IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Original Article

# Psychiatric Outcomes in Patients with Trigeminal Neuralgia Treated with Anticonvulsants and Antidepressants: A Retrospective Cohort Study Using a National Database

Ashley Deng,[1] Priya Kaneria,[1] Eduardo Espiridion.[2]

## Abstract

**Background:** Trigeminal Neuralgia (TN) is a chronic craniofacial condition characterized by intense, sporadic shocks of pain through the trigeminal nerve. The unpredictable and severe nature of these episodes can be physically and mentally debilitating, significantly affecting the quality of life and often leading to anxiety, depression, and sleep disorders. This study investigated the psychiatric outcomes of anxiety, depression, and sleep disorders in TN patients who were treated with both anticonvulsants and antidepressants, compared to those who were treated only with anticonvulsants, to explore a multi-modal approach for addressing both pain and psychiatric symptoms. **Methods:** A retrospective analysis of electronic health records was conducted using TriNetX, a collaborative health network encompassing over 250 million patient records worldwide. The analysis included 15,129 patient records, comparing two cohorts of TN patients. **Results:** After adjusting for demographic factors, both cohorts were predominately female (73%), white (70%), and about 59 years of age. The results indicated that patients taking both anticonvulsants and antidepressants had higher risk, odds, and hazard ratios for developing depression (RR 10.448, OR 10.906, HR 10.763), anxiety (RR 2.680, OR 3.210, HR 3.013), and sleep disorders (RR 3.595, OR 3.696, HR 3.697) compared to those taking only anticonvulsants. **Conclusion:** Despite limitations including inability to assess dosage and severity of pain, these findings suggest that concurrent use of anticonvulsants and antidepressants may exacerbate psychiatric symptoms in TN patients. However, these effects might improve with appropriate dosage adjustments, highlighting the need for including dosage adjustments and monitoring.

## Introduction

Craniofacial pain and disease encompass a range of conditions affecting the head, face, and neck, such as temporomandibular join (TMJ) disorders, headaches, and facial pain. Among these, chronic forms like Trigeminal Neuralgia (TN) present significant clinical challenges due to their debilitating nature, marked by intense, electric-shock-like facial pain.[1] The pain severely impacts quality of life, both physically and mentally.[2]

The pathophysiology of TN includes classical (primary), secondary, and idiopathic causes. Classical TN often arises from trigeminal nerve root compression, typically by the superior cerebellar artery, leading to demyelination and heightened nerve excitability.[3,4] These changes disrupt voltage-gated sodium channel (VGSC) conductance, resulting in the abnormal nerve activity that underpins TN's hallmark sharp pain.[3] Secondary TN stems from identifiable conditions like multiple sclerosis or brain tumors. Idiopathic TN lacks a clear etiology, highlighting the need for further research into unexplained cases.

The diverse causes of TN, ranging from nerve compression to idiopathic cases, underscore the complexity of managing this condition. These variations not only influence the severity of pain but also contribute to the high prevalence of psychiatric and sleep-related comorbidities in affected individuals. Recognizing this interplay, the treatment options outlined in this study focus on pharmacological strategies aimed at alleviating TN symptoms while addressing its primary comorbidities—anxiety, depression, and sleep disorders.

The American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) recommends anticonvulsants, such as carbamazepine and oxcarbazepine, as first-line treatments for classical TN. These drugs alleviate neuropathic pain by stabilizing electrical activity in the nervous system through mechanisms such as blocking voltage-gated sodium channels (VGSCs), modulating calcium channels, and balancing excitatory and inhibitory neurotransmitters.[2] While

[1] B.S. Second-year Medical Student. Drexel University College of Medicine, West Reading, USA.

[2] MD. Reading Tower Health Hospital, Reading, USA.

**About the Author:** *Ashley Deng and Priya Kaneria are second-year medical students at Drexel University College of Medicine in West Reading, USA. Ashley is a Medical Student Summer Research Fellow and Co-Chair of DUCOM's largest student run service organization, Health Outreach Project. Priya is passionate about investigating quality of life outcomes across diverse fields, including cardiology and psychiatry. Her research focuses on understanding how clinical interventions impact patient-centered outcomes, using real-world data to drive meaningful insights.*

**Correspondence:**

Ashley Deng

Address:50 Innovation Way-Wyomissing, PA 19610- USA

Email: asd328@drexel.edu.

*Editor: Francisco J. Bonilla-Escobar*
*Student Editors: Esraa Kamal Eldin Elbadawi Babiker & Eleni Georgiadi*
*Copyeditor: xx*
*Proofreader: Amy Phelan*
*Layout Editor: Daniela Collazos*

*Submission: May 29, 2024*
*Revisions: Jul 11, Sep 9, Nov 7, Nov 13, Nov 20, Nov 27, 2024*
*Responses: Jul 18, Sep 16, Nov 13, Nov 20, Nov 22, Dec 16, 2024*
*Acceptance: Jan 27, 2025*
*Publication: Mar 28, 2025*
*Process: Peer-reviewed*

commonly used in epilepsy, these mechanisms are effective in reducing abnormal nerve excitability in TN.

