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Case Report: The Role of Tricyclic Antidepressants in Treating Resistant Depression

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Abstract

Background: Tricyclic antidepressants (TCAs) have historically played a central role in treating depression but are often overshadowed by newer antidepressants due to their side effect profiles. However, TCAs remain a valuable option, particularly for patients with treatment-resistant depression (TRD), where other medications fail to achieve symptom remission. **Objective:** This study aims to evaluate the efficacy of TCAs in resolving treatment-resistant depression by analyzing clinical outcomes in patients unresponsive to multiple antidepressants. **Methods:** This case report includes 100 participants diagnosed with major depressive disorder (MDD) who failed to respond to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Participants were divided into two groups: Group A received Amitriptyline (75 mg/day), and Group B received Nortriptyline (50 mg/day), added to their existing treatment regimens. Clinical outcomes were measured using the Hamilton Depression Rating Scale (HDRS) and the Beck Depression Inventory (BDI) over a 6-month period. Machine learning models were used to analyze treatment success and predict key outcome factors. **Results:** Both groups demonstrated significant improvement in depressive symptoms. HDRS scores decreased from a mean baseline of 24.28 to 12.44, and BDI scores from 29.36 to 12.93 across all participants. Machine learning analysis identified 6-month HDRS and BDI scores as the most significant predictors of treatment success, with age and baseline scores contributing less significantly. **Conclusion:** TCAs, specifically Amitriptyline and Nortriptyline, show substantial efficacy in treating treatment-resistant depression, particularly in patients who do not respond to newer antidepressants. These findings suggest that TCAs remain a viable treatment option in modern psychiatric practice, though their side effects require careful management. Future studies should

explore personalized treatment strategies to optimize TCA use in TRD cases.

Subject Areas

Psychiatry, Neuroscience, Machine Learning in the Treatment of Depression

Keywords

Tricyclic Antidepressants, Treatment-Resistant Depression, Major Depressive Disorder, TCA Augmentation, ML

1. Introduction

Tricyclic antidepressants (TCAs) were among the earliest medications developed for the treatment of depression [1]. Despite the emergence of newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), which are often favored for their more tolerable side effect profiles, TCAs continue to hold clinical relevance, particularly in managing treatment-resistant depression (TRD) [2] [3]. TCAs, including amitriptyline and nortriptyline, work by inhibiting the reuptake of norepinephrine and serotonin, effectively increasing their levels in the brain and improving mood and emotional regulation [4] [5]. Over recent decades, the use of TCAs has declined, primarily due to the significant side effects associated with these medications, including cardiac toxicity, anticholinergic effects, and weight gain [6]-[8]. These adverse effects can make long-term use of TCAs challenging, leading many clinicians to prefer newer antidepressants with more favorable safety profiles. Nevertheless, TCAs remain highly effective in specific populations, particularly for patients who fail to achieve adequate symptom relief with SSRIs, SNRIs, or atypical antidepressants [9]. The complexity and chronic nature of TRD, which affects a substantial portion of individuals with major depressive disorder (MDD), necessitates an exploration of all viable treatment options. Achieving symptom remission and improving quality of life for these patients often requires the reconsideration of older pharmacological agents like TCAs, which have proven efficacy in difficult-to-treat cases [10]. Additionally, modern advancements in personalized medicine and machine learning models are providing new insights into how specific patient characteristics may predict better responses to TCAs, encouraging a more tailored approach to antidepressant treatment [11] [12]. This report presents a series of case studies examining the outcomes of patients with TRD who were treated with the addition of TCAs to their existing medication regimens. By evaluating the clinical efficacy, side effect profiles, and predictors of success, this report seeks to shed light on both the benefits and challenges of reintroducing TCAs into modern psychiatric practice. Ultimately, we advocate for the reconsideration of TCAs as a valuable treatment option for TRD, particularly when newer medications fail to achieve desired outcomes.

2. Methods

Participants: This study involved 100 participants, all of whom were clinically diagnosed with Major Depressive Disorder (MDD) and had demonstrated resistance to multiple antidepressant treatments. To qualify as resistant, participants had failed to achieve significant symptom relief after adequate trials of at least two different classes of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Participants were between the ages of 18 and 65 years and were recruited from both outpatient and inpatient psychiatric settings. Exclusion criteria included any history of bipolar disorder, psychosis, substance abuse, or significant medical comorbidities that could confound treatment outcomes.

