Original Article

Tramadol-Induced Seizures in Adolescents and Young Adults in Bangkok: Clinical Features and Emergency Management

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Objective: The authors aimed to describe the substances involved in those young people with seizures and to characterize their clinical presentation, clinical course as well as management in the Emergency Department [ED] and their outcomes.

Materials and Methods: This was a retrospective study. Patients aged 10 to 26 years from September 2011 to November 2013 with substance related seizures were included. The authors excluded those with a history of severe head injury within one month, suspected alcohol withdrawal, and prior history of a known cause of seizures. Two independent ED nurses abstracted the data. Inter-rater reliability was tested and the kappa was 0.84.

Results: Over the 27-month-period, 56 cases aged 10 to 26 years with a history of seizure were included. Eighty percent were male. The median age was 17 years old. Almost 90% of patients ingested tramadol, mainly for recreational purposes. Half of them ingested tramadol alone, the other half ingested it in combination with promethazine (25%), hydroxyzine (16%) and diphenhydramine (5%). The median dose of tramadol was 400 mg. All seizures were generalized tonic clonic. Sixteen percent (6/37) had serotonin syndrome. Serum creatinine was found elevated in 28%. Plasma glucose was low in 2 cases. Most cases (77%) were observed in the ED (median 10 hours) and were discharged home safely without any unscheduled revisit or recurrent seizures.

Conclusion: Cases with tramadol-induced seizures were commonly seen among adolescents and young adults in Bangkok during the study period. Elevated serum creatinine level seemed relatively common.

Keywords: tramadol, recreational, serotonin syndrome, promethazine, prescription drug abuse

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In 2012 and 2013, an unexpected increase in the number of cases presenting to our Emergency Department [ED] with substance induced seizures was encountered. Almost all of them were adolescents or young adults. They often reported using tramadol or a mixture of tramadol and another medication namely cough and cold preparations. Those medications were widely available in pharmacies throughout Thailand.

Data regarding clinical course and ED management of tramadol induced seizures especially in adolescents and young adults from tramadol misuse are still limited. Most existing studies were done in adults and in those with intentional self-harm[1-3]. There had been no studies which focused on the adolescents and young adults especially in the abuse setting. Regarding the drug overdose in children, there was a report with a large number of tramadol intoxications in children[4], however, the number of seizures were limited and the clinical course were not described in detail.

In the present study, the authors aimed to describe the substances involved in those young people who were brought to our ED with seizures and to characterize their clinical presentation, clinical course as well as our ED management and outcomes for this

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specific age group.

Materials and Methods

This was a retrospective descriptive study which was conducted at a public tertiary teaching hospital in a suburb area of Bangkok. The hospital contains around 900 beds and the ED has around 70,000 visits annually. The majority of patients are lower, working, or lower middle class. The authors searched the ED consultation and Medical Toxicology logbooks for the medical records of adolescents and young adults aged 10 to 26 years old who were brought to the ED of the institution from September 1, 2011 to November 30, 2013 with drug or substance related seizures. The seizures had to develop within 24 hours after the last drug or substance exposure for the patients to be included in the study. The authors excluded those with a history of severe head injury within the past month, those with suspected alcohol withdrawal, and those with a prior history of a known cause of seizures such as intracranial process or epilepsy.

Types and doses of drugs used were self-reported by patients or their friends. Tramadol is well known and easily identified as a half green-half yellow capsule. For cough and cold syrups, patients were asked to identify what brand they used. Sometimes those products were shown as photos (presented by the patients themselves) or sometimes the authors requested their friends or families to bring the bottles. Dose of tramadol ingestion was estimated from what a patient reported to the physician or nurse. For example, when one said he put 10 capsules of tramadol (50 mg/capsule) with 1.5 L of Coke, the authors further asked the patient to estimate how much he drank from the bottle. If he said "half of it", then the estimated ingested dose would be around 250 mg. As a result, the dose of tramadol ingested was from an estimation. The authors did not attempt to estimate doses of other substances including cough and cold preparations and caffeine from soft drinks or tea. Urine or serum drug screen was usually not sent since neither detects tramadol. More sophisticated labs such as liquid or gas chromatography were not done because they do not provide additional value in terms of immediate medical care and these tests are quite expensive at our settings. The authors controlled quality of this retrospective chart review by several means in addition to having clear inclusion and exclusion criteria. The authors developed a standard data collection form and data abstraction protocol. The authors trained two chart abstractors who were also experienced ED nurses and had worked in the ED for more than 5 years. However, these two nurses were blinded to the objectives of the present study in an effort to reduce any selection bias as suggested by Gearing RE et al[5]. The authors assessed the quality of data abstraction by having a training session using standardized mock charts, standard definitions of our work, and by using the standard data record form. Finally, inter-rater reliability was tested from 10 medical records and the kappa was 0.84 before the process of data abstraction from those eligible medical records began.

