CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Review Article*

A COMPREHENSIVE REVIEW ON TRAMADOL OVERDOSAGE

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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.

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Please cite this article in press Santosh Uttangi et al, ***A Comprehensive Review On Tramadol Overdosage.,*** *Indo Am. J. P. Sci, 2023; 10 (01).*

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 it's 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 -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 -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 to 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 POISIONING:

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 tranquillizers 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 -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 FATALITES:

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 POISIONING:

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 antiserotoninergic 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.

REFERENCE:

1. Kaye AD (2015) Tramadol, pharmacology, side effects, and serotonin syndrome: a review. Pain Physician 18:395–400

2. Taghaddosinejad F, Mehrpour O, Afshari R, Seghatoleslami A, Abdollahi M, Dart RC (2011) Factors related to seizure in tramadol poisoning and its blood concentration. J Med Toxicol 7:183
3. Rahimi HR, Soltaninejad K, Shadnia S (2014) Acute tramadol poisoning and its clinical and laboratory findings. J Res Med Sci 19:855
4. Randall C, Crane J (2014) Tramadol deaths in Northern Ireland: a review of cases from 1996 to 2012. J Forensic Leg Med 23:32–36
5. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R (2017) Trends in tramadol: pharmacology, metabolism, and misuse. Anesth Analg 124:44–51
6. Kovelowski CJ, Raffa RB, Porreca F (1998) Tramadol and its enantiomers differentially suppress c-fos-like immunoreactivity in rat brain and spinal cord following acute noxious stimulus. Eur J Pain 2:211–9
7. Moore PA (1999) Pain management in dental practice: tramadol vs. codeine combinations. J Am Dent Assoc 130:1075–9
8. Tobias JD (1997) Seizure after overdose of tramadol. South Med J 90:826–7
9. Moore KA, Cina SJ, Jones R, et al (1999) Tissue distribution of tramadol and metabolites in an overdose fatality. Am J Forensic Med Pathol 20:98–100
10. Sansone RA, Sansone LA (2009) Tramadol: seizures, serotonin syndrome, and coadministered antidepressants. Psychiatry (Edgmont) 6:17–21
11. Goeringer KE, Logan BK, Christian GD (1997) Identification of tramadol and its metabolites in blood from drug-related deaths and drug-impaired drivers. J Anal Toxicol 21:529–37
12. Clarot F, Goullé JP, Vaz E, Proust B (2003) Fatal overdoses of tramadol: is benzodiazepine a risk factor of lethality? Forensic Sci Int 134:57–61
13. Moore KA, Cina SJ, Jones R, et al (1999) Tissue distribution of tramadol and metabolites in an overdose fatality. Am J Forensic Med Pathol 20:98–100
14. Reeves RR, Cox SK (2008) Similar effects of tramadol and venlafaxine in major depressive disorder. SouthMed J 101:193–5
15. Yalcin I, Aksu F, Bodard S, et al (2007) Antidepressant-like effect of tramadol in the unpredictable chronic mild stress procedure: possible involvement of the noradrenergic system. Behav- Pharmacol 18:623–631
16. Grond S, Sablotzki A (2004) Clinical pharmacology of tramadol. Clin Pharmacokinet 43:879–923
17. Klingmann A, Skopp G, Pedal I, et al (2000) Distribution of morphine and morphine glucuronides in body tissue and fluids—postmortem findings in brief survival. Arch Kriminol 206:38–49
18. Moore KA, Cina SJ, Jones R, et al (1999) Tissue distribution of tramadol and metabolites in an overdose fatality. Am J Forensic Med Pathol 20:98–100
19. Musshoff F, Madea B (2001) Fatality due to ingestion of tramadol alone. Forensic Sci Int 116:197–9
20. Spiller HA, Gorman SE, Villalobos D, et al (1997) Prospective multicenter evaluation of tramadol exposure. J Toxicol Clin Toxicol 35:361–4
21. U.S. Food and Drug Administration (2011) Dear healthcare professional letter. Medical Product Safety Information [MedWatch]. http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM213266.pdf [accessed 2011 June 04]
22. Fass J (2010) Comment: effect of scheduling tramadol as acontrolled substance on poison center exposures to tramadol. Ann Pharmacother 44:1509
23. Bäckstrom BG, Classon G, Löwenhielm P, Thelander G (2010) Krypton—new, deadly Internet drug. Since October 2009 have nine young persons died in Sweden. Lakartidningen 107:3196–7
24. Gaubert S, Vié M, Damase-Michel C, et al (2009) Dextropropoxyphene withdrawal from a French university hospital: impact on analgesic drug consumption. Fundam Clin Pharmacol 23:247–52
25. Marquardt KA, Alsop JA, Albertson TE (2005) Tramadol exposures reported to statewide poison control system. Ann Pharmacother 39:1039–44
26. Tashakori A, Afshari R (2010) Tramadol overdose as a cause of serotonin syndrome: a case series. Clin Toxicol (Phila) 48:337–41
27. Shadnia S, Soltaninejad K, Heydari K, et al (2008) Tramadol intoxication: a review of 114 cases. Hum Exp Toxicol 27:201–5
28. Ripple MG, Pestaner JP, Levine BS, Smialek JE (2000) Lethal combination of tramadol and multiple drugs affecting serotonin. Am J ForensicMed Pathol 21:370–4.

