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Review Article

**A COMPREHENSIVE REVIEW ON TRAMADOL  
OVERDOSAGE****J.S. Venkatesh<sup>1</sup>, Dr. Santosh Uttangi<sup>2</sup>, Shyno Sunny<sup>\*3</sup>, Sheril K S<sup>\*4</sup> and  
Sumanth S<sup>\*5</sup>.**<sup>1</sup> Head of Department, Department of pharmacy practice, S.C.S College of Pharmacy,  
Harapanahalli.<sup>2</sup> Assistant Professor, S.C.S College of Pharmacy, Harapanahalli.<sup>3-5</sup> Pharm D Interns, S.C.S College of Pharmacy, Harapanahalli.**Article Received:** November 2022    **Accepted:** December 2022    **Published:** January 2023**Abstract:**

*It is possible to anticipate a considerable rise in tramadol prescriptions as well as a rise in tramadol overdoses and poisonings. When taken in excess, the synthetic opioid tramadol can have a number of negative effects, including some that can be fatal. These include loss of consciousness, seizures, serotonin syndrome, and, less frequently, hypotension and cardiovascular failure.*

**Corresponding author:****Dr.Santosh Uttangi,**Assistant Professor, S.C.S. College of Pharmacy,  
Harapanahalli, Karnataka, India

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**INTRODUCTION:**

One of the most frequently recommended central nervous system (CNS) analgesics used internationally is tramadol. It is frequently given to relieve mild to severe pain [1]. In several nations [2,3,4], it is one of the most frequently prescribed opioids. In various nations, tramadol has been designated as a prohibited substance due to an increase in overdoses and fatalities linked to the drug over the past ten years [4]. In contrast to other opioids, tramadol was once thought to have a lower risk of overdose, constipation, and addiction. However, some studies have suggested that phenotypic variations may be responsible for its analgesic and side effect profile [5]. The objectives of this article were to review the clinical features attributed to tramadol poisoning and to discuss its life-threatening risks in order to improve patient management.

Keywords Tramadol · Poisoning · Seizure · Serotonin syndrome

**PHARMACOLOGY**

A synthetic analogue of codeine is tramadol [6,7]. Tramadol exhibits a dual mode of action that involves suppression of serotonin and norepinephrine reuptake as well as weak agonistic actions at the  $\mu$ -opioid receptor [8]. N-desmethyl and O-desmethyl tramadol are the two major metabolites of tramadol that have been measured [9]. While tramadol has a 10-fold lower analgesic impact than codeine due to its lower affinity for  $\mu$ -opioid receptors, its active metabolite, O-desmethyl tramadol, has a much higher affinity (up to 200-fold) [10] and twice the analgesic effectiveness of the parent drug. The combination of these effects contributes to the analgesic effects of tramadol [11]. Tramadol has a low affinity for opioid receptors and also inhibits norepinephrine and serotonin reuptake, which results in analgesia by stifling nociceptive impulses in the spine [12,13]. Due to the structural similarity between tramadol and venlafaxine, it is possible that it will function similarly to antidepressants [14,15].

Tramadol is quickly and virtually entirely absorbed after oral administration [16]. The active ingredient is released over the course of 12 hours by sustained-release tablets, which also have a bioavailability of 87-95% and peak concentrations after 4.9 hours. About 20% of tramadol plasma protein binding. Postmortem studies [17,18] have shown that tramadol is dispersed in blood, liver, kidney, and brain samples but not in muscles. Like morphine, it accumulates substantially more in the bile than in the liver and kidney tissues. The distribution of tramadol is consistent with a volume of 3 l/kg [19]. The primary

metabolic pathways for tramadol are O- and N-demethylation as well as conjugation processes, which result in glucuronides and sulphates. The kidneys are primarily responsible for excreting tramadol and its metabolites. The average half-life of elimination is roughly 6 hours. While cytochrome P450 (CYP) 2D6 catalyses the O-demethylation of tramadol, CYP2B6 and CYP3A4 catalyse the N-demethylation. Tramadol's pharmacokinetic parameters exhibit a great deal of heterogeneity, which can be partially attributed to CYP polymorphism.

**TRAMADOL POISONING:**

Tramadol was initially marketed as being quite safe and having a low risk of abuse [7,20]. Later on, though, opposing evidence has come to light. The Food and Drug Administration has issued a safety notice for this medication that includes specific warnings for people who are also using tranquilizers or antidepressants, as well as people who drink too much alcohol, have emotional disorders, or suffer from depression. Additionally emphasised were potential abuse, misuse, and diversion [21]. Tramadol has lately been proposed to be included to Schedule IV of the Controlled Substances Act [22].

Tramadol overdose complications are disproportionately more common. Instead of its opioid effects, tramadol's monoamine uptake inhibition appears to be responsible for a large portion of the toxicity in tramadol overdose [20]. Tramadol-related problems are occurring more frequently. This problem has been helped by online prescriptions, initial safety-focused marketing, reduced misuse and diversion risk, and dextropropoxyphene withdrawal in hospital settings [20,23,24].

