

Causes, nature and toxicology of tramadol-associated deaths reported in the peer-reviewed literature

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

3
4

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20

1 **Abstract**
2

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

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

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

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

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

22 **Impact of findings on practice**

23 ➤ The healthcare professionals who are responsible for tramadol prescriptions, should be adequately
24 supported and trained on their side-effects and its dual mechanism of action.

25 ➤ The risks associated with ingesting tramadol along with serotonin reuptake inhibitors (SRIs), monoamine
26 oxidase inhibitors (MAOIs), alcohol, and CNS depressants should be acknowledged

27 **Introduction**

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

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

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

15 Metabolism of tramadol is facilitated by cytochrome P450 (CYP450) enzymes [4]. CYP450 polymorphisms
16 predict the toxicity of tramadol [2,19]. The variation is likely to be attributed to genetic differences in CYP2D6
17 activity. Different CYP2D6 genotypes result in different responses [2,20]. Patients with renal failure can be given
18 tramadol, though the dose should be reduced in these patients and those with liver cirrhosis [22-24]. Evidence
19 suggests that poor metabolizers of CYP2D6 are commonly found in European Caucasians (7%) and 1% in
20 Orientals [21]. The risk of tramadol toxicity is higher in people who metabolise the drug very rapidly (ultra-rapid
21 metabolisers) [20], yielding elevated plasma levels of O-desmethyltramadol (ODT) [2,19,25]. ODT is the major
22 active metabolite of tramadol, which has double the potency for pain management compared to the parent drug
23 [3]. Although UMs experience better pain relief than extensive metabolisers [26], they are also more likely to
24 experience more nausea than the latter group [25].

25 In England, a remarkable increase by approximately 5.2 million between 2005 and 2012 in tramadol prescriptions
26 measured by the number of Daily Defined Doses (DDD) was reported [27]. In addition to the managing the
27 concerns related to the frequency of tramadol prescriptions, the risk to benefit ratio should be considered during
28 its administration [28]. Moreover, tramadol is one of the most prominent causes of poisoning with an increased
29 tendency to commit suicide among adult males with a prior history of drug addiction and mental health issues
30 [9,11]. Consequently, The Misuse of Drugs Act 1971 and the Misuse of Drugs Regulations 2001 in the United

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

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

15

16 **Aims of the review**

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

19 **Methods**

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

22

23 **Data sources and searches**

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

1 **Study selection**

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

8 **Data Extraction, quality assessment and synthesis**

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

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

18 **Results**

19 **Search Results**

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

24 **Quality Assessment**

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

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

3 **Demography**

4 In the included studies, a total of 181 deaths have been recorded. Most of the deaths occurred in Northern Ireland
5 of UK (n=127, 70.2 %). The remaining cases were identified around rest of the Europe (n= 36), USA (n= 12), and
6 one case in the Republic of Ireland (Appendix 1). Tramadol intoxication was more common among males (n=
7 116, 64.1%).

8 **Routes of administration**

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

11 **Cause of deaths**

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

17 Of the 181 reported deaths, the cause of tramadol intoxication was reported to be suicidal in 54 cases (29.8%)
18 and 50 cases (27.6%) as tramadol overdose. Tramadol alone as the cause of death had been confirmed in 8 cases
19 (4.4%) in the case reports, and it was the only substance that was detected in 37 cases (20.4%) mentioned in the
20 case series. In the case of 127 deaths associated with mixed toxicity, the most identified drugs were
21 benzodiazepines (44.9%), antidepressant drugs (17.6%), and a range of opioids (14.8%), details of which can be
22 found in Table 4. Of those commonly misused drugs alongside tramadol, 20 possess the potential to result in
23 serotonin syndrome [39]. There was one natural death where toxicological analysis identified the presence of
24 tramadol. Moreover, there was one case of accidental death or death from injuries, such as decapitation [2].

25 **Nature of deaths**

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

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

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

10 **Toxicology**

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

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

19 **Discussion**

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

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

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

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

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

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

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

8 The unintentional nature of many tramadol deaths has been reported and it is important to consider that the drug
9 can be acquired through illicit means [9]. The healthcare professionals who are responsible for tramadol
10 prescriptions, should be adequately supported and trained on their side-effects and its dual mechanism of action
11 [9]. Pharmacists may be well placed to offer meaningful intervention and support for people using opioid
12 medicines and tramadol for chronic, non-cancer pain in both community pharmacy and primary and secondary
13 care. It is worth noting that patients with long-term conditions such as hypertension are more likely to have a
14 comorbid diagnosis of depression [41]. Consequently, it is important not to preclude the presence of serotonin
15 syndrome, arising from the concurrent use of tramadol and antidepressants [2, 9]. Tramadol should therefore only
16 be prescribed where necessary, and these prescriptions should be issued in accordance with the local regulations
17 and policies. In patients with tramadol overdose, drug screening for opioids is usually negative. Therefore, the
18 screening for tramadol must be applied to all types of basic toxicological tests.

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

22

23 **Limitations**

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

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

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

9 **Conclusion**

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

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17 **Declarations**

18 **Ethics approval and consent to participate**

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

20 **Consent for publication**

21 Not applicable.

22 **Availability of data and materials**

23 All data have been provided within the manuscript

24 **Competing interest**

25 The authors declare that they have no conflict of interest.

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27 Not applicable.

28 **Authors Contributions**

1 Author EC developed the research question. Author SA conducted the searches and extracted the data. Both EC
2 and SA analysed the data and did the quality assessment. Authors EC, SA, VP and MHN contributed to the
3 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 (<i>n</i> = 1) Cardiorespiratory arrest (<i>n</i> = 1) Dizziness hypothermia 34C (<i>n</i> = 1) Not reported (<i>n</i> = 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 (<i>n</i> = 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 (<i>n</i> = 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 (<i>n</i> = 1) Cardiopulmonary arrest followed by death (<i>n</i> = 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 (<i>n</i> = 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 (<i>n</i> = 1)	No
Randall and Crane, 2014 [9].	Northern Ireland/U K	127	Case series	Suicide (48) Overdose (34) Not reported (45)	Not reported	Range: 1.85–88.8 Mean: Not reported	Seizures (<i>n</i> = 1) Multi-organ or liver failure (<i>n</i> = 8) Acute liver failure (<i>n</i> = 3) Not reported (<i>n</i> = 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 (<i>n</i> = 1) Respiratory depression (<i>n</i> = 2)	No
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1 **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?	✓	✓	✓	✓	✓	✓	✓	✓
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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?	-	-	-	-

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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%

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

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2 **FIGURE 1:** Prisma flow diagram

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