29. Daubin C, Quentin C, Goullé JP, et al (2007) Refractory shock and asystole related to tramadol overdose. Clin Toxicol (Phila) 45:961–4
30. Jick H, Derby LE, Vasilakis C, Fife D (1998) The risk of seizures associated with tramadol. Pharmacotherapy 18:607–11
31. Gasse C, Derby L, Vasilakis-Scaramozza C, Jick H (2000) Incidence of first-time idiopathic seizures in users of tramadol. Pharmacotherapy 20:629–34
32. Gardner JS, Blough D, Drinkard CR, et al (2000) Tramadol and seizures: a surveillance study in a managed care population. Pharmacotherapy 20:1423–31
33. Labate A, Newton MR, Vernon GM, Berkovic SF (2005) Tramadol and newonset seizures. Med J Aust 182:42–4.
34. Jovanovic-Cupic V, Marinovic Z, Nesic N (2006) Seizures associated with intoxication and abuse of tramadol. Clin Toxicol (Phila) 44:143–6
35. Boyd IW (2005) Tramadol and seizures. Med J Aust 182:595–6
36. Kahn LH, Alderfer RJ, Graham DJ (1997) Seizures reported with tramadol. JAMA 278:1661
37. Márquez-Romero JM, Zermeño-Pohls F, Soto-Cabrera E (2010) Convulsive status epilepticus associated with a tramadol overdose. Neurologia 25:583–5
38. Tashakori A, Afshari R (2008) Tramadol induced seizure: can it be predicted? Proceedings of 7th Annual Congress of the Asia Pacific of Medical Toxicology, Chandigarh, India, 8-10 December 2008, p. 27.
39. Thundiyil JG, Kearney TE, Olson KR (2007) Evolving epidemiology of drug induced seizures reported to a poison control center system. J Med Toxicol 3:15–9
40. Afshari R, Maxwell SR, Bateman DN (2007) Hemodynamic effects of methadone and dihydrocodeine in overdose. Clin Toxicol (Phila) 45:763–72
41. Afshari R, Maxwell SR, Webb DJ, Bateman DN (2009) Morphine is an arteriolar vasodilator in man. Br J Clin Pharmacol 67:386–93
42. Afshari R, Tashakori A, Shakiba AH (2008) Tramadol overdose induced CPK rise, haemodynamic, and electrocardiographic changes, and seizure. Clin Toxicol 46:5, 369 [Abstract]
43. Cole JB, Sattiraju S, Bilden EF, et al (2010) Isolated Tramadol Overdose Associated with Brugada ECG Pattern. Pacing Clin Electrophysiol. 2010 Oct 7. [Epub ahead of print]
44. Talaie H, Panahandeh R, Fayaznouri M, et al (2009) Doseindependent occurrence of seizure with tramadol. J Med Toxicol 5:63–7
45. Garrett PM (2004) Tramadol overdose and serotonin syndrome manifesting as acute right heart dysfunction. Anaesth Intensive Care 32:575–7
46. Afshari R, Ghoshkhaneh H (2009) Tramadol overdose induced seizure, dramatic rise of CPK and acute renal failure: a case report. J Pak Med Assoc 59:178
47. Wang SQ, Li CS, Song YG (2009) Multiply organ dysfunction syndrome due to tramadol intoxication alone. Am J Emerg Med 27:903.e5-7
48. De Decker K, Cordonnier J, Jacobs W, et al (2008) Fatal intoxication due to tramadol alone: case report and review of the literature. Forensic Sci Int 175:79–82
49. Loughrey MB, Loughrey CM, Johnston S, O'Rourke D (2003) Fatal hepatic failure following accidental tramadol overdose. Forensic Sci Int 134:232–3
50. Jones D, Story DA (2005) Serotonin syndrome and the anaesthetist. Anaesth Intensive Care 33:181–7
51. Hernandez AF, Montero MN, Pla A, Villanueva E (1995) Fatal moclobemide overdose or death caused by serotonin syndrome? J Forensic Sci 40:128–30
52. Mahlberg R, Kunz D, Sasse J, Kirchheiner J (2004) Serotonin syndrome with tramadol and citalopram. Am J Psychiatry 161:1129
53. Kesavan S, Sobala GM (1999) Serotonin syndrome with fluoxetine plus tramadol. J R Soc Med 92:474–5
54. Gonzalez-Pinto A, Imaz H, DeHeredia JL, et al (2001) Mania and tramadol-fluoxetine combination. Am J Psychiatry 158:964–5
55. Lange-Asschenfeldt C, WeigmannH, Hiemke C, Mann K (2002) Serotoninsyndrome as a result of fluoxetinein a patient with tramadol abuse: plasma level-correlated symptomatology? J Clin Psychopharmacol 22:440–1
56. Karunatilake H, Buckley NA (2006) Serotonin syndrome induced by fluvoxamine and oxycodone. Ann Pharmacother 40:155–7
57. Gnanadesigan N, Espinoza RT, Smith R, et al (2005) Interaction of serotonergic antidepressants and opioid analgesics: is