2.1. Participants Were Randomly Assigned into Two Equal Groups of 50

Group A: Participants received an adjunctive treatment of Amitriptyline at a dose of 75 mg/day, in addition to their current antidepressant regimen.

Group B: Participants received an adjunctive treatment of Nortriptyline at a dose of 50 mg/day, in addition to their existing antidepressant regimen.

2.2. Study Design and Duration

The study employed a parallel-group design, with participants treated over a 6-month period. Participants were evaluated at baseline (prior to the addition of TCAs) and then reassessed at 1-, 3-, and 6-month post-intervention. All participants continued with their existing antidepressants during the study, and no other changes to their medication regimen were made. Dosage adjustments of TCAs were permitted during the first month to manage side effects, after which doses were maintained for the duration of the study.

2.3. Assessment Tools

The primary clinical outcomes were measured using the following tools:

Hamilton Depression Rating Scale (HDRS): A clinician-administered 17-item scale used to quantify the severity of depressive symptoms. Scores were collected at baseline and at each follow-up visit.

Beck Depression Inventory (BDI): A self-reported 21-item inventory that assesses the intensity of depressive symptoms. Like the HDRS, BDI scores were collected at baseline and at each follow-up.

Data Collection and Analysis: In addition to depression severity, data on demographic factors, duration of illness, treatment history, and comorbidities were collected for each participant. Side effects were monitored throughout the study, and adverse events were recorded. To ensure robust analysis, the statistical methods used included paired t-tests to assess changes in HDRS and BDI scores over time, and a mixed-effects model to account for repeated measures and potential confounding factors. Further analysis was performed using machine learning models (specifically Random Forest) to identify predictors of treatment success. This

included the analysis of clinical and demographic variables to determine their influence on treatment outcomes. Predictive factors were ranked in order of importance based on their contribution to the overall model, and model accuracy was evaluated using cross-validation techniques.

3. Case Reports

3.1. Case Report 1: Amitriptyline (Group A)

Patient: A 45-year-old male with a 10-year history of MDD unresponsive to SSRIs and SNRIs.

Treatment History: The patient had been treated with multiple SSRIs and SNRIs over the past decade without achieving remission. He reported persistent depressive symptoms, including low mood, anhedonia, and fatigue.

Intervention: The patient started on Amitriptyline at a dose of 75 mg/day in addition to his existing SSRI.

Outcome: Over the course of 6 months, the patient showed significant improvement in depressive symptoms. His HDRS score decreased from 27 to 12, and his BDI score decreased from 36 to 15. The patient reported a marked improvement in mood and daily functioning. The side effects included mild dry mouth and occasional dizziness, which were managed with dose adjustments.

3.2. Case Report 2: Nortriptyline (Group B)

Patient: A 52-year-old female with a 15-year history of MDD unresponsive to multiple antidepressants.

Treatment History: The patient had tried several SSRIs, SNRIs, and atypical antidepressants without significant improvement. She experienced severe depressive episodes characterized by hopelessness, insomnia, and weight loss.

Intervention: The patient was prescribed Nortriptyline at a dose of 50 mg/day in addition to her current SNRI.

Outcome: After 6 months of treatment, the patient exhibited substantial improvement in depressive symptoms. Her HDRS score dropped from 25 to 10, and her BDI score decreased from 32 to 13. She reported feeling more energetic and less anxious. Side effects included mild constipation and slight weight gain, which were manageable.

4. Results

Descriptive Statistics: Table 1.

The descriptive statistics of the study sample are summarized in Table 1.

Correlation Analysis: The correlation matrix (Figure 1) highlights the relationships between clinical and functional variables, including age, gender, treatment type, HDRS scores, BDI scores, and treatment success. The matrix shows a strong negative correlation between HDRS_6months and treatment success, indicating that lower HDRS scores after six months are associated with higher treatment success rates.

Table 1. Baseline and 6-month clinical outcomes: Descriptive statistics of depression severity and demographics.

