Causes, nature and toxicology of tramadolassociated deaths reported in the peerreviewed literature

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Causes, nature and toxicology of tramadol associated deaths reported in the peer-reviewed literature: A systematic review of case studies and case series

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Abstract

Background: Despite the increased reporting of tramadol poisoning, the nature and toxicology of tramadol associated deaths have not been adequately subjected to systematic evaluation. This study aims to investigate the causes, nature and toxicology of tramadol associated deaths by systematically reviewing the case studies and case series published in the peer-reviewed journals.

Methods: Scopus, Embase, and Medline, Google Scholar were searched from inception until 30th May 2020 to identify the case studies and case series published in English that reported tramadol associated deaths. Data on number of deaths, routes of administration, toxicological data and any concomitant drug usage were extracted. The Joanna Briggs Institute's quality assessment tool was used to assess the quality of included studies.

Results: The initial searches identified 451 articles. Of these, 12 (eight case studies and four case series) studies were considered in the review which represented a total of 181 deaths with UK (n=127) and Sweden (n=17) reporting most deaths. Intentional suicide was the cause of tramadol poisoning in 54 of the 181 cases. Data on routes of administration was often missing, however, most common related to oral route (15.5%). Mixed drug toxicity was among the causes of reported deaths (n= 127, 70.2%), where most cases were receiving other CNS depressants, especially benzodiazepines. However, tramadol, as the sole cause of death, was reported in 8 cases. The mean level of blood tramadol for the deaths was 10.6 µg/ml.

Conclusion: The unintentional nature of many tramadol deaths has been reported and it is important to consider that the drug can be acquired through illicit means. Healthcare practitioners need to build a strong understanding about tramadol's possible toxicity and should take caution when using tramadol in combination with other drugs.

Keywords: Tramadol, toxicity, poisoning, overdose, death, mortality, case studies, and case series.

Impact of findings on practice

- The healthcare professionals who are responsible for tramadol prescriptions, should be adequately supported and trained on their side-effects and its dual mechanism of action.
- The risks associated with ingesting tramadol along with serotonin reuptake inhibitors (SRIs), monoamine oxidase inhibitors (MAOIs), alcohol, and CNS depressants should be acknowledged

Introduction

Tramadol is the world's most prescribed synthetic pain treatment that is used globally for chronic or moderate-to-severe pain [1]. Compared to opioids, tramadol exerts analgesia but with fewer side effects [2,3]. Tramadol is

commercially available as a racemic mixture, which is a 1:1 combination of two enantiomers that bind weakly to the μ class of opioid receptors and exert synergistic benefits in terms of pain management [4]. The (+) enantiomer increases the release of serotonin, whereas the (-) enantiomer inhibits the reuptake of noradrenaline. [4-6] Therefore, tramadol has two modes of action responsible for its central analgesic effects [7]. However, tramadol is also associated with increased abuse and dependence, besides causing death [2,8]. This may occur as a single drug or in combination with other drugs [2,9-11].

Tramadol can be administered in the form of tablets, oral drops, or as an injection [12]. Oral administration is the most common method of giving the drug [3]. The bioavailability of an oral dose of tramadol is 75%, which may rise to 100% with a programmed schedule [12,13]. Therapeutic doses of tramadol range from 50 to 100 mg (50 mg oral and 50-100 mg intramuscular [IM]) and may be administered up to three or four times a day [14]. Generally, doses exceeding 400 mg/day are unnecessary [15,16]. Information from the International Association of Forensic Toxicologists states that in adults, therapeutic blood levels of tramadol are between 0.1 and 0.8 mg/L, whereas toxic levels are between 1 and 2 mg/L [15]. Lethal concentrations typically exceed 2 mg/L, indicating that the therapeutic, toxic, and lethal levels of tramadol are somewhat close together [15,17,18].