Although antidepressants are sometimes added to manage TN-related comorbidities like depression and anxiety, no clinical trials have directly examined the efficacy of combining anticonvulsants and antidepressants for TN. Existing literature typically focuses on either drug class alone.[6-7] However, evidence from psychiatric treatments suggests that combining these medications may have synergistic benefits. For instance, the combination of lamotrigine (an anticonvulsant) and antidepressants has shown promising results in treating bipolar disorder, suggesting potential relevance for TN treatment.[8] Nonetheless, studies often lack dosage-specific analyses or considerations for the complex interplay between pharmacological treatments and comorbidities such as sleep disorders. The potential for combined pharmacological therapies is particularly relevant given the high prevalence of psychological comorbidities in TN, such as depression, anxiety, and sleep disorders.

**Comorbidities**

**Anxiety & Depression:** Chronic pain of TN exacerbates psychological consequences including depression and anxiety. A nationwide retrospective cohort study found that individuals with TN are three times more likely to experience clinical have depression and anxiety compared to controls.[5] In fact, patients with TN demonstrated higher levels of these conditions compared to those with atypical face pain.[9]

Physicians may prescribe antidepressants in addition to anticonvulsants to counter mood changes in regard to anxiety and depression. Notably, depressive disorders and mania are rarely seen as complications of treatment in patients given carbamazepine alone due to its chemically similar component to tricyclic antidepressants.[10] However, it is still uncertain if incorporating antidepressants in conjunction with anticonvulsants would further reduce anxiety and depression stemming from social or physiological consequences.

**Sleep Disorders:** Sleep disorders represent a prevalent and impactful comorbidity in individuals suffering from TN. The interplay between TN and sleep disturbances is complex, often resulting in a bidirectional relationship that exacerbates the symptoms of both conditions.

Individuals with TN frequently experience disturbances in sleep patterns. [11]The intensity and frequency of TN pain episodes, characterized by sudden, electric shocks on one side of the face, can disrupt sleep continuity and quality. In a study assessing quality of life in 298 patients diagnosed with TN, a construct validity analysis revealed a correlation between deteriorating sleep, energy, and appetite.[12] If sleep disturbances are prolonged among individuals with TN, heightened depression and anxiety could be a likely occurrence.[13]

Relating to TN treatment, anticonvulsants can either have no effect or an improved effect on sleep. For first line pharmacological treatments such as carbamazepine, sleep is not notably affected with patients with epilepsy. However, oxcarbazepine has shown as either worsening or having no effect for patients with epilepsy.[11] There is inconclusive evidence of the performance of anticonvulsants on enhancing sleep with patients with TN. Antidepressants, commonly prescribed to manage mood disorders associated with chronic pain, can influence sleep architecture. While these medications may be effective in addressing depression and anxiety in TN patients, they can have adverse effects on rapid eye movement (REM) sleep, potentially worsening sleep disorders. In fact, it was shown that most antidepressants suppress REM in both healthy and depressed patients.[14]

TN is a complex condition with varied manifestations, including psychological and sleep-related symptoms. Insights into the efficacy of combined pharmacological interventions can guide treatment plans, offering clinicians evidence-based tools to tailor therapeutic approaches to individual patient needs. The study aims to evaluate the efficacy of anticonvulsant drugs in the treatment TN and to explore the benefits of adding antidepressants to the treatment regimen through the impact on the psychiatric symptoms anxiety, depression, and sleep disorders. The study hypothesizes that combining anticonvulsants and antidepressants will lead to improved psychiatric outcomes and better management of psychological and sleep-related symptoms in TN patients.

## Methods

**Data set:** This study utilized a retrospective cohort design to examine the long-term psychiatric outcomes in patients diagnosed with Trigeminal Neuralgia (TN) and treated with anticonvulsants, with or without antidepressants. Data were obtained from the TriNetX Collaborative Network, which includes de-identified electronic health records from 61 U.S.-based healthcare organizations over a 20-year period. Two cohorts were established based on treatment regimens, and psychiatric outcomes were assessed over a 5-year follow-up period post-diagnosis. Propensity score matching was applied to minimize confounding variables, ensuring comparable baseline characteristics across cohorts. Statistical analyses included risk ratios, odds ratios, and hazard ratios, accounting for time-to-event outcomes using the Cox proportional hazards model.

**Study Population:** The study was run using only the United States Collaborative Network in the TriNetX database. This included 61 Health Care Organizations (HCOs). All patients included in the study were diagnosed with Trigeminal Neuralgia (ICD-10 CM: G50). A time constraint of 5 years after the first day of diagnosis was used. We believe this period is sufficient to capture potential chronic psychiatric effects of TN and the ongoing impact of anticonvulsant and antidepressant treatment. Additionally, only patients diagnosed within the last 20 years were included. This is because TriNetX is most comprehensive

following the wide-spread implementation of EPIC electronic health record around 2006. Cohort 1 was defined as patients diagnosed with TN (ICD-10 CM: G50) and prescribed anticonvulsants medication (VA: CN400) and antidepressant medication (ATC: N06A). Cohort 2 was defined as patients diagnosed with TN (ICD-10 CM: G50) and prescribed anticonvulsants medication (VA: CN400) without antidepressant medication (ATC: N06A).

