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Original Research Article

The Role of Mu Opioid and GABA Receptors in Tramadol-Induced Seizures: A Comprehensive Literature Review and Hypothesis Generation

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Abstract: Tramadol, a widely prescribed analgesic for moderate to severe pain, has raised concerns due to its association with an increased risk of seizures. This literature review aims to explore the role of pharmacokinetics in tramadol-induced seizures. A comprehensive literature review was conducted, analyzing studies ranging from cross-sectional and cohort studies to case reports and animal research. The results indicate a complex relationship between tramadol dosage and seizure risk, with some studies suggesting a dose-dependent risk while others highlight individual variability and genetic predispositions. Based on the reviewed literature, we hypothesize that individuals with downregulation or low expression of Mu opioid and GABA receptors are at an increased risk for tramadol-induced seizures due to altered neurotransmitter modulation and impaired inhibitory control over neuronal excitability. This study emphasizes the need for cautious tramadol prescription and suggests further research into biomarkers that could predict seizure risk in patients taking tramadol.

Keywords: Mu Opioid Receptor, GABA Receptor, Tramadol, Seizure, Hypothesis.

INTRODUCTION

Tramadol is prescribed to relieve moderate to severe pain management in patients [1]. Tramadol produces satisfactory analgesia against various types of pain [2]. The opioid analgesic potency of a given dose of tramadol is influenced by an individual's CYP genetics [3]. Tramadol-induced seizures usually occur at high doses whereas seizure reported with low-dose oral tramadol (37.5 mg) [4]. Tramadol has been associated with an increased risk of seizures [5-7]. This adverse effect is particularly concerning in patients who use Tramadol for off-label purposes or without an underlying pain condition. Clinical observations have reported seizure incidents in patients taking tramadol, even without a prior history of epilepsy or seizure disorders. The pharmacological properties of Tramadol, along with patient-specific factors, may contribute to this heightened seizure risk [8]. This review examines the current literature on tramadol-induced seizures with a focus on Mu opioid and GABA receptor expression.

METHODOLOGY

A comprehensive search of databases such as PubMed, Web of Science, and Scopus was conducted to collect studies related to tramadol-induced seizures. The inclusion criteria were studies that discussed tramadol's pharmacodynamics, and clinical cases reporting seizures as an adverse effect.

We performed a systematic search of electronic databases, including PubMed, Web of Science, and Scopus, using keywords such as "tramadol," "seizures," "epilepsy," "neurotoxicity," "GABA receptor," and "opioid receptors." The search was limited to studies published in English. We

included studies that specifically addressed the occurrence of seizures following tramadol use. All the types of studies considered such as cross-sectional studies, prospective cohort studies, case reports, animal studies, and nested case-control studies.

For each selected study, we extracted the following information: Reference number and authors, methodology, number of patients involved, and manifestations related to tramadol-induced seizures.

By following this methodology, we aimed to provide a thorough understanding of the potential seizure-inducing effects of tramadol and identify areas where further research is needed.

RESULT

Our literature review yielded a diverse range of studies that provided insights into the seizure-inducing potential of tramadol. The findings from the included studies are summarized in Table 1 below.

Table 1: Studies included in the literature review

Ref	Authors	Methods (Patient number)	Manifestations
[5]	P. Pedramfar	cross-sectional study (106)	Tramadol may provoke seizures in patients with epilepsy and also in previously healthy people even within the recommended dose ranges.
[6]	R. Boostani	prospective cohort study (28)	the neurotoxicity of tramadol commonly manifests as generalized tonic clonic seizures most frequently within 24 hours after tramadol intake
[7]	N. Bekjarovski	Case report (1)	Tramadol prescription, use and abuse are connected with the risk of developing seizures.
[9]	R. Raffa	Animal study	Tramadol seizures were increased by naloxone at high tramadol doses. No synergistic effect on seizure induction was observed between concomitant tramadol and codeine or morphine.
[10]	F. Taghaddosinejad	cross-sectional study (401)	Seizure was significantly correlated to higher reported dose.
[11]	S. Shadnia	retrospective cohort study (100)	The risk of multiple seizures in tramadol poisoning is low.
[12]	Richard L	nested case-control study (96753)	Tramadol was not associated with an increased risk of seizure defined by inpatient and outpatient diagnoses. Tramadol was associated with a higher risk of seizure at the highest level of tramadol exposure than at low or moderate daily doses.
[13]	Camille Lagard	Animal study	Tramadol-induced seizures mainly involve GABAergic pathway.

