

## AIM OF THE WORK

**This study was conducted to fulfill the following objectives:**

**General objective:**

Studied the epidemiologic and clinical pattern of tramadol intoxication in order to help in early diagnosis and management.

**Specific objectives:**

1. Studied the epidemiologic, clinical and laboratory patterns of tramadol overdose among users.
2. Determined 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 includes:**

1. All patients with tramadol overdosed who were recorded in medical records and files from the period of 1/1/2012 till 30/6/2012 (n = 63).
2. All patients with tramadol overdosed who were admitted during the period from 1/10/2012 till 31/3/2013 (n = 59).

### **Exclusion criteria**

Fully alert patient without signs and symptoms of over-dosage before admission after adequate remaining in emergency department (ED) managed as outpatient and not included in the study population.

## METHODS

### Study design:

Descriptive epidemiological two study designs was approached:

1. Retrospective study by record reviewing.
2. Follow up case series study.

### Research setting:

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

### Field work

The field work was carried out from November 2012 till April 2013.

### Data collection tools and sources:

Data were obtained from conscious patients if possible and from their relatives by using the following research tools.

1. A structured interview format was used to collect socio demographic data.
2. A clinical examination sheet was used to record clinical data.
3. A transfer sheet was used to collect laboratory data and patients' outcomes from medical records & files that were completed by hospital specialists or interns.

### The following data were collected for each patient:

#### ➤ Data in interview format:

- Personal history: sociodemographic 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.

Maximum recommended dosage for this medication is 400 mg per day, for adults over the age of 17. Toxic dose was 400 – 700 mg while fatal dose was 700 – 1000 mg.

#### ➤ Data in clinical examination sheet: Appendix 1

- General examination signs: consciousness level, vital signs.
- Systemic examination signs: neurological signs, cardiovascular signs, respiratory signs, gastrointestinal signs, genitourinary signs, skin signs.

#### ➤ Data transferred from medical records and patients' files included:

- Laboratory parameters if available: complete blood picture (CBC)<sup>(82)</sup>, random blood glucose, liver function, renal function<sup>(83)</sup>, electrocardiogram (ECG).
- Emergency management: decontamination, supportive treatment, narcain injection.
- Days of hospital stay.

- Outcome (prognosis): complete recovery and discharge, put under observation, ICU admission, death either directly or due to complications even if in the emergency room.

### **Data collection:**

- **Getting permission:** The permission of the head of Alexandria Poison center at the Main University Hospital was obtained.
- **A pilot study:** was conducted (on 15 patients) to test the validity of the study tools, identify any administrative obstacles and estimate the average time needed for data collection. Those excluded from the statistical analysis.

### **Feedbacks of the pilot study indicated that:**

1. The research tools could be easily and quickly completed.
2. The average time estimated to fill the formats was 35 minutes.
3. There was a good cooperation from the managers of the units, nurses and colleagues.

### **Field work**

All data tools needed were printed. The field work covered a time period starting from November 2012 till April 2013. The researcher worked according to a definite schedule (3 days/week, 2 hours/day). Interviewing process took 10 minutes per patient. Questions were clearly explained in a standard way to minimize error in interviewing. Clinical examination spent nearly 15 minutes per patient. Transferring data from records took around 10 minutes for each patient. All patients were cooperative thus making the response rate 100%.

### **Ethical considerations**

The Ethical Committee of the Faculty of Medicine has approved the conduction of the present study. A written consent was taken from patients/ relatives before beginning the process of data collection following a thorough explanation of the purpose and aims of the study. Assurance of confidentiality and anonymity was ensured. Data obtained names of patients and their responses remained undisclosed by the researcher. After data analysis and final report writing, data sheets were shredded and disposed of.

### **Data management**

Following data collection, raw data was coded and scored and a coding instruction manual was prepared. Data was fed to the computer and statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 18.0). Significance of the obtained results was judged at the 5% level of significance.<sup>(82)</sup>

### **Data processing**

Complete confidentiality was maintained while the data were being processed. This stage had two major objectives:

1. Clean data by performing a series of comprehensive checks, making corrections whenever possible. Different statistical procedures (frequencies, means, standard deviations, and median, and cross tabulations) were used to check the validity of data and spot any error.

2. Produce analytic results. This involved the recording of variables into forms required for analysis.

## Data analysis

The following statistical measures were used:

- 1- Descriptive Statistics such as frequency distribution, mean, median, and standard deviation to describe selected socio demographic and clinical profile of the studied patients.
- 2- Multivariate logistic regression analysis was conducted to determine the independent predictor variables of adverse outcome for the studied patients with tramadol over dosage. The regression models included 4 sets of predictors' namely socio demographic, lifestyle, poisoning circumstances and clinical data. Dichotomous socio demographic variables included in the final model were; age (years), gender, SES, and residence. Lifestyle variables were smoking, alcohol consumption, and illicit drug use. Poisoning circumstances included past history of psychiatric troubles, previous suicidal attempts, reason for tramadol use, poisonous amount, mode of poisoning, pre-hospital care. Clinical data were disturbed conscious, receiving recommended treatment, days of hospital stay. This model explains 53% of variables predicting adverse outcome of tramadol over-dosage ( $R^2=0.525$ ) with significant overall model  $\chi^2_{15} = 43.020$ ,  $p < 0.001$ .

## Time table

### A. Preparatory phase:

#### i. Reviewing the literature:

The past and current literature related to tramadol over-dosage were reviewed to guide in the preparation of the study proposal and study tools from August 2011 to the end of September 2011.

#### ii. Developing instruments:

Research tools were developed in October 2012 to be tested in the pilot study.

#### iii. Patient recruitment & record reviewing:

The number of tramadol over-dosage patients in PC was obtained from the Hospital medical records of 2012 during November 2012.

#### iv. Obtaining approval:

Approval of the study was obtained in September 2012.

### Pilot survey:

The pilot study was conducted on December 2012.

### B. Data collection phase:

Started from 1st October 2012 and lasted to 31st March 2013.

### C. Analysis and tabulation:

The analysis started on September 2013 and lasted till February 2014.

### D. Final report:

Final report writing started on March 2014 and continued until approved by supervisors to be submitted for evaluation and determining the date for discussion.

**Time table of the study**

Year 1 (2011)												
Activity	Jan.	Feb.	Mar.	Apr	May.	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Preparatory phase												
-literature review												
Year 2 (2012)												
-getting approval												
-developing data collection instruments												
-sampling												
-Pilot study												
Data collection phase												
Year 3 (2013)												
Data collection phase												
Analysis and tabulation phase												
Year 4 (2014)												
Analysis and tabulation phase												
Report writing												

## RESULTS

The present 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 includes:

1. Patients with tramadol overdoses who were admitted from 1/1/2012 to 30/6/2012. Sixty three patients (A retrospective study).
2. Patients with tramadol overdoses who were admitted from 1/10/2012 to 31/3/2013. fifty nine patients (A prospective study).

### The results were presented in the following sections:

1. Section (I):General characteristic:
  - Socio demographic data.
  - Life style habits.
  - Poisoning conditions.
  - General signs.
  - Systemic signs: Neurological signs, Cardiovascular signs, Respiratory signs, Gastrointestinal signs, Skin signs and Genitourinary signs.
  - Investigations.
  - Emergency management.
2. Section (II):Patients' outcomes:
  - Predictors of adverse outcomes of tramadol overdose.

### Section (I):

#### Socio demographic data:

As regard sociodemographic characteristics of the studied patients (**Table 2**), shows that age of patients included ranged between 18.0 and 40.0 years with the mean of  $29.9 \pm 6.9$  years. (**Graph 1**) illustrates age distribution among the studied patients. More than half (52.5%) were in the age group 30-40 years. More than a third (34.4%) aged between 20 and <30 years. The least proportion (13.1%) were <20 years old. Of all patients, males constituted 71.3% (n=87) while females represented 28.7% (n=35) (**Graph 2**).

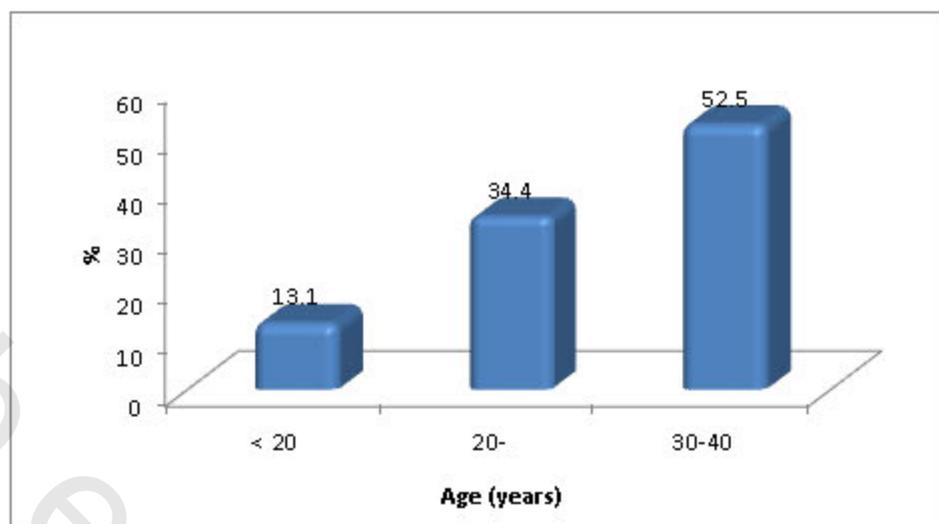
More than half of the studied patients (61.5%) were middle socioeconomic status (SES) and more than a third (35.2%) had poor SES. Only 3.3% were of high SES (**Graph 3**).

