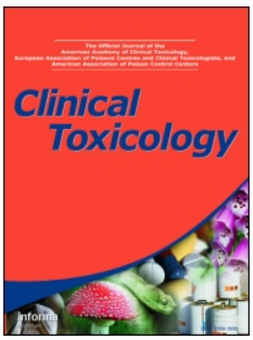

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Brian Patrick Murray, Joseph E. Carpenter, Camille A. Dunkley, Tim P. Moran, Musa Alfaifi, Waleed S. Alsukaiti & Ziad KazziOn Behalf of the Toxicology Investigators Consortium (2019): Seizures in tramadol overdoses reported in the ToxIC registry: predisposing factors and the role of naloxone, Clinical Toxicology, DOI: 10.1080/15563650.2018.1547826

To link to this article: https://doi.org/10.1080/15563650.2018.1547826

Published online: 24 Jan 2019.

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2018.1547826

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CLINICAL RESEARCH

Seizures in tramadol overdoses reported in the ToxIC registry: predisposing factors and the role of naloxone

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ABSTRACT

Importance: Tramadol prescriptions have increased as fewer schedule II and III drugs are prescribed. There has been a concomitant increase in overdoses and adverse events recorded in the National Poison Data System. Seizure activity after tramadol overdose or therapeutic use is a well-documented adverse event. The primary objective is to evaluate the characteristics associated with seizures following single agent tramadol ingestion. Secondarily we aim to compare the rate of seizures in individuals treated, and not treated, with naloxone.

Methods: We searched the Toxicology Investigators Consortium data registry for all cases of single agent tramadol ingestions from 01/01/2014 through 12/31/2017. Descriptive statistics were used to evaluate characteristics associated with increased risk of seizures. Binary logistic regressions were used to evaluate the associations between seizures and age, race, acuity, intent, toxidromes, symptoms, and treatments.

Results: There were 80 single ingestion tramadol cases entered into the registry. Seizures developed in 42 (52.5%) patients. Asian patients (OR = 7.2, 95% CI: 1.9–27.3, $p = .004$) and patients abusing or misusing tramadol (OR = 3.2, 95% CI: 1.2–8.3, $p = .02$) more likely to develop seizures. Patients exhibiting an opioid toxidrome were significantly less likely to develop seizures (OR = 0.12, 95% CI: 0.03–0.60). Ingestion of tramadol as a means of self-harm and age were not associated with an increased risk of seizures. There was no significant association between naloxone administration and seizures (OR = 0.30, 95% CI 0.07–1.25).

Conclusions: Based on data from the ToxIC registry, tramadol induced seizures are more likely in Asian patients and those abusing or misusing the medication. There was no association found between the development of seizures and the use of naloxone.

ARTICLE HISTORY
Received 30 July 2018
Revised 2 November 2018
Accepted 7 November 2018
Published online 25 January 2019

KEYWORDS
Tramadol; seizure; overdose; naloxone; ToxIC

Introduction

Opioid prescribing started to decrease in the early 2010s [1,2], at least in part due to the reclassification of hydrocodone as a schedule II drug, the revised guidance for opioid prescribing by the Centers for Disease Control and Prevention (CDC), and the increased awareness of the ongoing opioid epidemic [3–5]. This shift in prescribing patterns is associated with an increase in prescribing of schedule III/IV analgesics, such as the schedule IV analgesic tramadol [6–9]. Tramadol is a less potent μ-agonist than morphine and is generally considered to be a "safer" opioid alternative [10]. Along with the increased number of tramadol prescriptions, there has also been a two-fold increase in the number of calls to poison centers related to tramadol ingestions such that calls have increased from 5965 in 2006 to 12,108 in 2016 [11,12].