Metabolism of tramadol is facilitated by cytochrome P450 (CYP450) enzymes [4]. CYP450 polymorphisms predict the toxicity of tramadol [2,19]. The variation is likely to be attributed to genetic differences in CYP2D6 activity. Different CYP2D6 genotypes result in different responses [2,20]. Patients with renal failure can be given tramadol, though the dose should be reduced in these patients and those with liver cirrhosis [22-24]. Evidence suggests that poor metabolizers of CYP2D6 are commonly found in European Caucasians (7%) and 1% in Orientals [21]. The risk of tramadol toxicity is higher in people who metabolise the drug very rapidly (ultra-rapid metabolisers) [20], yielding elevated plasma levels of O-desmethyltramadol (ODT) [2,19,25]. ODT is the major active metabolite of tramadol, which has double the potency for pain management compared to the parent drug [3]. Although UMs experience better pain relief than extensive metabolisers [26], they are also more likely to experience more nausea than the latter group [25].

In England, a remarkable increase by approximately 5.2 million between 2005 and 2012 in tramadol prescriptions measured by the number of Daily Defined Doses (DDD) was reported [27]. In addition to the managing the concerns related to the frequency of tramadol prescriptions, the risk to benefit ratio should be considered during its administration [28]. Moreover, tramadol is one of the most prominent causes of poisoning with an increased tendency to commit suicide among adult males with a prior history of drug addiction and mental health issues [9,11]. Consequently, The Misuse of Drugs Act 1971 and the Misuse of Drugs Regulations 2001 in the United

Kingdom were amended on the 10th June 2014 to reclassify certain drugs, including tramadol, that has then been classified as Schedule 3 controlled [27].

Many symptoms have been reported following tramadol overdose, including agitation, ataxia, blurred vision, coma, hypertension, hypo- and hyperreflexia, itching, lethargy, oedema, palpitation, perspiration, bradycardia, and respiratory depression [10,11,29,30]. Nausea, constipation, dizziness, headaches, and vertigo are typical features of acute tramadol toxicity [10,29,31]. Compared to other opioid toxicity, miosis is less common, affecting no more than a third of patients; this is likely to be related to the drug's inhibition of serotonin and noradrenaline reuptake [32,33]. Following tramadol overdose, asystole, cardio-respiratory depression, liver failure, and resistant shock are the most common mechanisms of death [10,11,18,23]. The compounds that when co-administered with tramadol, are most likely to result in death include ethanol, propranolol, and trazodone; co-administered CNS depressants, such as barbiturates, benzodiazepines, and serotonergic drugs are particularly risky [9,10,15,18]. Despite the increased reporting of tramadol poisoning, the nature and toxicology of tramadol associated deaths have not been adequately subjected to systematic evaluation. Such knowledge is imperative in the understanding and prevention of tramadol related harm and designing interventions focused on drug prescribers and users.

Aims of the review

This review aims to systematically review the causes, characteristics, routes of administration, and toxicology of tramadol associated deaths by using the case studies and case series published in peer-reviewed journals.

Methods

This study has been reported based on PRISMA guideline for reporting systematic reviews and meta-analysis (see appendix 1 for PRISMA checklist).

Data sources and searches

Searches were conducted using search terms "Tramadol", "toxicity", "death", "case studies," "case series," in three databases Scopus, Embase, and Medline and Google Scholar from inception until 30th May 2020. In addition, the first 20 pages of Google Scholar and the reference lists of the retrieved articles were screened to ensure no relevant articles were missed.

Study selection

Articles were imported into Endnote to carry out the initial screening. Inclusion and exclusion criteria were applied to screened titles and abstracts. All duplicated articles were deleted. The full texts of articles deemed to be relevant were retrieved. Case studies and case series published in English language and reporting tramadol-related deaths of adults aged 16 years or older were retained. Excluded articles included those that focused on tramadol analogues or products mixed with tramadol. Furthermore, abstracts, conference proceedings, and articles published in a language other than English language were not included in the review.

Data Extraction, quality assessment and synthesis

A pair of independent reviewers (SA and EC) screened the articles for eligibility, firstly at the title and then at the full-text level. Any differences were resolved through discussion. A data extraction tool was developed to extract information from the articles reporting the number of deaths, routes of administration, toxicological data, and any concomitant drug usage (see table 1 for characteristics of included studies). The Joanna Briggs Institute's quality assessment tool (JBI) was used to assess the quality of included studies [34].