The cross-sectional studies by P. Pedramfar [5], and F. Taghaddosinejad [10], indicated a correlation between tramadol use and seizure occurrence, with a significant association found with higher doses. R. Boostani's [6], prospective cohort study highlighted the acute neurotoxicity of tramadol, often resulting in generalized tonic-clonic seizures shortly after intake.

N. Bekjarovski's [7], case report underscored the risk associated with tramadol prescription and misuse, while R. Raffa's [9], animal study suggested that naloxone could exacerbate tramadol-induced seizures at high doses.

S. Shadnia's [11], retrospective cohort study provided evidence that multiple seizures are an uncommon outcome in cases of tramadol poisoning, contrasting with Richard L's nested case-control study which suggested that high levels of tramadol exposure increase seizure risk.

These results collectively suggest that while tramadol is effective for pain management, its use is not without risks, particularly concerning seizures which can occur even within recommended dose ranges or more frequently at higher doses.

DISCUSSION

The findings from our literature review suggest a complex relationship between tramadol use and seizure risk. While some studies, such as those by Pedramfar [5], and Taghaddosinejad [10], indicate a dose-dependent risk of seizures, others like Richard L's nested case-control study [12], suggest that the risk is not uniformly increased across all levels of tramadol exposure.

The prospective cohort study by Boostani [6], highlights the acute neurotoxic potential of tramadol, with seizures frequently occurring within 24 hours of intake. This immediate response suggests a direct pharmacological effect of tramadol on neuronal excitability. However, Shadnia's retrospective cohort study [11], provides a contrasting perspective, indicating that the risk of multiple seizures is low, which could imply that certain patient-specific factors or genetic predispositions play a role in seizure development.

The case report by Bekjarovski [7] underscores the individual variability in response to tramadol, further complicating the understanding of its seizure-inducing potential. This is supported by Raffa's animal study [9], which suggests that naloxone can increase seizure risk at high doses of tramadol, indicating an opioid-receptor-mediated mechanism.

Tramadol enhances inhibitory effects on pain transmission both by opioid and monoaminergic mechanisms [14]. Tramadol acts as an agonist on the opioid and GABA receptors and it also inhibits the muscarinic, serotonin, and nicotinic acetylcholine receptors, as well as the reuptake of norepinephrine and serotonin [15-18]. Additionally, it increases serotonin release [19]. These actions suggest that these receptors are likely involved in tramadol's mechanisms of action (Fig. 1).

The effects of different types of medications on seizure activity are well-documented. Opioid receptor agonists have been found to not exhibit a direct relationship with seizures, but high doses can induce seizures [20, 21]. The opioid analgesic potency of a given dose of tramadol is influenced by an individual's CYP genetics [3]. On the other hand, GABA receptor agonists can reduce seizures by enhancing inhibitory neurotransmission [22].

Muscarinic receptor inhibitors do not have a direct association with seizure development, although they may influence seizure susceptibility [23, 24]. Inhibiting serotonin receptors can have either pro- or antiepileptic effects [25, 26], while inhibition of nicotinic acetylcholine receptor ion-channels with mecamylamine can inhibit seizure-like activity [27]. Norepinephrine reuptake inhibitors may be linked to decreased seizure threshold, although duloxetine, which inhibits NE reuptake, is not associated with seizures [28, 29]. Lastly, selective serotonin reuptake inhibitors (SSRIs), which inhibit serotonin reuptake, are known to potentially cause seizures, with a reported seizure incidence of 1.9% [30, 31].