Tramadol overdoses have been linked to serotonin syndrome (SS) [10,20,26,45,50]. Although the precise prevalence of tramadol overdose-induced SS is unknown, it is most likely below 5% in hospital settings [26]. SS can happen after taking one dose of tramadol, but it seems to be more likely after heavy use, overdose, or when taking other drugs at the same time, especially antidepressants. There was no correlation between the frequency of SS and the reported tramadol overdose dose.

Other drugs that cause SS may work better when used with tramadol [51]. Tramadol monotherapy may cause it, although combinations with the drugs citalopram [52], fluoxetine [53-55], fluvoxamine [56], moclobemide-clomipramine [51], mirtazapine [57], paroxetine [58-61], sertraline [62-64], and

venlafaxine [65,66] have been shown to reduce the risk of SS. We are confident that the true rate of tramadol-induced SS may be significantly greater than currently reported, if agitation, tachycardia, disorientation, and hypertension were taken into account as potential mild SS symptoms, which are commonly ignored in clinical settings.

In addition to increased serotonin synthesis, decreased serotonin metabolism, increased serotonin release, inhibition of serotonin reuptake (e.g. SSRIs), and direct agonism of serotonin receptors, SS may also develop as a result of excessive serotonergic agonism of serotonin receptors in the central and peripheral nervous systems [67–69]. Along with its effect on  $\mu$ -opioid receptors, tramadol also promotes pre-synaptic serotonin release and inhibits serotonin reuptake [26,69]. Otherwise, SSRIs can prevent the CYP2D6 isoenzyme from metabolising tramadol, leading to therapeutic tramadol overdose and, in those who are vulnerable, idiosyncratic SS induction.

#### **BIOLOGICAL FEATURES:**

Creatinine phosphokinase may increase as a result of a tramadol overdose (CPK). Although CPK increase can occur without a seizure, it is more pronounced and may be linked to acute renal failure in seizure cases [35,40,46,47]. There have been reports of an increase in white blood cell count [26]. Tramadol's interaction with oral anticoagulants has also been linked to bleeding concerns [70]. There are currently no biochemical indicators of SS, hence clinical presentation must be used to make the diagnosis [71].

Overdose deaths from tramadol are uncommon and only account for 1% of instances that are officially reported [9,12,26,48]. Combining tramadol with other medications, such as benzodiazepines and antidepressants, increases the risk of death [12,72,73].

#### **TRAMADOL FATALITIES:**

Patients on tramadol have a large therapeutic concentration range and interpersonal variability in tramadol concentrations [74]. Concentrations of 8 mg/l, 9.6 mg/l, 22.6 mg/l, or 38.3 mg/l have been reported in fatal instances [10,18,48,73], exceeding the typical therapeutic range of 0.1-0.3 mg/l by at least 30 times.

#### **MANAGEMENT OF TRAMADOL POISONING:**

Supportive therapies such supplementary oxygen supply, fluids, and diazepam to calm agitation or seizures should be the main emphasis of

management. Additionally, patients should be watched for a possible increase in CPK and acute renal failure, which may occur a few days later [46]. Some patients might need to be hospitalised to the intensive care unit for tracheal intubation and mechanical ventilation [20,25–27]. Only patients admitted within two hours of the ingestion and in the absence of any contraindications should undergo gastrointestinal decontamination. If not contraindicated or if the patient is intubated, several doses of activated charcoal should be recommended in critically poisoned individuals after ingesting large amounts of slow-release drugs. Tramadol-related cardiovascular failure can occasionally cause extremely severe episodes of refractory shock and asystole that necessitate extracorporeal life support.

Tramadol combined with other medicines and mydriasis patients are more likely to experience seizures. Both serotonin and adrenaline may have a role in these. Even if there has been no prior seizure, empirical, early treatment with benzodiazepines in these situations may benefit individuals with tramadol overdose [26]. In situations when mild SS is underdiagnosed, empirical benzodiazepines may also be beneficial. The treatment of SS is supportive, involving stopping serotonin-related medications and applying external cooling [71]. The majority of patients who need to be admitted to the intensive care unit (ICU) will recover in 12 to 24 hours [69]. Useful antiserotonergic medications include parenteral chlorpromazine and oral cyproheptadine, which blocks the 5HT1A and 5HT2 receptors.

#### **CONCLUSION:**

Tramadol-related complications are on the rise, and the removal of dextropropoxyphene from the market may exacerbate this trend. Tramadol abuse and diversion should not be overlooked. Limiting access to this medication and replacing it with less harmful opioids would benefit the general population in low and middle income countries where there are fewer law enforcement mechanisms. To avoid an increase in tramadol-related morbidity and mortality among acutely poisoned patients, strict toxicological surveillance should be implemented.

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