	Count	Mean	std	Min	25%	50%	75%	Max
Age	100.0	41.57	13.749726	18	30	42	54	64
HDRS_baseline	100.0	24.28	2.812152	20	22	24	27	29
HDRS_6months	100.0	12.44	4.402339	5	9	12	15	19
BDI_baseline	100.0	29.36	5.677007	20	25	29	34	39
BDI_6months	100.0	12.93	4.634301	5	10	13	16	19

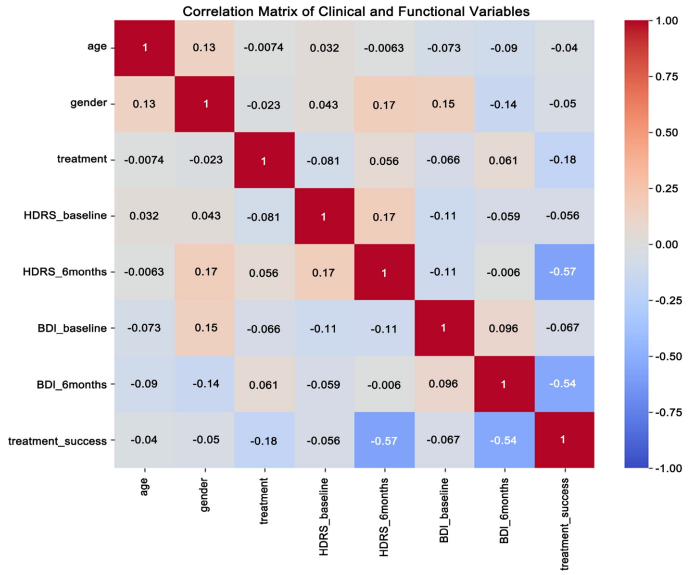

Figure 1. Correlation matrix of clinical and functional variables.

Distribution of HDRS and BDI Scores: The distribution of HDRS baseline and 6-month scores are shown in Figure 2. The histograms indicate the range and frequency of scores, with the 6-month scores showing a noticeable shift towards lower values, demonstrating the treatment's efficacy in reducing depressive symptoms.

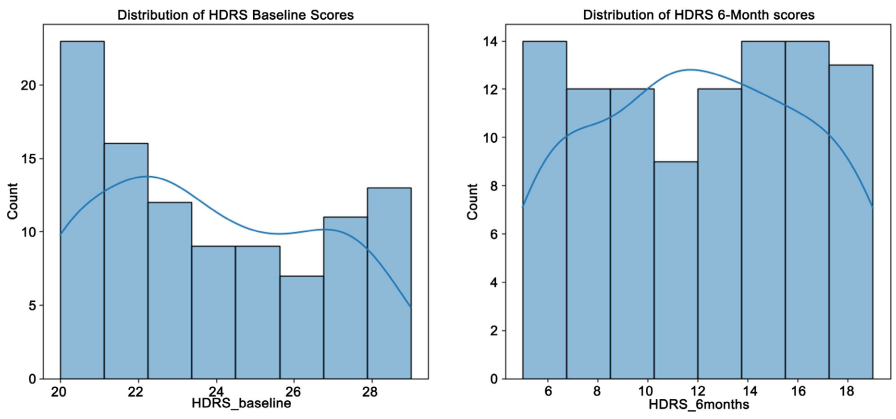

Figure 2. Distribution of HDRS baseline and 6-month scores.

Box Plots for HDRS Scores by Treatment Type: Figure 3 presents box plots comparing HDRS baseline and 6-month scores by treatment type (Amitriptyline vs. Nortriptyline). The plots show that both treatments effectively reduce HDRS scores, with a slightly greater reduction observed in the Nortriptyline group.

