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Prospective and Retrospective Study of Pattern of Tramadol Overdosed Patients Admitted to Alexandria Main University Hospital

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Abstract

Background: *Tramadol is one of the analgesic drugs, related to opioid. It is a centrally acting synthetic analgesic compound that is not derived from natural sources. Tramadol produces its anti-noceptive and analgesic effects via opioid and non-opioid mechanisms. The opioid component involves low affinity to μ-opioid receptors and the non-opioid component inhibits the reuptake of serotonin and norepinephrine neurotransmitters. Initially this new opioid painkiller medication was introduced as having safe and low abuse liability and widely used throughout the word. However, after a while, it was revealed that this agent has significant risks when overdose occurs. Nowadays, tramadol abuse has become a common medical emergency. An increasingly alarming phenomenon of tramadol drug abuse has been demonstrated in the Egyptian community in the last four years. Although the issue of drug abuse is not a newcomer to the Egyptian society, tramadol has been associated with a wide range of drug abuse and its illegal drug transactions had made it easily accessible and readily provided at cheap costs despite of its being a scheduled drug. The alleged sexual potency effects of tramadol had also contributed greatly to its popularity and massive use especially among Egyptian youth.*

Aim of the work: *This study was carried out on all patients with tramadol overdoses admitted to the Alexandria Poison Center and Intensive Care Unit (I.C.U.) at Alexandria Main University Hospital from 1/1/2012 to 30/6/2012 and from 1/10/2012 to 31/3/2013. It aimed to study the epidemiologic, clinical and laboratory patterns of tramadol over dose among users. Also, it aimed to determine the possible association between these patterns and the patients' outcome.*

Keywords: *Tramadol, toxicity, overdose, abuse, Alexandria.*

INTRODUCTION

Tramadol is a centrally acting, synthetic opioid analgesic agent. It exerts its analgesic effect by inhibiting the re-uptake of norepinephrine and serotonin and also by weak opioid receptor agonism.(1) Tramadol is extensively metabolized by the liver and primarily excreted in the urine. Dose reduction is recommended in severe renal

impairment and liver cirrhosis. The most common side effects are dizziness, nausea, constipation and headache. Accidental overdose of tramadol may lead to fatal acute hepatic failure. [2, 3]

Tramadol has a low affinity to opioid receptors but its analgesic potency is only 5-10 times less than morphine, and is equal to pethidine. About 30% of the effect of tramadol could be antagonized by naloxone (pure narcotic antagonist). In addition, tramadol has a low potential for the development of tolerance, dependence as well as abuse. [3, 4, 5] Tramadol does not show serious adverse effects of traditional opioid analgesics such as respiratory depression or drug dependence. Therefore, its potential of abuse is thought to be lower or absent in comparison with other opioid analgesics. [6]

The potential adverse reactions of tramadol involve seizures and Serotonin Syndrome. Either of these reactions may occur with tramadol monotherapy, but both appear to be much more common with either abuse/overdose or in combination with other drugs, particularly antidepressants. [7,8] Respiratory depression with opiates is due in part to decreased brainstem response to CO, and the hypoxic drive, and to a blunted increase in respiratory drive associated with increased airway resistance.[8,9]

Therefore, knowledge of the modal of poisoning with tramadol will help in early diagnosis and management of poisoning which in turn should result in reduction of morbidity and mortality. The present study was undertaken to provide such information.

This study was conducted to fulfill the following objectives:

General objective: To study the epidemiologic and clinical pattern of tramadol intoxication in order to help in early diagnosis and management.

Specific objectives: To study the epidemiologic, clinical and laboratory patterns of tramadol overdosage among users and to determine the association between these patterns and patients' outcome.

PATIENTS

Target population: This study was carried out on all patients with tramadol overdoses admitted to the Alexandria Poison Center and Intensive Care Unit (I.C.U.) at Alexandria Main University Hospital. This included: Patients with tramadol overdoses who were admitted from 1/1/2012 to 30/6/2012 and patients with tramadol overdoses who were admitted from 1/10/2012 to 31/3/2013.