A narrative synthesis was undertaken due to heterogeneous data. The narrative synthesis focused on geographical distribution, nature, causes, and toxicology of tramadol associated deaths. Every piece of data in the narrative synthesis was visualised using tables of counts and percentages, except for the toxicology data. In the latter case, this was presented in the form of means and ranges.

Results

Search Results

A total of 451 articles were identified and following the removal of duplicates (n=17), the remaining 434 articles were screened. Of these, 12 (eight case studies and four case series) studies were considered in the review (8 case studies: [16], [35], [15], [23], [36], [22], [11] and [30], and 4 case series: [2], [37], [38] and [9]) (Figure 1). These studies reported a total of 181 deaths with UK (n=127) and Sweden (n=17) reporting most deaths.

Quality Assessment

The quality of the included studies was assessed using the Joanna Briggs Institute's tools [34]. Overall, the quality of the case studies was deemed to be good. Most of the studies provided demographic details, patient's clinical status on presentation, diagnostic tests or assessment methods and the results, adverse events or unanticipated events, patient histories and take away lessons. The intervention or treatment procedure and post-intervention

clinical conditions were clearly described in two articles only. The quality of the case series was variable (Tables 2 and 3).

Demography

In the included studies, a total of 181 deaths have been recorded. Most of the deaths occurred in Northern Ireland of UK (n=127, 70.2 %). The remaining cases were identified around rest of the Europe (n= 36), USA (n= 12), and one case in the Republic of Ireland (Appendix 1). Tramadol intoxication was more common among males (n= 116, 64.1%).

Routes of administration

The administration route of tramadol was clearly illustrated in 29 cases, with the most common form of administration being oral (n= 28, 15.5%); one case was recorded as intravenous administration (0.55%).

Cause of deaths

Although the exact cause of death was not reported in most of the studies, amongst the recorded causes were mixed drug toxicity (n= 127, 70.2%), tramadol, and alcohol intoxication (n= 36, 19.8%), and another drug toxicity (n= 4, 2.2%). There is, however, evidence to suggest that deaths can occur from the administration of tramadol alone [11,22,23,30,35,36]. In addition, there were challenges associated with the distinguishing of cases where tramadol had been prescribed from those where it was not administered legitimately.

Of the 181 reported deaths, the cause of tramadol intoxication was reported to be suicidal in 54 cases (29.8%) and 50 cases (27.6%) as tramadol overdose. Tramadol alone as the cause of death had been confirmed in 8 cases (4.4%) in the case reports, and it was the only substance that was detected in 37 cases (20.4%) mentioned in the case series. In the case of 127 deaths associated with mixed toxicity, the most identified drugs were benzodiazepines (44.9%), antidepressant drugs (17.6%), and a range of opioids (14.8%), details of which can be found in Table 4. Of those commonly misused drugs alongside tramadol, 20 possess the potential to result in serotonin syndrome [39]. There was one natural death where toxicological analysis identified the presence of tramadol. Moreover, there was one case of accidental death or death from injuries, such as decapitation [2].

Nature of deaths

Data relating the nature of tramadol-related deaths in the included studies were generally incomplete and vague, except one case where the nature of deaths was described in detail [36].

De Decker et al. reported a case of a young patient who was known to be using tramadol and was identified in an unconscious state. As suggested by various patients who were on the initial patient's ward, the patient had taken

a benzodiazepine before sleeping, and snored throughout the night. However, during the next morning, another patient noticed that he had apnoea, and so he raised this to the attention of the physicians and nurses. When the health professionals arrived, asystole was identified, and the patient began to receive advanced life support. Once the patient had been resuscitated, massive hepatic failure took place along with signs of multiple organ failure. The patient was admitted to the hospital's intensive care unit (ICU). Based on a chest X-ray, consolidation of the left lower lobe was observed, which necessitated a bronchoscopy. Based on the laboratory results, both acute renal failure and acute hepatic failure were indicated. Investigation of the serum on ICU admission indicated the presence of tramadol. However, acute renal failure could not be prevented, which progressed to multiple organ failure. After two days, the patient died. [36].

