REVIEW ARTICLE

A review on tramadol toxicity: mechanism of action, clinical presentation, and treatment

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Abstract

Aims As an analgesic that acts upon the central nervous system (CNS), tramadol has gained popularity in treating moderate to severe pain. Recently, it has been increasingly reported as a drug of misuse with intentional overdoses or intoxications. This review focuses on tramadol intoxication in humans and its effects on different systems.

Subject and method This narrative review provides a comprehensive view of the pharmacokinetics, mechanism of action, and incidence of tramadol toxicity with an in-depth look at its side effects. In addition, the main approaches to the management of tramadol poisoning are described.

Results Tramadol poisoning can affect multiple organ systems: gastrointestinal, central nervous system (seizure, CNS depression, low-grade coma, anxiety, and over time anoxic brain damage), cardiovascular system (palpitation, mild hypertension to life-threatening complications such as cardiopulmonary arrest), respiratory system, renal system (renal failure with higher doses of tramadol intoxication), musculoskeletal system (rhabdomyolysis), endocrine system (hypoglycemia), as well as, cause serotonin syndrome. Seizure, a serious nervous disturbance, is more common in tramadol intoxication than with other opioids. Fatal tramadol intoxications are uncommon, except in ingestion cases concurrent with other medications, particularly CNS depressants, most commonly benzodiazepines, and ethanol.

Conclusion With the increasing popularity of tramadol, physicians must be aware of its adverse effects, substantial abuse potential, and drug interactions, to weigh its risk–benefit ratio for pain management. Alternative therapies might be considered in patients with a previous overdose history to reduce risks for adverse outcomes.

Keywords Tramadol · Intoxication · Poisoning · Toxicity · Overdose

Introduction

Tramadol is one of the most commonly prescribed central nervous system (CNS) analgesics used globally. It is widely prescribed for the treatment of moderate to severe pain [1]. It is one of the most widely prescribed opioids in many countries [2–4]. Because of an increased incidence of tramadol-related overdoses and deaths in the last decade, it has been classified as a controlled substance in several countries [4]. It was thought that tramadol had a lower risk for overdose, constipation, and addiction than other opioids, but some studies propose that phenotypic differences can contribute to its analgesic and side effect profile [5].

The International Narcotics Control Board review of 2013, revealed that tramadol abuse was problematic for several countries (32 out of 77 countries responding) [6]. However, recent studies have increasingly reported tramadol as

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a drug of misuse with intentional overdoses or intoxications [3, 4, 7–10]. While much is known about tramadol's efficacy for pain, there is increasing evidence from post-marketing surveillance indicating significant side effects. In 2004, the Australian Adverse Drug Reactions Advisory Committee received several adverse events due solely to tramadol use. These reactions suggest that the decision to prescribe tramadol should be carefully considered [11]. Tramadol is responsible for severe intoxications leading to consciousness disorder (30%), seizures (15%), agitation (10%), and respiratory depression (5%) [12]. Easy availability of prescription opioids in some countries may be contributing to increased drug-related health problems, hospitalizations, and mortality [8]. This review focuses on a variety of aspects of tramadol intoxication in humans and its effects on different systems.

Methods

In this review, several databanks, including PubMed, Web of Science, Scopus, Embase, and Google Scholar were searched using MESH headings and a combination of relevant keywords including tramadol, poisoning, intoxication, and overdose. Two researchers independently searched the databases mentioned above until 30 May 2020. No limitations were considered in the year or language of studies. Papers published in English or having an abstract in English were included. Titles and abstracts of retrieved articles were initially examined by two reviewers independently (O.M and S.N). The literature search was explicitly targeted toward studies focusing on tramadol's side effects on different body systems.

Case-control, cohort, cross-sectional, animal studies, and case reports were assessed. To find additional relevant articles, reference lists from the identified studies were also examined. The screening was performed after exclusion of duplications. Moreover, articles with inadequate data pertaining to the study objectives, as well as editorials, and conference papers, were excluded. Of the citations retrieved, one hundred eighteen studies were included in this narrative review. Papers 11, 13, 38, and 56 included original studies on humans, case reports, animal studies, and reviews, respectively.

Results

Incidence

An abuse rate of 69 per thousand persons per year has been reported for tramadol, with a dependence rate of 10% among the abusers [13]. Young male adults were more frequently involved in tramadol abuse and intoxication than females.

Moreover, the most common route of poisoning was oral (> 98%), which is consistent with the most commonly available form of tramadol [2, 3, 7].

