Assessment of Cases of Acute Tramadol Toxicity as Regards Clinical, Laboratory and Management Procedures in Some University Hospitals in Cairo

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ABSTRACT

Tramadol, a widely used opioid in recent years, is a centrally acting analgesic drug that has been used clinically for the last two decades to treat pain in humans. Tramadol also has antitussive activity. Tramadol is a centrally acting analgesic which is extensively used in the management of moderate to severe pain. It slightly affects opioid receptors and inhibits the reuptake of norepinephrine and serotonin in the CNS**.**

The aim of this study was to evaluate the clinical manifestations, the laboratory findings, the different lines of treatment and the outcome of cases presented with acute toxicity by tramadol overdoses. This study was carried out at Al-Azhar University Emergency Hospitals in Cairo (El-Hussein And Bab El-Shaaria University Hospitals) and Ain Shams University Hospitals on one hundred subjects in the period from July 2016 to February 2018. Toxicological screening was done for every patient by rapid lateral flow chromatographic immunoassay for detection of tramadol and its principal metabolites in human urine by special kits at a cut off level of 1000 ng/ml. In this study, 95% of studied cases fully recovered and 5% died.

Keywords*:* Tramadol; substance of abuse; urine screening.

INTRODUCTION

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic used in the treatment of moderate to severe pain. It has a low affinity to opioid receptors and inhibits the reuptake of norepinephrine and serotonin. Its analgesic effect is partially blocked by Naloxone [(1)]**.**

It possesses weak agonist actions at the microopoid receptor, and inhibits the reuptake of norepinephrine [(2)].

Tramadol, a widely used opioid is a centrally acting analgesic drug that has been used clinically for the last two decades to treat pain in humans. Tramadol also has antitussive activity [(3)]**.**

Tramadol use is largely considered safe by physicians. The most common reported side effects are dizziness, nausea, constipation and headache. However, Tramadol toxicity may be underestimated; several deaths have been reported when Tramadol was ingested alone in overdose [(4)]**.**

The most common symptoms of acute tramadol overdose are central nervous system (CNS) depression, nausea, vomiting, tachycardia and seizures. Higher doses can be associated with classic opioid toxicity features of coma, respiratory depression and cardiovascular collapse [(5)]**.**

According to the data of the International Association of Forensic Toxicologists, therapeutic blood levels in adults range from 0.1–0.8 mg/L, toxic level was between 1–2 mg/L and lethal concentration was higher than 2 mg/L [(5)]**.**

Toxicology databases state that the treatment should still be naloxone to antagonize the opioid effects of tramadol [(6)]**.**

The aim of this study was to evaluate the clinical manifestations, the laboratory findings, the different lines of treatment and the outcome of cases presented with acute toxicity by tramadol overdoses.

SUBJECTS AND METHODS

This study included a total of one hundred subjects presented with acute toxicity by tramadol overdoses, at Al-Azhar University Emergency Hospitals in Cairo (El-Hussein and Bab El-shaaria University Hospitals) and Ain Shams University Hospitals. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between July 2016 to February 2018.

Patients' Inclusion Criteria: 18 years old or more, male or female having definite history of Tramadol intake given either by the patients themselves or their relatives. They had Positive laboratory parameter for qualitative detection of Tramadol in urine.

Patients' Exclusion Criteria: subjects below 18 years old, with no definitive history of tramadol intake and negative laboratory parameter for qualitative detection of tramadol in urine. Patients with history of chronic liver or renal disease were also excluded.

All patients enrolled in this study were subjected to history and thorough clinical examination. From each patient, collection of 3 ml

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of arterial blood for arterial blood gases and 10 ml of venous blood for biochemical and toxicological analysis were taken. 10 ml urine samples were also collected at the time of admission and before receiving any treatment. Catheterization was done if the patient was unable to void urine or comatose.

T**he following laboratory studies were done:**

I- Qualitative detection of Tramadol in urine:

It was done by rapid lateral flow chromatographic immunoassay for detection of tramadol and its principal metabolites in human urine according to the method of [7]**.**

II- Confirmatory urine test:

For detection of Tramadol and/or its metabolites in biological samples were done by gas chromatography/mass spectrometry (GC/MS).

III- Arterial Blood Gases (ABGs) Analysis:

They were analyzed using Rapid lab 855 of Bayer Company for assessment of the following (pH, PCO2, PO2, SO2 and HCO3).