Exclusion criteria were designed to reduce confounding effects from pre-existing psychiatric conditions that independently influence the likelihood of developing chronic psychiatric sequelae. Specifically, patients with bipolar disorder (ICD-10 CM: F31), depressive episode (ICD-10 CM: F32), or persistent mood affective disorders (ICD-10 CM: F34) were excluded. These conditions were chosen due to their established and direct associations with anxiety, depression, and sleep disorders, which were primary outcomes of interest. While these exclusions aimed to isolate the psychiatric effects specifically attributable to TN and its treatment, other psychiatric comorbidities or chronic illnesses were not excluded due to low prevalence in the dataset, as determined during cohort analysis. However, the absence of exclusions for other conditions like chronic pain, personality disorders, or substance use disorders could introduce residual confounding. Additionally, socioeconomic status could not be assessed. Although propensity score matching addressed demographic and some clinical factors (e.g., age, sex, race, and ethnicity), the inability to control for additional variables, such as chronic illnesses or pain severity, due to data limitations (e.g., lack of natural language processing) may limit the generalizability of the findings.

The psychiatric outcomes that were assessed were a diagnosis of 'Major depressive disorder, recurrent (ICD-10 CM:F33)', 'Anxiety, dissociative, stress-related, somatoform and other non-psychotic mental disorders (ICD-10 CM:F40-F48)', and 'Sleep disorders not due to a substance or known physiological condition (ICD-10 CM:F51).' Acute depressive episodes were not included in the outcome analysis as the study was aimed to observe long-term outcomes ***(Figure 1).***

**Statistical Analysis:** Measures of association and survival were assessed using the TriNetX platform. Patients diagnosed with the studied outcomes prior to the indexed event were excluded. Risk ratio (RR), which compares the probability of achieving a defined outcome between two cohorts, was extrapolated as well as odds ratio (OR), the probability of an event occurring divided by the probability of the event not occurring was also compared between cohorts. RR was particularly relevant due to the binary nature of the outcomes of interest (yes/no). OR was necessary for comparing more rare conditions. Hazard ratios (HR), which calculate how quickly an outcomes occurs over time, were calculated using the Cox Proportional hazards model. The Cox model directly estimates the HR. HR is particularly valuable for its ability to incorporate time as a factor, clarifying differences in the speed of outcome occurrence. By leveraging the Cox proportional hazards model alongside RR and OR calculations, the study ensured a comprehensive analysis of both the association and timing of psychiatric outcomes in relation to treatment regimens.

## Results

Cohort 1 included TN patients treated with both anticonvulsants and antidepressants, while Cohort 2 included those treated with anticonvulsants alone. Patients with pre-existing conditions such as bipolar disorder, depressive episodes, or persistent mood disorders were excluded to avoid confounding factors. Both cohorts were propensity score-matched on variables like sex, age, race, and ethnicity. The central symbol indicated effect size (RR, OR, HR) with the horizontal line representing 95% confidence intervals. An effect size greater than 1 suggests increased association of the outcome ***(Figure 1).***

Our study initiated with 15,238 TN patients on a combined regimen of anticonvulsants and antidepressants, alongside 23,408 TN patients exclusively on anticonvulsants. After a 1:1 Propensity Score Match, each cohort comprised 15,129 patients. Post-matching, both cohorts showed a balanced profile: mean age of 59 years, 73% female representation, 71% non-Hispanic or Latino, and 70% white ***(Table 1).***

After matching for age, sex, race, and ethnicity, risk ratio and odds ratio were calculated. Results indicate that patients with TN taking anticonvulsants and antidepressants had a higher risk and odds for development of depression, anxiety, and sleep disorders than their counterparts taking only anticonvulsants. Depression shows a particularly high increase in risk (RR= 10.448) when taking anticonvulsants and antidepressants concurrently rather than taking anticonvulsants alone ***(Table 2).***

Similarly, patients with TN taking both anticonvulsants and antidepressants demonstrated a markedly higher hazard ratio in depression, anxiety, and sleep disorder development compared to their counterparts only taking anticonvulsant. Based off the Cox proportional hazards model, larger chi-square values generally indicate stronger evidence of an association between the medication and the outcome. The chi-square and the p-value indicate whether the medication had a significant impact on the determined outcomes. A p-value <0.05 is generally significant. For depression and anxiety, the larger chi-square value ($\chi 2$= 6.276, 36.777 respectively) compounded with their corresponding p-value (p-value = 0.01, <0.01 respectively) indicate that combination anticonvulsant and antidepressant therapy show statistically significant impact on time to development of depression and anxiety ***(Table 3).***