Toxicology

The toxicology data was included in 11 studies. However, there was considerable variation in the tramadol concentrations in the blood samples. Based upon the cases included in 11 of the 12 articles, the mean tramadol concentration in the blood of all deaths was 10.6 mg/L (range 0.05 – 134 mg/L). As indicated in table 5, research based on post-mortem toxicological typically includes blood samples drawn from multiple sites, such as the femoral and heart.

The findings of the current review indicate that the highest tramadol levels occurred in cases of mixed drug toxicity and were ranging from 0.88 mg/L to 134 mg/L (mean= 35.62 mg/L). This was followed by intoxication by tramadol alone which were ranging from 3.7 mg/L to 61.83 mg/L (mean= 20.76 mg/L).

Discussion

To the author's knowledge, this is the first review that has systematically assessed the causes, characteristics, routes of administration and toxicology of tramadol associated deaths. Most of the deaths were reported in UK [9]. Minimal detail was offered in the included case studies and case series relating to the routes of administration. Nevertheless, the studies which reported routes of administration, majority of the deaths were attributed to the oral route. Additionally, for one patient who received tramadol through the intravenous route of administration, Oertel et al argued that the distribution pattern was the same as the patients who received an oral route of tramadol administration [38].

Tramadol concentration in the peripheral blood and heart specimens did not indicate a notable difference, where the ratio amounted to 1.36. This was also in accordance with the drug's lack of sequestration in the liver. Comparable to morphine, tramadol accumulation was significant in the bile [35]. However, in tramadol

intoxications that resulted in death, femoral blood is generally the desired specimen for post-mortem analysis. This stems from the fact that it is not exposed to post-mortem distribution to the same degree [40].

This study anticipated that the largest concentrations of tramadol would be located in the blood samples of patients whose deaths had been attributed entirely to tramadol alone, rather than its administration in conjunction with other drugs. In other words, the absence of any CNS depressants, such as benzodiazepine, was deemed to require the administration of a larger dose of tramadol to result in fatality. However, this supposition was not supported by the results of this review. The findings of the current review indicate that the highest tramadol levels were (mean= 35.62 mg/L) ranging from (0.88 mg/L to 134 mg/L) occurred in cases of mixed drug toxicity [15]. This was followed by intoxication by tramadol alone, which was ranging from 3.7 mg/L to 61.83 mg/L (mean= 20.76 mg/L) [11]. The threshold at which tramadol acquired a toxic nature ought to have been modified by the presence of the respiratory and CNS depressing effects. Whilst the results of the review lack statistical significance and include a substantial overlap of their range, they do indicate that a multiplicity of variables must be considered when reviewing toxicological analyses. The identification of the highest tramadol concentrations in cases of mixed drug toxicity remains ambiguous. The characteristics of the patients who died from mixed drug toxicity may have some relevance. For example, a history of drug abuse might have increased the opioid tolerance of some patients and thereby elevated the toxic threshold [9].

No concentration greater than 134 mg/l has been reported in this review, and this concentration is regarded as being more than 60 times the toxic level. No indication accounts for this concentration, and although post-mortem redistribution may be implicated, it was not deemed as significant. Additionally, for three cases, the tramadol concentrations in the patient's blood exceeded the toxic concentration. However, it is not possible to attribute any of these deaths solely to tramadol since bromazepam was co-detected at toxic concentrations [15].

Most studies discussed concentrations of tramadol metabolites. Specifically, O-desmethyltramadol (ODT), which comprises a primary tramadol metabolite, is frequently recorded in blood toxicology following the administering of tramadol [2]. Hence, many studies in this review indicated the usefulness of ODT as a means of recognising the fact with which death occurred in the wake of tramadol being administered.

Although the exact cause of death was not reported in most of the studies, amongst the recorded causes were mixed drug toxicity, tramadol, and alcohol intoxication and another drug toxicity. Evidence suggest that deaths can occur from the administration of tramadol alone [11,22,23,30,35,36] or from the coadministration of tramadol with serotonin reuptake inhibitors (SRIs), monoamine oxidase inhibitors (MAOIs), alcohol or CNS depressants (please cite relevant references). The risks associated with coadministration of tramadol and these drugs should be acknowledged to emphasise the possible risk of death at levels that are lower than those linked to tramadol-only poisonings.

