side effects related to its abuse and poisoning have been reported [4]. Statistics indicate that the abuse of tramadol is increasing in Iran [5] so that the use of tramadol has been reported as one of the most common causes of drug poisoning in recent years [6].

In most cases, tramadol overdose is not a threat to life; however, if accompanied by a seizure, the increased mortality has rarely been reported [7]. The recommended maximum dose of tramadol is 400 mg, and its overdose in the acute phase can lead to myositis, respiratory depression, seizure, hypotonicity, and acidosis. Side effects can be fatigue, vertigo, headache, visual impairments, nausea, vomiting, sweating, xerostomia (dry mouth), constipation, heart failure, and hallucination [8]. The seizure is a significant side effect of tramadol consumption and can occur following the therapeutic or toxic doses of the drug [7, 9].

One of the most dangerous side effects in patients with tramadol poisoning is the seizures. Because most physicians hospitalize these patients for fear of the second seizure, a substantial financial cost is forced on the health system. Regarding the increasing consumption of tramadol in the Iranian community and many reports of tramadol poisonings along with seizures and respiratory problems, this study aimed to investigate the characteristics of tramadol-induced seizures in the referred patients to Imam Reza and Ghaem hospitals in Mashhad.

## 2. Materials and Methods

In this cross-sectional descriptive study, the sampling of patients was initiated after approval by the Ethics Committee of Mashhad University of Medical Sciences. So that, all patients who were hospitalized with tramadol poisoning from May to September 2017 in the Emergency Departments of Ghaem and Imam Reza hospitals, were evaluated if they have presented the inclusion criteria of age between 18 to 50, hospitalization for more than 12 hours, visiting an emergency medicine specialist, and

performing routine emergency care. Patients with a recent history of epilepsy and head trauma were excluded from the study.

After recording the patients' profile, inpatient follow-up, clinical status and related parameters, including side effects induced by poisoning, clinical status, seizure frequency, location of seizure incident, consumed dosage of tramadol, age of patients, the examination of urine toxins test, tramadol consumption history, seizure history following tramadol consumption, etc. were collected based on patients' records and documents of observations of physicians and nurses. All patients were treated according to a single guideline. Patients were monitored for up to 12 hours for the frequency of repeated seizures. Data analysis was performed using SPSS version 23 and descriptive statistical (mean, percentage, standard deviation, and frequency) and inferential statistical tests (Kruskal-Wallis, Mann-Whitney, and Chi-square) were conducted at the significant level ( $P < 0.05$ ).

## 3. Results

A total of 350 patients referred to the hospitals, of which 185 patients (52.9%) were male, and 165 patients (47.1%) were female. The average age of the patients was 23.4 years. The youngest was 18, and the oldest was 47 years old. A total of 337 patients (96.3%) have had seizures outside the hospital, and 13 patients (3.7%) inside the hospital. The average number of seizures was 1.22, with a minimum of one and a maximum of three. Also, 281 patients (80.3%) had only one seizure, 60 (17.1%) experienced two seizures, and 9 (2.6%) experienced three seizures. Among the patients, 22 (6.3%) patients had apnea following tramadol use, and 7 (2%) lost their consciousness (Table 1).

The average dose consumed was  $1171.4 \pm 802.77$  mg, the minimum dose consumed, which had caused the seizure was 200 mg, and the maximum dose was 4000 mg.

According to the examination of urine toxins test, 269 patients (76.9%) had only used tramadol, but 50 patients (14.3%) opium, 17 (4.9%) benzodiazepine, and 14 (4%) patients amphetamine along with tramadol.

Among the patients, 157 (44.9%) have reported the history of using tramadol, and 17 patients (4.9%) had seizure history after consuming tramadol (Table 2).

The average dose of tramadol consumed was significantly different in patients who have had one or two or three times seizure(s) outside the hospital ( $P = 0.002$ ). There was also a

**Table 1.** Demographic characteristics of the patients

Variables	No. (%)
Male	185 (52.9)
Female	165 (47.1)
Seizure outside the hospital	337 (96.3)
Seizure inside the hospital	13 (3.7)
One seizure	281 (80.3)
Two seizures	60 (17.1)
Three seizures	9 (2.6)
The occurrence of apnea	22 (6.3)
Loss of consciousness	7 (2)

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**Table 2.** Frequency of drug use and seizure records following drug consumption

Variables	No. (%)
Tramadol use history	Yes 157 (44.9)
	No 193 (55.1)
Case history of seizure incident following the tramadol use	Yes 17 (4.9)
	No 333 (95.1)

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significant difference between the average consumed doses in patients who have experienced two or three seizures inside the hospital ( $P=0.002$ ) (Table 3).

Tramadol consumed average doses were 1144.5 mg, 2017.7 mg, and 511.1 mg in patients who had one,

two, and three seizure(s), respectively. According to the Kruskal-Wallis statistical test, there is a significant relationship between the dose consumed and the number of seizures ( $P=0.001$ ) (Table 4).