Suicide attempts have been reported as the most common cause of intoxication (52–80%), followed by abuse (18–31%), and unintentional intoxication (1–11%) [2, 7, 14, 15]. A history of chronic tramadol abuse or opioid dependence was reported in at least 20% of cases of tramadol poisoning [2, 16–18]. A previous history of suicide attempts, substance abuse, and mental disorders played an important role in intentional intoxications [2, 7]. Previous literature also reported an association of tramadol intoxication with self-induced injuries and borderline personality disorders [19, 20].

Tramadol metabolism

The liver metabolizes tramadol by *N*- and *O*-demethylation mediated by the cytochrome P450 pathways (particularly CYP2D6) and is mainly excreted through the kidneys [1]. Therefore, any impairment in these systems or concurrent use of other medications that also are metabolized through the same hepatic pathways may cause overdose or intoxication. Wu et al. studied the metabolism of tramadol and subsequently produced metabolites. They detected 26 metabolites for tramadol due to liver metabolism, consisting of 14 metabolites from phase I of liver metabolism (M1 to M11 and M31 to M33) and 12 metabolites from phase II (7 glucuronides—M12 to 18—and 5 sulfonates—M19 to 23) [21]. Following oral administration of tramadol, out of 26 metabolites, only 23 metabolites were identified in the urine [21, 22]. At the same time, M31 to M33 were identified only in liver microsomes [21]. Among these 26 metabolites detected in humans, M12, M19 to M23, and M33 were not detected in mice or dogs [22]. Its metabolites result from tramadol metabolism by the liver, of which only *O*-desmethyl tramadol (M1) and *O,N*-di-desmethyl tramadol (M5) are pharmacologically active. M1 is the result of *O*-demethylation by cytochrome P450 2D6 (CYP2D6) [23].

Selective analysis of tramadol and M1 showed (–)-M1 levels were generally higher than (+)-M1 levels [24]. CYP2B6 and CYP3A4 are responsible for the *N*-methylation of tramadol to *N*-desmethyl tramadol (M2) [25]. M1 and M2 may then be broken down into secondary metabolites, *N,N*-didesmethyl tramadol (M3) and *N,O*-didesmethyl tramadol (M5), and then to *N,N,O*-tridesmethyl tramadol (M4) [24]. Following bioactivation in the liver, M1 is released into the bloodstream, enters the central nervous system, and stimulates μ -opioid receptors. In phase II metabolism, M1 is inactivated by glucuronidation in the liver, mostly via UGT2B7 and UGT1A8 [24] (Fig. 1).

Various metabolizer phenotypes (MP) are predictable by genetic variants in CYP2D6. It has been reported that

Fig. 1 Schematic diagram of tramadol metabolism

the CYP2D6 genotype affects the plasma levels of tramadol and its metabolites, as well as, tramadol efficacy and adverse drug reactions [26–28]. The CYP2D6 phenotype is classified into different groups based on the metabolizer status, including ultra-rapid metabolizers (UMs), extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs). EMs carry two active CYP2D6 alleles, IMs one inactive and one reduced activity CYP2D6 allele, and PMs two inactive CYP2D6 alleles. A minimum of three active CYP2D6 alleles are carried by UMs [24]. It has been reported that UMs are more prone to experience the side effects of tramadol [29]. PMs may contain higher tramadol concentrations, and the simultaneous use of CYP2D6 or CYP3A4 inhibitors such as fluoxetine, paroxetine and quinine could cause substantial drug interactions [24]. Genetic polymorphism of CYP2D6 accounts for major inter-individual differences in tramadol metabolism, its peak blood levels, and clinical presentations with therapeutic doses or overdoses [30, 31]. Polymorphic CYP2D6 action has been reported to be determinative of tramadol's pharmacokinetics and pharmacodynamics via hepatic phase I *O*-demethylation

of (+)-tramadol to (+)-*O*-desmethyl tramadol. This could elucidate the broad range of tramadol toxic doses reported in the literature [32]. Individuals with Middle Eastern and African ethnicities are more likely to be UMs in comparison with North American and Middle European people (21–29% vs. 1–5%, respectively) [33]. Consequently, more sedation, opioid effect, and adverse effects are expected in the former group [34].

An individual's CYP genetics influence the opioid analgesic potency of an administered dose of tramadol. PMs experience small conversions to active M1 opioid metabolites and UMs, experiencing a higher opioid analgesic effect. The importance of CYP metabolism should lead to considering pharmacogenomic tools before the administration of tramadol in clinical centers [5].

Moreover, tramadol is considered as an efficient probe for CYP2D6 phenotyping [35]. Pederson et al. found that 50 mg of tramadol has potential as a CYP2D6 phenotype probe using the 8-h urinary ratio of (–)-M1/(+)-M1 concentrations. In addition, they reported a metabolic ratio of 2.0 or higher for PMs [35].