Tramadol is a unique synthetic drug; its chemical structure and pharmacologic activity are similar to those of the atypical antidepressant venlafaxine. The primary mechanism of action of the parent compound is serotonin and norepinephrine reuptake inhibition as well as weak μ-receptor agonism. The active metabolite *o*-desmethyltramadol is primarily responsible for the μ-receptor agonism [13]. The metabolism of tramadol to *o*-desmethyltramadol is facilitated by the hepatic enzyme CYP2D6, the activity of which varies widely between individuals [14]. Overdoses of tramadol are associated with seizures [15–18], serotonin syndrome [10], and CNS depression [19]. Seizures have been noted to occur in 14%–35% of tramadol poisoned patients [18,20–23] and can occur even with therapeutic use [24]. This may be due to tramadol's inhibitory effect on GABA receptors at high doses [25], a characteristic shared by morphine [26], which has anticonvulsant activity at low doses and is proconvulsant at high doses [27], as well as meperidine, propoxyphene, and pentazocine [28]. The interplay between opioid activity and seizure activity is complex, and likely related to the specific effect of the κ-, δ-, and μ-opioid receptors. κ-receptors are primarily found on glutamatergic neurons, yielding a net inhibitory effect, while δ- and μ-receptors are often located on neurons that exert inhibition on glutamatergic neurons; thus, their activation results in a net disinhibition [29].

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Even though seizure activity from tramadol has been associated with higher doses [10], the occurrence of seizures from tramadol may not be dose-dependent. Talaie et al. [21] reported, in a study of 120 tramadol poisoned patients, that the highest number of seizures occurred at doses between 500 and 1000 mg, and that there was no association between increasing doses and increased seizure activity.

While there is evidence that tramadol ingestion may induce seizures, it is currently unclear what risk factors, if any, distinguish between those who do and those who do not develop seizures. The primary purpose of this study is to evaluate the characteristics associated with seizures following single agent tramadol ingestion.

Of particular interest to us is the effect of naloxone administration. It has been hypothesized that naloxone reduces the rates of seizure in tramadol poisoned patients [20,30–33]. This is, however, controversial, as two studies have suggested that naloxone may actually increase the risk of developing seizures [34,35]. The secondary objective of our study is to compare the rate of seizures in tramadol poisoned individuals treated with naloxone and those not treated with naloxone.

Methods

Study setting and design

This study was an analysis of data collected by the Toxicology Investigators Consortium (ToxIC), a prospective multicenter registry, with participating sites in the United States, Canada, Israel, and Thailand, [36] that is sponsored by the American College of Medical Toxicology [37]. Cases entered into the registry have been evaluated at the bedside by a Medical Toxicologist. This study was approved by the ToxIC Research Board and was determined to be exempt from review by our Institutional Review Board (IRB).

Inclusion/exclusion criteria

The electronic database was queried for all cases involving a tramadol exposure from 01/01/2014 through 12/31/2017. Only single-agent exposure cases were included in this study. All reasons for ingestion, ages, and subject races were included. Cases were excluded if there was a multi-agent exposure, if the evaluation was for a withdrawal syndrome, or if the signs and symptoms were not deemed to be "likely" due to the toxicological exposure, as determined by the Medical Toxicologist evaluating the patient at bedside.

Statistical analysis

Categorical variables were described using percentages and 95% confidence intervals (95% CI). Continuous variables were described using medians and interquartile ranges. Categorical demographic variables were compared across the Seizure and No-Seizure groups using the χ^2 test or Fisher's exact test when the expected cell count was less than five. Continuous demographic variables were compared across the Seizure and No-Seizure groups using the Mann–Whitney *U* test. Binary logistic regressions were used to evaluate the associations between seizures and toxidromes, symptoms, and treatments. Unadjusted relationships between variables are presented as odds ratios (ORs) with corresponding 95% CI. Across the data set, 6.01% of data points were missing and the pattern of missingness was consistent with missing completely at random mechanisms ($p > .9$). Missing data were imputed using fully conditional specification, an iterative method that relies on Markov Chain Monte Carlo procedures. Analyses were conducted using SPSS v24 (IBM; Armonk, NY, USA).

Table 1. Demographics of patients who experienced and did not experience seizures.