METHODS

Study design:

Descriptive epidemiological two study designs were approached:

1. A retrospective study by record reviewing.
2. A follow up case series study.

Research setting:

Alexandria Poison Center (APC) and Intensive Care Unit (I.C.U.) at Alexandria Main University Hospital.

Data collection tools and sources:

Data were obtained from conscious patients or their relatives.

1. Transfer sheet used to collect data from medical records that was completed by hospital specialists or interns.
2. Interview format to collect socio-demographic data.
3. Clinical examination sheet to record clinical data and patients' outcomes from patients' files.

The following data were collected for each patient:

i. **Data in interview format:**

- Personal history: socio demographic study including age, sex, residence, psychiatric troubles, previous suicidal attempts, life style habits, reason for using Tramadol.
- Poisoning condition: amount, mode of poisoning, route of poisoning, pre-hospital management, time elapsed since admission.

ii. **Data in clinical examination sheet:**

- General examination signs: consciousness level, and vital signs.

- Systemic examination signs: neurological signs, cardiovascular signs, respiratory signs, gastrointestinal signs, genitourinary signs, and skin signs.
- Laboratory parameters if available: random blood glucose, complete blood picture (CBC), liver function, renal function, and electrocardiogram (ECG).
- Emergency management: decontamination, supportive treatment, and Narcan injection.
- Outcome (prognosis): complete recovery and discharge, put under observation, ICU admission, death either directly or due to complications even if in the emergency room.

RESULTS

I. Socio-demographic data:

As regards age distribution, this study showed that the average age of patients of tramadol overdose ranged between 18.0-40.0 years with the mean of 29.77±6.94 years. More than half (52.5%) were in the age group 30-40 years (Fig. 1).

Among a total of 122 tramadol overdose, males constituted 71.3% (n=87) while females represented 28.7% (n=35) (Fig. 2).

More than half of the studied patients (61.5%) were middle socioeconomic status (SES) and more than a third (35.2%) had poor SES. Only 3.3% were of high SES (Fig. 3).

The majority of the studied patients (81.1%) were urban inhabitants while the rest (18.9%) were rural one (Fig. 4).

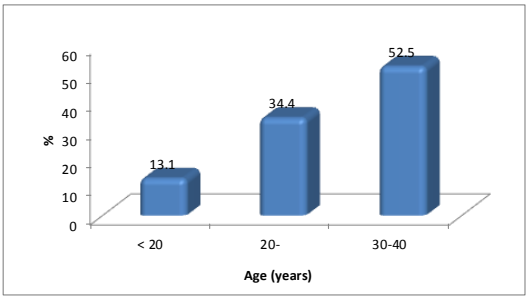

Fig. 1: Percent distribution of tramadol overdosed patients (n = 122) by age group.

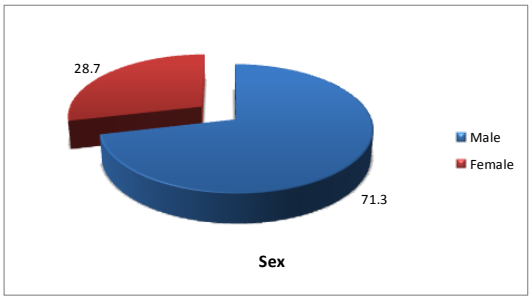

Fig. 2: Percent distribution of tramadol overdosed patients (n = 122) according to sex.

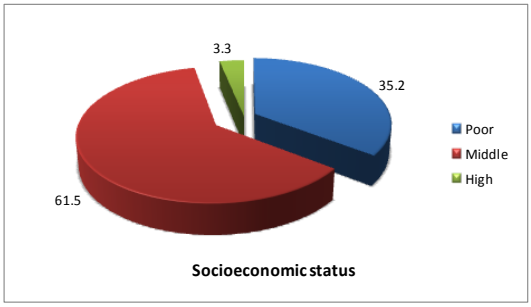

Fig. 3: Percent distribution of tramadol overdosed patients (n = 122) according to socioeconomic status.