Mechanism of action

Tramadol has both opioid and non-opioid mechanisms of action. It is an agonist of the opioid (mainly μ -opioid) and gamma-aminobutyric acid (GABA) receptors and inhibits the reuptake of serotonin (SSRI) and norepinephrine (SNRI) [23] (Fig. 2). Tramadol is a racemic mixture of (+) and (−) enantiomers with different affinities for the opioid receptors and various impacts on serotonin and norepinephrine reuptake. Therefore, their ratio may affect the threshold of tramadol therapeutic and toxic effects. Enantiomer (+) is the opioid part, but it also accelerates serotonin release and prevents its reuptake. Enantiomer (−) is considered to be a norepinephrine reuptake inhibitor (SNRI) [2].

Of the identified tramadol metabolites, M1, M2, and M5 are the main ones. Moreover, M1 has a greater inhibitory effect against amine reuptake and is largely responsible for analgesic as well as adverse effects in intoxicated patients [3, 36]. Overall, analgesic activity is caused by two tramadol enantiomers ([+]-tramadol and [−]-tramadol), along with metabolite M1 [24]. *In-vitro* and clinical studies have shown that the metabolite M1 is significantly more potent than tramadol μ -opioid receptors in binding and producing analgesia. At the same time, the parent drug is only a weak μ -opioid receptor agonist [37, 38]. (+)-M1 has a significantly higher affinity for the μ -opioid receptor ($K_i = 0.0034 \mu\text{M}$) than the parent drug (+/−)-tramadol ($K_i = 2.4 \mu\text{M}$) as well as (+/−)-M5 ($K_i = 0.1 \mu\text{M}$) and (−)-M1 ($K_i = 0.24 \mu\text{M}$) [37, 39]. Thus, tramadol's parent form exhibits about a 700-fold lower affinity than its (+) M1 metabolite. The (+/−)-tramadol also inhibits

the reuptake of serotonin neurotransmitters (by binding to transporter hSERT) and norepinephrine (by binding to transporter hNET). The racemic tramadol binds to hNET and hSERT with K_i values at 14.6 and 1.19 μM , respectively [40] (Table 1).

The half-lives of tramadol and M1 are 5–6 h and 7–9 h, respectively [23, 41]. Therefore, the longer elimination half-life of M1 may instigate bioaccumulation with regular dosing. Additionally, the results of one study showed that tramadol half-life is dose-dependent, which could explain the adverse consequences of severe overdoses [42].

Table 1 Evaluation of inhibitory constant (K_i) of binding activity in tramadol, tramadol enantiomers and metabolites at human MOR, NET, and SERT

	MOR K_i binding affinity (μM)	NET K_i binding affinity (μM)	SERT K_i binding affinity (μM)
Racemic tramadol	2.4	14.6	1.19
(+) Tramadol	1.33	NA	0.53
(−) Tramadol	24.8	0.43	NA
Tramadol (+) M1	0.0034	NA	NA
Tramadol (−) M1	0.24	NA	NA
Tramadol (+/−) M5	0.1	NA	NA

MOR μ -opioid receptor, NA not available, NET norepinephrine (noradrenaline) transporter, SERT serotonin transporter

Fig. 2 Potential mechanisms for tramadol induced seizure and serotonin syndrome. MAO-A monoamine oxidase A, GABA-A gamma-Aminobutyric acid type A

Clinical presentations of tramadol intoxication

Tramadol is available in different forms with a standard therapeutic dose of 50 mg orally, 100 mg rectally, and 50–100 mg parenterally. The maximum recommended daily dose is 400 mg [23]. It is commonly administered orally, rapidly and almost entirely absorbed, with peak effect reached within 2 h [43]. The therapeutic blood concentration of tramadol ranges from 0.1 to 0.3 mg/L. Moreover, toxic and possibly lethal blood concentrations have been reported at 1 and 2 mg/L, respectively [32]. Tramadol is disseminated into the spleen, lungs, brain, kidneys, and liver [44]. It can pass through the placental barrier and has been detected in breast milk in small amounts [23]. While the current evidence supports tramadol's efficacy and safety, there is an increasingly large amount of evidence regarding its adverse effects and fatal complications, even in the absence of interacting drugs [45].

The most commonly reported adverse effects are nausea, vomiting, CNS depression, seizure, dizziness, agitation, tachycardia, hypertension, reduced appetite, headache, itching, pruritus and rash, and gastric irritation, and skin eruption [3, 7, 14, 46, 47]. Rapid metabolizers of CYP may experience more adverse reactions (ARs) such as opioid toxidrome effects [5]. However, Pederson et al. found a weak correlation between ARs and the genotype and phenotype. However, they found that females are more susceptible to ARs of tramadol, and they found a slight reduction in CYP2C9, CYP2C19, and/or CYP1A2 activity in four female subjects with ARs of moderate-to-severe intensity such as headache, dizziness, nausea, and vomiting [48]. These observations almost certainly reflect unrecognized pharmacodynamic interactions of tramadol that can be observed despite the single-dose and low doses of the individual drugs. This may be understandable as tramadol has a complex metabolism with many detected metabolites with various effects.