Demographic	Total n/M	%	No seizure %/M	No seizure 95% CI/IQR	Seizure %/M	Seizure 95% CI/IQR
Race						
Asian	22	27.5	9.7	(3.2–24.8)	44.4	(29.9–60.1)
Black	9	11.3	13.9	(5.8–28.9)	8.0	(2.4–23.2)
Native American	5	6.3	8.7	(2.0–29.4)	5	(0.8–24.3)
Other	4	5	5.9	(0.7–36.3)	2.7	(0.4–17.2)
White	40	50	61.4	(43.1–76.5)	40.1	(26.3–55.9)
Age, M (IQR)	26	(17–49)	41.5	(19–53.5)	20	(17–41)
Hispanic	9	11.3	10.8	(2.4–37.1)	10.5	(4–24.8)
Gender						
Male	48	60.0	50.5	(34.8–66.2)	68.0	(52.4–80.3)
Female	32	40.0	49.5	(33.9–65.2)	32.0	(19.7–47.6)
Chronicity						
Acute	57.0	71.3	71.1	(54.0–83.7)	71.3	(55.5–83.2)
Acute on chronic	15.0	18.8	17.3	(7.7–34.4)	20.6	(10.6–36.0)
Chronic	8.0	10	11.5	(4.4–27.0)	8.1	(2.7–22.0)
Reason for overdose						
Self-harm	18	22.5	28.4	(16.2–44.9)	17.7	(8.7–32.6)
Abuse/misuse	43	53.8	39.0	(24.7–55.4)	67.0	(51.3–79.7)

M: median; IQR: interquartile range; 95% CI: 95% confidence interval.

Results

There were 33,393 cases reported in the ToxIC registry between 01/01/2014 and 12/31/2017 [36,38,39]. During this time period there were 85 cases of single-agent exposure to tramadol. As was observed in the National Poison Data System (NPDS) data [11,12], there was an increase in tramadol related cases in the ToxIC registry with no cases in 2014, 2.6 cases per 1000 in 2015 and 2016 and 5.2 cases per 1000 in 2017. Of the 85 patients with single ingestion tramadol poisonings, 80 were classified as having reactions that were "likely" caused by tramadol exposure, and five were excluded as their signs and symptoms were not thought to be due to their toxicologic exposure by the evaluating Medical Toxicologist. All exposures were by means of ingestion. The subjects were composed of 60% males. The median age was 26 years (IQR: 17–49 years). About 50% of the sample population was white and 22% were Asian (Table 1). There were 2.4 times as many subjects who abused or misused tramadol than those who took the medication in a suicide attempt. In total, 42 (52.5%) of the patients developed seizures.

Patient gender, chronicity of ingestion, and suicidal intent did not significantly differ between patients who had seizures and those who did not. The χ^2 evaluating the association between seizures and race was significant ($p = .02$). A binary logistic regression with race as the predictor (dummy-coded with "White" as the referent category) and seizure as the outcome revealed that Asian patients were more likely to

Table 2. Characteristics of patients who did and did not experience a seizure.

Characteristic	*n*	Total %	%	No seizure 95% CI	%	Seizure 95% CI	Odds ratio[a]	95% CI
Toxidromes								
Serotonin syndrome	9	11.3	13.2	(5.6–28.0)	7.2	(2.3–20.0)	0.51	(0.11–2.3)
Toxidrome–opioid	13	16.3	29.0	(16.8–45.2)	4.8	(1.2–17.2)	0.12	(0.03–0.60)
Symptoms								
CNS depression	21	26.3	38.4	(24.3–54.7)	15.3	(7.1–29.9)	0.29	(0.10–0.87)
Respiratory depression	9	11.3	13.2	(5.6–28.0)	8.9	(3.0–24.0)	0.65	(0.15–2.88)
Agitation	9	11.3	18.4	(9.0–33.9)	2.4	(0.3–15.1)	0.11	(0.01–0.93)
Myoclonus	10	12.5	23.7	(12.8–39.7)	3.2	(0.5–18.8)	0.11	(0.01–0.85)
Treatments								
Naloxone	11	13.8	20.5	(10.3–36.6)	7.2	(2.3–20.0)	0.30	(0.07–1.25)
Benzodiazepines	25	31.3	18.4	(9.0–33.9)	41.6	(27.7–57.0)	3.16	(1.13–8.83)

[a]Unadjusted odds ratio.
95% CI: 95% confidence interval.

suffer from a seizure (OR = 7.2, 95% CI: 1.9–27.3, $p = .004$). Lastly, patients who had seizures were more likely to have abused or misused tramadol. Initially, patients who had seizures were also found to be significantly younger than patients who did not, however further exploration of the associations between seizures, age, and race revealed that Asian patients were, on average, younger than other patients (median age for Asian patients = 17; median age for other patients = 41; $p < .001$). This leaves open the possibility that confounding accounts for at least some of the association between seizures, age, and race. Therefore, an additional logistic regression including both race, age, gender, ethnicity, and toxidrome as predictors was conducted. This regression revealed that Asian patients were more likely to suffer from seizures (OR = 5.2, 95% CI: 1.06–24.2, $p = .04$) and that the opioid toxidrome is associated with lower likelihood of seizures (OR = 0.12, 95% CI: 0.02–0.71, $p = .02$); however, age was no longer associated with seizures (OR = 0.99, 95% CI: 0.97–1.03, $p = .77$).