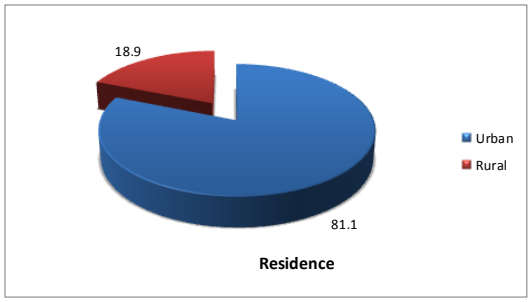

Fig. 4: Percent distribution of tramadol overdosed patients (n = 122) according to residence.

II. Life style habits: (Table 1)

The majority of the studied cases (95.9%) were active smokers. Only 2.5% were passive smokers. A minority (1.6%) were non-smoker. Most of the studied patients (82.0%) were not alcoholic and 18.0% consumed alcohol. More than three quarters of the studied individuals (76.2%) have not used other illicit drugs.

Table 1: Frequencies analysis regarding life style habits (n= 122).

Life Style Habits:		
Smoking	No.	%
Never	2	1.6
Active	117	95.9
Passive	3	2.5
Alcohol	No.	%
No	100	82.0
Yes	22	18.0
Illicit drug use	No.	%
No	93	76.2
Yes	29	23.8

III. Poisoning conditions: (Table 2)

More than two-thirds of the studied patients had psychiatric troubles mainly in the form of depression (68.9%). Vast majority of the studied patients (94.3%) did not have any previous suicidal attempts. Self-medication was reported by most of the studied patients (97.5%) whereas only three individuals (2.5%) were using prescribed medications.

Regarding poisonous amount, just less than two-thirds of the studied patients (63.9%) reported intake of non-toxic doses (<400mg). Nearly a third (33.6%) reported toxic doses intake. Only 2.5% reported intake of fatal doses

Accidental poisoning was reported in most of the studied individuals (94.3%), while suicidal poisoning was found in (5.7%). Ingestion was reported as the only route of administration in all studied individuals (100%). As regard prehospital management, the majority of patients included in the study (82%) did not receive any prehospital management. Only 18.0% received such care

Table 2: Poisoning circumstances of tramadol overdosed patients (n= 122).

Poisoning circumstances	No. (n = 122)	%
Past history of psychiatric troubles		
No	38	31.1
Yes	84	68.9
Previous suicidal attempts		
No	115	94.3
Yes	7	5.7
Reason for using tramadol		
Intentional (or self-medicated)	119	97.5
Therapeutic	3	2.5
Poisonous amount #		
Non- toxic	78	63.9
Toxic	41	33.6
Fatal	3	2.5
Mode of poisoning		
Accidental	115	94.3
Suicidal	7	5.7
Route of poisoning		
Ingestion	122	100.0
Prehospital care		
No	100	82.0
Yes	22	18.0

IV. General signs: (Table 3)

Glasgow coma score ranged between 9.0-15.0 with the mean of 12.9 ± 1.2. Pulse rate ranged between 56-149 beat/min with the mean of 102.8±20.3 beat/min. Temperature ranged between 36.6-37.8 degrees with the mean of 37.2±0.4 degrees. The mean respiratory rate of the studied patients was 21.5±3.5 breath/min indicating tachypnea (a minimum of 16.0 and maximum of 28 breath/min).

Table 3: Vital signs of tramadol overdosed patients (n= 122).

Clinical sign	Reference value	Minimum	Maximum	Mean± Std. Deviation
Glasgow Coma Score #	3-15	9.0	15.0	12.9±1.2
Pulse (beat/minute)	60-100	56.0	149.0	102.8±20.3
Systolic blood pressure (mmHg)	120-139	110.0	140.0	120.1±9.3
Diastolic blood pressure (mmHg)	80-89	60.0	90.0	76.9±8.2
Temperature (C^o)	36.5-37.2	36.6	37.8	37.2±0.4
Respiratory Rate (per minute)	12-16	16.0	28.0	21.5±3.5

V. Systemic signs:

Common clinical signs and symptoms of the studied patients with tramadol overdose is summarized in Fig. 5.

VI. Investigations:

Results of renal blood tests, random blood glucose, complete blood picture, and liver function tests were obtained for all participated patients and statistically analyzed (data not shown).