IV- Determination of Random Blood Sugar [8]**,** serum urea [9]**,** creatinine [9] and liver enzymes (ALT and AST) [10] by colorimetric method

RESULTS

Table (1): Distribution of demographic characteristics among all studied cases as regards sex, age, marital status, socioeconomic standard, residence and occupation.

Demographic data	No.	%
*** Sex**		
Males	89	89
Females	11	11
*** Age groups**		
18-30 years	56	56
31-45 years	35	35
More than 45 years	9	9
Mean±SD	27.12±8.45	
*** Marital Status**		
Married	59	59
Single	22	22
Divorced	19	19
*** Socio- economic standard distribution**		
High	9	9
Moderate	39	39
Illiterate	52	52
*** Residence**		
Rural areas	92	92
Urban areas	8	8
*** Distribution of occupation**		
Drivers	28	28
Manual workers	23	23
Employers	17	17
Unemployed	22	22
Nurses	4	4
Others	6	6

This table shows that males represent majority of cases, mean age group between subjects was (27.12±8.45), the majority of cases were married, of low socioeconomic standard, lives in rural areas, drivers and manual workers represent majority of the studied cases.

Table (2): Dose of Tramadol and delay time among the studied cases.

Parameters	Mean	Standard deviation	Range
Dose (g/dose)	1.66g	± 0.39	0.1-9g
Delay time (hour)	4.64hr.	1.15	1-24hr.

This table shows that the mean dose of Tramadol for cases in this study group was 1.66±0.39 gram (g) and the mean delay time was 4.64±1.15 hours.

Table (3): Distribution of studied cases according to the routes of administration.

Route of administration	Frequency	Valid Percent %
Oral	70	70
Intravenous	28	28
Other routes (rectal)	2	2
Total	100	100

This table shows that almost all the studied cases 70% were intoxicated through the oral route & about 28% by intravenous injection and about 2% other routes (rectal).

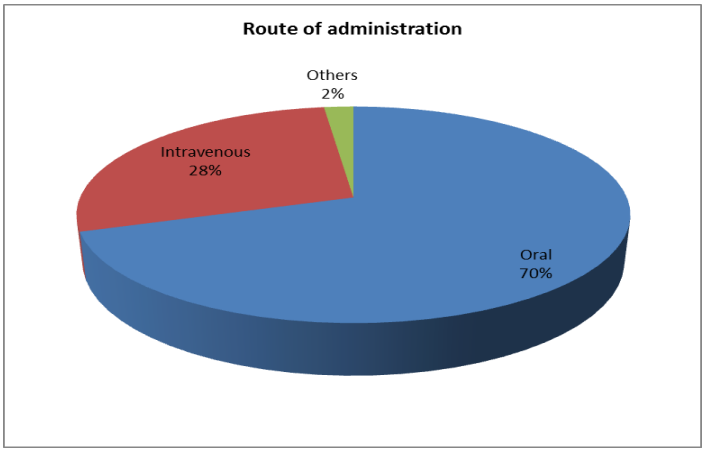

Figure (1): A Pie chart of the routes of administration distribution of the studied group

This figure shows that almost all the studied cases 70% were intoxicated through the oral route & about 28% by intravenous injection and about 2% other routes (rectal).

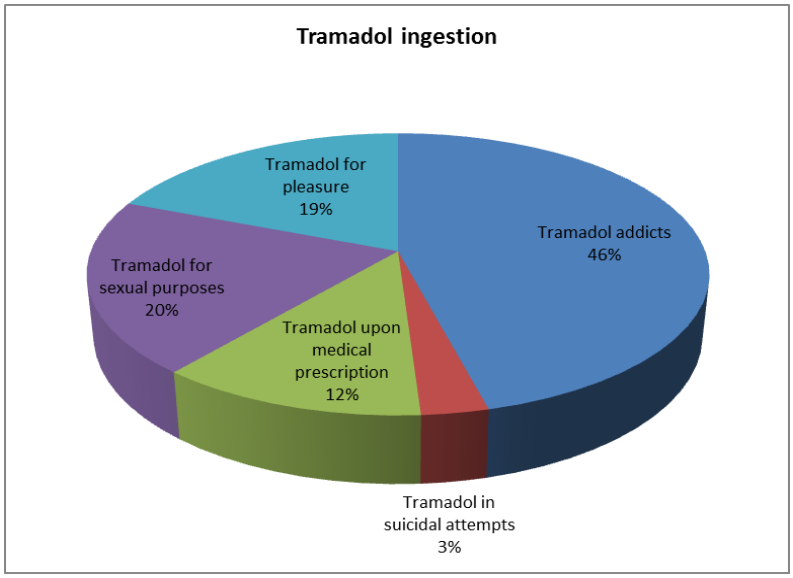

Figure (2): A bar chart showing distribution of studied cases according to the motives.