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

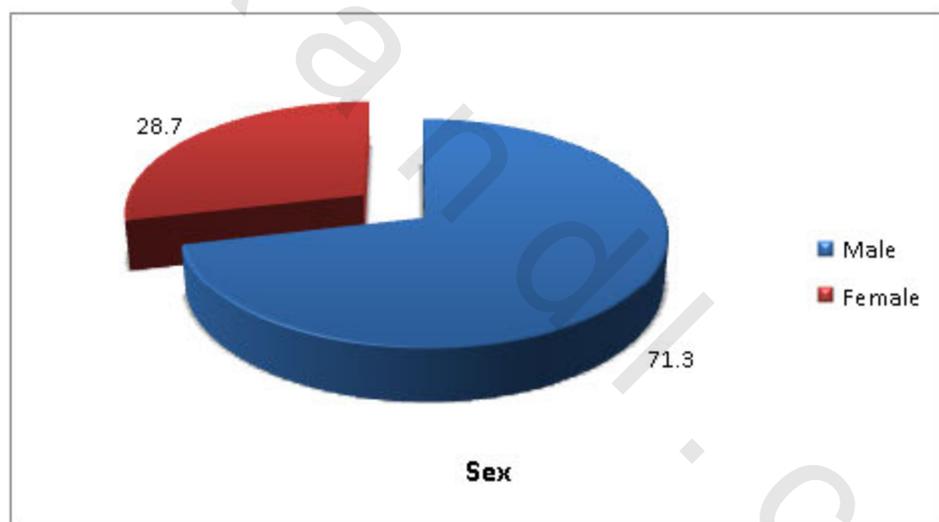
**Table (2):** Socio demographic characteristics of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital.

<b>Socio demographic data</b>	<b>No. (n = 122)</b>	<b>%</b>
<b>Age (years)</b>		
< 20	16	13.1
20-	42	34.4
30-40	64	52.5
<b>Minimum- Maximum</b>	18.0 – 40.0	
<b>Mean ± SD</b>	29.9 ± 6.9	
<b>Sex</b>		
Male	87	71.3
Female	35	28.7
<b>Socioeconomic status</b>		
Poor	43	35.2
Middle	75	61.5
High	4	3.3
<b>Residence</b>		
Urban	99	81.1
Rural	23	18.9

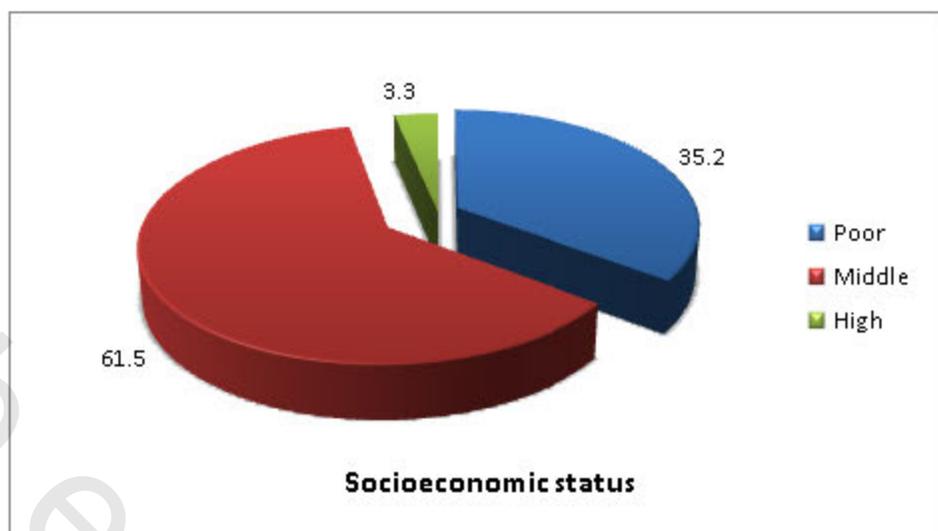
Socioeconomic (SE) status was assessed by development of SE index that is based on a composite measure of patient's education, occupation, residence and average monthly income



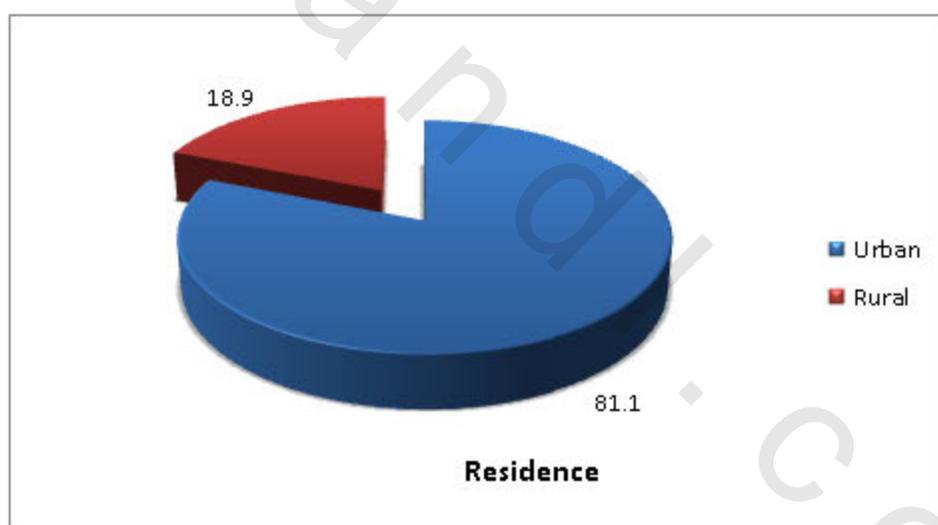
**Graph (1):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital by age group



**Graph (2):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to sex



**Graph (3):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to socioeconomic status



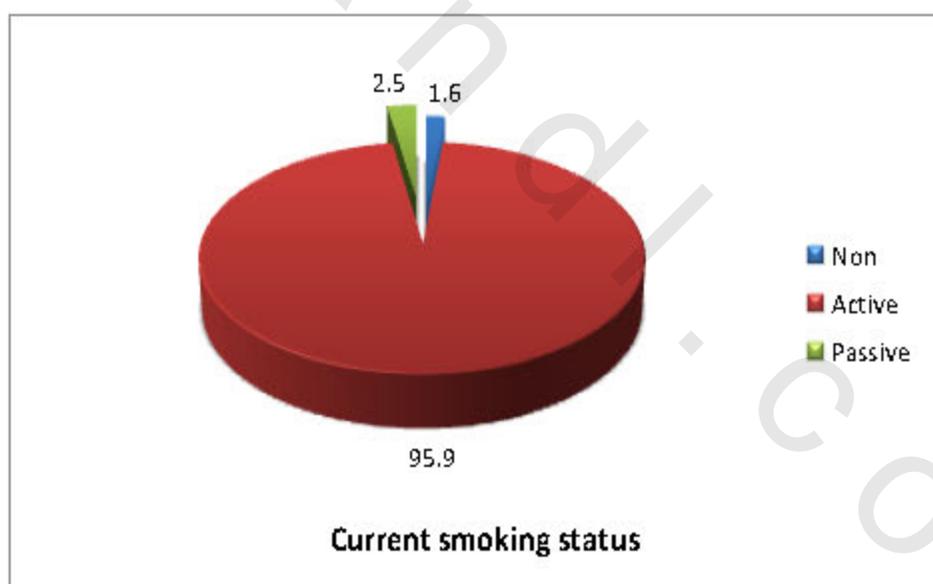
**Graph (4):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to residence