Finally, we created a summary figure that shows the comparative OR, RR, and HR of depression, anxiety, and sleep disorder when comparing cohort 1, TN patients taking concurrent anticonvulsants and antidepressants, and cohort 2, patients only taking anticonvulsants. Notably, all associated risks were over the value of 1, with depression being the most at-risk outcome ***(Figure 2).***

***Table 1.*** Characteristics of Study Population Prior to and After Propensity Match.

| Variables | Before Matching | | | After Matching | | |
|---|---|---|---|---|---|---|
| | AC+AD (n=15,238) | AC (n= 23,408), Control | p-value | AC+AD (N = 15,129) | AC (n = 15,129, control) | p-value |
| **Age at index date +/- SD** | 58.8 +/- 16.9 | 61.6 +/- 16.9 | <0.001 | 59.0 +/- 16.7 | 59.0 +/- 16.9 | 0.665 |
| **Gender** | | | | | | |
| Female | 11119 (73.0%) | 15122 (64.6%) | <0.001 | 11010 (72.8%) | 11018 (72.8%) | 0.918 |
| Male | 3644 (23.9%) | 7380 (31.5%) | <0.001 | 3644 (24.1%) | 3646 (24.1%) | 0.979 |
| **Ethnicity** | | | | | | |
| Hispanic or Latino | 1053 (6.9%) | 1959 (8.4%) | <0.001 | 1053 (7.0%) | 1028 (6.8%) | 0.570 |
| Not Hispanic or Latino | 10914 (71.6%) | 15882 (67.8%) | <0.001 | 10810 (71.5%) | 10796 (71.4%) | 0.859 |
| Unknown Ethnicity | 3271 (21.5%) | 5567 (23.8%) | <0.001 | 3266 (21.6%) | 3305 (21.8%) | 0.587 |
| **Race** | | | | | | |
| White | 10936 (71.8%) | 15767 (67.4%) | <0.001 | 10832 (71.6%) | 10811 (71.5%) | 0.770 |
| Black or African American | 1526 (10.0%) | 2628 (11.2%) | <0.001 | 1526 (10.1%) | 1608 (10.6%) | 0.122 |
| Asian | 316 | 870 | <0.001 | 316 | 322 | 0.810 |
| American Indian or Alaska Native | 55 | 72 | 0.370 | 55 | 40 | 0.123 |
| Native Hawaiian or Other Pacific Islander | 19 | 58 | 0.039 | 19 | 10 | 0.095 |

***Legend:*** *AC=anticonvulsant AD=antidepressant*

***Figure 1***. Selection Criteria for Retrospective Cohort Study.

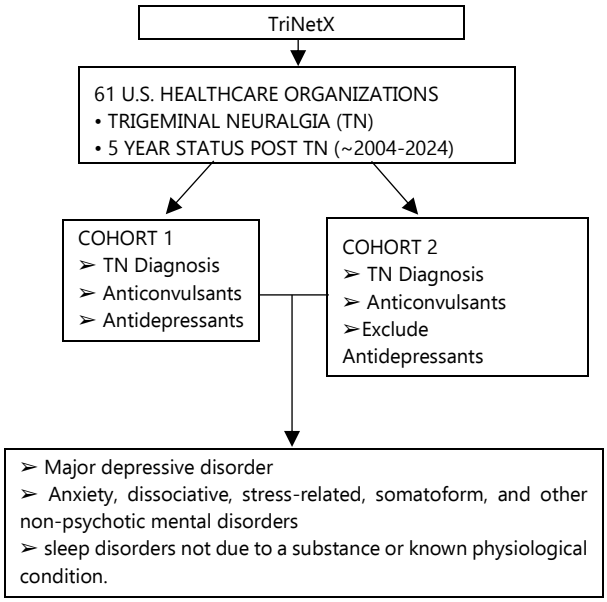
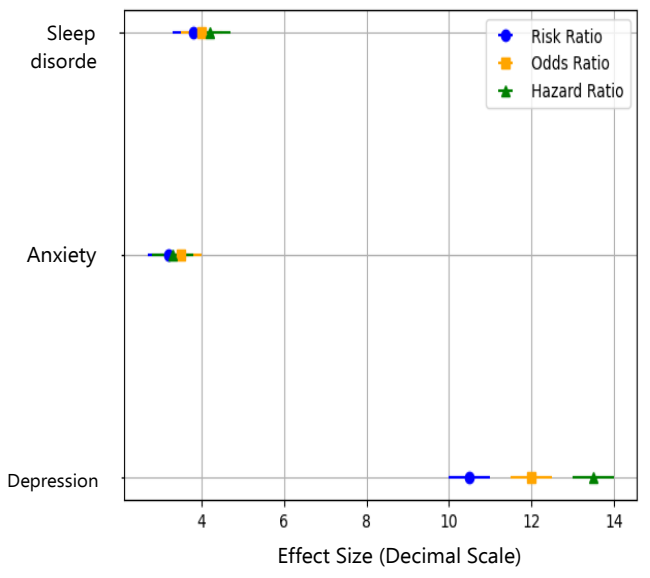