The unintentional nature of many tramadol deaths has been reported and it is important to consider that the drug can be acquired through illicit means [9]. The healthcare professionals who are responsible for tramadol prescriptions, should be adequately supported and trained on their side-effects and its dual mechanism of action [9]. Pharmacists may be well placed to offer meaningful intervention and support for people using opioid medicines and tramadol for chronic, non-cancer pain in both community pharmacy and primary and secondary care. It is worth noting that patients with long-term conditions such as hypertension are more likely to have a comorbid diagnosis of depression [41]. Consequently, it is important not to preclude the presence of serotonin syndrome, arising from the concurrent use of tramadol and antidepressants [2, 9]. Tramadol should therefore only be prescribed where necessary, and these prescriptions should be issued in accordance with the local regulations and policies. In patients with tramadol overdose, drug screening for opioids is usually negative. Therefore, the screening for tramadol must be applied to all types of basic toxicological tests.

Further research to expand the knowledge of tramadol interactions with other drugs should be considered. Future studies on the complications of tramadol and its metabolites based on their serum concentrations will produce a greater amount of high-quality data on this issue.

Limitations

This study has some limitations. The bioactivation of tramadol to ODT occurs by CYP2D6, and substantial differences exist in terms of the amount and efficiency of CYP2D6 enzymes, which were not acknowledged in the present review. With these observations in mind, it would be worthwhile to consider isoenzyme metabolism in an analysis of tramadol-associated deaths. Additionally, although this study's target population consisted of adults, children have also been known to die due to tramadol exposure. Furthermore, since studies from non-

indexed journals and unpublished articles were excluded from the review, the comprehensiveness of the literature search may not be as high as would be desirable. The study did not explore the possible impact of confounding factors such as age, gender, employment and education on the study outcomes and the study findings should therefore be interpreted with caution.

In almost all cases, data were not offered on the subjects' symptoms prior to death. Several subjects died while hospitalised, and the deaths generally occurred without witnesses. Most concomitant drugs can lead to serotonin syndrome, and while this was not examined in the present review, the link between this condition and death must be considered.

Conclusion

This systematic review has demonstrated that tramadol should remain controlled and should be cautiously administrated. Healthcare practitioners need to build a strong understanding about tramadol's possible toxicity and should take caution when using tramadol in combination with other drugs.

Declarations

Ethics approval and consent to participate

This work did not require ethics approval and consent to participate.

Consent for publication

Not applicable.

Availability of data and materials

All data have been provided within the manuscript

Competing interest

The authors declare that they have no conflict of interest.

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Authors Contributions

Author EC developed the research question. Author SA conducted the searches and extracted the data. Both EC and SA analysed the data and did the quality assessment. Authors EC, SA, VP and MHN contributed to the preparation of the manuscript.

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1 **Tables**

2 **Table 1: Data extracted from the included case series and case studies**

Study ID	Country	No. of tramadol-related deaths reported	Study design	Cause of tramadol intoxication (no. of pts)	Route of tramadol administration (no. of pts)	Tramadol Concentration from Specified Blood Source (mg/L)	Findings in tramadol-intoxicated patients	Evidence of concomitant drugs
Georinger et al, 1997 [2].	USA	12	Case series	Undetermined (7) Accidental (3) Suicide (2)	Not reported	Range: 0.03-22.59 Mean: 2.41	Not reported	Yes
Michaud et al, 1999 [16].	Switzerland	1	Case report	Overdose	oral	38.3	Not reported	yes
Musshoff and Madea, 2001 [35].	Germany	1	Case report	Overdose	oral	Femoral blood= 9.6 Heart blood= 13.1	Organ failure and respiratory depression	No

Clarot et al, 2003 [15].	France	4	Case report	Not reported	Not reported	Range: 0.88–134 Mean: 35.62	Bloody vomit (*n* = 1) Cardiorespiratory arrest (*n* = 1) Dizziness hypothermia 34C (*n* = 1) Not reported (*n* = 1)	Yes
Loughrey et al, 2003 [23].	Ireland	1	Case report	Overdose	Oral	3.7	Liver failure, Dyspnoea, cyanotic and hypotensive, lactic acidosis, hypoxia and hypoglycaemia. Followed by cardiorespiratory arrest, shortly after admission to ER (*n* = 1)	No
Tjäderborn et al, 2007 [37].	Sweden	17	Case series	Not reported (9) Overdose (8)	Oral (7) Not reported (10)	Range: 1.1–12.0 Mean: 3.74	Not reported	Yes