**Life style habits: (Table 3)**

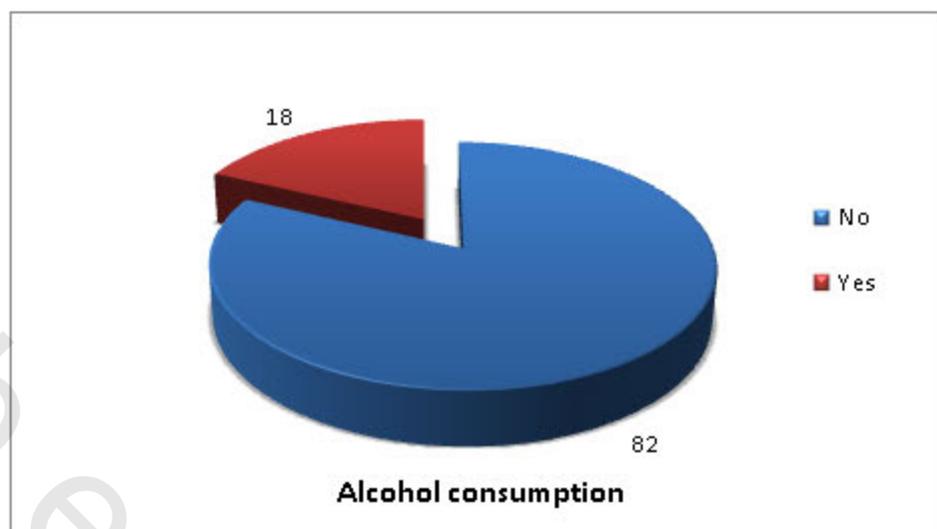
(Graph 5) illustrates that the majority of the studied cases (95.9%) were active smokers. Only 2.5% were passive smokers. A minority (1.6%) were non-smoker. Most of the studied patients (82.0%) were not alcoholic and 18.0% consumed alcohol (Graph 6). More three quarters of the studied individuals (76.2%) did not use illicit drug. However, more than a fifth (23.8%) were drug abusers (Graph 7).

**Table (3):** Lifestyle habits of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital

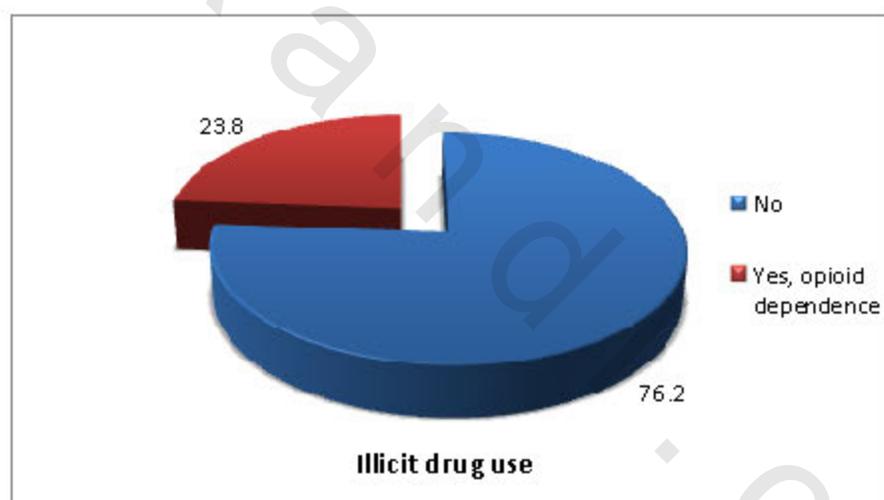
Life style habits	No. (n = 122)	%
<b>Current smoking status</b>		
Non	2	1.6
Active	117	95.9
Passive	3	2.5
<b>Alcohol consumption</b>		
No	100	82.0
Yes	22	18.0
<b>Illicit drug use</b>		
No	93	76.2
Yes, opioid dependence	29	23.8



**Graph (5):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to current smoking status



**Graph(6):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to alcohol consumption



**Graph (7):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to illicit drug use

### Poisoning conditions:(Table 4)

More than two-thirds of the studied patients had psychiatric troubles mainly depression (68.9%) as reported (**Graph 8**). Vast majority of the studied patients (94.3%) did not have any previous suicidal attempts (**Graph 9**). Self medication was reported by most of the studied patients (97.5%) while only three individuals (2.5%) were using prescribed medications(**Graph 10**).

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 (**Graph 11**).

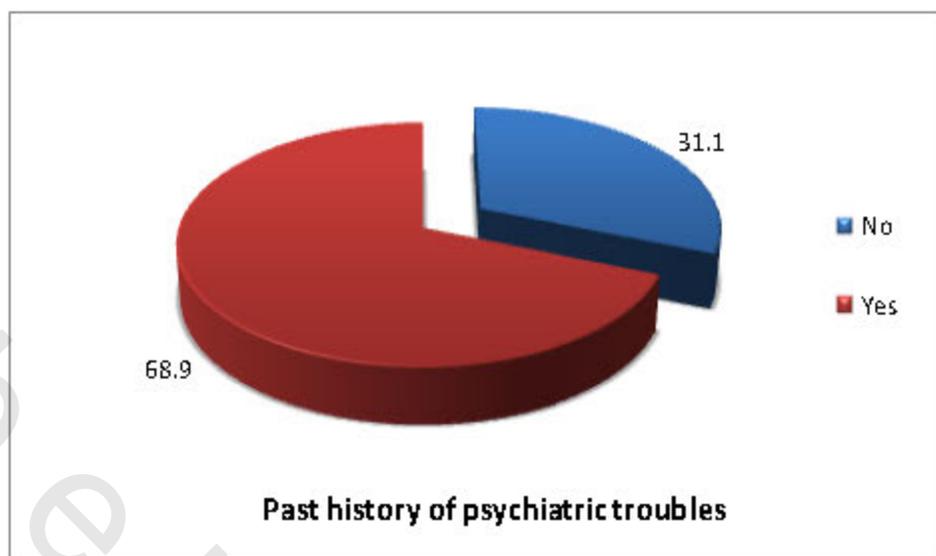
Accidental poisoning was reported by most of the studied individuals (94.3%), while suicidal poisoning was mentioned by 7 cases (5.7%) (**Graph12**). Ingestion was reported as the only route of poisoning in all of the studied individuals. As regard prehospital management, the majority of patients included in the study (82%) did not receive any prehospital management. Only 18.0% received such care (**Graph13**).

**Table (4):** Poisoning circumstances of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital

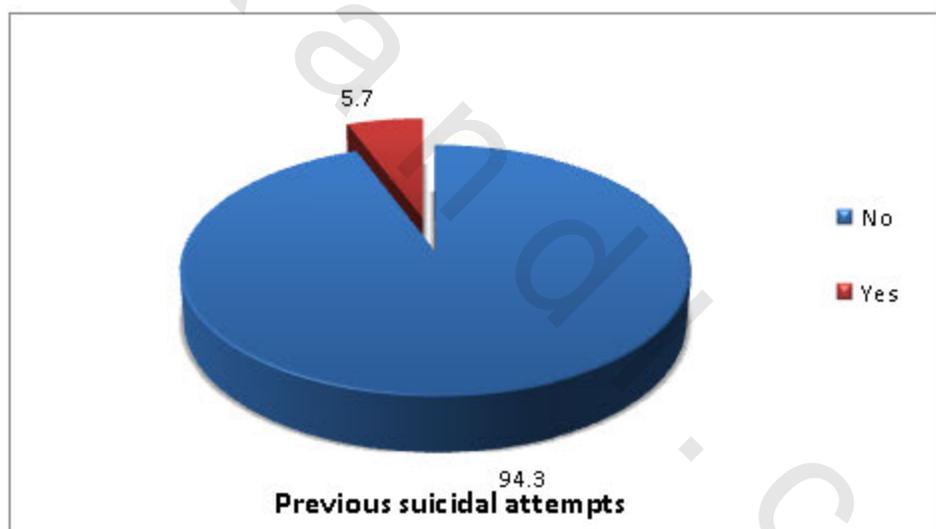
Poisoning circumstances	No. (n = 122)	%
<b>Past history of psychiatric troubles</b>		
No	38	31.1
Yes	84	68.9
<b>Previous suicidal attempts</b>		
No	115	94.3
Yes	7	5.7
<b>Reason for using tramadol</b>		
Intentional (or self medicated)	119	97.5
Therapeutic	3	2.5
<b>Poisonous amount #</b>		
Non- toxic	78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

-Pre-hospital care included supportive measures such as oxygenation and intravenous fluids.