This figure shows that the majority of the studied cases about 46% of Intoxicated cases were Tramadol addicts and 3% ingested Tramadol in suicidal attempts while only12% of Intoxicated cases were receiving Tramadol upon medical prescription & 20% 0f intoxicated cases were receiving tramadol for sexual purposes and 19% 0f intoxicated cases were receiving tramadol for pleasure.

Table (4): Distribution of the studied cases according to the co-ingested drugs.

Co-ingested drugs	Frequency	Valid Percent %
Absent	35	35
Sildenafil	20	20
Cannabis	18	18
Alcohol	10	10
Parkinol	5	5
Antibiotics	5	5
Antipsychotics	4	4
Benzodiazepines	3	3
Total	100	100

This table shows that the most common drugs co ingested with Tramadol among studied cases were Alcohol, Benzodiazepines, sildenafil and Cannabis.

Table (5): Pulse, blood pressure, respiratory rate, temperature and O_2 saturation among the studied cases.

Parameters	Mean	Standard Deviation	Range
Pulse (beat/minute)	96.12	±15.35	35-140
Systolic Blood Pressure (mmHg)	115.54	±13.92	50-160
Diastolic Blood Pressure (mmHg)	72.31	±10.42	30-100
Respiratory Rate (breath/minute)	11.85	±2.39	3-25
Temperature (ºC)	36.98	±0.31	36-38.5
O_2 Saturation (%)	85.71	±21.34	5-99

This table shows that in the studied cases the mean pulse was 96.1±15.3 beat/minute, the mean systolic blood pressure was 115.5±13.9 mmHg, the mean diastolic blood pressure was 72.3±10.4mmHg, the mean respiratory rate was 11.85±2.39 breath/minute, the mean temperature was 36.9±0.3ºC and the mean O_2 saturation measured by pulse oxymetery was 85.7±21.3%.

Table (6): Skin manifestations among studied cases.

Parameters	Frequency	Valid Percent %
Normal	69	69
Sweating	21	21
Cyanosis	7	7
Pruritis	3	3
Total	100	100

This table shows that as regard the skin manifestations, the majority of studied cases % showed no abnormal skin manifestations while % of cases were presented with sweating and only % were presented with cyanosis.

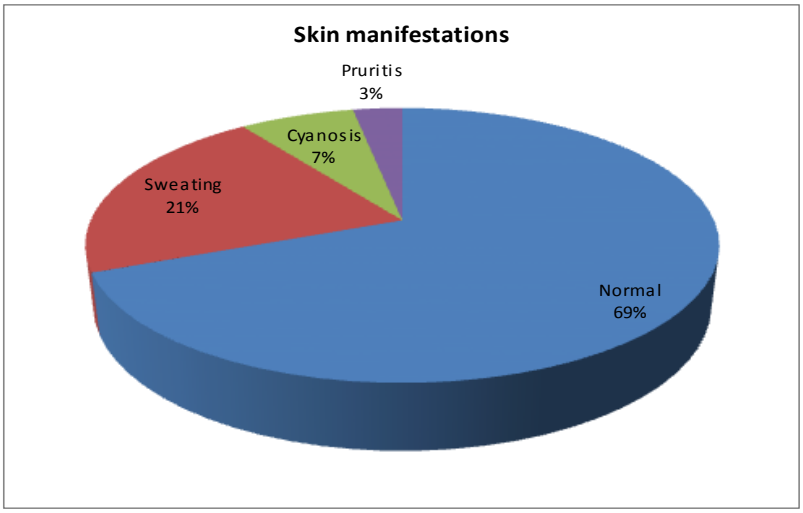

Figure (3): A pie chart of the skin manifestations among the studied cases.