ECG findings (Table 4) have shown that only 3 patients (2.5%) had irregular rhythm. Normal P-wave was found in the majority of the studied individuals 119 (97.5%), while flattened P-wave was detected in only one patient (0.8%) and inverted P-wave was detected in 2 patients (1.6%). Normal QRS-wave was reported in 65.6% of patients (n=80), whereas 22.1% (n=27) had shortened QRS-wave and 15 patients (12.3%) had prolonged QRS-wave. T-wave was normal in the majority of the studied individuals 120 (98.4%), while flattened T wave was detected in 2 patients(1.6%). Nearly two-thirds of the studied patients (65.6%) had normal PR interval, whereas 22.1% (n=27) had shortened PR interval and 15 patients (12.3%) had prolonged interval.

Table 4: ECG findings of tramadol overdosed patients (n= 122).

ECG findings	No. (n = 122)	%
Heart rate		
<60	2	1.6
60-100	71	58.2
>100	49	40.2
Rhythm		
Regular	119	97.5
Irregular	3	2.5
P-wave		
Normal	119	97.5
Flattened	1	0.8
Inverted	2	1.6
QRS-wave		
Normal	80	65.6
Prolonged	15	12.3
Shortened	27	22.1
T-wave		
Normal	120	98.4
Flattened	2	1.6
ST segment		
Normal	120	98.4
Depressed	2	1.6
PR interval		
Normal	80	65.6
Prolonged	15	12.3
Shortened	27	22.1