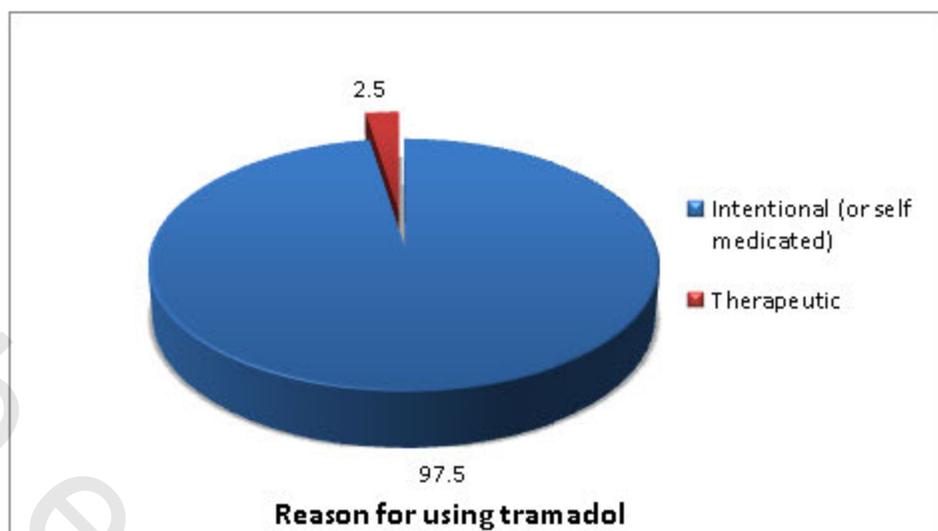
# Maximum recommended dosage for this medication is <400 mg per day, for adults over the age of 17. Toxic dose was defined as 400-700 mg while fatal dose was 700-1000 mg



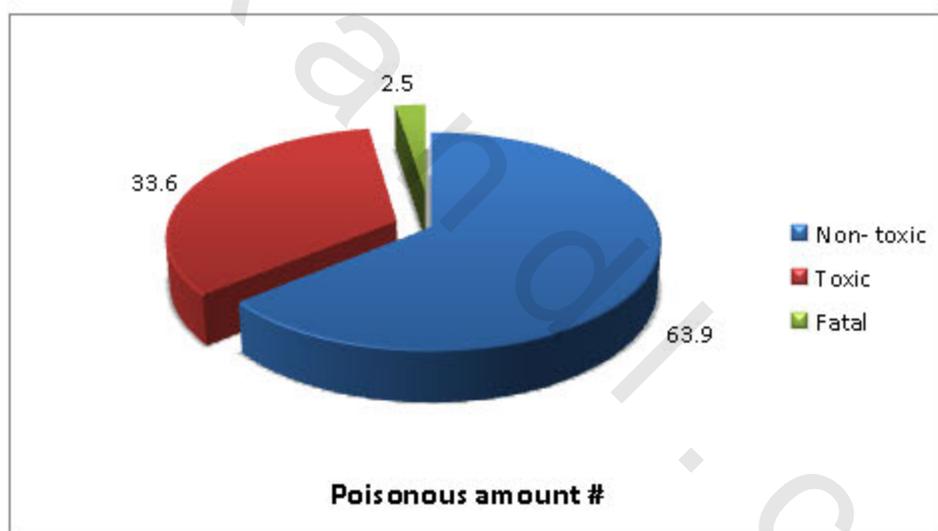
**Graph (8):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to psychiatric troubles



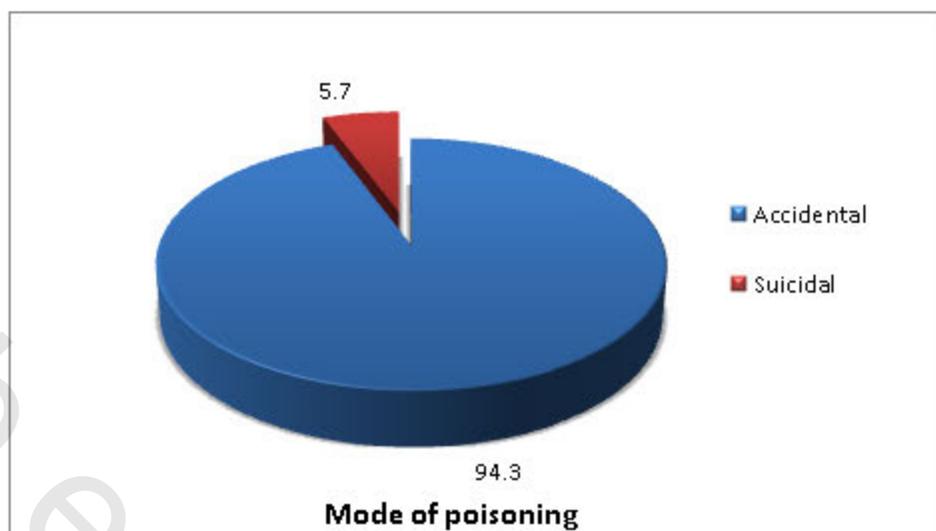
**Graph (9):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to previous suicidal attempts



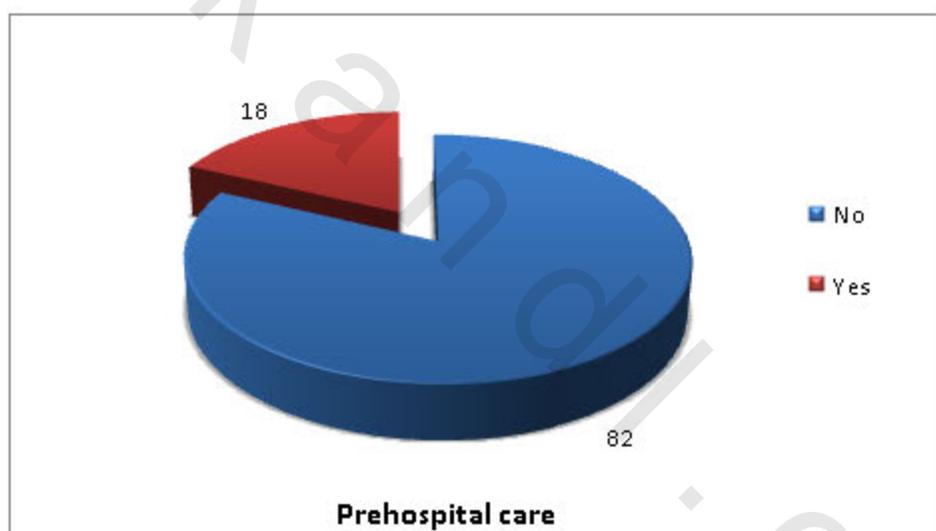
**Graph (10):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to reason for using tramadol



**Graph (11):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to poisonous amount



**Graph (12):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to mode of poisoning



**Graph (13):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to prehospital management

## Examinations

### General signs:

(Table 5) shows conscious status and vital signs of tramadol overdosed patients.

### Glasgow coma score:

Glasgow coma score ranged between 9.0-15.0 with the mean of  $12.9 \pm 1.2$ .

### Vital signs:

Pulse rate ranged between 56 -149 beat/min with the mean of  $102.8 \pm 20.3$  beat/min. Systolic blood pressure ranged between 110.0-140.0 mmHg with the mean of  $120.1 \pm 9.3$  mmHg. Diastolic blood pressure ranged between 60.0-90.0mmHg with the mean of  $76.9 \pm 8.2$  mmHg. Temperature ranged between 36.6-37.8 degrees with the mean of  $37.2 \pm 0.4$  degrees. The mean respiratory rate of the studied patients was  $21.5 \pm 3.5$  breath/min indicating tachypnea (a minimum of 16.0 and maximum of 28 breath/min).

Table (5): Vital signs of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital

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

	1	2	3	4	5	6
<b>Eye</b>	Does not open eyes	Opens eyes in response to <u>painful stimuli</u>	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
<b>Verbal</b>	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
<b>Motor</b>	Makes no movement	Extension to painful stimuli ( <u>decerebrate response</u> )	Abnormal flexion to painful stimuli ( <u>decorticate response</u> )	Flexion / Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

# The scale is composed of three tests: eye, verbal and motor responses. The three values separately as well as their sum are considered. The lowest possible GCS (the sum) is 3 (deep coma or death), while the highest is 15 (fully awake person).