Results

Over the 27-month-period, 92 patients between the ages of 10 and 26 years old with a history of seizure were identified. Thirty-six cases were excluded for the following reasons: unavailable medical records (9 cases), patients transferred to another hospital before diagnosis (8 cases), intracranial process (6 cases), known history of epilepsy (5 cases), undetermined cause (5 cases), and alcohol withdrawal (4 cases). Finally, 56 cases were included in the study (Figure 1).

During the first 9 months of the study period, from September 2011 to May 2012, the authors rarely encountered drug-induced seizures in our ED. Since June 2012, the number of adolescent and young adult cases presenting with drug-induced seizures rose dramatically through the end of the study period. This number increased 4.2-fold during the second 12-month-period of our study (September 2012 to August 2013) as compared to the first 12-month-period (September 2011 to August 2012), as seen in Figure 2 (42 cases vs. 10 cases).

Of the 56 cases included in the study, the majority were male (80%). The youngest was 13 years old, the oldest was 25, with the median age of 17 (IQR: 16 to 19) (Table 1). Most of the patients were students. Almost 90% of them ingested tramadol and their main stated reason for doing so was recreational. Half of them ingested only tramadol, the other half used tramadol in combination with other medications such as promethazine (25%), hydroxyzine (16%) and diphenhydramine (5%).

Seizures were generalized tonic clonic in 100% of cases. All patients had only a single episode of seizure, except for one case. This was a 14-year-old girl who ingested an unknown amount of a mixture of tramadol, promethazine, and a soft drink. Because pediatricians did not think the multiple episodes of seizures in this case could be explained solely from

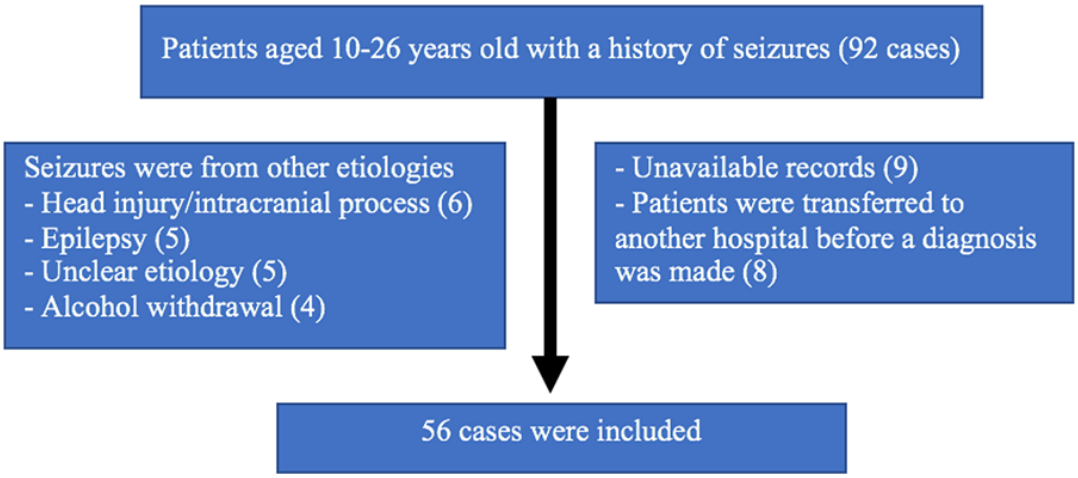

Figure 1. Study population inclusion and exclusion.