A triad of opiate overdoses (i.e., miosis, respiratory depression, and decreased level of consciousness) can be observed in tramadol intoxication. Unlike opioids, tramadol can lead to hypertension, tremor, irritability, and increased deep tendon reflexes [7, 49]. Poisoning may also lead to multiple organ failure, coma, cardiopulmonary arrest, and death [45]. In the following section, the adverse effects of tramadol on different systems will be delineated (Fig. 3).

Gastrointestinal system

Nausea and vomiting have been reported as common presenting symptoms with both therapeutic doses and overdoses [7, 10, 11, 14, 50]. These symptoms usually resolve within 24 h with supportive care and early administration of charcoal [51].

Results of an animal trial demonstrated that the main hepatic histopathologic finding with therapeutic doses of tramadol was vacuolization in tubular cells [52]. Although uncommon, acute liver failure following tramadol intoxication has been reported [4, 36], which is usually in a setting of multiple organ failure. Management of tramadol-associated liver failure is mainly supportive. No evidence is available regarding the uses of molecular absorbent recirculating systems [36]. Hyperamylasemia in a patient with tramadol overdose was likely due to hypoxemia and lactic acidosis [53].

Central nervous system

CNS symptoms of tramadol poisoning include, but are not limited to, CNS depression, low-grade coma, anxiety, and seizure [3, 7, 10, 34, 54–56]. Seizure as a serious nervous disturbance is more common in tramadol intoxication than with other opioids [2, 9–11, 34, 54, 55, 57–67] (Table 2) and the detailed mechanism of tramadol-induced seizure requires further investigation [2]. The incidence of seizure has been reported to be 8–81% with tramadol overdose [2, 3, 7, 9–11, 14, 34, 50, 54, 68, 69] and it may occur in infants and children, as well [63, 70]. The pharmacological reasons for such a high seizure risk are unclear; most patients will have a normal EEG and CT scan of the brain [9, 34].

Tramadol induced seizures may occur in the first 6 h after ingestion of tramadol [2, 9, 14, 64]. Seizures are typically of the tonic–clonic type [2, 7, 9, 34], single [2, 10, 59], and occur at doses as low as 50–100 mg [9, 66, 71]. Although controversial, it seems that tramadol-induced seizures are dose-dependent; however, a seizure may occur with its therapeutic use, abuse, or overdose [2, 9, 14, 66]. They have been reported more frequently in higher doses [2, 3, 7, 23, 61, 67]; therefore, higher doses of tramadol could be considered a risk factor [67, 72]. Patients with recurrent seizures ingested, on average double the tramadol dose of single seizure patients [10]. In contrast, some studies reported a non-significant difference of serum tramadol concentrations between patients with seizures and those without seizures [2, 17, 73, 74].

The seizure risk is most significant in those with an existing seizure disorder or a history of previous seizures [2, 4, 66]. In addition, the highest seizure rate (54.4%) has been reported in patients with a history of tramadol abuse or intoxication, as well as, in chronic tramadol users (44%) [34]. Tramadol may also increase the seizure risk with concurrent use of serotonergic medications [1].

There is controversy about the effect of benzodiazepines (BZD) and naloxone in tramadol-related seizures. Some studies found a decreased risk of seizure in patients who co-ingested BZDs [11] and also in rats administered a combination of diazepam and tramadol [12]. In contrast, other researchers proposed an increase in morbidity and

Fig. 3 The adverse effects of tramadol on different systems

possibly lethality of tramadol overdoses when BZDs were used. [15]. On the other hand, while the evidence could not support the preventive effect of naloxone in such patients [54], seizures may be precipitated by injecting naloxone, accompanying high doses of tramadol [2, 7, 31, 60, 75]. Interestingly, recent meta-analyses have shown that the occurrences of seizures was not related to naloxone administration [67]. Along with serotonin, other possible systems have been proposed as being involved in precipitating tramadol-induced seizures, including histaminergic,

dopaminergic, opioid and GABAergic neurotransmission [12]. Inhibition of GABAergic neurons and activation of glutamatergic neurons lead to seizures. Tramadol and metabolite M1 inhibit GABAA receptors at high concentrations and NMDA receptors at clinical concentrations [76]. Neurotoxicity after tramadol exposure is associated with serotonin and norepinephrine reuptake inhibition. However, the potent inhibition of GABA-A receptors at high doses of tramadol may explain the decreased seizure threshold [67] (Fig. 2).