### **Systemic signs**

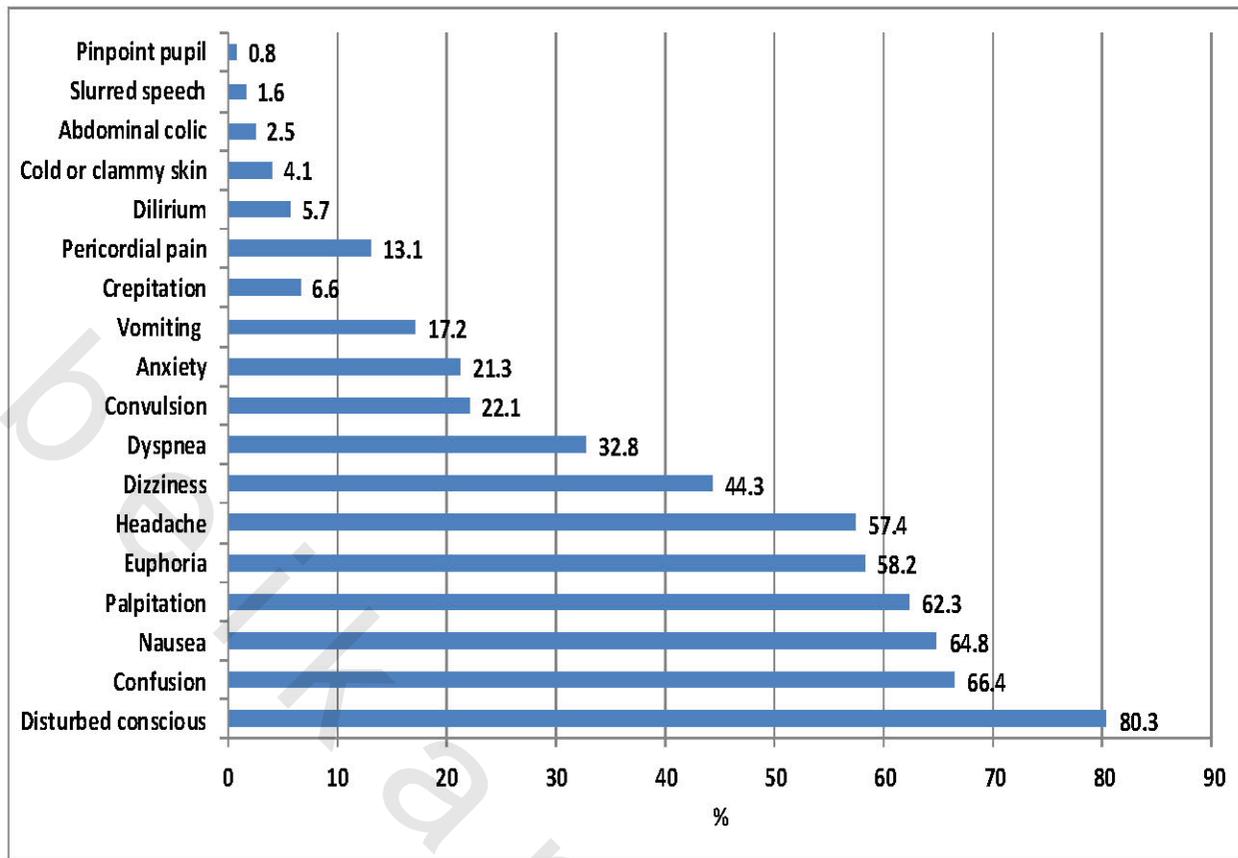
(Tables 6-a,6-b) and (Graph 14) show common clinical signs and symptoms of the studied patients with tramadol overdose.

### **Neurological signs: (Table 6-a)**

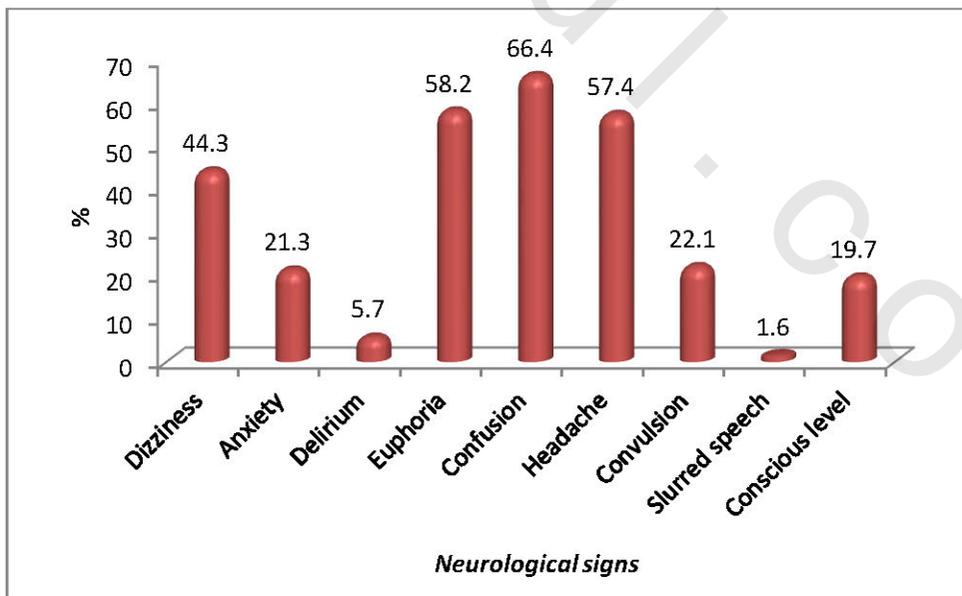
As regard conscious level, most of the studied individuals (80.3%) had disturbed consciousness but not comatose while, 19.7% of patients were fully conscious. Normal pupil size was seen in the majority of patients included in the study (91.8%), whereas constricted pupil was detected in 9 cases (7.4%) and pinpoint pupil was observed in only one patient (0.8%). Dizziness was reported by 54 patients (44.3%) while 55.7% of patients did not suffer from dizziness. More than a fifth of patients (21.3%) had anxiety. Delirium was reported as complain in only 7 cases (5.7%). More than half of the studied individuals (58.2%) reported euphoria. Confusion was detected in 66.4% of the study group. Seventy patients (57.4%) suffered from headache. More than a fifth of patients (22.1%) had convulsion. Slurred speech was detected in only 2 patients of the studied group (1.6%). (Graph 15)

Table (6-a): Clinical presentation on admission of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital

Clinical presentation	No. (n = 122)	%
<b>Neurological signs</b>		
<b>Conscious level</b>		
Fully- alert	24	19.7
Disturbed-conscious	98	80.3
<b>Pupil</b>		
Normal	112	91.8
Constricted	9	7.4
Pinpoint	1	0.8
<b>Dizziness</b>		
No	68	55.7
Yes	54	44.3
<b>Anxiety</b>		
No	96	78.7
Yes	26	21.3
<b>Delirium</b>		
No	115	94.3
Yes	7	5.7
<b>Euphoria</b>		
No	51	41.8
Yes	71	58.2
<b>Confusion</b>		
No	41	33.6
Yes	81	66.4
<b>Headache</b>		
No	52	42.6
Yes	70	57.4
<b>Convulsion</b>		
No	95	77.9
Yes	27	22.1
<b>Slurred speech</b>		
No	120	98.4
Yes	2	1.6



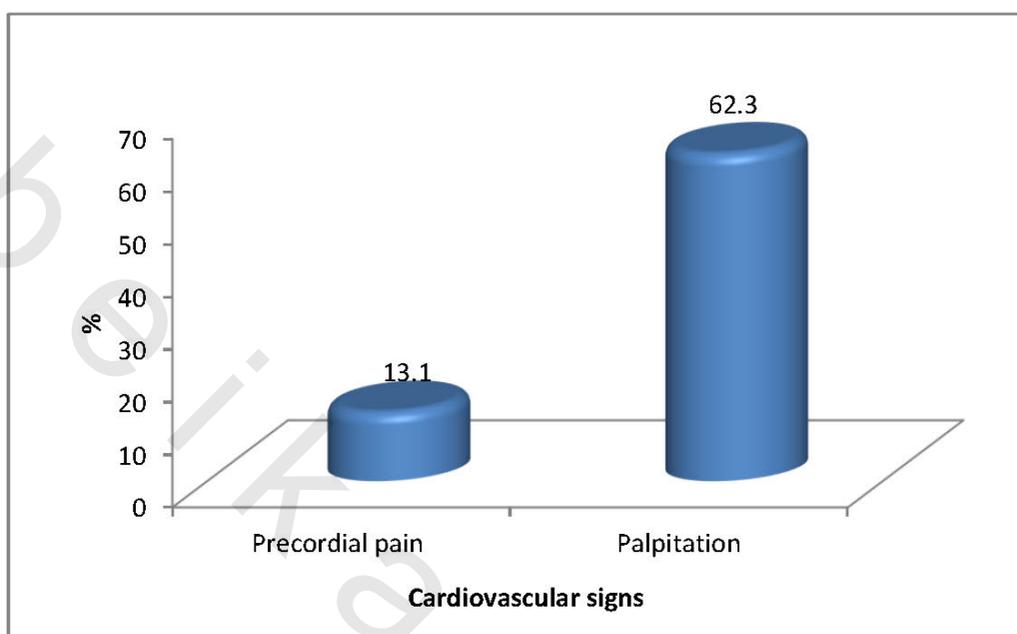
**Graph (14):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to common clinical presentation.