This figure shows that as regard the skin manifestations, the majority of studied cases % showed no abnormal skin manifestations while % of cases were presented with sweating and only % were presented with cyanosis.

Table (7): Neurological manifestations among the studied cases.

Parameters	Frequency	Valid Percent %
Normal	40	40
Drowsiness	22	22
Tremors	18	18
Convulsions	6	6
Agitation and Convulsions	4	4
Coma	3	3
Hallucination and Convulsions	3	3
Drowsiness and Convulsions	2	2
Coma and Convulsions	2	2
Total	100	100.0

This table shows that as regards the neurological manifestations, 40% of studied cases showed no abnormal neurological manifestations while the total percent of cases presented with drowsiness and coma was 22 and 3 respectively with the mean GCS (13.40) and the total percent of cases presented with convulsions was 6. Agitation, hallucination and tremors were manifested separately only in 25% of studied cases**.**

Table (8): GCS in the studied cases.

Parameter	Mean	Standard Deviation
GCS	13.40	3.29

This table shows that the mean GCS (13.40) among the studied cases.

Table (9): Arterial Blood Gas analysis among the studied cases.

Parameters	Frequency	Valid Percent %
Normal	58	58
Respiratory acidosis	28	28
Combined respiratory and metabolic acidosis	7	7
Metabolic acidosis	5	5
Respiratory alkalosis	2	2
Total	100	100

This table shows that there was a slight difference in percentage between the normal arterial blood gas analysis (58%) and the abnormal findings (28%) among studied cases and that respiratory acidosis represented the majority of the abnormal findings (representing 28% of studied cases).

Table (10): Laboratory parameters among studied cases.

Investigations	Mean	Standard Deviation	Range
Random Blood Sugar (mg/dl)	97.75	±24.31	29-310
Aspartate aminotransferase AST(IU/L)	23.86	±5.12	12-90

Alanine aminotransferase ALT(IU/L)	20.94	±4.36	10-79
Urea(mg/dl)	29.08	±6.80	23-120
Creatinine (mg/dl)	0.923	±0.220	0.5-8.3

This table shows that Random Blood Sugar (97.7±24.3), serum AST (23.8±5.1), ALT (20.9±4.3), Urea (29±6.80), Creatinine (0.9±0.22) and Creatine levels were within normal range among cases in this study.

Table (11): GIT decontamination among studied cases.

Method of GIT decontamination	Frequency	Valid Percent %
Gastric lavage and Activated charcoal	60	60
Activated charcoal only	30	30
No decontamination done*	10	10
Total	100	100

This table shows that the method of GIT decontamination in 60% of studied cases was gastric lavage and activated charcoal while 30% was given activated charcoal only and no decontamination was done in 10%.

Table (12): Speceific medications taken among studied cases.

Medications	Frequency	Valid Percent
Valium	13	13
Atropine	3	3
Adrenaline	2	2
Anti allergic medications	2	2
Dormicum	5	5

This table shows that some specific medications as Valium, Atropine, Adrenaline, Dormicum and anti-allergic medications were given in 13%, 3%, 2%, 2% and5% of studied cases respectively.

Table (13): Distribution of studied cases according to the duration of hospital stay.

Duration (hours)	Frequency	Valid Percent %
Less than 12	28	28
12 or more but less than 24	39	39
24 and more	43	43
Total	100	100

This table shows that 28% of studied cases stayed at the hospital less than 12 hours, 39% stayed 12 hours or more but less than 1 day and 43% stayed for 24 hours or more.

Table (14): Outcome of cases in this study.

Parameters	Frequency	Valid Percent
Full recovery	95	95
Death	5	5
Total	100	100

This table shows shows that 97% of studied cases fully recovered and 3% died.

Discussion

Tramadol is a centrally acting analgesic which is extensively used in the management of moderate to severe pain. It slightly affects opioid receptors and inhibits the reuptake of norepinephrine and serotonin in the CNS [(11)].

Tramadol can be administered orally, rectally, or parenterally (intravenous, intramuscular and subcutaneous) [(12)]. Its standard therapeutic doses are 50 mg orally, 50–100 mg by injection and 100 mg rectally. The total daily dose should not exceed 400 mg [(1)].

This prospective study was performed on acutely intoxicated patients with Tramadol admitted to Al-Azhar and Ain Shams university hospitals

In this study, 100 Tramadol intoxicated cases were evaluated as regards clinical picture, laboratory investigations and management procedures.

