**REVIEW ARTICLE**

**Journal of Otorhinolaryngology and Facial Plastic Surgery 2023;9 (1):1-6.**
https://doi.org/10.22037/orlfps.v9i1.47125

# Tramadol Toxicity and Its Implications for Brain Disorders: A Narrative Review

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## Article Info

**Article Note:**
Received: November 2023
Accepted: December 2023
Publish Online: December 2023

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**Keywords:**
Tramadol;
Oxidative stress;
Neuroinflammation;
Neurodegeneration.

## Abstract

Tramadol is widely used in the management of moderate to moderately severe pain due to its unique dual mechanism of action as a weak μ-opioid receptor agonist and as an inhibitor of serotonin and norepinephrine reuptake. However, it seems that this medication may possess neurotoxicity, especially in misuse, overdose, or chronic use. This review highlights current knowledge on the neurotoxic effects of tramadol, outlining the mechanisms of both its acute and chronic effects on seizure induction, serotonin syndrome, oxidative stress, neuroinflammation, and neurotransmitter dysregulation. Patients susceptible to the adverse effects from such neurotoxicity-geriatric, pediatric, or with previous neurological disorders-also come into focus, with personalized clinical approaches being recommended. It also touches on the possible connections of chronic tramadol use with neurodegenerative disorders such as Alzheimer's and Parkinson's diseases and gives the implications for public health and clinical practice. The future directions of research are outlined: large-scale epidemiological studies, biomarker development, alternative pain management strategies, and enhanced regulatory frameworks. This review therefore addresses these gaps to guide safer use of tramadol and improving our understanding of its long-term consequences on brain health.

**Conflicts of Interest:** The Authors declare no conflicts of interest.
**Please cite this article as:** Sadrinasab S, Mousavi Nejad SA, Aliaghaei A. Tramadol Toxicity and Its Implications for Brain Disorders: A Narrative Review. J Otorhinolaryngol Facial Plast Surg 2023;9(1):1-6. https://doi.org/10.22037/orlfps.v9i1.47125

## Introduction

Tramadol is a synthetic opioid analgesic that has gained prominence in the world due to its effectiveness in the treatment of moderate to moderately severe pain. Introduced in the 1970s, tramadol differs from traditional opioids by its dual mechanism of action: it is a weak μ-opioid receptor agonist and also inhibits serotonin and norepinephrine reuptake. These properties confer a degree of analgesia, putatively with a lower risk of dependence and respiratory depression compared to conventional opioids (1). On the other hand, the more recent ubiquity of tramadol has revealed a far more complex profile, namely, one of increasing misuse, dependency, and toxicity rates. Epidemiological data clearly show that tramadol use is rapidly rising worldwide, especially in the Middle East, Africa, and some parts of Asia, where regulations are less tight (2). In such regions, factors like the affordability of, and access to, tramadol have promoted widespread non-medical use associated with significant public health burdens.

Although tramadol is clinically useful, it is not devoid of risks. Indeed, its pharmacological profile-while accounting for its efficacy in analgesia-prevents it from misuse and addiction. Consequently, tramadol dependence

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has developed into one of the significant drug dependency concerns globally in both developing and developed nations (3). While the abuse potential is lower than that of many other opioids, such as morphine or oxycodone, repeated tramadol administration leads to physical dependence and tolerance and a whole host of withdrawal symptoms. Its unique serotonergic and noradrenergic activities confer additional neuropsychiatric risks not seen with typical opioid drugs. These risks, in addition to the relatively high incidence of seizures associated with its overdose or misuse, suggest the necessity for a closer investigation of tramadol's action on the CNS (4).

Chronic tramadol addiction produces profound effects on the CNS, disrupting normal neurochemical homeostasis. With chronic use, there is a great degree of neuroadaptive change, including alterations in opioid receptor density, neurotransmitter release, and synaptic plasticity (5, 6). Such changes underlie the tolerance and withdrawal developments, the hallmarks of opioid dependence. This dimension of tramadol use uniquely impacts CNS function by modulating serotonin and norepinephrine pathways. Dysregulation of these pathways has been implicated in mood disorders, anxiety, and the observed cognitive dysfunctions in users of tramadol in the chronic phase (7, 8).

As tramadol displays its pharmacological activity primarily on the brain, this organ is especially prone to tramadol's toxicity. So, the dual action of tramadol on the opioid and monoaminergic systems makes a person at greater risk for adverse neuropsychiatric events, most notably seizure, serotonin syndrome and mood dysregulation (9). In addition, oxidative stress and neuroinflammation have also been implicated in the mechanisms of neuronal injury and dysfunction due to repeated exposure to tramadol (10). These effects are mainly concerning in chronic use, where cumulative toxicity may contribute to long-term brain damage.