**Table 3.** Comparison of tramadol consumed dose in three groups of patients divided by the number of seizures outside and inside the hospital

Variables	Number of Seizures	Number of Patients	Mean±SD	Result of the Kruskal-Wallis Test
Outside the hospital	1	281	1144.841±5.2	$\chi^2=12.60$ $P=0.002$
	2	53	1317.552±0.5	
	3	3	533.230±3.9	
Inside the hospital	1	0	-	$\chi^2=9.57$ $P=0.002$
	2	7	2000.230±0.9	
	3	6	500.275±0.7	

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**Table 4.** Comparison of tramadol consumed dose in three groups of patients based on the number of seizures

Variables	Mean±SD	Result of the Kruskal-Wallis Test
One seizure	1144.5±841.2	$\chi^2=23.557$ P=0.001
Two seizures	2017.7±568.6	
Three seizures	511.1±247.2	

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The patients with one seizure have experienced it outside the hospital. In the case of patients with two seizures, 53 (88.3%) have had both seizures outside the hospital, and 7 (11.7%) have experienced the second seizure inside the hospital. In the case of patients with three seizures, 3 patients (33.3%) have had all three seizures outside the hospital, and 6 (66.7%) have experienced the second and third seizures inside the hospital. According to the Chi-square test, there is a significant relationship between the number of seizures and the location of the seizure incident (P=0.001).

#### 4. Discussion

Currently, patients who refer to the hospital complaining of taking tramadol, are being monitored in the emergency room for several hours, depending on the clinical status and concomitant use of other drugs. Then if their seizure and clinical condition are being controlled and stable, they get discharge [10]. This study aimed to investigate the characteristics of tramadol-induced seizures.

In the present study, the average age of patients was 23.4 years. The average age of patients in the studies of Delirrad et al., Jovanović, and Abbasi et al. were respectively 23.29, 22.2, and 23.23 years, which are close to the present study and may indicate the prevalence of this phenomenon among the young people [10, 11, 12]. The youth are also more likely to abuse drugs such as tramadol since they are more involved in risky behaviors. The availability of the drug, not knowing the side effects of tramadol, and the recommendation of peer groups and friends to take tramadol as a common painkiller have increased the use of this drug in Iran. This situation mostly underscores the importance of education about the dangers and side effects of random use of addictive drugs at the community level, especially young people [7, 13].

In the present study, tramadol consumption was higher in men. In Bushehri et al. study, tramadol consumption was also higher in men [14]. Also, the results of Mood et al., Farzaneh et al., Okazi et al., Shokrzadeh et al., Delirrad et al., Talaei et al. support the results of the present

study [5, 6, 11, 16-18]. But the results of by Spiller et al. study and Marquardt et al. in the USA were different, in which women had been poisoned more than men due to the cultural differences between Iran and USA regarding the tendency of women to use drugs [19, 20]. Tramadol is also more commonly prescribed in other countries as a painkiller and can lead to unwanted poisoning, but in our country, tramadol is abused, and adult patients (especially women) use it like other drugs with the aim of suicide. In the present study, the Mean±SD consumed dose of tramadol was 1171.4±802.77 mg.

In the studies of Mood et al., Taghaddosi Nejad et al., and Delirrad et al., the Mean±SD consumed dose of tramadol were 2006±7466, 1151±1353, and 2347.36±1837.35 mg, respectively [6, 11, 21]. In this study, the minimum dose consumed of tramadol that caused seizure was 200 mg and the maximum dose of 4000 mg among the patients. In a retrospective study done by Klarout et al. in the USA, the minimum consumed dose of tramadol that resulted in seizure was 500 mg, and the minimum dose that caused coma and respiratory depression was 800 mg [22]. In the study of Mood et al., the minimum consumed dose and the maximum dose consumed were reported to be 100 and 10000 mg, respectively [6].

In Jovanović et al. study, the lowest and highest doses associated with seizures were respectively 250 and 2500 mg [12]. Farzaneh et al. reported the minimum dose of 100 mg related to seizure [15], and in Mehrpour et al. study, two cases of seizures with the doses of 100 mg were reported [23]. Also, in the investigations conducted by Spiller et al. and Marquardt et al., the minimum doses related to seizure were reported to be 500 mg and 800 mg, respectively [19, 20]. Besides, in Delirrad et al. research, the tramadol consumption was 100 mg, and the maximum consumed dose was 8000 mg [11]. These differences can be attributed to the independence of seizure incident from the consumed dose in patients with tramadol poisoning.

In the present study, 44.9% of patients had a history of tramadol use. The percentages of patients who reported the history of tramadol use were 78.5%, 34%, 66.4%,

and 58.7% in the study of Bushehri et al., Mood et al., Farzaneh et al., and Abbasi et al., respectively [6, 10, 14, 15]. The frequent consumption of tramadol may be due to excessive dependence on the drug. It appears that these results indicate the drug abuse by young people. Also, the ease of access and preparation of suicide is one of the essential aspects in this area and should be considered.