Socio demographic data

In this study, the mean age for cases was 27.12 ± 8.45 years.

This result is in agreement with ***Shadnia et al.***[(11)], ***Marquardt et al.***[(12)], ***Petramfar and Haghighi*** [(14)], ***Tashakori and Afshari*** [(15)] ***and Ahmadi et al.***[(16)] who had approximately similar results. This can be explained as adolescence is one of the most vulnerable stages of life, a time typified by puberty and stresses at home, community and in personal relationships.

On the contrary, ***Tja¨derborn et al.***[(2)] study reported that the mean age was 44 years (range 18–78years).

In this study, males represented the majority of cases (89%) in comparison to females (11 %).

This result is in agreement with ***Shadnia et al.***[(11)], ***Petramfar and Haghighi***[(14)], ***Tashakori and Afshari***[(15)], ***Ahmadi et al.***[(16)] ***and. Talaie et al.***[(17)] .This can be explained by the increased tramadol abuse in males and its alleged enhancement of sexual performance.

This disagrees with ***Marquardt et al*** [(13)] who found that female intoxicated patients were represented at a higher rate than males. This was reported as well by ***Varnik et al.***[(18)] who found that females were highly represented in his study which might reflect a gender preference of women to rely on drug overdose as a means of self-harm, whereas men may be more likely to inflict physical self-harm.

In the present study, there were distribution of cases residences in Cairo governorate (60%), Giza governorate (37%) and other governorates (3%). This can be explained by the characteristic location of poison control centers in between these governorates.

- **Toxicity data**

According to this study, the mean dose of Tramadol was 1.66±1.76 gram.

This finding was similarly observed by ***Shadnia et al.***[(11)] who noticed that the range of dosage used was between 100 and 14000 mg with an average of 1650 mg and by ***Tashakori and Afshari***[(15)] who observed that the alleged mean dose ingested was 1481 ±1499 mg, which ranged from 150 to 9375 mg.

In controversy to this study, ***Petramfar and Haghighi***[(14)] stated that in their study the mean dose of ingested Tramadol was 363.2 ± 303.1mg.

In the present study, the mean delay time was 4.64±4.31 hours.

This result is in agreement with ***Shadnia et al.***[(11)] who observed that the time between ingestion and admission ranged from 0.5 to 24 hours with average of 6.12 hours. This can be attributed to the fact that the peak plasma concentration after orally administered Tramadol is reached in 1-3 hours for regular release preparations and in 5 hours for sustained release products ***(Ardakani and Rouini***[(19)]

In this study, almost all cases (70%) were intoxicated through the oral route, (28%) through the parenteral route and about (2%) by other routes.

This result in accordance with ***Shadnia et al.***[(11)] ***and Tashakori and Afshari***[(15)] This can be explained as the oral dosage forms are the most available pharmaceutical forms of Tramadol in pharmacies and the most easily administered.

According to this study, the majority of intoxicated cases were Tramadol addicts (46%) while only (3%) of intoxicated cases ingested Tramadol in suicidal attempts and(12%) of Intoxicated cases were receiving Tramadol upon medical prescription& (20%) 0f intoxicated cases were receiving tramadol for sexual purposes &(19%) 0f intoxicated cases were receiving tramadol for pleasure.

This result doesn't agree with ***Shadnia et al.***[(11),] ***Marquardt et al.***[(13)] ***Ahmadi et al.***[(16)] ***and Fariba et al.***[(20)]who stated in their studies that suicide was the most common mode of poisoning for both men and women followed by abuse.

In the present study, the most common drugs co ingested with Tramadol were sildenafil, Cannabis, alcohol and benzodiazepines.

On the contrary with this study ***Shadnia et al.***[(11)] ***and Ahmadi et al.***[(16)] have observed that

benzodiazepines were the most common co ingested drugs.

On the contrary, ***Tja¨derborn et al.***[3] and ***Fariba et al.***[20] noticed that the most common co-ingested drugs were opioids.

Investigational data

In this study, regarding the Arterial Blood Gas analysis, respiratory acidosis was represented in 28% of cases; combined respiratory& metabolic acidosis and metabolic acidosis were represented in 7% and 5% respectively.