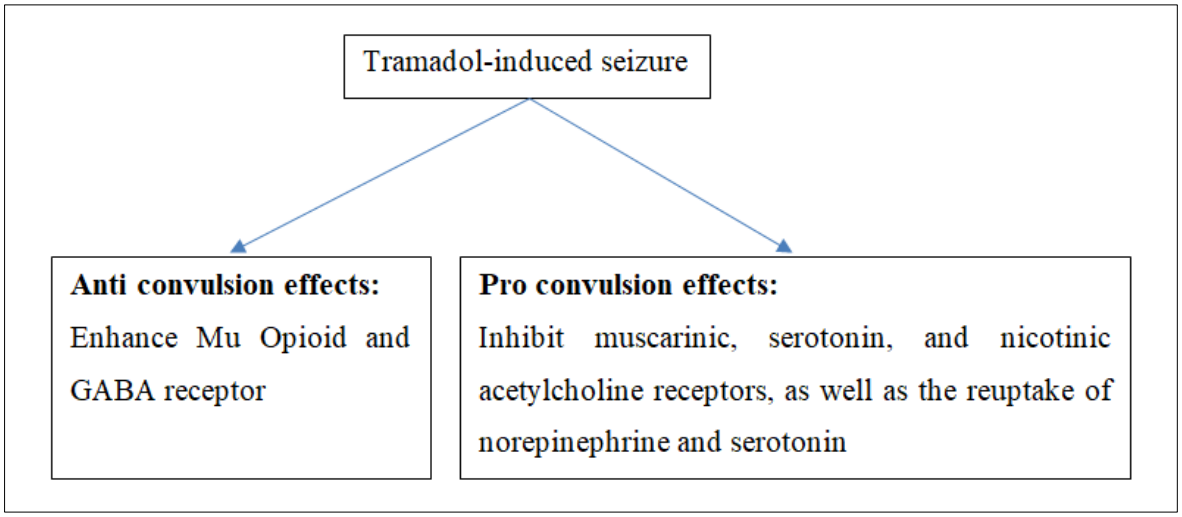

Figure 1: proconvulsion and anticonvolsion mechanisms of Tramadol

Overall, it appears that when seizures are induced by tramadol, the drug's anticonvulsant mechanisms, such as the stimulation of mu and GABA receptors, may not work effectively. This could be due to lower expression of these receptors in some individuals compared to others. One study showed Mu receptor expression decreases after maternal opioids in neonatal rats [32]. Tramadol has proconvulsant effect mediated by opioid receptor histamine release [33]. Decreased GABA receptor expression is linked to increased susceptibility to seizures [34]. Tramadol induces seizures through GABA receptor inhibition at high concentrations (35). Ethanol-induced deficits in GABAA receptor subunits affect seizure susceptibility [36]. Tramadol-induced seizures mainly involve GABAergic pathway [13]. It emphasizes the need for careful patient selection and monitoring when prescribing tramadol. The influence of genetic factors, such as CYP genetics, on tramadol's analgesic potency and seizure risk cannot be overlooked. Future research should focus on identifying biomarkers that predict seizure risk in

patients taking tramadol, especially expression of Mu and GABA receptors. This would enable personalized medicine approaches to mitigate this serious adverse effect.

CONCLUSION

In conclusion, this review highlights the need for a deeper understanding of the genetic and molecular factors contributing to tramadol-induced seizures. Future research should focus on identifying biomarkers for seizure risk in patients prescribed tramadol, particularly regarding Mu opioid and GABA receptor expression levels.

Hypothesis

Based on the reviewed literature, we hypothesize that individuals with downregulation or low expression of Mu opioid and GABA receptors are at an increased risk for tramadol-induced seizures due to altered neurotransmitter modulation and impaired inhibitory control over neuronal excitability.

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