Table 2 Studies on tramadol-induced seizures excluding case reports

References	Study	Patients (n)	Gender	Age (years)	Dose	Cause of intoxication	Note
Ryan [11]	Retrospective cases series	71	39% M, 61% F	Median: 41 (range: 17–69)	> 400 mg (median: 1000 mg)		Seizures were dose-related and occurred in 8 patients; one of them co-ingested a benzodiazepine
Eirazi-Mood [54]	Prospective cohort	104	67% M, 33% F	Mean: 26.3			The incidences of seizure were 14.1% vs. 5.1% between patients received naloxone (18.3% of patients) and those who did not, respectively
Farajidana [59]	Retrospective	232			Mean: 1420 ± 1120 mg	Therapeutic and overdose	Seizure episodes occurred once (89.2%), twice (9.1%), and three times (1.7%). The prevalence of trauma was 24.6%
Shadnia [10]	Retrospective cohort	100	82% M, 18% F	Mean: 23.3 ± 7.7	Mean: 1160 ± 985 mg (range, 100–7000 mg)	93% with suicidal intent	7% had recurrent seizures and all patients recovered without sequelae; 3–15% co-ingested other drugs; The mean dose in those patients who had recurrent seizures were approximately 2000 mg and in those with only a single seizure, it was approximately 1100 mg
Taghaddosinejad [2]	Prospective case series	401	83% M, 17% F	Mean: 22.9 (range, 14–50)	Mean: 1510 mg ± 1350 (range, 200–7000 mg)	51.9% intentional overdoses	71% of patients experienced just one seizure; 30.2% of patients had a history of seizure; 3–13% of seizure cases co-ingested other medications or chemicals

Table 2 (continued)

References	Study	Patients (n)	Gender	Age (years)	Dose	Cause of intoxication	Note
Petramfar [66]	Cross-sectional study	106	96.2% M, 3.8% F	Mean: 26.7 ± 6.9	Mean: 363 ± 303 (range, 50–1500 mg)	18.9% therapeutic and 81.1% abused	86.8% had new-onset provoked seizure(s) induced by tramadol and in 13.2%, tramadol ingestion was considered as a precipitating factor in the setting of previously-known epilepsy
Talaie [9]	Cross-sectional study	132	73.5% M, 26.5% F	24.13 (range 15–69)	Mean: 2060 mg	Tramadol overdose	The seizure occurred in 46.2% of patients (all were generalized tonic-clonic seizures); Most patients with seizure used tramadol in the dose range of 500–1000 mg; Mean tramadol dose was lower among females than males (1706 mg vs. 2413 mg), but the difference was statistically insignificant
Jovanovic-Cupic [34]	Prospective	57	82.5% M, 17.5% F	22.3 (range 16–43 years)	250–2500 mg	Tramadol abuse or intoxication	Tonic-clonic seizures occurred in 54.4% of patients, which were single in 45%; Seizures occurred within 24 h after tramadol intoxication in 84% of patients; Compared to addicts without seizures, the abusers with seizures were younger
Farzaneh [60]	Case-Control	124	92%M, 8% F	27	–	Tramadol overdose	In the naloxone group, the incidence of seizure was higher than in the control group. The possibility of seizure occurrence was significantly higher in naloxone group than the control group

Table 2 (continued)

References	Study	Patients (n)	Gender	Age (years)	Dose	Cause of intoxication	Note
Goodarzi [62]	Cross-sectional study	54	–	26.48	Range: 200–11,000 mg Mean: 3250 mg	–	The route of poisoning in all of patients was oral. 20.4% required intensive care unit (ICU) during treatment. The mortality rate was 7.4%. There was a significant difference between male and female according to coma grading. The significant difference between number of seizure and ingested dose, ICU admission, and mortality was observed. There was also a significant difference between mortality and ingested dose and ICU admission
Rahimi [3]	Cross sectional	144	77% M 23% F	23.7 ± 6.9 (range = 15–57)	1970 ± 233 mg (range: 100–20,000 mg)	Tramadol overdose	Seizure (47.91%) was the most frequent symptom. There was correlation between ingested dose and seizure (OR: 2.7, 95% CI: 1.03–7.09)
Abbasi [136]	Cross sectional	150	94% M, 6% F	23.23 ± 5.94 (17–52)	NM	Tramadol overdose	No differences were observed between patients with seizure and without seizure in terms of ingested dose. seizures were more likely to occur in males and patients with a previous history of tramadol use
Eizadi mood [137]	Cross-sectional	184	76.6% M, 23.4% F	24 ± 7 years	2010 ± 7470 mg (100–10,000)	Tramadol overdose	Significant relationships between tramadol dose and seizure no significant differences between males and females in terms of seizure

Table 2 (continued)