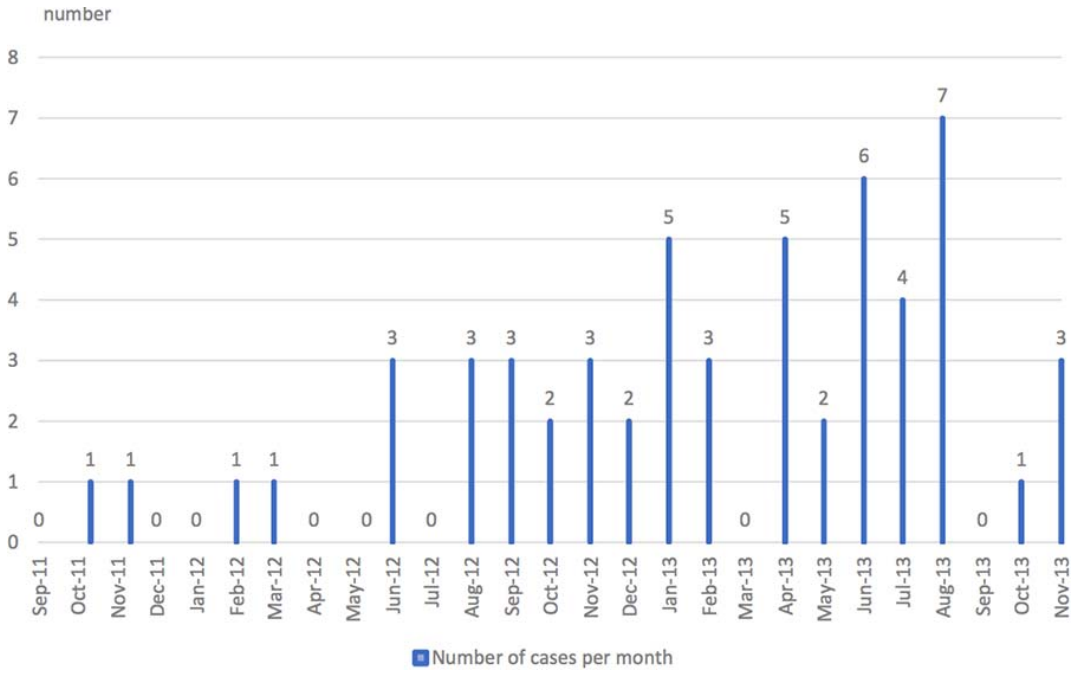

Figure 2. Number of cases per month.

tramadol ingestion which usually causes a single seizure, she was admitted and underwent further investigations, including an EEG and finally she was diagnosed with epilepsy and was discharged home on antiepileptic medication.

Eighty-eight percent (49/56) of seizing patients had a history of tramadol ingestion (Table 1).

The ingested tramadol dose ranged from 100-1,500 mg with a median of 400 mg (IQR: 300 to 500 mg) (Table 2). The minimum dose of 100 mg of tramadol ingestion was reported in four male cases aged 18, 18, 19, and 19 years old.

For those with tramadol induced seizures (49 cases), 37 cases (76%) had enough information to further determine the presence of serotonin syndrome. Based on Hunter's criteria for serotonin syndrome, only

Table 1. Epidemiology and patient characteristics

Gender	
Male	45 (80%)
Age (years old)	
Median (IQR) = 17 (16 to 19)	
Min = 13	
Max = 25	
Occupation	
Student	47 (84%)
Employee	8 (14%)
State enterprise employee	1 (2%)
Past medical history	
No known disease	30 (54%)
Allergy	2 (4%)
G6PD deficiency	1 (2%)
No data	23 (41%)
Type of drug used before seizures	
Tramadol	49 (88%)
Promethazine	18 (33%)
Hydroxyzine	10 (19%)
Diphenhydramine	3 (6%)
Characterization of drug use (n = 56)	
Single drug use	30 (54%)
Tramadol	23 (41%)
Promethazine	4 (7%)
Hydroxyzine	1 (2%)
Combination	26 (46%)
Tramadol + Promethazine	14 (25%)
Tramadol + Hydroxyzine	9 (16%)
Tramadol + Diphenhydramine	3 (5%)
Unknown drug	2 (4%)
Beverages mixed with drug (n = 55)	
No mixing	22 (40%)
Soft drink	25 (45%)
Tea	4 (7%)
Alcohol + soft drink	2 (4%)
Alcohol	1 (2%)
Energy drink	1 (2%)
Purpose of drug use (n = 55)	
Recreation or party with friends	49 (89%)
Therapeutic reason	4 (7%)
Self-harm	2 (4%)
Number of seizure episode (n = 56)	
Once	55 (98%)
More than once*	1 (2%)
Type of seizure (n = 36)	
Generalized tonic clonic	36 (100%)
ED disposition (n = 56)	
ED observation then discharged home [median of observation duration (IQR) = 10 h (7 to 13 h)]	43 (77%)
Against medical advice	5 (9%)
Hospital admission	4 (7%)
Transfer	4 (7%)
ED revisit or scheduled follow-up after ED observation	0 (0%)
ED revisit (n = 43)	
Came back for scheduled follow-ups (n = 27)	20 (74%)