De Decker et al, 2008 [36].	Belgium	1+7 (2 of them were recorded before) 8	Case report, Case series	Overdose (3) Not reported (5)	Oral (3) Not reported (5)	Range: 1.6-15.1 Mean: 8.75	Tachycardia, coma, hypoglycemia, metabolic acidosis, and multiple Organ failure (*n* = 1)	No
De Backer, et al. 2010 [22].	Belgium	2	Case Report	Suicide overdose (2)	Not reported	Case 1: 7.7 mg/L Case 2: 48.34 mg/L	Pulmonary edema (*n* = 1) Cardiopulmonary arrest followed by death (*n* = 1)	No
Oertel et al, 2011 [38].	Germany	7	Case series	Undetermined (7)	Oral (6) IV (1)	Heart blood Range: 0.24-25.8 Mean: 7.09	Heart failure left and one right Organ failure (*n* = 2)	Yes

						Venous blood Range: 0.06-8.67 Mean: 3.22		
Barbera et al, 2013 [11].	Italy	1	Case report	Suicide Overdose (1)	Oral	Range: 3.7 to 61.83 Mean: 20.76	Vital functions depression, respiratory depression, bradypnea or bradycardia to cardiac arrest (*n* = 1)	No
Randall and Crane, 2014 [9].	Northern Ireland/UK	127	Case series	Suicide (48) Overdose (34) Not reported (45)	Not reported	Range: 1.85–88.8 Mean: Not reported	Seizures (*n* = 1) Multi-organ or liver failure (*n* = 8) Acute liver failure (*n* = 3) Not reported (*n* = 115)	Yes

Gioia et al, 2017 [30].	Italy	2	Case report, Case series	Suicide (2)	Not reported	Case1: Peripheral= 32 Heart= 23.9 Case2: Peripheral= 5.8 Heart= 7.5	Pulmonary edema (*n* = 1) Respiratory depression (*n* = 2	No

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Table 2: Quality assessment of the included case studies

	Michaud et al, 1999	Musshoff and Madea, 2001	Clarot et al, 2003	Loughrey et al, 2003	De Decker et al, 2008	De Backer, et al. 2010	Barbera et al, 2013	Gioia et al, 2017
Were Patient's demographic characteristics clearly described?	✓	✓	✓	✓	✓	✓	✓	✓
Was the Patient's history clearly described and presented as a timeline?	✓	✓	✓	✓	✓	✓	✓	✓
Was the current clinical condition of the Patient on presentation clearly described?	✓	✓	✓	✓	✓	✓	✓	✓
Were diagnostic tests or assessment methods and the results clearly described?	✓	✓	✓	✓	✓	✓	✓	✓
Was the intervention(s) or treatment procedure(s) clearly described?	N/A	N/A	N/A	N/A	✓	✓	N/A	N/A
Was the post-intervention clinical condition clearly described?	N/A	N/A	N/A	N/A	✓	✓	N/A	N/A
Were adverse events (harms) or unanticipated events identified and described?	✓	✓	✓	✓	✓	✓	✓	✓

Does the case report provide takeaway lessons?	✓	✓	✓	✓	✓	✓	✓	✓

1

Yes	**No**	**Unclear**	**Not applicable**
✓	×	-	N/A

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4 **Table 3: Quality assessment of the included case series**

	Georinger et al, 1997	Tjäderborn et al, 2007	Oertel et al, 2011	Randall and Crane, 2014
Were there clear criteria for inclusion in the case series?	✓	✓	✓	✓
Was the condition measured in a standard, reliable way for all participants included in the case series?	✓	✓	✓	✓
Were valid methods used for identification of the condition for all participants included in the case series?	✓	✓	✓	✓
Did the case series have consecutive inclusion of participants?	✓	✓	✓	✓
Did the case series have complete inclusion of participants?	✓	✓	✓	✓