Approximately 11% of the subjects developed serotonin syndrome; however, the association between the development of serotonin syndrome and the development of seizures was nonsignificant. CNS depression, agitation and myoclonus were all associated with decreased odds of having a seizure (Table 2). Sixteen percent of the subjects exhibited an opioid toxidrome. These subjects were somewhat – though, non-significantly – more likely to be treated with naloxone (OR 3.9, 95% CI 0.94–16.4) and were less likely to develop seizures (OR 0.12, 95% CI 0.03–0.60). However, the association between naloxone administration and seizures was nonsignificant (OR 0.30, 95% CI 0.07–1.25).

Discussion

In our sample, 52.5% of patients developed seizures. This is higher than previously reported by Eizadi-Mood [20], Ryan [40], and Almalki [41] who found rates of seizures of 12.5% in tramadol poisoned patients admitted to an inpatient unit, 10% in patients poisoned with at least 400 mg and admitted to an inpatient unit, and 9% using the National Poison Data System, respectively. This greater rate of seizures may be due to the fact that the subjects reported to the ToxIC registry had potentially a more severe illness because they required emergency department evaluation or admission and bedside evaluation by a medical toxicologist. On the other hand, NPDS data includes subjects who may or may not have actually been poisoned and may not have even been evaluated at a medical treatment facility. Additionally, the number of patients who abuse or misuse tramadol may account for this large discrepancy in reported percentage of seizures. These other studies did not list the reason for ingestion, while we found 54% abused or misused tramadol. From our own data, there is a higher risk of seizures from abuse and misuse, potentially due to a more chronic ingestion, rather than an acute single overdose.

We found that Asian patients were more likely to develop seizures, which has not been previously reported. We hypothesize this may be due to altered CYP2D6 metabolism. The frequency of the reduced function allele *CYP2D6*10* is elevated in Asian populations and may be present in 40%–50% of individuals [42–44]. This allele causes slower drug metabolism [42], has been associated with prolonged mean serum half-life of tramadol in homozygous individuals compared with normal or heterozygous subjects [45], and is correlated with increased doses of tramadol for post-surgical pain control [43]. The parent compound is known to cause serotonin and norepinephrine reuptake inhibition [13]; its prolonged presence may in part explain the increased seizure frequency in this population due to increase risk from serotonergic toxicity.

Some research suggests that age is an important risk factor for developing seizures. Seizures occur most often in adults aged 25 with a range of 25–44 years [10]. Eizadi-Mood [20] found that there was an increased risk of seizures as a patient's age increased following tramadol ingestion, with an odds ratio of 2.09. However, this was not replicated in the present sample. The unadjusted comparison suggested that younger patients were more likely to develop seizures; however, this appears to be attributable to confounding with patient race. When adjusted for race, the association between age and seizures was no longer significant.

The association between the diagnosis of serotonin syndrome and seizures was non-significant. In prior studies, seizures occurred at a higher rate in co-ingestions with other serotonergic agents, likely reflecting a synergistic effect with the serotoninergic activity of tramadol [10,46]. It is unknown if these subjects are more likely to be treated with benzodiazepines, the mainstay of treatment for serotonin syndrome, thereby preventing the development of seizures, additionally it is possible that the patients were misdiagnosed with

serotonin syndrome, although, as they were all evaluated at bedside by a medical toxicologist, this possibility is less likely.

Patients acutely intoxicated with tramadol may present with an opioid toxidrome, and therefore might be empirically treated with naloxone, a μ-receptor antagonist [47]. Prior studies performed in animal models and in Middle Eastern countries, where tramadol use and abuse are high, have shown that naloxone may decrease the incidence, duration, and severity of seizures associated with tramadol overdose [20,30–33]. In particular, Eizadi-Mood [20] reported that of the 140 tramadol poisoned patients admitted to the Clinical Toxicology Department of Isfahan University, only 5% of patients developed seizures when naloxone was administered, compared with 14% who developed seizures when naloxone was not administered.