***Figure 2.*** Summary Forest Plot of RR, OR, and HR for Depression, Anxiety, and Sleep Disorder Outcomes.



## Discussion

Our study examined the relationship between antidepressant use in conjunction with anticonvulsants and its impact on observed psychiatric symptoms. Utilizing RR, OR, and HR analyses, our findings provide comprehensive insights into the potential implications of this treatment approach across different mental health conditions. In chronic depression, patients undergoing antidepressant and anticonvulsant therapy demonstrated a risk ratio of 10.448, revealing an over tenfold increased risk compared to the comparison cohort. This extremely high RR could be due to unaccounted comorbidities or mediation side effects. However, exclusion of patients with pre-existing mood disorders (such as bipolar disorder or depressive episodes) was designed to minimize confounding by these conditions. However, the decision to exclude only these specific conditions and not others could be too narrow, potentially missing other underlying mental health disorders that predispose patients to depression. This relationship should be further investigated. For generalized anxiety, the risk ratio stood at 2.680, indicating a nearly threefold higher risk in the exposed group. Sleep disorders exhibited a risk ratio of 3.595, emphasizing a more than threefold elevated risk in patients receiving this combined treatment. By examining hazard ratios, our study revealed that combined anticonvulsant and antidepressant therapy versus only anticonvulsant therapy only had a significant impact on time to development of anxiety and depression. The chi-squared and p-value for sleep disorders was not significant. These findings collectively suggest a potential lack of benefit in improving psychiatric symptoms with antidepressant use alongside anticonvulsants, prompting careful consideration by clinicians in treatment decisions for this patient population. The consistency across RR, OR, and HR for each outcome reinforces the reliability of these findings

Chronic pain is heavily associated with increased risk for psychiatric symptoms. Trigeminal nerve branch afferents (V1,V2,V3) convey sensation from the face and mouth to the trigeminal ganglion located in Meckel's cave in the temporal bone. From there, the neurons travel to the lateral pons of the brain stem where they synapse with the second order neuron that ascends to the thalamus.

The enter/exit point on the lateral pons is often the site of nerve compression, potentially by the superior cerebellar artery. The second order neuron projects to the somatosensory cortex and limbic structures including the amygdala, hypothalamus, and anterior cingulate gyrus.[15] Similarly, limbic structure activity modulation has been implicated in depression and anxiety. Furthermore, thalamus and hypothalamus receive projections from the reticular activating system, causing arousal. Stimulation of these areas can lead to hyperarousal and interrupted sleep structure. In addition to the anatomical overlap in structure, there is a convergence of neurotransmitters between pain and psychiatric symptoms, with serotonin and norepinephrine playing pivotal roles.[16] Our findings substantiate the fundamental connection between psychiatric symptoms and pain, echoing the intricate interplay of neuroanatomy and neurotransmitter pathways.

***Table 2.*** Risk Ratio and Odds Ratio of Psychiatric Outcomes of Patients Taking Concurrent Anticonvulsants and Antidepressants Versus Anticonvulsants Only.

| Outcome | Risk Ratio | 95% CI | Odds Ratio | 95% CI |
|---|---|---|---|---|
| **Depression** | **10.448** | (8.14, 13.41) | **10.906** | (8.478,14.027) |
| **Anxiety** | **2.68** | (2.528, 2.840 | **3.21** | (3.002, 3.433) |
| **Sleep disorder** | **3.595** | (3.018,4.282) | **3.696** | (3.094, 4.415) |

***Table 3.*** Hazard ratio of psychiatric outcomes of Patients Taking Concurrent Anticonvulsants and Antidepressants Versus Anticonvulsants Only.

| Outcome | Hazard Ratio | 95% CI | $\chi^2$ | df | p |
|---|---|---|---|---|---|
| **Depression** | **10.763** | (8.376, 13.831) | 6.276 | 1 | 0.01 |
| **Anxiety** | **3.013** | (2.831, 3.208 | 36.777 | 1 | <0.01 |
| **Sleep Disorder** | **3.697** | (3.099,4.41) | 0.021 | 1 | 0.88 |

Anatomical and chemical overlap contributes to the reciprocal relationship between pain and psychiatric symptoms, meaning patients with chronic pain often will develop psychiatric symptoms which can then exacerbate pain. In fact, 30-45% of patients with chronic pain experience depression.[17] Anticonvulsants, mainly carbamazepine, are a first line defense for treating TN pain. Carbamazepine acts by stabilizing electrical activity in the brain, mainly through decreasing Na+ channel conductance. Carbamazepine, along with other anticonvulsants, have been associated with improving pain symptoms in TN patients.[18] However, they may be associated with increasing prevalence of depression as they work to decrease excitation of neurons by increasing inhibitory neurotransmitter release or decreasing excitatory conductance or neurotransmitter.[19] Depression is often listed as a side effect for many anticonvulsants drugs. It is not unreasonable to expect providers to prescribe antidepressants to address these symptoms. Antidepressants work through increasing mood-enhancing monoamine neurotransmitters, mainly serotonin and norepinephrine, through selective reuptake inhibition. However, a common side effect of antidepressants is insomnia through the increase in wakefulness neurotransmitters serotonin and norepinephrine