* This was the only one case who had 4 episodes of seizures and was finally diagnosed with epilepsy and was continued on antiepileptic medication

Table 2. Pharmaceutical products and doses reported by patients

Pharmaceutical product*	Dose (mg)
Tramadol (n = 46)	400 (300 to 500)**
Diphenhydramine	150 (0)***
Hydroxyzine	125 (68)***
Promethazine	53 (32)***

*All products were taken by mouth; **Median (IQR); ***Mean (SD)

Table 3. Clinical parameters in patients with seizures and tramadol use (n = 49)

Body temperature (n = 34)	
<38 c	33 (97.1%)
≥38 c	1 (2.9%)
Ankle clonus (n = 40)	
Absent	22 (55.0%)
Present	18 (45.0%)
1 to 4 beats	9 (22.5%)
>4 beats	1 (2.5%)
Unknown count	8 (20.0%)
Deep tendon reflex of ankles (n = 43)	
1+	1 (2.3%)
2+	30 (69.8%)
3+	11 (25.6%)
4+	1 (2.3%)
Glasgow coma scale score at presentation (n = 46)	
≤8	1 (2.2%)
9 to 13	1 (2.2%)
14 to 15	44 (95.6%)
Serotonin syndrome [Hunter's criteria] (n = 37)	
Inducible clonus and sweating	6 (16.2%)
Spontaneous clonus	0 (0%)
Ocular clonus and either agitation or sweating	0 (0%)
Tremor and hyperreflexia	0 (0%)
Limb hypertonicity and BT >38 c and either ocular clonus or inducible clonus	0 (0%)

6/37 cases (16%) had serotonin syndrome (Table 3).

However, all of the 6 cases had only a mild form of serotonin syndrome [inducible clonus + sweating (nobody had agitation)] and the outcomes were benign. None of those cases were admitted (Table 4).

Regarding the investigations (Table 5), 14 out of 50 cases with available serum creatinine concentrations (Cr) had elevated values based on their normal reference ranges by age and sex (available below

Table 4. Patients with serotonin syndrome

Case #	Age	Hunter'scriteria	Tramadol dose (mg)	Co-ingestion	ED observation (hours)	CK	Cr	Hospital admission (Yes/No)
29	18	Clonus + sweating	250	Hydroxyzine	12 h	-	1.0	No
30	19	Clonus + sweating	100	Hydroxyzine	8 h	153	1.3	No
32	19	Clonus + sweating	833	Promethazine	6 h	-	1.3	No
42	15	Clonus + sweating	150	None	7 h	-	1.0	No
50	19	Clonus + sweating	100	None	10 h	-	0.9	No
55	20	Clonus + sweating	500	None	8 h	-	1.1	No

ED = emergency department; CK = creatine kinase; Cr = creatinine

the table). Twelve of those were male and the highest concentration was 1.7 mg/dL. Serum creatine kinase concentrations [CK] were available in only 8 cases ranging from 147 to 846 U/L. There were two cases with hypoglycemia (serum glucose <60 mg/dL), 29 and 56 mg/dL, respectively. No one had serum sodium <130 mmol/L, potassium <3.0 mmol/L, magnesium <1.8 mmol/L, and calcium <8.0 mmol/L. Brain CT scan was done in only 8 cases and they were all negative. EEG was done in the only case who had four episodes of seizure and the result was positive for epilepsy.

Approximately 80% (43/56) of patients were only observed shortly in the ED [median (IQR) = 10 hours (7 to 13)] and were discharged home without hospital admission. Six out of 43 patients (14%) who were observed in the ED were referred to psychiatry. None of the discharged ED cases returned to the ED without unscheduled plans for follow-ups or another episode of seizures within one week. For those who came back for the planned follow-ups, no one reported having another seizure after the ED discharge (Table 1).