The rationale of the current review is the increasing use and misuse of tramadol worldwide, in addition to the growing evidence on its neurotoxicity. While tramadol holds great therapeutic promise, its contributions to neuropsychiatric and probably neurodegenerative disorders through adverse impacts on CNS functioning have been inadequately explored. This review gathers the current knowledge on tramadol toxicity and its implications on brain health, focusing on its underlying mechanism, clinical manifestations, and links to long-term neurological outcomes.

**Potential Mechanisms Involved in Neurotoxic Impacts of Tramadol**

There is an emerging body of evidence for tramadol's neurotoxic potential, mediated via a number of mechanisms. For instance, acute tramadol toxicity most often presents with seizures even at therapeutic doses in the vulnerable population (11). Furthermore, the serotonergic effect of tramadol can induce serotonin syndrome, characterized by confusion, agitation, and even seizures and coma in its severe form (12). While with chronic use of tramadol, other mechanisms, such as neurodegenerative and neuropsychiatric pathologies, may also rise (13). Each of the mechanisms mentioned above is discussed separately in the sections that follow as a way of fully elaborating on the neurotoxic effects of tramadol.

**1. Seizure Induction and GABAergic Inhibition**

Tramadol has consistently been associated with increased seizure risk, a product of its ability to modulate GABAergic and glutamatergic neurotransmission. By inhibiting the release of GABA, tramadol decreases inhibitory capacity in the brain and predisposes neurons toward hyperexcitability (14). The increased activity of glutamate further exacerbates excitatory transmission, thus increasing the risks of seizure development (15). Clinical evidence has shown that even therapeutic doses of tramadol may induce seizures in susceptible

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individuals, especially those with previous episodes of epilepsy or receiving other proconvulsant drugs concomitantly (16). Furthermore, the propensity for seizure with tramadol is dose-dependent; meaning higher doses increase this adverse effect (17).

**2. Serotonin Syndrome and Monoaminergic Dysregulation**

Serotonin syndrome is a serious condition that is related to tramadol's serotonergic activity, especially when taken with other serotonergic agents like SSRIs. Symptoms include a triad of cognitive, autonomic, and somatic symptoms: agitation, hyperthermia, and hyperreflexia (18). Mechanistically, the inhibition of serotonin reuptake by tramadol increases synaptic serotonin levels, causing overstimulation of postsynaptic serotonin receptors (19). Preclinical models have determined that excessive serotonergic stimulation disrupts neuronal signaling and contributes to neurotoxicity (20). This is a mechanism that calls for caution in co-administering tramadol with other serotonergic drugs.

**3. Oxidative Stress and Mitochondrial Dysfunction**

Chronic exposure to tramadol has been implicated in the generation of oxidative stress, which is one of the key factors in neuronal injury (21). The generation of oxidative stress follows the imbalance in the generation of reactive oxygen species and in the brain's antioxidant systems. Such tramadol-induced oxidative stress has damaged the DNA, proteins, and lipids within neurons and has eventually brought about an insult to cell integrity (22). Furthermore, studies have shown that tramadol disrupts mitochondrial function, impairs ATP production, and enhances ROS generation (23).

Mitochondrial dysfunction is a hallmark of neurodegenerative diseases such as Alzheimer's and Parkinson's, suggesting a possible link between tramadol use and long-term neurodegeneration (24).

**4. Neuroinflammation and Microglial Activation**

Another vital mechanism implicated in the neurotoxicity of tramadol is neuroinflammation. Chronic treatment with tramadol activates microglial cells, the resident immune cells of the brain, leading to the release of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, which further enhance neuronal injury by facilitating apoptosis and disrupting synaptic function (25, 26). This process might explain the role of tramadol in the development of neurodegenerative diseases since sustained neuroinflammation has already been widely recognized as one of the driving forces for neuronal loss and cognitive decline (27).

**5. Dysregulation of Neurotransmitter Systems**

tramadol can modulate both opioid and monoaminergic systems, among others, disrupting the normal neurotransmitter balance that is crucial to CNS function. According to research, long-term use of tramadol changes the density and sensitivity of μ-opioid receptors, thus leading to tolerance and dependence (28). Its effects on serotonin and norepinephrine pathways were related to mood disturbances, anxiety, and cognitive dysfunctions, especially among chronic users (29, 30). The altered state of these neurotransmitter systems in relation to neuronal circuitry remains an active research area for understanding the long-term health effects of tramadol on the brain.

**6. Potential Role in Neurodegeneration**

The possible neurotoxic cumulative effects of tramadol raise concern regarding its potential role as an accelerator for neurodegenerative processes. Preclinical findings show the worsening of oxidative injury and neuroinflammation with mitochondrial dysfunction, all of which can be considered hallmarks of neurodegeneration after exposure to tramadol (31). Although a cause-and-effect relationship has yet to be established, these findings could point out that chronic use of tramadol may be implicated in the development

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or progression of a range of diseases, including Alzheimer's and Parkinson's disease (32). More studies are needed to clarify these relationships and to explore possible protective strategies.