**Graph (15):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to neurological signs.

**Cardiovascular signs: Table (6-b)**

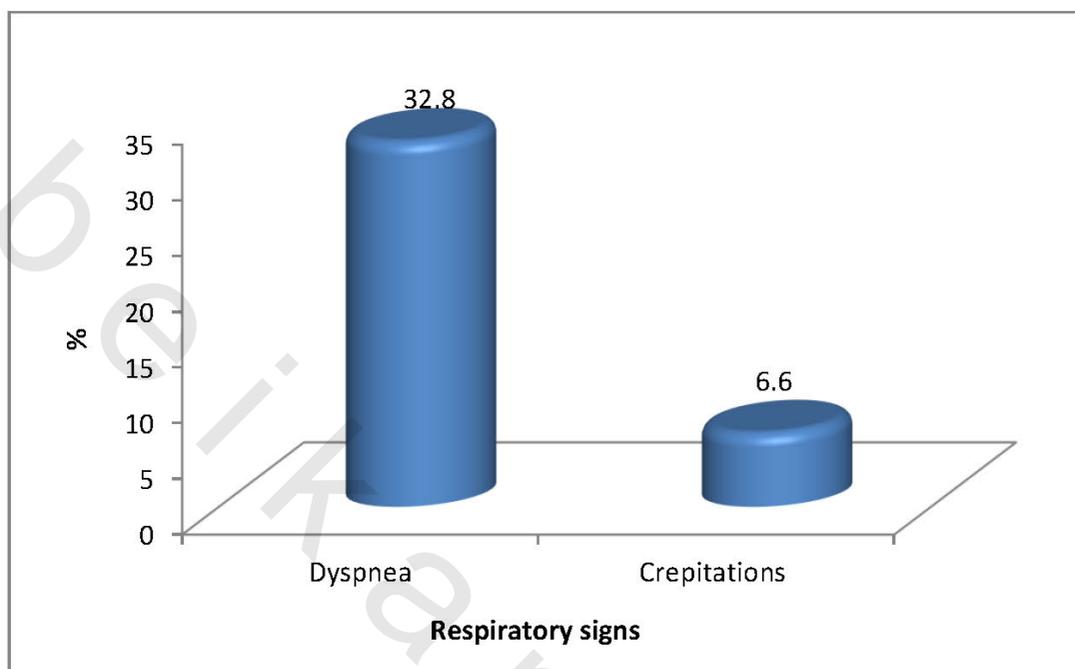
Precordial pain was reported by more than a tenth of cases 13.1%. less than two-thirds patients (62.3%) complained of palpitation. None of the patients had syncope or cardiac arrest (**Graph 16**).



**Graph (16):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to cardiovascular signs

**Respiratory signs: Table (6-b)**

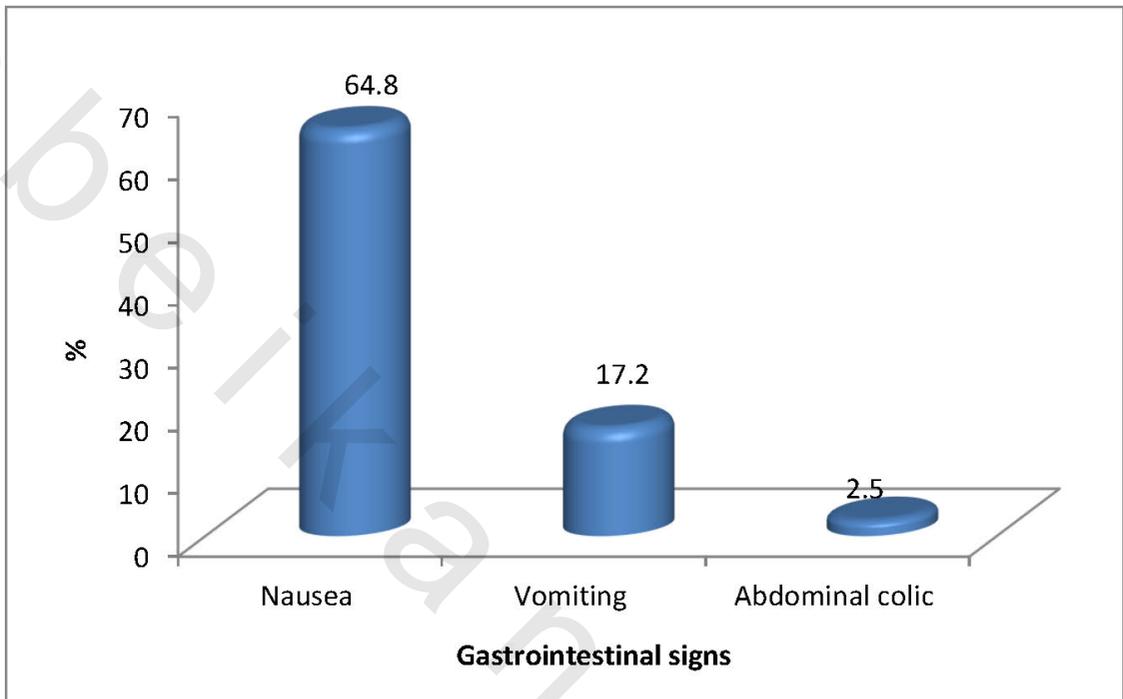
Dyspnea was detected in 40 patients (32.8%). None of the patients had cough. Crepitations were found in only 8 (6.6%) of the studied patients. There were no rhonchi or stridor detected in any patient of the studied group (**Graph 17**).



**Graph (17):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to some respiratory signs

**Gastrointestinal signs: Table (6-b)**

None of the studied patients had anorexia. Nausea was reported in nearly two-thirds patients of the studied group (64.8%). Only 21 of the patients, suffered from vomiting (17.2%). Abdominal colic was reported as a complain in only three patients (2.5%). None of the studied individuals had either diarrhea or constipation (**Graph18**).



**Graph (18):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to some gastrointestinal signs

**Skin signs: Table (6-b)**

Hypothermia was detected in only 4.1% of the studied patients (n=5). There were no other skin signs such as cyanosis, redness, hotness, rash or diaphoretic skin detected.

**Genitourinary signs: Table (6-b)**

None of the following genitourinary manifestations; dysuria, oliguria, anuria, renal colic, or haematuria were detected in the studied patients.

**Table (6-b):** Clinical presentation of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital(continue)

Clinical presentation	No.	%
<i>Cardiovascular signs</i>		
<b>Precordial pain</b>		
No	106	86.9
Yes	16	13.1
<b>Palpitation</b>		
No	46	37.7
Yes	76	62.3
<i>Respiratory signs</i>		
<b>Dyspnea</b>		
No	82	67.2
Yes	40	32.8
<b>Crepitation</b>		
No	114	93.4
Yes	8	6.6
<i>Gastrointestinal signs</i>		
<b>Nausea</b>		
No	43	35.2
Yes	79	64.8
<b>Vomiting</b>		
No	101	82.8
Yes	21	17.2
<b>Abdominal colic</b>		
No	119	97.5
Yes	3	2.5
<i>Skin signs</i>		
<b>Cold or clammy skin</b>		
No	117	95.9
Yes	5	4.1

**Investigations: Table (7)**

**Renal functions tests:**

Urea level in blood ranged between 4.3-8.5mg/dLwith a mean of 6.4±1.3 mg/dL.Creatininelevel in blood ranged between 0.8-1.3 mg/dLwith a mean of 1.082±0.2 mg/dL.

**Random blood glucose:**

Random blood glucose level ranged between 80.0-120.0mg/dLwith the mean of 101.9±11.9 mg/dL.

**Complete blood picture:**

Haemoglobin level ranged between 13.5-15.5 g/dL with a mean of 14.6±0.6 g/dL. Haematocrit level ranged between 40.0-45.0 % with the mean of 42.4±1.7 %. Red Blood Cells ranged between 4.5-5.7×10<sup>6</sup>/μLwith the mean of 5.1±0.4×10<sup>6</sup>/μL.Platelets count ranged between 151.0-446.0×1000 mm<sup>3</sup>with the mean of 309.9±85.8×1000 mm<sup>3</sup>. White Blood Cells ranged between 4.0-10.4×1000 mm<sup>3</sup> with the mean of 7.3±1.9×1000 mm<sup>3</sup>.regarding differential leucocytesneutrophils ranged between 40.0-60.0%with the mean of 50.5±5.9 %. Lymphocytes ranged between 20.0-40.0%with the mean of 30.8±6.2 %. Eosinophils ranged between 1.0-4.0%with the mean of 2.4±1.1 %. Basophils ranged between 0.5-1.0 % with the mean of 0.7±0.2 %.

**Liver functions tests:**

ALT ranged between 17.0-35.0U/L with the mean of 25.8±5.1 U/L. AST ranged between 19.0-35.0 U/L with the mean of 27.3±4.5 U/L.

