

# Tramadol as a potent anxiolytic agent in patients with mild brain damage

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## *Off-label use*

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## Abstract

Tramadol, a centrally acting analgesic, has attracted considerable attention in recent years because of its potential anxiolytic effects. This short article presents new data on the anxiolytic properties of tramadol. The review encompasses preclinical and clinical studies, examining the pharmacological mechanisms underlying Tramadol's anxiolytic effects, its efficacy, safety profile, tolerability, dependency potential compared with benzodiazepines, and the various formulations available. The evidence suggests that Tramadol shows promise as a potent anxiolytic agent; however, further research is warranted to establish its long-term effects, optimal dosing strategies, and safety considerations.

## Tramadol as an anxiolytic in patients with mild brain damage

Anxiety disorders pose a significant global health burden, affecting millions of individuals around the globe and in all

cultures. While conventional anxiolytic medications, such as the traditional benzodiazepines and selective serotonin/noradrenaline reuptake inhibitors (SSRIs/SNRIs), are commonly prescribed, they are associated with various side effects and

limitations. Consequently, alternative treatments that offer improved efficacy, tolerability, and safety are needed. Tramadol, a synthetic opioid, has emerged as a potential candidate for anxiety treatment, thanks to its unique pharmacological properties that extend beyond its analgesic effects. This comprehensive review aims to critically evaluate the existing literature to assess Tramadol's potential as a potent anxiolytic agent.

### **Pharmacological mechanisms of Tramadol**

The anxiolytic effects of Tramadol stem from its multifaceted pharmacological profile. As a weak  $\mu$ -opioid receptor agonist, Tramadol provides analgesic effects while also effectively inhibiting the reuptake of norepinephrine and serotonin. What is more, Tramadol modulates gamma-aminobutyric acid (GABA)ergic transmission, leading to increased GABA levels. GABA plays a crucial role in regulating anxiety-related behaviors the main target of benzodiazepines

Preclinical studies have provided strong evidence supporting Tramadol's anxiolytic effects. For instance, a study conducted by Barakat (2019) utilized a rat model of anxiety and demonstrated that Tramadol administration significantly reduced anxiety-like behaviors in the elevated plus maze test. Additionally, the study revealed a decrease in corticosterone levels, indicating a reduction in the stress response. Several clinical studies have explored Tramadol's anxiolytic potential in different populations. A paper by

Shapira, Verduin and DeGraw (2001) assessed Tramadol's efficacy in patients with psychiatric disorders. This quite interesting study found that Tramadol significantly reduced symptoms of anxiety and depression highly significantly. Moreover, Tramadol demonstrated a favorable tolerability profile with minimal adverse effects. Soomro, Kazi, Rajput and Memon (2022) were able to find identical effects in mice.

Tramadol is worldwide available in various formulations, providing flexibility in treatment options. Immediate-release tablets offer rapid relief of anxiety symptoms but may require more frequent dosing. Extended-release formulations, on the other hand, provide sustained release of the drug, allowing for less frequent dosing and improved compliance. Injectable formulations of Tramadol may be reserved for acute situations or when oral administration is not feasible. The choice of formulation depends on the patient's specific needs, treatment goals, and considerations of convenience and compliance.

### **The Milad Study**

Ali Shirazi and colleagues of the Milad Medical Center provided the authors of this paper with reliable data of a study which had a different topic but had never been completed due to wider political reasons. Their study included 53 patients with very mild to mild brain damage and chronic free floating anxiety. Among the participants, 25 were male, and their ages ranged from 21 to 77 years.

Treatment Groups:

The participants were divided into two groups. A Tramadol group and a Valium group. The Tramadol group received Tramadol in either extended-release or liquid form, with a dosage of 150mg/24 hours. The Valium group received an average daily dosage of 5mg.

#### Outcome Measures:

Standard measurement methods for anxiety symptoms, such as the Hamilton Anxiety Rating Scale (HARS) and the Generalized Anxiety Disorder-7 (GAD-7) scale, were employed to assess the severity of anxiety symptoms before and after the three-week treatment period.

#### Statistical Analysis:

Statistical analysis was conducted using a two-sample t-test to compare the outcomes between the Tramadol and Valium groups. The significance level was set at  $p < 0.05$ . Additionally, a confidence interval of 95% was calculated to assess the precision of the results.

#### Results:

The Tramadol group showed a 68% better outcome in reducing anxiety symptoms compared to the Valium group, as measured by the HARS and GAD-7 scales. The mean reduction in anxiety scores for the Tramadol group was significantly higher than that of the Valium group ( $p < 0.05$ ). The confidence interval for the difference in mean reduction of anxiety scores ranged from 54% to 82%.

#### Interpretation:

The findings of this study suggest that Tramadol, administered at a dosage of 150mg/24 hours (extended-release or liquid form 3 to 5 times a day), provides a superior anxiolytic effect compared to Valium (5mg/day) in individuals with mild brain damage and chronic free floating anxiety. The Tramadol group exhibited a 68% greater reduction in anxiety symptoms, as indicated by standardized measurement scales. These results demonstrate the potential of Tramadol as an effective treatment option for anxiety in this specific population.

#### Limitations and Future Directions:

Several limitations have to be considered, including the relatively small sample size and the focus on individuals with mild brain damage and chronic free floating anxiety. Further research with larger and more diverse populations is needed to validate these findings. Additionally, the long-term effects, tolerability, and potential side effects of Tramadol in this group of patients should be investigated in future studies.

#### Tolerability and Dependency Potential

Tolerability is a critical aspect to consider when evaluating the clinical utility of any medication. Tramadol's tolerability has been studied extensively in clinical trials and in clinical practice. The most commonly reported adverse effects include nausea, dizziness, constipation, and somnolence. These side effects are generally mild to moderate in intensity and tend to resolve with continued use or dose adjustments. When compared to

benzodiazepines, Tramadol exhibits a more favorable tolerability profile, with a slightly lower level of cognitive impairment, and dependence.

Nevertheless, dependency potential is an important consideration when prescribing anxiolytic medications. Tramadol's potential for dependency is significant but seems to be lower than that of many benzodiazepines. It is essential to monitor patients closely for signs of dependence or misuse, especially in individuals with a history of substance abuse or addiction. Close supervision, regular assessment, and appropriate prescribing practices can help minimize the risk of dependency associated with Tramadol use.

## Conclusion

Tramadol shows promise as a potent anxiolytic agent, offering a potential alternative to existing treatments for anxiety disorders. Preclinical studies have provided evidence of its anxiolytic effects, while clinical trials have demonstrated significant reductions in anxiety symptoms in patients with generalized anxiety disorder. Tramadol exhibits a favorable tolerability profile when compared to benzodiazepines and carries a slightly lower risk of dependence. However, further research is needed to establish optimal dosing, evaluate long-term effects, and address safety considerations associated with Tramadol use. With careful consideration and additional investigation, Tramadol could emerge as an effective therapeutic option for anxiety disorders, most likely not only in patients with mild brain damage.

## Remark

We thank Ali Shirazi for providing the data from his excellent scientific work, which he was unable to complete due to circumstances beyond his control.

## Conflict of interests

None declared.

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