References	Study	Patients (n)	Gender	Age (years)	Dose	Cause of intoxication	Note
Farzaneh [138]	Cross-sectional	122	89.5% M, 10.5% F	27.0 ± 7.2 years	2210 ± 1170 mg (range: 800–15)	Tramadol overdose	Seizure had no relationship with gender, age, and history of addiction to tramadol ingested dose of tramadol was not different between two groups of patients with seizure and without seizure
Ahmadimanesh [139]	Cross-sectional	120	75.8% M, 24.1% F	22.8 ± 5.8 years (range: 14–37 years)	Median (IQR) with seizure: 1000 (475, 2000) without seizure: 1000 (500, 1850)	Tramadol overdose	Seizure correlated with gender and concentrations of tramadol. There was no significant difference between the groups of patients with and without seizure in the median of ingested dose. Co-ingestion of other opioids and a history of sedative-hypnotics use resulted in lower incidences of seizure. history of tramadol use and/or addiction to opioids do not influence seizure occurrence
Mohammadpour [73]	Cross-sectional	121	67.7% M, 32.3% F	25 (14–35) year	500 and 800 mg were the lowest and highest doses, in seizure group.	Tramadol users	There was no significant difference in tramadol concentrations between the seizure and non-seizure groups
Ahmadi [140]	Cross-sectional	546	75.6% M, 24.4% F	22.5 ± 6.25 (range = 13–80)	40.7% ingested lower than 1000 mg	Tramadol overdose	Seizure incidence in males was higher than females There was significant correlation between Tramadol dosages and occurrence of seizure

Table 2 (continued)

References	Study	Patients (<i>n</i>)	Gender	Age (years)	Dose	Cause of intoxication	Note
Murray [141]	Cross-sectional	80	60% M, 40% F	26 (IQR: 17–49) years	NM	Tramadol overdose	Seizure occurred in 52.5% There was no significant difference in tramadol concentrations between males and females Seizure and naloxone administration had no relationship
Nasr [74]	Cross-sectional	100	80% M, 20% F	26.3 ± 12.1 years	NM	Tramadol overdose	Seizure occurred in 46% There was no significant relationship between tramadol blood levels and seizures
Adree [17]	Cross-sectional	102	86.2% M, 13.8% F	26.24 ± 9.50 (range: 5–55 years)	Mean dose of seizure group: 686 ± 318 mg (300–1500)	Tramadol overdose	Seizure occurred in 27.4% There was significant relationship between ingested dose and seizures There was no significant relationship between tramadol concentration and seizure

Cardiovascular system

Cardiac manifestations are expected in tramadol intoxication. Experimental studies demonstrated a negative inotropic effect [77] and histological changes including alterations in cell morphology, inflammatory cell infiltrates, and cell death [78] with high doses of tramadol. The mechanisms underlying the cardiac effect of tramadol at high doses have not been completely understood. Inhibition of L-type calcium channels by tramadol enantiomers (~60%) has been shown, but the racemic mixture produced significantly less effect (~30%). A direct effect on calcium channels or activation of a receptor-modulating calcium current has been proposed rather than activation of opioid receptors [79].

Cardio-toxicity symptoms range from palpitation and mild hypertension to life-threatening complications such as cardiopulmonary arrest. However, such severe manifestations are uncommon and were observed only at high doses of tramadol (> 5 g) or in CYP2D6 UMs [7, 11, 14, 50, 80–84]. As a treatment option, extracorporeal life support (ECLS) has been successfully used in refractory cardiogenic shocks [81, 83, 84]. In another report, a tramadol poisoned patient with clinical signs of acute pulmonary hypertension and right heart failure was observed [82].

In a report of tramadol-intoxicated patients without a previous history of heart disease, the most common types of ECG changes were sinus tachycardia (33%), a dominant S wave in leads I and aVL (28%), right axis deviation (24%), QTC prolongation (18%), QRS widening (6%), and right bundle branch block (RBBB) (5%). Increased PR interval occurred in none of the patients [49]. Brugada pattern and sinus bradycardia occur rarely [49, 85, 86]. Another study demonstrated right axis deviation (32%), sinus tachycardia (31%), QTC prolongation (25%), prominent R waves in lead aVR (22%), QRS widening (8%), and complete or incomplete RBBB (5%) in intoxicated patients [86]. Additionally, the authors concluded that the risk of seizures could not be predicted according to the changes found on ECG at presentation. None of the studies found a relationship between the ECG changes and the amount of drug ingested, or a history of tramadol use. In contrast, some studies proposed that tramadol induced seizure could lead to cardiac complications and reported higher levels of troponin I and creatine phosphokinase in patients experiencing seizures, compared to non-seizure subjects [73].