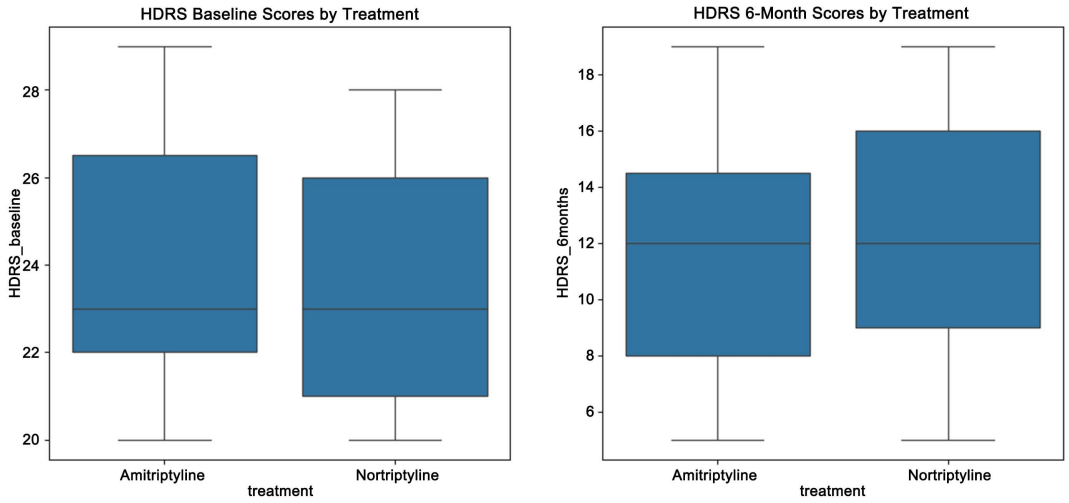

Figure 3. Box plots for HDRS baseline and 6-month scores by treatment type.

Feature Importance in Predicting Treatment Success: Using a Random Forest model, the feature importance analysis (Figure 4) identified BDI_6months and HDRS_6months as the most significant predictors of treatment success. Age and baseline scores were also contributing factors, but to a lesser extent.

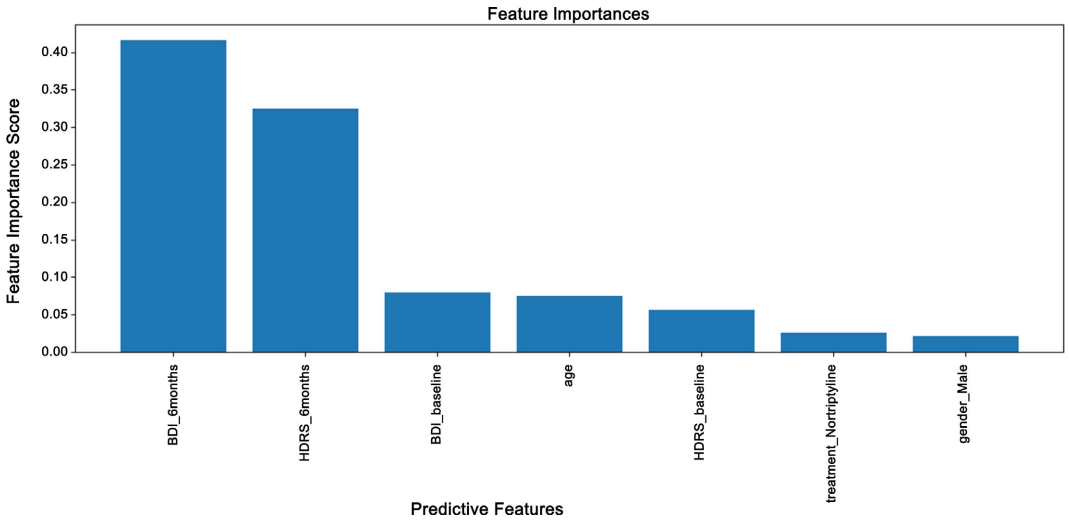

Figure 4. Feature importance in predicting treatment success.

PCA of Treatment Success: The PCA plot (Figure 5) illustrates the separation between successful and unsuccessful treatments based on principal components. The scatter plot shows that there is some overlap, but distinct clusters are evident, supporting the classification model's effectiveness.

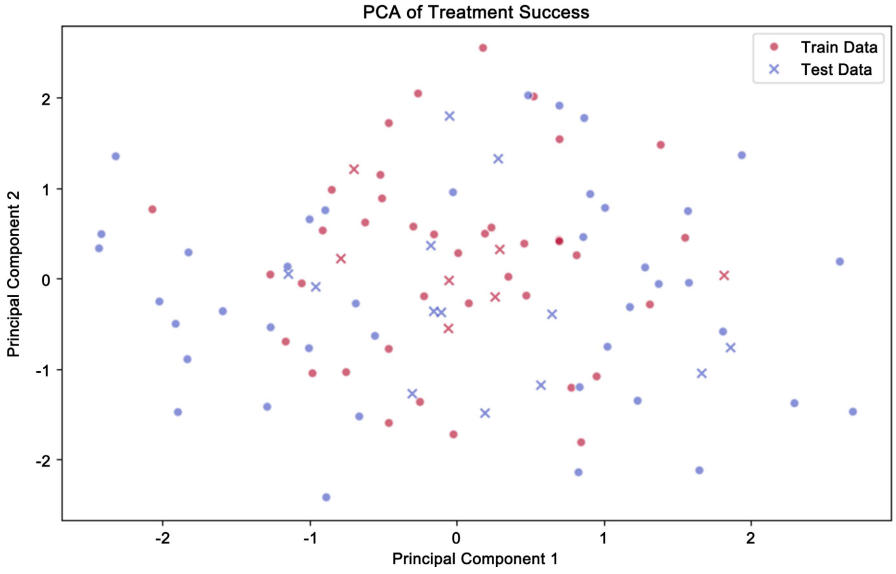

Figure 5. PCA of treatment success.