Was there clear reporting of the demographics of the participants in the study?	✓	✓	✓	✓
Was there clear reporting of clinical information of the participants?	✓	✓	-	✓
Were the outcomes or follow up results of cases clearly reported?	N/A	N/A	N/A	N/A
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	✓	✓	✓	✓
Was statistical analysis appropriate?	-	-	-	-

1

Table 4: **Drugs Suspected in tramadol-Associated Deaths Classified as a Mixed Drug Toxicity**

Drug class	**Drug**	**Total Number Reported in Toxicology**	**% of the total tramadol associated deaths reported in the included studies (n=181)**
Benzodiazepine	Alprazolam n= 4 Bromazepam n= 2 Diazepam n= 70 Flunitrazepam n= 3	79	43.65%
Non-benzodiazepine	Zopiclone n= 2	2	1.1%
Alcohol	Alcohol n= 55	55	30.4%
Muscle relaxants Carbamate	Carisoprodol n= 1	1	0.5%
Barbiturate	Phenobarbital n= 1	1	0.5%
Phenothiazine Antipruritic	Alimemazine n= 3	3	1.7%
Antidepressant/Antipsychotic	Venlafaxine n= 3 Doxepin n= 1 Amitriptyline n= 5 Desipramine n= 1 Nortriptyline n= 3 Trazodone n= 1 Mirtazapine n= 4 Propiomazine n= 3 Sertraline n= 4 Nitrazepam n= 2	31	17.1%

	Flunitrazepam n= 3 Trimipramine n= 1		
	Gamma-hydroxybutyrate n= 1	1	0.5%
Opioids	Morphine n= 7 Ethylmorphine n= 1 propoxyphene n= 8 Codeine n= 6 Hydrocodone n= 1 Methadone n= 1 Heroin n= 2	26	14.4%
Beta blocker Antihypertensive	Propranolol n= 1	1	0.5%
Hypnotic/Tranquiliser	Meprobamate n= 2 Levomepromazine n= 1	3	1.7%
Antiepileptic	Carbamazepine n= 2	2	1.1%
Morphinan sedative	Dextromethorphan n= 1	1	0.5%
Analgesics/antipyretics	Paracetamol n= 6	6	3.3%
Antihistamines	Promethazine n= 1 Hydroxyzine n= 1 Doxylamine n= 1	3	1.7%
CNS stimulant/anorectic	Amphetamine n= 3	3	1.7%

Table 5: The toxicology data extracted from the included case reports

Patient Demographic (Gender, Age)	Route of Administration	Cause of Death	Tramadol Concentration from Specified Blood Source	Evidence of concomitant drugs
Female, 30 [16]	Oral	Mixed Drug Toxicity	Femoral: 38.3 mg/l	Yes
Male, 26 [35]	Oral	Tramadol Overdose	Femoral: 9.6 mg/L Heart: 13.1 mg/L	NO
Male, 36 [15]	Not reported	Mixed Drug Toxicity	Femoral: 134 mg/l	Yes
Male, 42 [15]	Not reported	Mixed Drug Toxicity	Femoral: 0.88 mg/l	Yes
Male, 58 [15]	Not reported	Mixed Drug Toxicity	Femoral: 3 mg/l	Yes
Male, 24 [15]	Not reported	Mixed Drug Toxicity	Femoral: 1.90 mg/L	Yes

Male, 67 [23]	Oral	Tramadol Overdose	Autopsy: 3.7 mg/L	NO
Male, 28 [36]	Oral	Multiple organ failure Tramadol Overdose	Femoral: 5.2 mg/L	NO
Male, 17 [22]	Not reported	Tramadol Overdose	Peripheral: 7.7 mg/L	NO
Female, 75 [22]	Not reported	Tramadol Overdose	Peripheral: 48.34 mg/L	NO
Female, 48 [11]	Oral	Tramadol Overdose	Femoral: 61.83 mg/L	NO
Male, 48 [30]	Not reported	Tramadol Overdose	Peripheral: 23.9 mg/L Heart: 32 mg/L	NO
Male, 17 [30]	Not reported	Tramadol Overdose	Peripheral: 5.8 mg/L Heart: 7.5 mg/L	NO

FIGURE 1: Prisma flow diagram