In summary, tramadol-induced neurotoxicity involves a complex interplay of mechanisms such as seizure induction, serotonin dysregulation, oxidative stress, neuroinflammation, and neurotransmitter imbalance. Understanding these mechanisms is critical for developing targeted interventions to mitigate the adverse effects of tramadol on brain health.

**Vulnerable populations**

Certain groups of patients tend to be more sensitive to the neurotoxicity associated with tramadol. The elderly are particularly mentioned in this regard, considering that excessive exposure increases the risk of neurological complications, with increased chances of having seizures and cognitive dysfunction (33). This hyper-influence can occur due to the decreased hepatic metabolism and renal clearance that comes with age, risking accumulation of tramadol and its active metabolites within the body. Changes in the central nervous system may occur after taking tramadol, even at minimal doses, especially among elderly patients who have any neurological disorder baseline such as epilepsy, a history of traumatic brain injury, or stroke in the recent past. Again, the risk is extended to younger ages due to the incomplete development of metabolic enzymes that would distort tramadol metabolism, hence deviating from the expected pharmacokinetics and increasing susceptibility to toxicity (34).

In addition to age, concurrent use of other drugs along tramadol increases the chances of adverse neurological outcomes. Polypharmacy, especially in old age, increases the likelihood of drug-drug interactions, leading to enhanced neurotoxic effects of tramadol (35). Furthermore, when used with other CNS depressants, serotonergic agents, or proconvulsant drugs, the relative risk of serious adverse events, such as serotonin syndrome, respiratory depression, and seizures, is much increased (18). These issues take on even more significance when one considers careful patient selection and monitoring during tramadol therapy.

**Implications for Clinical Practice**

On a clinical level, all this evidence linking the drug tramadol to neurological disorders underscores the necessity for reassessing its application, particularly in high-risk groups. Clinicians should focus on individualized risk assessments, taking into account patient-specific features such as age, comorbidities, and concomitant drug exposure. Dose adjustment and therapeutic drug monitoring may be useful to minimize risk of neurotoxicity, particularly in vulnerable populations. Moreover, educating patients on the signs and symptoms of tramadol-related adverse events helps with early detection and management, thus possibly averting severe complications.

**Future Directions**

With adequate proof of tramadol neurotoxicity, there are certain gaps for future research efforts. Firstly, large-scale epidemiological studies have to be initiated so that they can quantify the prevalence of tramadol-induced neurological disorders. Such studies should report data from populations characterized by varied genetic, metabolic, and environmental backgrounds as this would assist in identifying certain risk factors and prevention models.

Second, mechanistic investigations are needed to define the exact molecular pathways that underlie tramadol's neurotoxic action. Neuroimaging and biomarker development may help to understand the early events of neuronal injury caused by tramadol, which will, in turn, enable timely therapeutic interventions. Biomarkers of oxidative stress or neuroinflammation might help develop neuroprotective agents that counter these processes. Third, well-desired clinical trials on the appraisal of alternative pain management strategies in a population at high risk for

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neurotoxicity from tramadol are needed. Such a multimodal approach to pain management may thus provide a safer yet effective treatment with comparable pain-relieving properties and reduced neurotoxic risks. The inclusion of cognitive-behavioral therapy or physical rehabilitation within treatment protocols could also be considered to reduce the dependency on opioids and potentially avoid disastrous outcomes. Lastly, regulatory frameworks must be stricter to control tramadol abuse and misuse. An improved pharmacovigilance system can make early detection of newly emerging trends in adverse events related to tramadol possible, and allow timely responses from a public health perspective. On equal measure, education of health providers and the general public is critical in limiting the risks associated with tramadol.

## Conclusion

The wide range of use and abuse of tramadol has put its neurotoxic potential into sharp focus. While it remains effective for the analgesia of many patients, its association with seizures, serotonin syndrome, oxidative stress, and neuroinflammation ushers in a word of caution, especially in vulnerable populations. While preliminary, the evidence associating tramadol with neurodegenerative processes underlines the importance of ongoing research in the elucidation of these associations and the identification of potential interventions. Clinicians must strike a balance between the benefits of tramadol and its risks, using strategies such as assessment of individual risk, dose adjustment, and education to minimize adverse outcomes. Meanwhile, researchers and policymakers play essential roles advancing our knowledge about the pharmacological mechanism of tramadol (particularly in the CNS) and in taking appropriate initiatives to protect public health. By addressing these challenges, tramadol can be continued as a valuable therapeutic tool while minimizing its impact on neurological health.

## Acknowledgments

We are grateful Hearing Disorders Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Financial Support

The authors declared that there was no external funding support forthis study.

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