Respiratory apnea (6.2%) was the most common cause of patients' referral to hospitals. In a study conducted on 190 poisoning cases with tramadol in the USA, the most commonly reported clinical symptom was respiratory distress that occurred in 27.4% of poisoned patients [24]. In the studies of Mood et al. [6], Bushehri et al. [14], Shokrzadeh et al. [17], Delirrad et al. [11], Mood et al. [6], Farzaneh [15], and Marquardt [20], the most common causes of patients' referral was the loss of consciousness. Regarding these reports, it appears that the symptoms of poisoning with tramadol are due to the inhibitory effects of tramadol on catecholamines and serotonin reabsorption rather than to the opioid effects of the drug. Dysphonia, tachycardia, vertigo, and hypertension all can indicate mild serotonin syndrome. Also, consuming high doses of tramadol causes severe involvement of the nervous system, but not the cardiovascular system [24].

In the present study, the examination of urine toxins test indicated that 76.9% of patients had only used tramadol, and respectively 50, 17, and 14 patients had consumed opium, benzodiazepine, and amphetamine along with tramadol. In the study of Bushehri et al. [14], 41 patients (17.6%) did not take a concomitant drug with tramadol, 185 patients (79.4%) had concomitant drug use along with tramadol, and 7 (3%) had uncertain status. In Mood et al. study [6], 100 patients (54.3%) had only used tramadol, and the rest had taken other medications in addition to tramadol; the most common drugs were clonazepam and acetaminophen. In Delirrad et al. study [11], 38 patients (15%) reported concomitant use of other drugs, and 213 patients (83.9%) had used only tramadol. The reason for taking tramadol with other drugs or medications may be the fact that the aim of the majority of patients was committing suicide; hence, they had accidentally used other medicines in addition to tramadol [15].

In the present study, the rate of seizure following tramadol use was 4.9 (n=17) (Table 2), which was the most important seizure factor in drug poisonings in Isfahan (25%), Ardabil (28.3%), Urmia (41.3%), Tehran (46.2%), Gorgan (35.1%) and France (27.4%) [6, 11, 15, 17, 18, 20].

In this study, there was a significant relationship between the consumed dose of tramadol and seizure outside

and inside the hospital (Table 3). The results of the present study are consistent with the studies of Mood et al. [6], Marquardt et al. [20], and Abbasi et al. [10]. In the investigations of Farzaneh et al. [15], Tashakkori et al. [25], Delirrad et al. [11], the amount of consumed dose of tramadol was not significantly correlated with the seizure, which does not support the results of the present study.

In the present study, there was no significant relationship between the previous history of addiction to tramadol and the seizure incidence. The results of the present study are consistent with the studies of Farzaneh et al. [15] and Taghaddosi Nejad et al. [21]. Studies by Jovanovic-Cupic et al. [12] and Marquardt et al. [20] indicate a relationship between tramadol addiction and the seizure incidence, which does not support the results of the present study.

In the present study, 80.3%, 17.1%, and 2.6% of patients had respectively one, two, and three seizures. In Jovanović-Čupić et al. study, 45% of patients who experienced seizures, had only one seizure, and 55% of them had more than one seizure [12]. In Abbasi et al. study [10], the patients were divided into two groups according to the frequency of seizures: patients with one seizure and patients with two and more seizures. In the first group, the time interval between drug use and seizure was approximately 3.5 hours. However, in patients who had two or more seizures, the occurrence time of the first seizure was less than one hour, and the occurrence time of second seizure was reported to be less than three hours. In other words, the probability of the second seizure was less, and its time interval with the first seizure was less than two hours.

The patients with one seizure experienced it outside the hospital. In the patients who had two seizures, both seizures occurred outside the hospital in 88.3% of cases, and inside the hospital in 11.7% of patients. Among the patients who had three seizures, 33.3% had all three seizures outside the hospital, and 66.7% of them had the second and third seizures inside the hospital. Abbasi et al. study indicates that the average seizure time is less than the average time of referral, indicating that at least the first seizure was before the referral, and patients had referred to the treatment center after the first seizure [10].

## 5. Conclusion

The results of the present study suggested no significant relationship between the consumed dose and location of seizure incident (outside and inside the hospital). The consumed doses of tramadol are different in the patients who have had two or three seizures, but this difference is

not dose-dependent. In other words, by increasing dose, the number of seizures does not increase, and there is no significant relationship between the amount of consumed dose and the number of seizures.

## Ethical Considerations

### Compliance with ethical guidelines

All ethical principles were considered in this article.

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### Author's contributions

All authors contributed in preparing this article.

### Conflict of interest

The authors declared no conflict of interest.

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