Respiratory system

Respiratory depression was not seen with therapeutic uses of tramadol [14]. It is more likely to happen when tramadol is taken with alcohol or other CNS depressants [4, 11]. Although respiratory depression and apnea in oral pure tramadol poisoning is reported [87]. Anoxic brain damage

may eventually happen secondarily to respiratory depression or arrest [36].

A large dose of tramadol, similar to other opioids, may cause central apnea. Studies within the same ethnic group demonstrated an apnea rate of 3.6% in adults vs. 15% in pediatric tramadol-intoxicated patients [16, 88]. Renal impairment or patient's genetic background, such as being an UMs, could also be predisposing factors [89].

There is no evidence that tramadol directly targets the lungs. However, a solitary case of acute respiratory distress syndrome (ARDS) and pulmonary edema has been reported [90, 91]. Studies with animals and humans have shown an increase of apneic threshold and a decrease in total CO₂ sensitivity due to tramadol [92, 93]. Naloxone reversed these effects dramatically, while over half of the expected respiratory depression was maintained in animals after naloxone pretreatment [92].

Respiratory depression could happen at doses just above the therapeutic dose in children (2 mg/kg), and it has been more common among children presenting with respiratory acidosis. Moreover, it has been reported that the occurrence of apnea was statistically independent of the ingested dose in children [88] and dose-dependent in adults [16]. Therefore, the observation time of 12 h was recommended for all asymptomatic children who have ingested greater than the therapeutic dose of tramadol [88].

Renal system

There are only a few case reports of renal failure with higher doses of tramadol intoxication [54, 57, 90]. An experimental study found only minimal renal histopathologic changes limited to tubular cells with chronic therapeutic doses of tramadol. In addition, blood urea nitrogen (BUN) and creatinine levels remained unchanged [52]. It has been proposed that tramadol induced seizure can lead to renal complications and kidney biochemical parameters which were reported to be significantly higher in patients experiencing seizures compared to the non-seizure patients [73].

Musculoskeletal system

Rhabdomyolysis and increased creatine phosphokinase (CPK) are rare but serious complications in tramadol intoxication [3, 57, 94, 95]. These observations have been proposed as a consequence of seizure but could not be confirmed in other studies [3]. It is important to diagnose and treat rhabdomyolysis quickly to prevent acute renal failure and life-threatening complications. Tongue laceration in a tramadol-poisoned unconscious patient is also considered a clinical indicator of generalized tonic-clonic seizures [96].

Endocrine system

Another possible major side effect of tramadol overdose is hypoglycemia in adults [97–99] and children [100] that seems to be dose-independent [97, 98]. In diabetic rats, the activation of μ -opioid receptors by tramadol enhanced the use of glucose and decreased hepatic gluconeogenesis that caused it [101]. Some studies also reported hyperglycemia due to tramadol poisoning [98, 102, 103]. It has been suggested that monoaminergic pathways, which are effective on the analgesic action of tramadol, may have a role in the hyperglycemic effects of the drug [103]. Serial blood glucose level monitoring has been suggested for early detection and management of hypo and hyperglycemia in tramadol overdose and intoxication [98]. A recent systematic review revealed that hypoglycemia is more likely to occur after tramadol use with both therapeutic use and in overdose. Importantly, all studies on tramadol use in diabetes reported hypoglycemia [104].

Serotonin syndrome (SS)

Tramadol PMs are at risk for elevated (+) tramadol levels, which has serotonergic reuptake inhibition activity [1]. An animal study found a potential for serotonin-like syndrome with tramadol alone in rodents lacking one or two copies of serotonin transporter. This finding may indicate genetic susceptibility to serotonin syndrome. In humans, however, serotonin syndrome is unlikely in isolated tramadol intoxication and has been reported in co-ingestion with other medications, especially serotonergic antidepressants and atypical antipsychotics [1, 11]. Pre-treatment with benzodiazepine such as chlordiazepoxide and diazepam could prevent tramadol overdose-induced serotonin syndrome as demonstrated in some animal and human studies [12, 94, 105]. In addition, the occurrence of serotonin syndrome in an infant intoxicated with tramadol has been reported [106]. Fujimoto et al. (2015) suggested that tramadol-induced seizures were not associated with inhibition of serotonin uptake and that these seizures were distinct from serotonin syndrome [107]. A potential mechanism for tramadol induced serotonin syndrome has been illustrated in Fig. 2.