serotonin syndrome going undetected? J Am Med Dir Assoc 6:265–9
58. Egberts AC, ter Borgh J, Brodie-Meijer CC (1997) Serotonin syndrome attributed to tramadol addition to paroxetine therapy. Int Clin Psychopharmacol 12:181–82
59. Lantz MS, Buchalter EN, Giambanco V (1998) Serotonin syndrome following the administration of tramadol with paroxetine. Int J Geriatr Psychiatry 13:343–45
60. Llinares-Tello F, Escriva-Moscardo S, Martinez-Pastor F, Martinez-Mascaraque P (2007) Possible serotoninergic syndrome associated with coadministration of paroxetine and tramadol. Med Clin (Barc) 128:438
61. John AP, Koloth R (2007) Severe serotonin toxicity and manic switch induced by combined use of tramadol and paroxetine. Aust N Z J Psychiatry 41:192–3
62. Mason BJ, Blackburn KH (1997) Possible serotonin syndrome associated with tramadol and sertraline coadministration. Ann Pharmacother 31:175–77
63. Sauget D, Franco PS, Amaniou M, et al (2002) Possible serotonergic syndrome caused by combination of tramadol and sertraline in an elderly woman. Therapie 57:309–10
64. Mittino D, Mula M, Monaco F (2004) Serotonin syndrome associated with tramadol-sertraline coadministration. Clin Neuropharmacol 27:150–1
65. Houlihan DJ (2004) Serotonin syndrome resulting from coadministration of tramadol, venlafaxine, and mirtazapine. Ann Pharmacother 38:411–13
66. Anonymous (2004) Venlafaxine + tramadol: serotonin syndrome. Prescrire Int 13:57–40
67. Sun-Edelstein C, Tepper SJ, Shapiro RE (2008) Drug-induced serotonin syndrome: a review. Expert Opin Drug Saf 7:587–96
68. Dvir Y, Smallwood P (2008) Serotonin syndrome: a complex but easily avoidable condition. Gen Hosp Psychiatry 30:284–7
69. Kitson R, Carr B (2005) Tramadol and severe serotonin syndrome. Anaesthesia 60:934–5
70. Hersh EV, Pinto A, Moore PA (2007) Adverse drug interactions involving common prescription and over-the-counter analgesic agents. Clin Ther 29(Suppl):2477–97
71. Boyer EW, Shannon M (2005) The serotonin syndrome. N Engl J Med 352:1112–20
72. Bynum ND, Poklis JL, Gaffney-Kraft M, et al (2005) Postmortem distribution of tramadol, amitriptyline, and their metabolites in a suicidal overdose. J Anal Toxicol 29:401–6
73. Michaud K, Augsburger M, Romain N, et al (1999) Fatal overdose of tramadol and alprazolam. Forensic Sci Int 105:185–9
74. Musshoff F, Madea B, Stuber F, Stamer UM (2006) Enantiomeric determination of tramadol and O-desmethyltramadol by liquid chromatography-mass spectrometry and application to postoperative patients receiving tramadol. J Anal Toxicol 30:463–7