Respiratory acidosis can be explained by **Hoffman**[21] who recognized that opioid agonists reduce ventilation by diminishing the sensitivity of the medullary chemoreceptors to hypercapnia. In addition to the loss of hypercarbic stimulation, opioids also depress the ventilatory response to hypoxia. The combined loss of hypercarbic and hypoxic drive leaves virtually no stimulus to breathe and apnea may follow.

This result is in accordance with ***Decker et al.***[22] who reported extreme acidosis in a 28-year old Caucasian man, treated with Tramadol for several months, presented by apnea.

Also, ***Chandrasekaran, et al.***[23] revealed mixed respiratory and metabolic acidosis. Respiratory acidosis was attributed to opioid like overdose and metabolic acidosis to selective serotonin syndrome toxicity.

Also, ***Gheshlaghi et al.***[24] observed severe metabolic acidosis (PH, 7.03; PCO2, 44.2 mmHg; HCO3, 13.2 mEq/l) in a19-year-old male after ingestion of one hundred 100mg tablets of Tramadol.

According to this study, Random Blood Sugar (97.7±35.3), serum AST (23.8±10.1), ALT (20.9±10.3), Urea (29±12.8), Creatinine (0.9±0.96) and Creatine Kinase-MB (14.12±3.35) levels were within normal range.

This is in accordance with ***Gheshlaghi et al.***[24] ***and Kung and Ng***[25] *who reported normal laboratory parameters mentioned above.*

In contrary with this study, ***Decker et al.***[22] reported acute hepatic as well as acute renal failure and also recognized hypoglycemia which was particularly demonstrated in rats.

Also, ***Tashakori and Afshari*** [15] showed higher mean for serum creatinine and glucose but lower mean for serum urea.

Treatment

In the present study, concerning the method of GIT decontamination, gastric lavage was done in 60% of cases, 30% of cases were given activated charcoal and no decontamination was done in 10% of cases.

This agrees with a study made by ***Tashakori and Afshari*** [15] that showed similar results.

However, ***Marquardt et al.***[13] used gastric lavage in 3.2% of cases and stated that the treatment should include early administration of charcoal and recognized that one child who ingested 300 mg and one who ingested 250 mg of Tramadol were given charcoal and did not manifest evidence of toxicity.

In this study, 40% of cases received supportive measures in the form of nasal oxygen and 5% needed mechanical ventilation.

This result agrees with ***Marquardt et al.***[13] who stated that 0.5% of cases were mechanically ventilated.

In the contrary, ***Tashakori and Afshari*** [15] reported that 78% of patients needed supplemental oxygen in their management.

In the present study, 45% of cases received Narcan as an antidote.

In accordance with the present study, ***Tashakori and Afshari*** [15] showed that 44% of patients were managed with Narcan. Also ***Marquardt et al.***[13] observed administration of Narcan in 5.8% of cases with successful response in 7 out of 8 cases.

In the present study, some specific medications as Valium, Atropine, Adrenaline, Dormicum and Anti allergic medications were given in 13%, 3%, 2%, 5% and2% of cases respectively.

As regard Valium administration, this finding is approximately similar to that observed by ***Tashakori and Afshari*** [15] and it is related to the occurrence of seizures among studied cases.

Concerning Adrenaline and Atropine, this is related to the finding that 3.1% of cases in this study died due to cardiorespiratory arrest.

Regarding the use of Dormicum and Anti allergic medications, this may be related to the presence of agitation and itching in 1.5% and 1.5% of cases respectively.

Outcome

In this study, 95% of studied cases fully recovered and 5% died.

This is in accordance with ***Shadnia et al.***[11] and ***Tashakori and Afshari*** [15] who showed that the mortality rates were 4.75% and 3.7% respectively that were also similar to a previous study done by ***Decker et al.***[22]**.**

Also, ***Ahmadi et al.***[16] reported that the mortality rate was 0.97% and that 90% of dead

cases were males, the mean age was 30 years, the most common cause of death was suicide (60%) and in 70% of cases symptoms of seizure were seen.

In the contrary, ***Tjaderborn et al.*** [3] recognized that of 297 cases of death due to intoxication, Tramadol was considered the cause of death in 148 (50%) cases.

The difference in mortality rates between this study and the above mentioned studies may be related to the increasing number of cases who co-ingested Tramadol with other drugs as central nervous system depressants, particularly benzodiazepines, barbiturates and drugs with serotonin effects ***Clarkson et al.***[12].

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