The attenuated risk of seizure following naloxone administration has been hypothesized to be related to the opioid-dependent GABA inhibitory pathway [48], where opioids inhibit GABAergic inhibitory postsynaptic currents [49]. However, in direct contradiction to this hypothesis, one murine study demonstrated that naloxone administration potentiated seizures at high tramadol doses [35] and a rat study showed a significantly increased rate ($p < .01$) and prolonged duration of tramadol induced seizures [34]. This potentiation of seizure activity has been proposed to be from direct naloxone antagonism of the $GABA_A$ receptor [50–52]. In the present study we were unable to demonstrate that the rates of seizure generation significantly decreased in association with naloxone administration. We did detect a non-significant decrease in seizure activity when naloxone was administered, which may have become significant with a larger sample size. Further studies are needed to further elucidate whether there is in fact a decreased risk of seizures following naloxone administration, which is a safe and relatively inexpensive means to prevent adverse events after tramadol poisoning.

Limitations

The limitations of this study are that it is a post-hoc analysis of previously prospectively collected data and the limited number and breadth of variables recorded in the registry. We were unable to determine, for example, if subjects had a history of seizure disorders, the time of seizure onset, how long after tramadol ingestion the naloxone was administered, the dose and route of naloxone administration, and its temporal relationship to seizures. Additionally, while the tramadol dose can be recorded, it was missing for nearly all of the entries thereby limiting analysis.

Similarly, the present study also included a small sample size. This limited the extent to which multivariate analyses could be conducted thereby allowing for the possibility that some of the associations were due to confounding. For example, the association between age and seizures in the present sample appears to be the result of confounding with race. Future work will need to control for other possible confounding variables.

We limited our inclusion criteria to those individuals with single-agent tramadol exposures, however both seizures and serotonin syndrome occur more commonly with concomitant exposure to serotonergic agents [10,46] and CYP2D6 inhibitors [53]. It is possible that the effect of naloxone is muted or potentiated by the addition of these agents. Despite the exclusion of co-ingestions, this study population experienced a higher incidence of seizures than has been previously reported following tramadol overdose. This may reflect a recruitment bias, as all subjects were sick enough to warrant a bedside consultation by a medical toxicologist. Lastly, this data set relies on voluntary entry by medical toxicologists and medical toxicology residents in-training. Given that less ill patients may have been entered at a lower rate than sicker patients, it is possible that the data set is incomplete and is skewed toward a severely ill patient population.

Conclusions

This study found significant increase in seizure activity in patients of Asian race who used tramadol as well as in patients who abused or misused tramadol. There was no association found between the diagnosis of serotonin syndrome or the use of naloxone and the development of seizures.

Disclosure statement

No potential conflict of interest was reported by the authors.

Disclaimer

The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of the Air Force Institute of Technology, the U.S. Air Force Office of the Surgeon General, the Department of the Air Force, the Department of Defense or the U.S. Government.

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References

[1] Levy B, Paulozzi L, Mack KA, et al. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. Am J Prev Med. 2015; 49:409–413.
[2] Kuo YF, Raji MA, Chen NW, et al. Trends in opioid prescriptions among part d medicare recipients from 2007 to 2012. Am J Med. 2016;129:221–230.
[3] Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep. 2016;65:1–49. Mar 18
[4] Guy GP, Jr., Zhang K, Bohm MK, et al. Vital signs: changes in opioid prescribing in the United States, 2006-2015. MMWR Morb Mortal Wkly Rep. 2017;66:697–704.
[5] Schultz S, Chamberlain C, Vulcan M, et al. Analgesic utilization before and after rescheduling of hydrocodone in a large academic level 1 trauma center. J Opioid Manag. 2016;12:119–122.
[6] Raji MA, Kuo YF, Adhikari D, et al. Decline in opioid prescribing after federal rescheduling of hydrocodone products. Pharmacoepidemiol Drug Saf. 2018;27:513–519.

[7] Seago S, Hayek A, Pruszynski J, et al. Change in prescription habits after federal rescheduling of hydrocodone combination products. Proc (Bayl Univ Med Cent). 2016;29:268–270.

[8] Oehler EC, Day RL, Robinson DB, et al. Has the rescheduling of hydrocodone changed ED prescribing practices?. Am J Emerg Med. 2016;34:2388–2391.