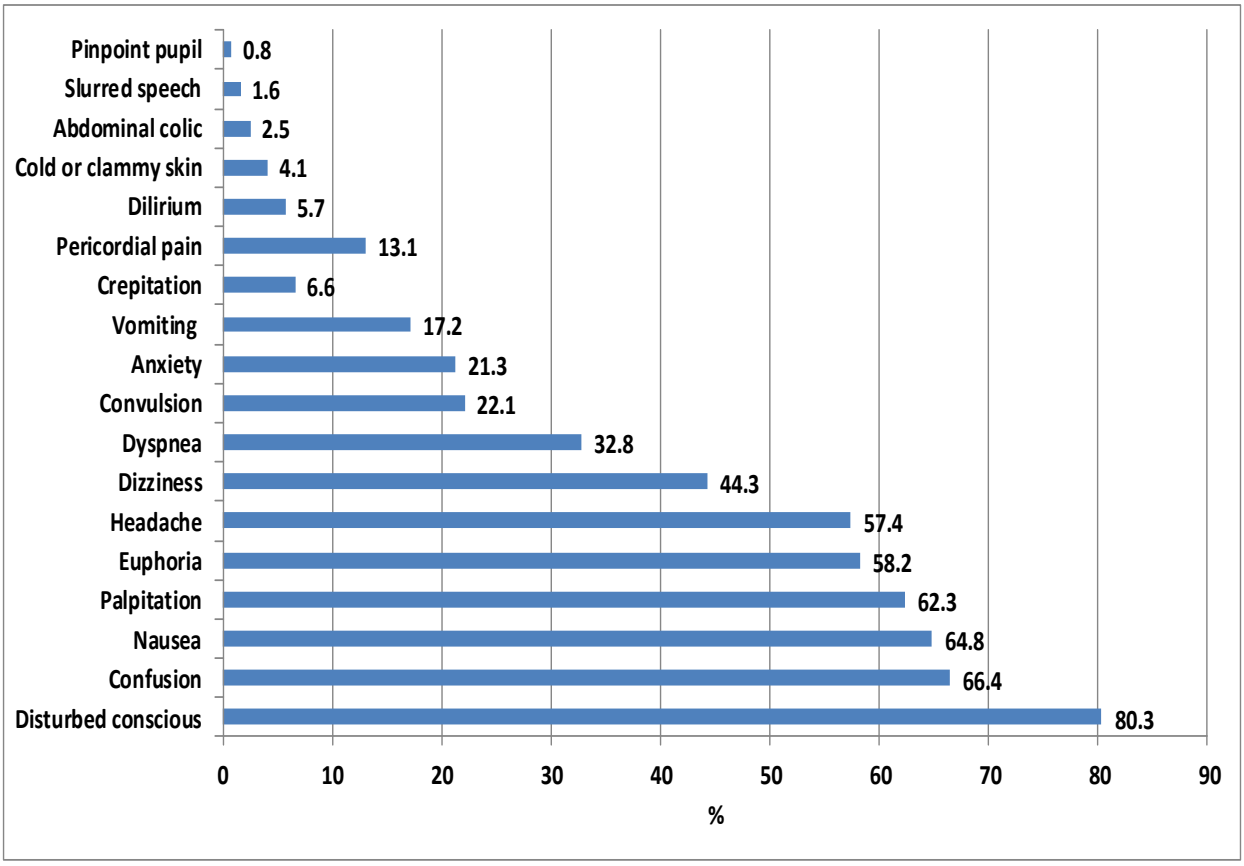

Fig. 5: Percent distribution of tramadol overdosed patients (n = 122) according to common clinical presentation.

VII. Lines of treatment:

The main lines of emergency management were utilized differently with varying patients according to their individual requirements (Fig. 6).

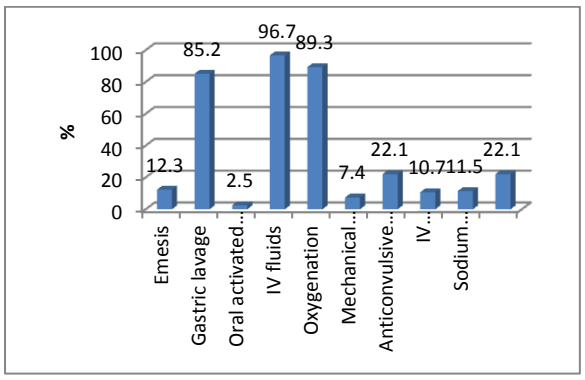

Fig. 6: Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University according to important recommended lines of treatment.

VIII. Prognosis: (Table 5)

Complete recovery and discharge was the fate in most of the studied individuals (72.1%), while (22.1%) required ICU admission and (5.7%) needed to be put under observation.

Table (5): Frequencies analysis regarding prognosis of the tramadol overdosed patients (n=122).

Prognosis	No.	%
Complete Recovery & Discharge	88	72.1
Put Patient Under Observation	7	5.7
ICU Admission	27	22.1
Total	122	100.0

IX. Predictors of adverse outcome of tramadol overdose:

Predictors of adverse outcome were determined after multivariate logistic regression analysis of variables contributing to adverse outcome of tramadol overdose patients (Table 6).

Table 6: Multivariate logistic regression analysis of predictors of adverse outcome of tramadol overdosed patients (n=122) admitted to Alexandria Main University Hospital.

Independent variable	OR	95% CI	P value
Block 1: Socio-demographic			
Gender (ref. female)	0.91	0.70 – 1.19	0.09
Age (years)	1.04	1.03 – 1.16	0.04*
Socioeconomic status (ref. poor)	0.88	0.67 – 1.17	0.13
Residence (ref. rural)	0.95	0.79 – 1.13	0.06
Block 2: Lifestyle habits			
Smoking (ref. no)	1.69	1.32 – 2.16	0.02*
Alcohol consumption (ref. no)	1.42	0.93 – 2.17	0.35
Illicit drug use (ref. no)	1.25	1.18 – 1.38	0.02*
Block 3: Poisoning circumstances			
Past history of psychiatric troubles (ref. no)	0.92	0.72 – 1.27	0.19
Previous suicidal attempts (ref. no)	0.89	0.71 – 1.35	0.23
Reason for using tramadol(ref. therapeutic)	1.62	1.42 – 2.64	0.03*
Poisonous amount(ref. non-toxic)	1.73	1.52 – 3.52	0.01*
Mode of poisoning (ref. accidental)	0.81	0.66 – 1.04	0.09
Pre-hospital care (ref. yes)	0.90	0.63 – 1.36	0.18
Block 4: Clinical characteristics			
Disturbed conscious(ref. no)	1.53	1.04 – 2.56	0.04*
Receiving recommended treatment (ref. yes)	0.72	0.59 – 1.54	0.18
Hospital stay (ref. one day)	0.93	0.82 – 1.74	0.39
*$\chi^2_{15} = 43,020$ overall model $P < 0.001$, Nagelkerke $R^2 = 0.525$			