Mortality

Tramadol-induced mortality is increasing in different countries [4, 91, 108–113]. Fatal tramadol intoxications are uncommon except in cases of co-ingestion with other drugs, particularly, the CNS depressants, most commonly benzodiazepines and ethanol [4, 7, 36, 80, 84, 114–123]. The majority of deaths have been reported before patients' arrival at hospitals. Consequently, the clinical course before death is not well known, and most cases occur without any

witnesses [36, 91, 116]. The most common cause of death is cardiopulmonary arrest [7, 9, 124, 125]. One potential mechanism of tramadol intoxication death could be attributed to respiratory depression induced by increased expression of GABA(A) α 1 and GABA(B)1 in the medulla oblongata solitary nucleus and ambiguous nucleus [126]. Addiction, depression, and previous history of seizure seem to be risk factors for tramadol associated mortality [4]. Curiously, fatal concentration of tramadol in the cases of co-ingestion were significantly lower (0.15 to 39 mg/L) in comparison with single tramadol poisoning. This low concentration of tramadol may overlap with the concentrations in therapeutic doses (0.1–0.3 mg/L) [4].

M1/M2 concentration ratio has been recommended to serve as an indicator of the time-lapse between the ingestion of tramadol and death with an M1/M2 concentration ratio of more than one, representing acute death. In contrast, a ratio of less than one displays a more extended time lapse [117, 127].

Tramadol blood concentration and its complications

Tramadol has an oral bioavailability of 68% after a single dose and 90–100% after multiple doses, reaching peak serum concentrations within 2 h [124]. It is well absorbed after oral administration (approximately 75%) [127]. The half-life of tramadol in overdose was reported as 9.24 h, which was positively correlated with higher concentrations [42]. The usual concentrations following 50–100 mg doses, range up to 0.3 mg/L [124], and toxic effects may occur at blood concentrations above 1 mg/L [127]. In pure tramadol poisoning induced fatal outcomes, blood tramadol concentrations of 1.6–61.8 mg/L have been reported [36, 115, 119, 127]. The minimum lethal dose reported in the literature is 1.6 mg/L. It reveals a lethal blood tramadol concentration several times higher than the normal therapeutic range of 0.1–0.3 mg/L. The literature regarding the relationship between tramadol serum concentrations and manifestations of tramadol overdose is limited. Some studies among patients with tramadol intoxication reported an elevated serum concentrations of tramadol and cardiac complications [81, 85].

Treatment

Treatment should be based on conservative approaches, including breathing, maintenance of airway, circulation, fluid resuscitation, oxygen therapy, and diazepam administration for managing seizure and agitation [57, 128, 129]. Patients should be examined for an increase in CPK and potential acute renal failure that may occur up to the following 2 days [57, 128].

Gastrointestinal decontamination should be carried out for referring patients within the first two hours after ingestion without any contraindications [7, 14, 50].

In severe toxicities that occur after ingestion of large amounts of sustained-release tramadol, multiple-dose activated charcoal may be a treatment of choice, if no contraindication is present [128, 130]. Because of the early onset of seizures following tramadol ingestion, it has been suggested to administer charcoal after securing the airway to avoid aspiration pneumonitis [14].

Intubation/ventilation and administration of naloxone are implemented to treat respiratory depression or tramadol-induced apnea [16, 70, 131, 132]. Some studies suggested that naloxone administration might cause seizure in tramadol intoxication and recommended against routine administration of naloxone for treating tramadol poisoning [10, 60, 133]. However, a recent meta-analysis showed that naloxone administration does not increase the risk of seizure in tramadol poisoned patients [67]. Seizures due to tramadol do not respond to naloxone but are relieved with benzodiazepines. Naloxone can be used for the treatment of post-seizure complaints [134]. A combination of diazepam/naloxone is reported as an efficient antidote to reverse tramadol-induced CNS toxicity [75]. Due to the low risk of multiple seizures in tramadol toxicity, anticonvulsant treatment should not be routinely prescribed even for cases of initial seizures [10].

Treatment of SS is also conservative and involves the withdrawal of the culpable drug and external cooling. Up to 42% of the patients are likely to require ICU, and most of them recover 12–24 h later [116]. Efficacy of intravenous lipid emulsion in tramadol poisoning in rabbits has been reported in some studies [135].

Conclusions

Tramadol poisoning can affect multiple organ systems, including the gastrointestinal, central nervous, cardiovascular, respiratory, renal, and endocrine systems, as well as, cause rhabdomyolysis and serotonin syndrome. Physicians must be aware of its adverse effects, substantial abuse potential, and drug interactions to weigh its risk-benefits for pain management. Alternative therapies might be considered in patients with a previous history of overdose to prevent further intoxications.

It is important to note that pharmacodynamics of tramadol including different enantiomers, genetic polymorphism, differences in affinity to the receptors, and metabolism play an important role in understanding why studies have failed to show a strong relationship between tramadol blood concentrations and occurrence of specific adverse effects. It also highlights the importance of dosage adjustment of tramadol

according to an individual's metabolic capacity, which is not currently practiced in most clinics.

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Compliance with ethical standards

Conflict of interest The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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