**Table (7):** Laboratory findings of tramadol overdosed patients (n=122) admitted to Alexandria Main University Hospital

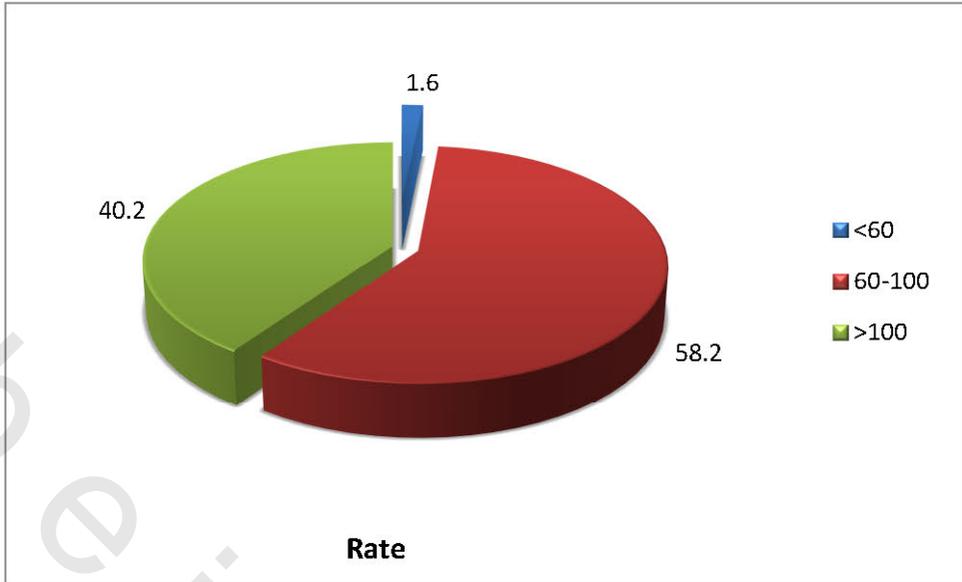
Lab. finding	Reference value	Minimum	Maximum	Mean± Std. Deviation
Urea (mmol/L)	2.9-7.1	4.3	8.5	6.4±1.3
Creatinine (mg/dL)	0.7-1.3	0.8	1.3	1.1±0.2
Random blood glucose (mg/dL)	70-110	80.0	120.0	101.9±11.9
Hg (g/dL)	Males:13-18 Females:12-16	13.5	15.5	14.6±0.6
Ht (%)	Males:41-51 Females:36-47	40.0	45.0	42.4±1.7
RBC (×10 <sup>6</sup> /μL)	Males:4.7-6.1 Females:4.2-5.4	4.5	5.7	5.1±0.4
Platelets (×1000 mm <sup>3</sup> )	150-400	151.0	446.0	309.9±85.8
WBC (×1000 mm <sup>3</sup> )	3.9-10.7	4.0	10.4	7.3±1.9
Neutrophils (%)	40-60	40.0	60.0	50.5±5.9
Lymphocytes (%)	20-40	20.0	40.0	30.8±6.2
Eosinophils (%)	1-4	1.0	4.0	2.4±1.1
Basophils (%)	0.5-1.0	0.5	1.0	0.7±0.2
ALT (U/L)	0-35	17.0	35.0	25.8±5.1
AST (U/L)	0-35	19.0	35.0	27.3±4.5

**Electrocardiogram (ECG):**(Table 8) reveals ECG findings of tramadol overdosed patients.

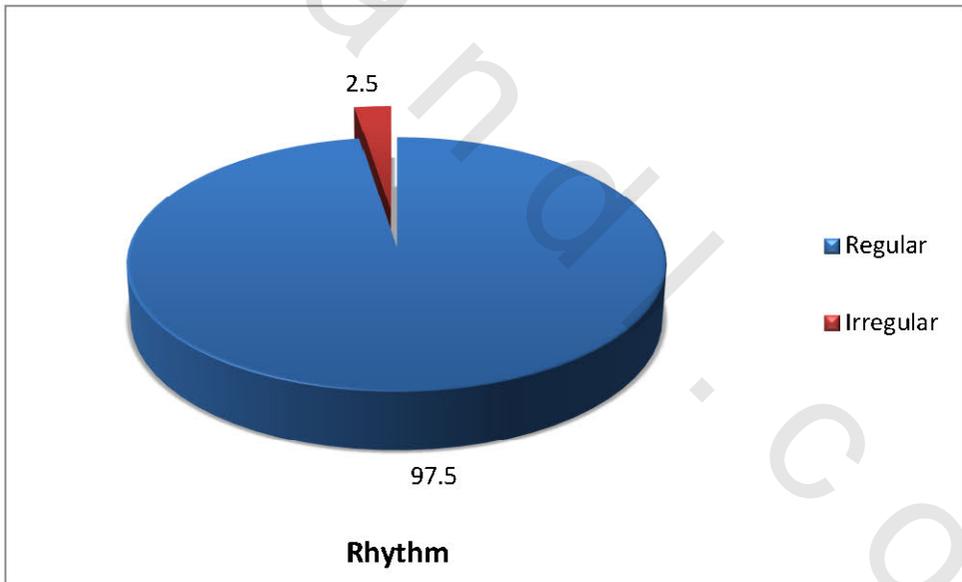
The heart rate was ranged between 60 and 100 beat/min in 58 % of cases (n=71), whereas 40.2 % 49 had the heart rate over 100. Only 2 patients (1.6%) had a rate below 60 beat/min(**Graph19**). Regular rhythm were found in most of the studied patients 119 (97.5%). Only 3 patients (2.5%) had irregular rhythm(**Graph20**). 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%)(**Graph21**). 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%). Normal ST segment was detected in the majority of the studied group (98.4%), while depressed ST segment was detected in only 2 cases (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 (8):** ECG findings of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital

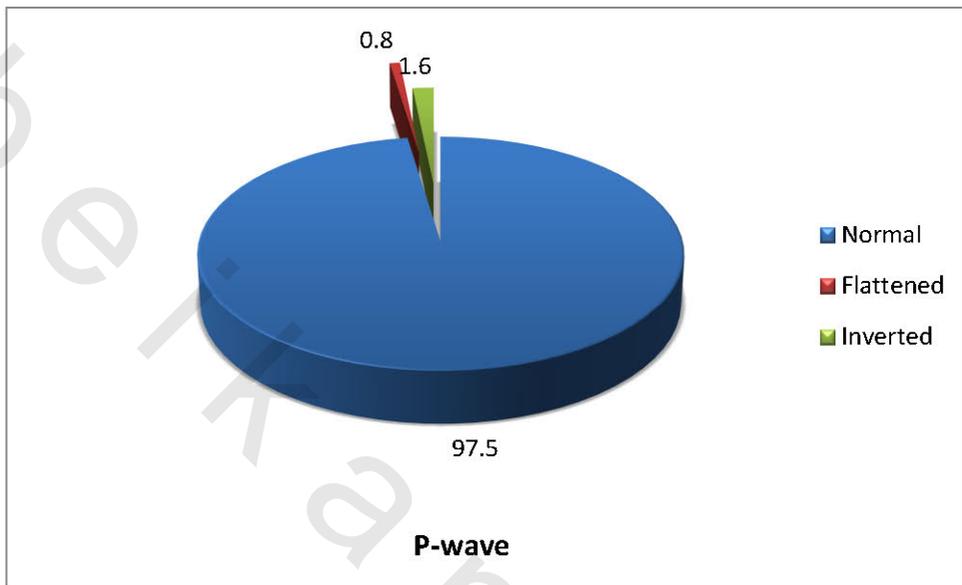
<b>ECG findings</b>	<b>No. (n = 122)</b>	<b>%</b>
<b>Heart rate</b>		
<60	2	1.6
60-100	71	58.2
>100	49	40.2
<b>Rhythm</b>		
Regular	119	97.5
Irregular	3	2.5
<b>P-wave</b>		
Normal	119	97.5
Flattened	1	0.8
Inverted	2	1.6
<b>QRS-wave</b>		
Normal	80	65.6
Prolonged	15	12.3
Shortened	27	22.1
<b>T-wave</b>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



**Graph(19):** Percent distribution of tramadol overdosed patients (n=122) admitted to Alexandria Main University Hospital according to heart rate



**Graph(20):** Percent distribution of tramadol overdosed patients (n=122) admitted to Alexandria Main University Hospital according to heart rhythm