Several recent studies have found combination therapy to be effective in managing chronic pain or neuralgia. A systemic review in 2022 that evaluated the efficacy, tolerability, and safety of different combination therapies for neuropathic pain found that pregabalin and tricyclic antidepressant, imipramine, therapy reduced pain by more than 50% in patients. [20] Another systemic

review focused on nonopioid drug therapy for cancer pain found that antidepressant duloxetine with opioid and pregabalin was more effective in reducing pain than only opioid and pregabalin alone.[21]

We hypothesize that several reasons could explain the increased association of psychiatric side effects with combination therapy. Interaction between antidepressants and anticonvulsants are complicated and may influence the pharmacokinetics and pharmacodynamics of each other. Pharmacokinetically, carbamazepine can act through enzyme induction to accelerate drug metabolizing enzymes.[19] This can reduce the efficacy of any other drug introduced into the system. Pharmacodynamically, carbamazepine can also cause hyponatremia.[22] This can be exacerbated by antidepressants, which have also been shown to cause hyponatremia.[23] Hyponatremia has been associated with psychiatric symptomatology and cognitive impairment.[24] There have been several case reports of patients presenting with depressive symptoms who were later observed to have serum sodium concentrations below normal 130 mEq/L. 25 Additionally, carbamazepine has been used as a mood stabilizer and in treatment of bipolar disorder, where addition of antidepressant may cause mood swings.[26]

Another hypothesis is serotonin syndrome. A significant pharmacological concern in the management of TN with combined anticonvulsant and antidepressant therapy is the potential for serotonin syndrome, a condition arising from excessive serotonergic activity in the central nervous system and peripheral tissues. Serotonin syndrome can occur when the introduction of certain anticonvulsants, which may increase extracellular serotonin release, is compounded by selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). SSRIs and SNRIs enhance serotonin levels by inhibiting its reuptake, leading to increased serotonin availability at synaptic junctions. The mechanism of serotonin syndrome also involves peripheral and central receptors, such as 5-HT2A and 5-HT1A, where overstimulation can result in autonomic dysregulation. Serotonin syndrome is associated with positive psychiatric symptoms including anxiety and insomnia.[27] Recent studies have shown that even mild cases of serotonin syndrome can manifest as anxiety and sleep disturbances, through inhibition of excitatory neurotransmission. This can modulate wakefulness and affective behavior, aligning with our findings.[28] The interaction between anticonvulsants and antidepressants, when not carefully managed, has the potential to exacerbate psychiatric symptoms.

The findings of our study, which suggest increased psychiatric risk with concurrent anticonvulsant and antidepressant treatment in trigeminal neuralgia (TN), should be viewed within the context of existing literature. While our study highlights significant risk ratios, especially for depression and anxiety, some research critiques the generalized association between these drug classes and psychiatric outcomes. For instance, anticonvulsants like carbamazepine and oxcarbazepine, while essential in TN management, are known to have mood-stabilizer properties that, in certain cases, could offset the risk of depressive symptoms when used appropriately.[29] The lack of dose specificity in our study could contribute to the stronger observed associations between combined treatment and adverse psychiatric outcomes.

Additionally, there is a significant variability in how patients respond to anticonvulsants and antidepressants due to genetic differences.[30] Polymorphisms in genes encoding P450 enzymes can significantly influence drug metabolism. Poor metabolizers may experience higher drug toxicity, increasing risk of psychiatric symptoms, while rapid metabolizers may clear the drugs too quickly, reducing their therapeutic efficacy. Moreover, stress has been shown to disrupt the normal functioning of CYP enzymes, potentially exacerbating these metabolic variations[30]. Furthermore, variations in serotonin transporter genes such as 5-HTTLPR can affect antidepressant efficacy and increase risk of serotonin syndrome[28]. Our study did not account for these genetic polymorphisms or environmental factors like stress, which may have introduced variability in the psychiatric outcomes observed. Future studies should aim to account for these variables, particularly by exploring the impact of individualized dosing strategies, pharmacogenetic testing, and environmental factors such as stress on psychiatric outcomes in patients receiving concurrent anticonvulsant and antidepressant therapy.

To our knowledge, this is the first and largest study to retrospectively study the psychiatric effect of antidepressants on TN patients using anticonvulsants. Due to the rarity of the disease, retrospective cohort review was necessary to compile adequate amounts of data per cohort. The study ultimately was able to compile 15,129 patients per cohort. Some limitations we encountered are generalizability and possible additional confounders. Due to the TriNetX platform, we were limited to the 61 Health care organizations that have opted to be a part of the platform in the U.S. Though ICD-10 codes is the standard in the U.S, there can be variability between providers on diagnostic coding. Additionally, though we matched cohorts for age, ethnicity, and sex, there may be additional confounders that we did not include such as chronic illnesses and pain severity. We did exclude the potential co-morbidities of bipolar disorder, depressive episode, and persistent mood affective disorders. TriNetX is developing their natural language processing ability which will benefit future studies in assessing continuous variables and psychiatric diagnoses that are assessed on specific scales and noted in the health record. We also did not account for dosages of medications. The appropriate balance between anticonvulsants and antidepressants may be particularly influential on reducing psychiatric symptoms. Due to the nature of a retrospective study, we cannot establish causality. Future long term follow up studies would be valuable in assessing effects over time.