DISCUSSION

Tramadol overdose has been one of the most frequent causes of drug poisoning in the recent years, especially in young adult males. As regard age, in the current study the mean age was 29.77±6.94 years. Similar findings were obtained by Zhang.et al., (2013).[10] since the mean age was 23.4±4.1 years in their study. Also other studies reported near mean age (22.7 years). [10,11]

This study, conducted on 122 patients, among which 87 (71.3%) were males and 35 (28.7%) were females. Hassanian HM et al., (2013) [12] reported similar finding where males predominated with a percentage of 70.1% according to his study. Fawzi et al., (2011) [13], found that adult population have higher prevalence (67.9%) compared to children that presented only (32.1%) of the studied cases. The male sex prevalence was also higher (77.2%) compared to females (22.8%) in the same study. Similarly, in Ahmadi et al., (2012) [11], patients with tramadol poisoning were identified as (78.5%) males and (21.5%) females. However, in a study conducted by Morteza, et al., (2012) [14], on 520 Tramadol intoxication patients during 2008-09 in kermanshah, the results showed that males were predominating (93.7% male and 6.3% female). Additionally, they demonstrated that, Tramadol intoxication was more common in young male patients (83.3%) where, 61.8% were between 20-40 years old. [14]

Regarding socioeconomic status and residence of patients involved in the current study, the higher percentage of cases 61.5% (n=75) were having middle socioeconomic status while poor status was reported in 35.2% (n=43) and high standards were only seen in 3.3% (n=4). Furthermore, most of the studied patients (81.1%) were living in the city while 18.9% were living in the village. In contrast, Fawzi et al., (2011) [13] found that most tramadol addicts being unemployed, low socioeconomic status, suburbs residents, uneducated or with minimal educational levels.

Investigating reasons for taking tramadol, it was shown that 97.5% were self-medicated and 2.5% were using tramadol as medically prescribed. Hundred percent of tramadol abusers reported in a

study by Zhang et al.,(2013)[10], were self-medicated. The reason for presentation was intentional self-poisoning in (68.4%), abuse in (27.8%) and (1.5%) had accidental poisoning according to the study conducted by Hassanian HM et al.,(2013) [12]. Petramfar et al., (2010) [15], found that 81% of patients abused tramadol and the rest of cases consumed it for therapeutic purposes.

Concerning life style habits of tramadol intoxicated patients in this study, most of the studied patients (95.9%) were active smokers, 82.0% did not drink alcohol. Seventy six percent of the studied individuals did not have any past history of drug abuse. In the study by Zhang.et al., (2013) [10], eighty seven percent of the sample had no previous history of drug abuse before tramadol abuse. Whereas, a past history of addiction to other substances was reported in 16.4% of patients according to the study conducted by Hassanian HM et al.,(2013) [12].

In the current study, the majority of the studied patients had psychiatric troubles (68.9%) as known by history taking.

Regards different lines of management performed in relation to the studied cases of tramadol intoxication, emesis was used for decontamination in (12.3%), gastric lavage was practiced in (85.2%), and activated charcoal was used in (2.5%). Intravenous fluids were administered in most of the studied individuals (96.7%). Oxygenation was needed in around 89% of the studied group. Mechanical ventilator was only required in (7.4%) of the studied group. Anticonvulsive therapy was required in (22.1%) of the studied patients. Intravenous hydrocortisone was only used in 13 cases (10.7%). Sodium bicarbonate was included in the treatment of 14 of the studied patients. Antidote usage was only needed in 22% of the studied group. Most of the studied samples (72.1%) required hospitalization for just one day, around 22% patients stayed for three days and 7 patients (5.7%) stayed in hospital for two days.

In the study conducted by Hassanian HM et al., (2013) [12], treatment for apnea included intubation and ventilation in 84.2%, naloxone administration in 15.8%. The treatment of tramadol overdose was mainly supportive, with careful monitoring. Symptom onset was rapid, requiring administration of activated charcoal within 1–2 hours of ingestion.