Discussion

Tramadol abuse or misuse has become more problematic for several years in several parts of the world such as the USA, UK, Africa, and the Middle-East[2,6,9]. Currently in Thailand, tramadol has not been scheduled as a narcotic according to the Narcotic Act[10] but tramadol has been controlled by the Drug Act as a dangerous drug, hence it requires a physician's prescription. Because it is widely available in pharmacies around the country and the law has not been strictly applied, some pharmacies have sold it to any customer, including adolescents, without a prescription. Our study showed that the popularity of tramadol abuse in Thailand started in the middle of 2012 and persisted throughout the study period until July 2013. In September 2013, the Thai FDA (Food and Drug Administration) took action by the following ways to halt this abuse: 1) restriction on manufacturers to dispense tramadol no more than 1,000 capsules per month per pharmacy, 2) pharmacies must file a report regarding tramadol dispensation every 4 months to the Thai FDA (instead of once yearly), 3) selling tramadol to those below 17 years of age is no longer permitted, 4) tramadol cannot be sold in quantities of more than 20 capsules per day per person[11]. Since 2014, the authors have observed a dramatic decline in tramadol-induced seizures in our ED.

Approximately 90% of the cases ingested tramadol before seizures, half of them ingested tramadol alone, but the other half took it in a combination with another medication namely cough and cold preparations containing substances such as promethazine, hydroxyzine, and diphenhydramine. All of these medications are histamine H-1 antagonists. Tramadol is available in the racemic form (± enantiomer). CYP 2D6 is the major enzyme that metabolizes tramadol to an active metabolite, O-desmethyltramadol (M1)[12]. Potschka et al has demonstrated in a rat model that the convulsive seizure was mainly caused by the parent compound of tramadol itself (the racemic form, ± enantiomer of tramadol), not the active metabolite M1 (O-desmethyltramadol)[13]. The M1 metabolite has a major role for analgesia and respiratory depression since it has higher affinity to the mu-receptor compared with the parent compound, but it has a minor role for convulsion. Interestingly, several histamine H-1 antagonists interact with tramadol through the inhibition of the CYP 2D6[14]. For example, promethazine is both a CYP 2D6 substrate and inhibitor[15] as a result

Table 5. Patients with elevated serum creatinine by age (n = 50)

Case #	Sex	Age	Cr (mg/dL)	BUN	CK	K	P	Ca	Mg	ED stay (hours)	Hospital admission
1	M	17	1.7	11	414	3.5	3.8	9.8	2.7	47	Admitted for 72 hours
2	M	18	1.5	9	225	3.5	-	-	-	48	Not admitted
3	M	18	1.5	9	-	3.8	2.9	8.3	3	9	Not admitted
4	M	20	1.5	10	-	3.0	3.5	9.4	2.3	12	Not admitted
5	M	19	1.4	9	702	5.9	5.3	10.8	2.6	27	Not admitted
6	M	18	1.4	11	-	3.2	3.6	9.7	2.5	9	Not admitted
7	M	19	1.4	7	-	3.8	6.0	9.6	2.7	16	Not admitted
8	M	15	1.2	9	-	3.5	4.1	9.8	2.3	5	Not admitted
9	M	15	1.0	9	-	4.0	2.8	9.3	2.1	7	Not admitted
10	M	15	1.0	9	-	4.0	2.8	8.7	2.1	7	Not admitted
11	M	15	1.0	8	-	3.3	5.9	9.7	2.1	7	Not admitted
12	M	15	1.0	7	-	3.3	3.5	10.1	2.7	2	Admitted for 24 hours
13	F	15	1.0	11	-	4.3	4.0	10.1	2.2	8	Not admitted
14	F	15	0.9	8	-	4.0	4.6	9.6	2.5	3	Transferred to another hospital

M = male; F = female; Cr = creatinine; BUN = blood urea nitrogen; CK = creatine kinase; K = potassium; P = phosphate; Ca = calcium; Mg = magnesium; ED = Emergency Department

Male serum creatinine reference ranges are as follows:

Age 12 to 13 years: 0.4 to 0.8 mg/dL

Age 14 to 15 years: 0.5 to 0.9 mg/dL

Age 16 years or older: 0.8 to 1.3 mg/dL

Female serum creatinine reference ranges are as follows:

Age 9 to 15 years: 0.4 to 0.7 mg/dL

Age 16 years or older: 0.6 to 1.1 mg/dL

(Reference: https://emedicine.medscape.com/article/2117892-overview)

it can potentially decrease the metabolism of tramadol, and thus promethazine prolongs the elimination half-life of tramadol. In addition, promethazine can also reduce seizure threshold[15]. By both mechanisms, decreased clearance of tramadol parent compound and decreased seizure threshold, promethazine and other anti H-1 substances may potentiate convulsion in those who co-ingested tramadol with anti-histamines.