Our study provides invaluable insights into a rare medical condition. This large-scale cohort analysis highlights the complexities of TN treatment, suggesting that while anticonvulsants are essential for pain management, the addition of antidepressants may exacerbate psychiatric symptoms in some patients. Clinicians should adopt a multi-modal approach

addressing both pain and psychiatric comorbidities. While anticonvulsants remain the primary treatment for managing pain, the addition of antidepressants may introduce risks that could potentially worsen psychiatric outcomes in certain patients.

To enhance patient care, clinicians should consider regular psychiatric monitoring for TN patients, especially those on combination therapies involving anticonvulsants and antidepressants. This could involve periodic mental health evaluations, structured screening for depression, anxiety, and sleep disorders, and timely adjustments to therapy as needed. Implementing these steps may help mitigate adverse psychiatric outcomes and allow for tailored treatment based on the patient's evolving needs.

Future studies should explore additional factors that may influence treatment outcomes, such as the impact of different dosages, specific antidepressant classes, and potential benefits of pharmacogenetic testing. This research could help clarify whether certain TN patients may be predisposed to psychiatric symptoms under specific treatment combinations. Prospective or controlled studies focusing on these variables could provide more precise guidance on optimizing therapy for TN patients with complex psychiatric profiles.

## Summary – Accelerating Translation

We present Psychiatric Outcomes in Patients with Trigeminal Neuralgia Treated with Anticonvulsants and Antidepressants: A Retrospective Cohort Study Using a National Database. Trigeminal Neuralgia (TN) is a debilitating condition characterized by sudden and intense facial pain, often described as shock-like. Beyond the physical toll, many TN patients struggle with mental health issues, such as anxiety, depression, and sleep disorders, which can further diminish their quality of life. Standard treatment for TN typically involves anticonvulsant medications to manage pain. However, some patients are also prescribed antidepressants to address coexisting psychiatric symptoms. While this combined approach might seem beneficial, it remains unclear how these medications interact and whether they improve or worsen mental health outcomes.

This study aimed to explore the impact of combining anticonvulsants and antidepressants on psychiatric outcomes in TN patients by comparing those treated with both medications to those treated only with anticonvulsants. Using TriNetX, a global database containing over 250 million patient records, researchers conducted a retrospective analysis of 15,129 TN patients. These patients were divided into two groups: one group received only anticonvulsant medications, while the other was treated with both anticonvulsants and antidepressants. The analysis examined the risk (relative risk, RR), odds (odds ratio, OR), and hazard ratios (HR) of developing anxiety, depression, and sleep disorders in each group, accounting for demographic factors such as age, gender, and race. The results showed that most patients in both groups were women (73%), white (70%), and around 59 years old. Patients who were treated with both anticonvulsants and antidepressants had a significantly higher likelihood of developing psychiatric conditions compared to those on anticonvulsants alone. Specifically, this group showed much higher risks of depression (RR: 10.448, OR: 10.906, HR: 10.763), anxiety (RR: 2.680, OR: 3.210, HR: 3.013), and sleep disorders (RR: 3.595, OR: 3.696, HR: 3.697).
These findings suggest that combining anticonvulsants and antidepressants may exacerbate psychiatric symptoms in TN patients rather than alleviate them. While this may seem counterintuitive, the results underscore the complexity of managing TN and its associated mental health challenges. It is possible that these outcomes could improve with more precise medication dosages and close monitoring of patients. This highlights the importance of personalized treatment plans and the need for further research to optimize the management of both pain and mental health in TN patients