Regarding outcome of the participated patients, complete recovery and discharge was the fate in the majority of cases (72.1%), while 27 patients (22.1%) required intensive care unit (ICU) admission and 7 patients (5.7%) needed to be put under observation. Ahmadi et al., (2012)[11], found that the duration of hospitalization for 94.2 % of cases was shorter than 48 hours. Their results also showed that 10% of the admitted cases have died. In Morteza et al., (2012) [14], 3.1% of patients had to be transferred to the ICU. Similarly, 15% of patients were admitted to the ICU in the study conducted by Spiller et al., (1997) [16]. In Shadnia et al., (2008)[6], the admission period ranged between 1 and 21 days with average of 2.75 days and around 7% of cases were admitted to the ICU in a different study.[11]

On doing multivariate logistic regression analysis of predictor variables contributing to adverse outcome of tramadol intoxicated patients, it was found that age, smoking, illicit drugs use, self-medication of tramadol, poisonous dose and state of consciousness were the main predictors of adverse outcome of tramadol overdose.

REFERENCES

1. Pothiawala S, Ponampalam R. Tramadol Overdose: A Case Report. Proceedings of Singapore Healthcare 2011; 20(3):219-23.
2. Loughrey MB, Loughrey CM, Johnston S, O'Rourke D. Fatal hepatic failure following accidental tramadol overdose. Forensic Sci Int 2003; 134(2-3):232-3.
3. De Decker K, Cordonnier J, Jacobs W, Coucke V, Schepens P, Jorens PG. Fatal intoxication due to tramadol alone: case report and review of the literature. Forensic Sci Int 2008; 175(1):79-82.
4. Eggers KA, Power I. Tramadol. Br J Anaesth 1995; 74(3):247-9.
5. Gillen C, Haurand M, Kobelt DJ, Wnendt S. Affinity, potency and efficacy of tramadol

and its metabolites at the cloned human mu-opioid receptor. Naunyn Schmiedebergs Arch Pharmacol 2000; 362(2):116-21.
6. Shadnia S, Soltaninejad K, Heydari K, Sasanian G, Abdollahi M. Tramadol intoxication: a review of 114 cases. Hum Exp Toxicol 2008; 27(3):201-5.
7. Sansone RA, Sansone LA. Tramadol: seizures, serotonin syndrome, and coadministered antidepressants. Psychiatry (Edgmont) 2009; 6(4):17-21.
8. Musshoff F, Madea B. Fatality due to ingestion of tramadol alone. Forensic Sci Int 2001; 116(2-3):197-9.
9. Houmes RJ, Voets MA, Verkaaik A, Erdmann W, Lachmann B. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. Anesth Analg 1992; 74(4):510-4.
10. Zhang H and Zhimin Liu. The Investigation of Tramadol Dependence with No History of Substance Abuse: A Cross-Sectional Survey of Spontaneously Reported Cases in Guangzhou City, China. Bio Med Research International. 2013; 25:1-6.
11. Ahmadi H, Rezaie M, Hoseini J. Epidemiology Analysis of Poisonings with Tramadol. J Forensic Res. 2012; 3:151-54.
12. Hassanian HM, Hoorvash F, Saeedeh S, Hamid O. Tramadol-induced apnea. Emergency Medicine. 2013; 31(1): 26-31.
13. Fawzi MM. Medicolegal Aspects Concerning Tramadol Abuse. The New Middle East Youth Plague: An Egyptian Overview 2010. J Forensic Res 2011; 2: 1-3
14. Morteza Rahbar Taromsari1, Ali Reza Badsar1, Farzaneh Bahrami, Khadije Jahanseir, Morteza Fallah Karkan. Clinical and Laboratory Findings in Patients with Tramadol Intoxication Referred to Razi Hospital During 2005-06. Iranian Journal of Toxicology. 2012; 6. 605-9.
15. Petramfar P, BorhaniHaghighi A. Tramadol Induced Seizure: Report of 106 Patients. Iranian Red Crescent Medical Journal. 2010;12(1):49-51.
16. Spiller HA, Gorman SE, Villalobos D, Benson BE, Ruskosky DR, et al. Prospective multicenter evaluation of Tramadol exposure. J Toxicol Clin Toxicol. 1997; 35: 361–364.