Tramadol can inhibit reuptake of serotonin and cause serotonin syndrome, according to some human studies[1,16]. However, a recent study from Australia reported that even after tramadol overdose (>400 mg), other adverse events such as seizures and respiratory depression were more common[3]. In the present study, 16% of those who ingested tramadol and had seizures had clinical pictures that were compatible with serotonin syndrome based on the Hunter's criteria. Nevertheless, all of them only had a mild form which consisted of inducible ankle clonus and sweating (no agitation). These cases needed no further treatment for their conditions. Only supportive care and short ED observation were required.

Regarding investigations in patients with tramadol overdose induced seizures, this study found unremarkable serum electrolytes, except for serum creatinine and blood glucose. It is reasonable that plasma glucose be checked in all cases presenting with seizures or altered mental status. There are an increasing number of reports that tramadol use is associated with hypoglycemia[17–20]. The possible 3 mechanisms for this include the reduction of hepatic gluconeogenesis, enhanced peripheral glucose utilization and increased hepatic insulin sensitivity due to tramadol[19,21,22]. The reason for elevated serum creatinine in some cases was unclear. It could be from various etiologies such as dehydration, rhabdomyolysis, or drugs. Finding exact causes of elevated serum creatinine in those cases was beyond the scope of the present study.

Based on this study where the majority of seizures were due to tramadol ingestion, the authors would suggest such patients be observed at least for 6 to 8 hours in the ED based on the 6-hour elimination half-life of tramadol in adults[23]. In fact, Vandenbossche et al[24] found that the elimination half-life of tramadol in pediatrics was shorter (5.19 vs. 5.72 hours) which was in concordance with another study on tramadol clearance which found it was faster in children and adolescents (12.0 mL/min/kg vs. 7.3 mL/min/kg)[25].

It was felt that patients could be safely discharged home after at least 6 to 8 hours of observation in the ED if they met all of the following criteria: 1) a thorough physical and neurological examination found no associated injury, 2) their mental status and vital signs had returned to normal, 3) there were no further seizures during the observation period, 4) all lab results came back normal. Most cases in the present study were observed in the ED for approximately 10 hours before discharge. The authors found no one returned to the ED as a result of recurrent seizures or complications. On the other hand, some cases may need more time for medical attention such as if they have rhabdomyolysis, acute kidney injury, fractures, dislocation, or if a cause of seizures is uncertain. As part of holistic care, however, after the medical conditions of those cases subsided, they should be offered drug rehabilitation or a psychiatry referral. Only 14% of our cases were scheduled for a psychiatry appointment and this should be improved.

The authors were aware of few limitations of the study. Being a retrospective study, there were a number of missing data from patient charts. The sample size of the present study was also relatively small. However, this study identified and analyzed data of 49 patients of tramadol induced seizures which was a large number compared with a study enrolling 7,334 cases with tramadol exposures, which identified only 24 patients with seizures[4].

Conclusion

Cases with tramadol-induced seizures were commonly seen among adolescents and young adults in Bangkok during the second half of the study period. Among the 49 cases with tramadol-induced seizures, 14 had elevated serum creatinine, six had mild serotonin syndrome, and two were hypoglycemic. At least six to eight hour ED observation seemed adequate especially for those who only had a single convulsive seizure and returned to their normal mental status with normal neurological and physical examination and had no serious associated injury.

What is already known on this topic?

Tramadol abuse has become more problematic and more common in several parts of the world. Because tramadol is an opioid, signs of opioid poisoning such as coma, respiratory depression, and pinpoint pupils can occur especially in case of overdose drug. Tramadol overdose, and occasionally with therapeutic doses, can cause seizures. Serotonin syndrome can occur in some severe cases due to its serotonergic property.

What this study adds?

Tramadol induced seizures is a common cause of seizure among adolescents and young adults who presented to the emergency room in Bangkok. The majority of patients had favorable outcomes and could be managed in the emergency room with short observatory period. The patients could be discharged home without hospitalization if they recovered to their normal mental status, physical examination, and laboratory results. ER revisits within one week after discharge due to the complications of seizures or repeated seizures were unlikely.

Potential conflicts of interest

The authors declare no conflict of interest.

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