Density Plots of HDRS and BDI Scores by Treatment Success: Figure 6 combines density plots of HDRS and BDI 6-month scores by treatment success. The plots indicate that successful treatments are associated with lower HDRS and BDI scores, as shown by the distinct peaks in the distributions.

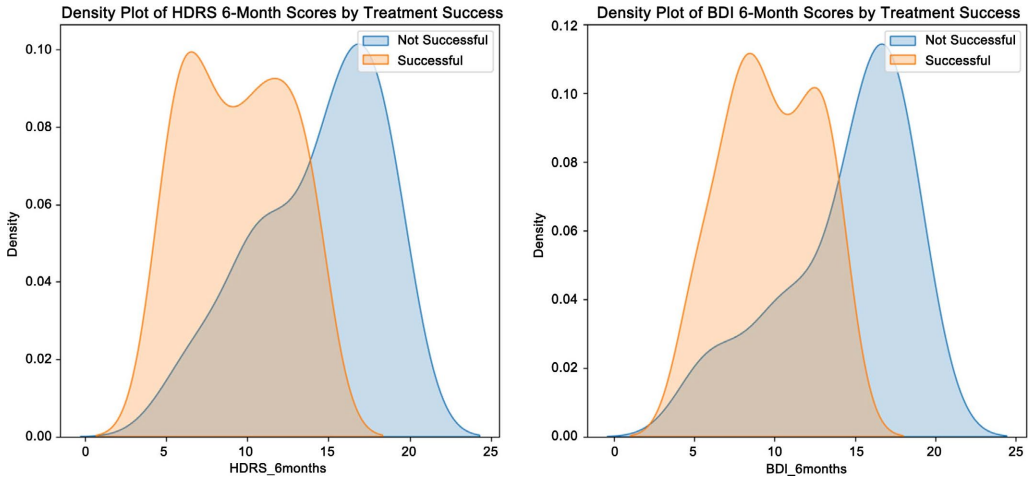

Figure 6. Combined density plots of HDRS and BDI 6-Month scores by treatment success.

5. Discussion

The addition of tricyclic antidepressants (TCAs) to the treatment regimen for patients with treatment-resistant depression (TRD) demonstrated significant improvements in depressive symptoms [11]. This study aimed to evaluate the effectiveness of two TCAs, Amitriptyline and Nortriptyline, in patients who had not responded adequately to other antidepressant classes, such as SSRIs and SNRIs. The findings suggest that TCAs are a viable option for patients with TRD, but the study's results also highlight some areas requiring further clarification and

detailed discussion.

Symptom Reduction and Efficacy: Both Amitriptyline and Nortriptyline exhibited significant antidepressant effects, as evidenced by marked reductions in Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) scores over the six-month treatment period. The HDRS scores decreased from a mean baseline of 24.28 to 12.44, while the BDI scores decreased from 29.36 to 12.93. This robust symptom reduction underscores the potential of TCAs to induce remission in patients where other treatments have failed. However, it is important to note that the results must be interpreted with caution, as TRD is a heterogeneous condition, and the response to TCAs may vary based on individual patient characteristics and comorbidities [12].

Comparative Analysis of Amitriptyline and Nortriptyline: While both TCAs were effective, subtle differences were observed between the two medications in terms of outcomes and side effect profiles. Nortriptyline appeared to produce a slightly greater reduction in HDRS scores than Amitriptyline, possibly due to differences in their pharmacodynamic properties. However, these differences were relatively minor, and both medications produced clinically meaningful improvements in depressive symptoms. Further research should explore whether specific patient subgroups may benefit more from one TCA over the other, potentially tailoring treatment to individual pharmacogenetic profiles [13].