## References

1. National Institute of Dental and Craniofacial Research (NIDCR). Craniofacial pain conditions. NIDCR. Available from: https://www.nidcr.nih.gov/research/data-statistics/craniofacial-pain-conditions. Accessed 2024 Jun 28.
2. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol.* 2008;15(10):1013–28.
3. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. Trigeminal neuralgia: new classification and diagnostic grading for practice and research. Neurology. 2016;87(2):220–8.
4. Miki K, Mori K, Hagiwara S, Tachibana M, Chiba K, Maeda M. Trigeminal neuralgia caused by a persistent primitive trigeminal artery variant and superior cerebellar artery. NMC Case Rep J. 2019;6(4):101–3.
5. Wu TH, Hu LY, Lu T, Chen PM, Chen HJ, Shen CC, et al. Risk of psychiatric disorders following trigeminal neuralgia: a nationwide population-based retrospective cohort study. J Headache Pain. 2015;16:64.
6. Tampi RR, Tampi DJ, Balachandran S, et al. Antipsychotics, antidepressants, anticonvulsants, melatonin, and benzodiazepines for behavioral and psychological symptoms of dementia: a systematic review of meta-analyses. Curr Treat Options Psych. 2017;4(1):55–79.
7. Vigo DV, Baldessarini RJ. Anticonvulsants in the treatment of major depressive disorder: an overview. Harv Rev Psychiatry. 2009;17(4):231–41.
8. Prabhavalkar KS, Poovanpallil NB, Bhatt LK. Management of bipolar depression with lamotrigine: an antiepileptic mood stabilizer. Front Pharmacol. 2015;6.
9. Araya EI, Claudino RF, Piovesan EJ, Chichorro JG. Trigeminal neuralgia: basic and clinical aspects. Curr Neuropharmacol. 2020;18(2):109–19.
10. Ware K, Tillery E, Linder L. General pharmacokinetic/pharmacodynamic concepts of mood stabilizers in the treatment of bipolar disorder. Ment Health Clin. 2016;6(1):54–61.
11. Lawthom C, Didelot A, Coppola A, Aledo-Serrano Á, Fazekas B, Sainz-Fuertes R, et al. The impact of epilepsy and antiseizure medications on sleep: findings from a large European survey in adults with epilepsy and matched controls. Epilepsy Behav. 2023;148:109000.
12. Luo Y, Zhang Y, Hu X, Zhang L, Wang J, Hu D, et al. A research on quality of life score (QOLS) of patients with trigeminal neuralgia (TN). *J Infect Public Health.* 2019;12(5):690–4.
13. Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. Dialogues Clin Neurosci. 2008;10(4):473–81.
14. Steiger A, Pawlowski M. Depression and sleep. Int J Mol Sci. 2019;20(3):607.
15. Huff T, Weisbrod LJ, Daly DT. Neuroanatomy, cranial nerve 5 (trigeminal). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482283/.
16. Yang S, Chang MC. Chronic pain: structural and functional changes in brain structures and associated negative affective states. *Int J Mol Sci.* 2019;20(13):3130.
17. Surah A, Baranidharan G, Morley S. Chronic pain and depression. Contin Educ Anaesth Crit Care Pain. 2014;14(2):85–9.

18. Di Stefano G, Truini A, Cruccu G. Real-world effectiveness and tolerability of carbamazepine and oxcarbazepine in 354 patients with trigeminal neuralgia. *Eur J Pain.* 2021;25(6):1229–35.
19. Punyawudho B, Cloyd JC, Leppik IE, Ramsay RE, Marino SE, Pennell PB, et al. Characterization of the time course of carbamazepine deinduction by an enzyme turnover model. Clin Pharmacokinet. 2009;48(5):313–9.
20. Afonso AS, Carnaval T, Cés SV. Combination therapy for neuropathic pain: a review of recent evidence. J Clin Med. 2021;10(16):3533.
21. Sohi G, Lao N, Caraceni A, et al. Nonopioid drug combinations for cancer pain: a systematic review. Pain Rep. 2022;7(2):e995.
22. Kaeley N, Kabi A, Bhatia R, Mohanty A. Carbamazepine-induced hyponatremia: a wakeup call. *J Fam Med Prim Care.* 2019;8(5):1786–8.
23. Lien YHH. Antidepressants and hyponatremia. Am J Med. 2018;131(1):7–8.
24. Bojdani E, Souza FD, Rajagopalan A, et al. Hyponatremia and psychiatric diseases. Weight Manag.
25. Sawant NS, Parkar SR, Rupani K, et al. Hyponatremia misdiagnosed as depression. Ann Indian Psychiatry. 2019;3(2):168.
26. Grunze A, Amann BL, Grunze H. Efficacy of carbamazepine and its derivatives in the treatment of bipolar disorder. *Medicina (Kaunas).* 2021;57(5):433.
27. Simon LV, Keenaghan M. Serotonin syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482377/.
28. Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. Ochsner J. 2013;13(4):533–40.
29. Rybakowski JK. Mood stabilizers of first and second generation. Brain Sci. 2023;13(5):741.
30. Pain O, Hodgson K, Trubetskoy V, Ripke S, Marshe VS, Adams MJ, et al. Identifying the common genetic basis of antidepressant response. *Biol* Psychiatry Glob Open Sci. 2021;2(2):115–26.

**Acknowledgments**

Drexel University College of Medicine and Reading Tower Health

**Conflict of Interest Statement & Funding**

The Authors have no funding, financial relationships or conflicts of interest to disclose.

**Author Contributions**

Conceptualization: A.D, E.E. Data Curation: A.D. Formal Analysis: A.D. Investigation: E.E. Methodology: A.D, P.K. Project Administration: P.K. Supervision: E.E. Validation: E.E. Writing - Original Draft: A.D, P.K. Writing - Review Editing: A.D, P.K

**Cite as**

Deng A, Kaneria P, Espiridion E. Psychiatric Outcomes in Patients with Trigeminal Neuralgia Treated with Anticonvulsants and Antidepressants: A Retrospective Cohort Study Using a National Database. Int J Med Stud. 2025 Jan-Mar;13(1):52-59.



**ISSN 2076-6327**

**This journal is published by Pitt Open Library Publishing**