[9] Haynes A, Kleinschmidt K, Forrester MB, et al. Trends in analgesic exposures reported to Texas Poison Centers following increased regulation of hydrocodone. Clin Toxicol. 2016;54:434–440.

[10] Hassamal S, Miotto K, Dale W, et al. Tramadol: understanding the risk of serotonin syndrome and seizures. Am J Med. 2018;131: 1382.e1–1382.e6.

[11] Bronstein AC, Spyker DA, Cantilena LR, Jr, et al. 2006 Annual report of the american association of poison control centers' national poison data system (NPDS). Clin Toxicol. 2007;45:815–917.

[12] Gummin DD, Mowry JB, Spyker DA, et al. 2016 annual report of the american association of poison control centers' national poison data system (NPDS): 34th annual report. Clin Toxicol. 2017; 55:1072–1252.

[13] Gong L, Stamer UM, Tzvetkov MV, et al. PharmGKB summary: tramadol pathway. Pharmacogenet Genom. 2014;24:374–380.

[14] Stamer UM, Musshoff F, Kobilay M, et al. Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther. 2007;82:41–47.

[15] Labate A, Newton MR, Vernon GM, et al. Tramadol and new-onset seizures. Med J Aust. 2005;182:423.

[16] Petramfar P, Haghighi A. Tramadol induced seizure: report of 106 patients. Iran Red Crescent Med J. 2010;12:49.

[17] Sansone RA, Sansone LA. Tramadol: seizures, serotonin syndrome, and coadministered antidepressants. Psychiatry (Edgmont). 2009;6: 17–21.

[18] Taghaddosinejad F, Mehrpour O, Afshari R, et al. Factors related to seizure in tramadol poisoning and its blood concentration. J Med Toxicol. 2011;7:183–188.

[19] Shadnia S, Soltaninejad K, Heydari K, et al. Tramadol intoxication: a review of 114 cases. Hum Exp Toxicol. 2008;27:201–205.

[20] Eizadi-Mood N, Ozcan D, Sabzghabaee AM, et al. Does naloxone prevent seizure in tramadol intoxicated patients? Int J Prev Med. 2014;5:302–307.

[21] Talaie H, Panahandeh R, Fayaznouri M, et al. Dose-independent occurrence of seizure with tramadol. J Med Toxicol. 2009;5:63–67.

[22] Marquardt KA, Alsop JA, Albertson TE. Tramadol exposures reported to statewide poison control system. Ann Pharmacother. 2005;39:1039–1044.

[23] Shadnia S, Brent J, Mousavi-Fatemi K, et al. Recurrent seizures in tramadol intoxication: implications for therapy based on 100 patients. Basic Clin Pharmacol Toxicol. 2012;111:133–136.

[24] Jick H, Derby LE, Vasilakis C, et al. The risk of seizures associated with tramadol. Pharmacotherapy 1998;18:607–611.

[25] Hara K, Minami K, Sata T. The effects of tramadol and its metabolite on glycine, gamma-aminobutyric acidA, and N-methyl-D-aspartate receptors expressed in Xenopus oocytes. Anesth Analg. 2005;100:1400–1405.

[26] Frenk H. Pro- and anticonvulsant actions of morphine and the endogenous opioids: involvement and interactions of multiple opiate and non-opiate systems. Brain Res. 1983;287:197–210.

[27] Shafaroodi H, Samini M, Moezi L, et al. The interaction of cannabinoids and opioids on pentylenetetrazole-induced seizure threshold in mice. Neuropharmacology. 2004;47:390–400.

[28] Hantson PE. Toxicant-induced seizures. In: Brent J, Burkhart K, Dargan P, et al., editors. Critical care toxicology: diagnosis and management of the critically poisoned patient. New York (NY): Springer; 2017. p. 447–473.

[29] Burtscher J, Schwarzer C. The opioid system in temporal lobe epilepsy: functional role and therapeutic potential. Front Mol Neurosci. 2017;10:245.

[30] Gilbert PE, Martin WR. Antagonism of the convulsant effects of heroin, d-propoxyphene, meperidine, normeperidine and thebaine by naloxone in mice. J Pharmacol Exp Ther. 1975;192:538–541.

[31] Prow NA, Irani DN. The opioid receptor antagonist, naloxone, protects spinal motor neurons in a murine model of alphavirus encephalomyelitis. Exp Neurol. 2007;205:461–470.