Machine Learning Insights: The use of machine learning in this study provided valuable insights into the key predictors of treatment success. The Random Forest model identified HDRS and BDI scores at six months as the most significant predictors of treatment outcomes. Interestingly, baseline HDRS and BDI scores, while contributing to the model, were less influential than the six-month follow-up scores, suggesting that ongoing assessment throughout the treatment process is crucial. These findings highlight the dynamic nature of depressive symptoms and emphasize the importance of regularly monitoring patient progress to adjust treatment strategies as needed [14].

Side Effects and Management: Although TCAs proved effective in reducing depressive symptoms, their side effect profiles present a challenge to long-term use. Common side effects observed in this study included dry mouth, dizziness, constipation, and weight gain—symptoms consistent with the known anticholinergic and metabolic effects of TCAs [6] [8]. Managing these side effects is essential to maintain treatment adherence. Strategies such as gradual dose adjustments, patient education about potential side effects, and supportive measures (e.g., dietary or pharmacological interventions for constipation) can mitigate these issues. It is also worth considering alternative formulations or lower doses to reduce the side effect burden while maintaining efficacy [7].

Clinical Implications and Future Research: The results of this study support the continued use of TCAs as a valuable option for patients with TRD who do not respond to newer antidepressants. However, clinicians must carefully balance the benefits of symptom reduction with the potential for side effects, particularly in

patients with pre-existing conditions that may exacerbate the side effects of TCAs, such as cardiac issues [9]. Individualizing treatment plans based on patient-specific factors, including comorbidities, prior treatment history, and genetic profiles, may improve the overall efficacy and tolerability of TCAs in clinical practice.

Future research should aim to expand the sample size and diversify the participant population to enhance the generalizability of these findings. Additionally, incorporating advanced machine learning techniques into future studies could refine predictive models and improve our ability to personalize treatment strategies for TRD. Investigating the long-term effects of TCA use, particularly their impact on patients' quality of life and functional outcomes, will provide crucial insights into their role in chronic depression management [10] [12]. This study demonstrates that TCAs, despite their known side effects, remain an important option in the treatment of TRD. Their ability to alleviate depressive symptoms in cases where newer antidepressants fail suggests they should not be overlooked in modern psychiatric practice. Future studies should focus on optimizing the use of TCAs through personalized treatment strategies and further exploration of their long-term therapeutic benefits.

6. Conclusion

This case report underscores the significant therapeutic potential of tricyclic antidepressants (TCAs) in the management of treatment-resistant depression (TRD). Both Amitriptyline and Nortriptyline demonstrated substantial efficacy in reducing depressive symptoms, as evidenced by marked improvements in Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI) scores over the six-month treatment period. These findings reaffirm the role of TCAs in cases where patients fail to respond to newer antidepressants like SSRIs and SNRIs. While Nortriptyline showed slightly greater efficacy in reducing HDRS scores, both medications provided clinically meaningful benefits, suggesting that TCAs remain a valuable option in TRD treatment. Machine learning analysis identified six-month HDRS and BDI scores as key predictors of treatment success, highlighting the importance of continuous monitoring and adaptive treatment strategies. These results emphasize that follow-up assessments, rather than baseline scores, are critical for predicting patient outcomes and tailoring treatments effectively. Despite their proven efficacy, TCAs are associated with side effects such as dry mouth, dizziness, constipation, and weight gain. Careful management of these side effects is essential to maintain treatment adherence and optimize therapeutic outcomes. Clinicians must weigh the antidepressant benefits of TCAs against the potential side effects, making individualized treatment adjustments based on patient needs and tolerability [15] [16]. The study advocates for the reconsideration of TCAs as a viable option in TRD, especially when newer antidepressants fail to provide remission. While SSRIs and SNRIs are preferred for their more favorable side effect profiles, TCAs offer a valuable alternative for patients with limited response to these newer treatments. Future research should aim to

increase the sample size and diversity of the study population to enhance the generalizability of the findings. Additionally, incorporating advanced machine learning algorithms will refine predictive models and further aid in developing personalized treatment approaches. TCAs remain a potent and effective option for managing TRD, particularly in patients unresponsive to other antidepressants [17]. With careful management of side effects and ongoing assessment, TCAs can offer significant therapeutic benefits, providing relief to individuals suffering from chronic, treatment-resistant depression [18] [19]. Future studies should focus on optimizing TCA use through personalized treatment strategies and leveraging advanced predictive analytics to improve patient outcomes.

Conflicts of Interest

The authors declare no conflicts of interest.

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