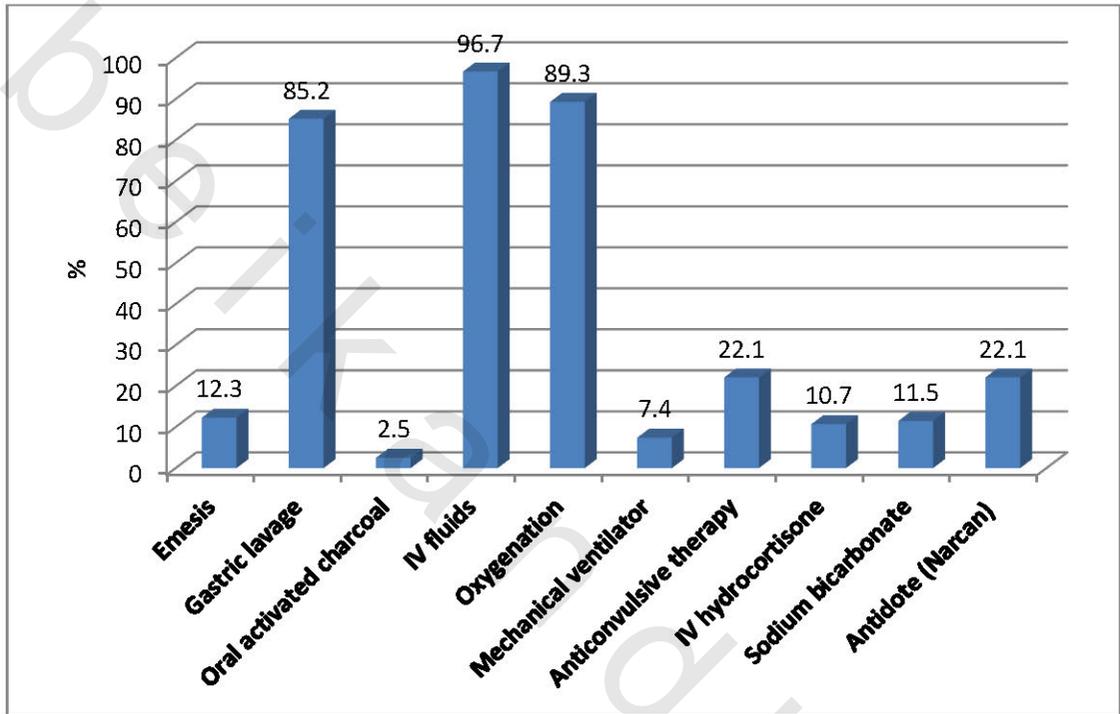
**Graph (21):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to p-wave.

**Emergency management:** (Table9) reveals the emergency treatment as recommended for the studied patients with tramadol overdose.

In most of the studied patients (85.2%), gastric lavage was the method used for decontamination. In more than a tenth (12.3%), emesis was used and in only 2.5% of patients, activated charcoal was used. Intravenous (IV) fluids were administered for most of the studied individuals 118 (96.7%). Oxygenation was done in 109 of the studied group (89.3%). Mechanical ventilator was required in only 9 cases (7.4%) of the studied group. Anticonvulsive therapy was given to 27 (22.1%) of the studied patients. IV hydrocortisone was only used for 13 (10.7%) patients. Sodium bicarbonate was included in the treatment of 14 (11.5%) patients. Antidote (narcane) usage was recommended in only 27 patients (22.1%) of the studied group (Graph22).

**Table (9):** Treatment of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital

Treatment	No. (n = 122)	%
<b>Decontamination</b>		
Emesis	15	12.3
Gastric lavage	104	85.2
Oral activated charcoal	3	2.5
<b>IV fluids</b>		
No	4	3.3
Yes	118	96.7
<b>Oxygenation</b>		
No	13	10.7
Yes	109	89.3
<b>Mechanical ventilator</b>		
No	113	92.6
Yes	9	7.4
<b>Anticonvulsive therapy</b>		
No	95	77.9
Yes	27	22.1
<b>IV hydrocortisone</b>		
No	109	89.3
Yes	13	10.7
<b>Sodium bicarbonate</b>		
No	108	88.5
Yes	14	11.5
<b>Antidote (narcan) usage</b>		
No	95	77.9
Yes	27	22.1



**Graph (22):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to important recommended lines of treatment.

**Duration of hospitalization: Table (10)**

Most of the studied samples 88 (72.1%) required hospitalization for just one day. However, more than a fifth (22.1%) stayed for three days. Only 7 patients (5.7%) stayed in hospital for two days.

**2. Section (II):**

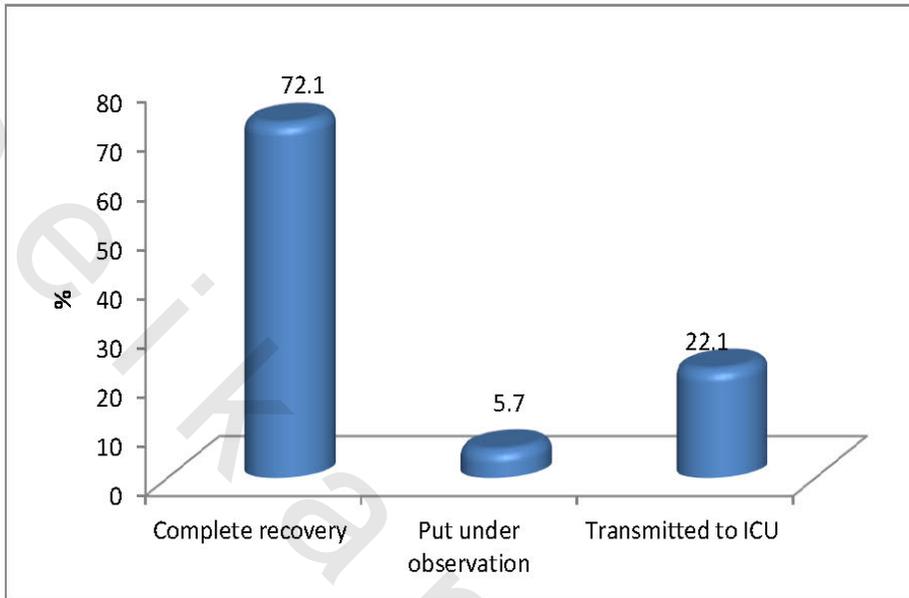
**Patients' outcome:**

In (Table 10), complete recovery and discharge was the fate for most of the studied samples 88 (72.1%). More than a fifth of patients (22.1%) required ICU admission because of slow, shallow breathing, apnea, coma or need for mechanical ventilation or intubation and 7 patients (5.7%) needed to be put under observation (Graph23). Thus adverse outcome represented (27.8%) of the studied patients.

**Table (10):** Outcome of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital

	No. (n = 122)	%
<b>Days of hospital stay</b>		
1.00	88	72.1
2.00	7	5.7
3.00	27	22.1
<i>Minimum – Maximum</i>	1 – 3	
<i>Mean ± SD</i>	1.9 ± 0.8	
<b>Outcome</b>		
Complete recovery & discharge	88	72.1
Put patient under observation	7	5.7
Transmitted to ICU #	27	22.1

# Because of slow, shallow breathing, apnea, or need for mechanical ventilation or intubation.



**Graph (23):** Percent distribution of tramadol overdosed patients (n = 122) admitted to Alexandria Main University Hospital according to the outcome

**Table (11):** 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
<b>Block 1: Sociodemographic</b>			
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
<b>Block 2: Lifestyle habits</b>			
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*
<b>Block 3: Poisoning circumstances</b>			
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
<b>Block 4: Clinical characteristics</b>			
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  $R^2 = 0.525$

OR = Adjusted Odds Ratio, CI = Confidence Interval

Dependent variable = adverse outcome (put under observation & transmitted to ICU), n = 34

\* Significant at 0.05 level.

### Predictors of adverse outcome of tramadol overdose:

(Table 11) shows multivariate logistic regression analysis of predictor variables contributing to adverse outcome of tramadol overdose patients.

- **Sociodemographic factors:**
  - Age of the studied patients significantly affects the adverse outcome (P=0.04). Older aged patients have the odds 1.04 of having the adverse outcome (OR=1.04, 95% CI=1.03-1.16).
  - However, gender, socioeconomic status and residence had no effect on the adverse outcome (P>0.05).
- **Life style habits:**
  - Smoking is significantly associated with the adverse outcome (P=0.02). Smokers had the odds of 1.69 time to have the adverse outcome (OR=1.69, 95% CI=1.32-2.16).
  - Illicit drug use is a significant factor contributing to the adverse outcome (P=0.02). Drug users is 1.25 likely to have adverse outcome (OR=1.25, 95% CI=1.18-1.38).
  - However, alcohol consumption had no effect on the adverse outcome (P=0.35).

- **Poisoning circumstances:**

- Self medication by tramadol was significantly associated with adverse outcome by 1.62 times (OR=1.62, 95% CI=1.42-2.64), P=0.03.
- Toxic or fatal doses of tramadol was a significant factor contributing to adverse outcome (P=0.01) intake of toxic or fatal doses is 1.73 likely to have adverse outcome (OR=1.73, 95% CI=1.52-3.52).
- However, past history of psychiatric troubles, previous suicidal attempts, mode of poisoning, or prehospital care had no effect on the adverse outcome (P>0.05).

- **Clinical characteristics:**

- Disturbed conscious was significant predictor contributing to the adverse outcome (P=0.04). Patients with disturbed conscious are 1.53 odds of having adverse outcome (OR=1.53, 95% CI=1.04-2.56).
- However, receiving the recommended treatment and days of hospital stay had no effect on the adverse outcome of tramadol overdose (P>0.05).