[32] Saidi H, Ghadiri M, Abbasi S, et al. Efficacy and safety of naloxone in the management of postseizure complaints of tramadol intoxicated patients: a self-controlled study. Emerg Med J. 2010;27:928–930.

[33] Yang L, Li F, Ge W, et al. Protective effects of naloxone in two-hit seizure model. Epilepsia. 2010;51:344–353.

[34] Lagard C, Malissin I, Indja W, et al. Is naloxone the best antidote to reverse tramadol-induced neuro-respiratory toxicity in overdose? An experimental investigation in the rat. Clin Toxicol. 2018;56:737–743.

[35] Raffa RB, Stone DJ. Unexceptional seizure potential of tramadol or its enantiomers or metabolites in mice. J Pharmacol Exp Ther. 2008;325:500–506.

[36] Farrugia LA, Rhyee SH, Calello DP, et al. The toxicology investigators consortium case registry-the 2016 experience. J Med Toxicol. 2017;13:203–226.

[37] Wax PM, Kleinschmidt KC, Brent J, et al. The toxicology investigators consortium (ToxIC) registry. J Med Toxicol. 2011;7:259–265.

[38] Rhyee SH, Farrugia L, Campleman SL, et al. The toxicology investigators consortium case registry–the 2014 experience. J Med Toxicol. 2015;11:388–409.

[39] Farrugia LA, Rhyee SH, Campleman SL, et al. The toxicology investigators consortium case registry-the 2015 experience. J Med Toxicol. 2016;12:224–247.

[40] Ryan NM, Isbister GK. Tramadol overdose causes seizures and respiratory depression but serotonin toxicity appears unlikely. Clin Toxicol. 2015;53:545–550.

[41] Almalki M, Almulhim K, Hon S, et al. Abstracts from the American College of Medical Toxicology (ACMT) Annual Scientific Meeting: tramadol exposures reported to NPDS. J Med Toxicol. 2017;13:42.

[42] Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics. 2002; 3:229–243.

[43] Wang G, Zhang H, He F, et al. Effect of the CYP2D6*10 C188T polymorphism on postoperative tramadol analgesia in a Chinese population. Eur J Clin Pharmacol. 2006;62:927–931.

[44] Gan SH, Ismail R, Wan Adnan WA, et al. Impact of CYP2D6 genetic polymorphism on tramadol pharmacokinetics and pharmacodynamics. Mol Diagn Ther. 2007;11:171–181.

[45] Gan SH, Ismail R, Wan Adnan WA, et al. Correlation of tramadol pharmacokinetics and CYP2D6*10 genotype in Malaysian subjects. J Pharm Biomed Anal. 2002 ;30:189–195. 5

[46] Kahn LH, Alderfer RJ, Graham DJ. Seizures reported with tramadol. JAMA. 1997;278:1661.

[47] Spiller HA, Gorman SE, Villalobos D, et al. Prospective multicenter evaluation of tramadol exposure. J Toxicol Clin Toxicol. 1997;35: 361–364.

[48] Rehni AK, Singh I, Kumar M. Tramadol-induced seizurogenic effect: a possible role of opioid-dependent gamma-aminobutyric acid inhibitory pathway. Basic Clin Pharmacol Toxicol. 2008;103: 262–266.

[49] Miura M, Saino-Saito S, Masuda M, et al. Compartment-specific modulation of GABAergic synaptic transmission by mu-opioid receptor in the mouse striatum with green fluorescent protein-expressing dopamine islands. J Neurosci. 2007;27:9721–9728.

[50] Dingledine R, Iversen LL, Breuker E. Naloxone as a GABA antagonist: evidence from iontophoretic, receptor binding and convulsant studies. Eur J Pharmacol. 1978;47:19–27.

[51] Svensson AI, Berntsson A, Eirefelt M, et al. Naloxone antagonizes GABA(A)/benzodiazepine receptor function in rat corticohippocampal synaptoneurosomes. J Neural Transm (Vienna). 2000;107: 261–270.

[52] Gruol DL, Barker JL, Smith TG. Naloxone antagonism of GABA-evoked membrane polarizations in cultured mouse spinal cord neurons. Brain Res. 1980;198:323–332.

[53] Gardner JS, Blough D, Drinkard CR, et al. Tramadol and seizures: a surveillance study in a managed care population. Pharmacotherapy. 2000;20:1423–1431.